Single Technology Appraisal

Tixagevimab plus cilgavimab for preventing COVID-19 [ID6136]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Tixagevimab plus cilgavimab for preventing COVID-19 [ID6136]

Contents:

The following documents are made available to stakeholders:

Access the **final scope** and **final stakeholder list** on the NICE website.

1. **Company submission** from AstraZeneca
   a. Submission
   b. Additional evidence

2. **Clarification questions and company responses**
   a. Clarification response
   b. CE and BI results at list price

3. **Patient group, professional group and NHS organisation submissions** from:
   a. Action for Pulmonary Fibrosis
   b. Anthony Nolan
   c. Blood Cancer UK
   d. Chronic Lymphocytic Leukaemia Support
   e. Crohn's & Colitis UK
   f. Clinically Vulnerable Families
   g. Evusheld for the UK
   h. Immunodeficiency UK
   i. Kidney Care UK
   j. Kidney Research UK
   k. Leukaemia Care
   l. Long COVID SOS
   m. LUPUS UK
   n. Lymphoma Action
   o. Multiple Sclerosis Trust
   p. Myeloma UK
   q. Scleroderma and Raynaud's UK
   r. Vasculitis UK
   s. UK CLL Forum
   t. UK Renal Pharmacy Group
   u. NHS England

4. **Expert personal perspectives** from:
   a. Antonio Pagliuca, Professor of Stem Cell Transplantation – clinical expert, nominated by AstraZeneca
   b. Jill Nicholson – patient expert, nominated by Blood Cancer UK

c. Steve Jones – patient expert, nominated by Action for Pulmonary Fibrosis
d. Sanjeev Patel, Consultant Rheumatologist - NHS England Clinical Advisor
e. Mohammed Asghar, ICS Prescribing Governance Lead – commissioning expert, nominated by Frimley Health & Care ICS

Mandy Matthews – commissioning expert, nominated by NHS England (see document 3u.)

5. External Assessment Report prepared by the School of Health and Related Research, University of Sheffield
a. EAG report
b. EAG critique of the additional company evidence
c. EAG addendum

6. External Assessment Report – factual accuracy check
a. Factual accuracy check of the EAG report
b. Factual accuracy check of the updated EAG report and the EAG critique of the additional company evidence

7. Correspondence between NICE and the MHRA regarding repeat dosing

8. Independent Advisory Group (IAG) report concerning the use of COVID-19 directed antibodies in the prophylaxis setting in the highest risk clinical subgroups

9. In Vitro Advisory Group (IVAG) report

10. NICE Managed Access feasibility assessment

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Tixagevimab–cilgavimab for preventing COVID-19 [ID6136]

Document B

Company evidence submission

November 2022

File name	Version	Contains confidential information	Date
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Table of Abbreviations

Abbreviation	Term
AE	Adverse events
AESI	Adverse events of special interest
APPG	All-Party Parliamentary Group
ARDS	Acute respiratory distress syndrome
CASP	Critical Appraisal Skills Programme
CDW	Corporate Data Warehouse
CEAC	Cost-effectiveness acceptability curve
CEV	Clinically extremely vulnerable
CI	Confidence interval
CKD	Chronic kidney disease
CLL	Chronic lymphocytic leukaemia
COPD	Chronic obstructive pulmonary disorder
COVID	Coronavirus disease
DCCI	Deyo-Charlson comorbidity index
DHSC	Department of Health and Social Care
DSMB	Data Safety Monitoring Board
EAG	Evidence Assessment Group
ECMO	Extracorporeal membrane oxygenation
EUA	Emergency Use Authorization
FDA	Food and drug administration
FVC	Forced vital capacity
HR	Hazard ratio
HRG	Health resource group
HRQoL	Health-related quality of life
HTA	Health technology assessment
ICEP	Incremental cost-effectiveness plane
ICER	Incremental cost-effectiveness ratio
ICI	Immunocompromised individuals
ICNARC	Intensive care national audit and research centre
ICU	Intensive care unit
IM	Intramuscular
IMP	Investigational medicinal product
IMV	Invasive mechanical ventilation

IQR	Inter-quartile range
ITT	Intention to treat
KTR	Kidney transplant recipients
LFO	Low-flow oxygen
LY	Life years
MAAE	Medically attended adverse events
MHRA	Medicines and Healthcare products Regulatory Authority
MHS	Meier hazards
MV	Mechanical ventilation
NICE	National institute for health and care excellence
NIV	Non-invasive ventilation
ONS	Office of National Statistics
OWSA	One-way sensitivity analysis
PAS	Patient access scheme
PASLU	Patient access schemes laison unit
PCR	Polymerase chain reaction
PEP	Post-exposure prophylaxis
PERR	Prior event rate ratio
PICOS	Population, interventions, comparators, outcomes and study
PrEP	Pre-exposure prophylaxis
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSA	Probabilistic sensitive analysis
PSS	Personal social services
PSSRU	Personal Social Services Research Unit
QALY	Quality-adjusted life years
QALYS	Quality adjusted life year
QoL	Quality of life
RCT	Randomised clinical trial
RNA	Ribonucleic acid
RR	Rate ratio
RRR	Relative risk reduction
RWE	Real-world evidence
SAE	Serious adverse events
SARS	Severe acute respiratory syndrome

ScHARR	School of health and related research
SD	Standard deviation
SLR	Systematic literature review
SM	Standardized mean
SMD	Standardised mean difference
SoC	Standard of care
SOTR	Solid organ transplant recipients
TLR	Targeted literature review
TTSR	Time to symptom resolution
US	United States
UTI	Urinary tract infection
VA	Veterans Affairs
VoC	Variant of concern
VOI	Variant of interest
WHO	World Health Organization
WTP	Willingness to pay

B1 Decision problem, description of the technology and clinical care pathway

B1.1 Decision problem

The decision problem addressed in this submission is presented in Table 1.

The submission focuses on a specific target population within Evusheld's marketing authorisation based on its expected use in UK clinical practice, as defined below. All other aspects of the decision problem align with the NICE scope.

1.1.1 Target population

Adults who are not currently infected with SARS-CoV-2 and who have not had a known recent exposure to a person infected with SARS-CoV-2 and:

- are at the highest risk of an adverse COVID-19 outcome, namely hospitalisation and death, or
- for whom COVID-19 vaccination is not recommended

The target population is clearly defined in clinical practice (as detailed in Section B1.3.5) and closely aligns with the 'subgroups to be considered' section of the NICE scope.

UK clinical experts advised that the target population represents people with the highest medical unmet need for prophylactic treatment and as such, is where Evusheld is anticipated to be used in UK clinical practice. See Section B1.3 for further details.

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults who are not currently infected with SARS-CoV-2 and who have not had a known recent exposure to a person infected with SARS-CoV-2 and: • who are unlikely to mount an adequate immune response to COVID-19 vaccination or • for whom COVID-19 vaccination is not recommended	Adults who are not currently infected with SARS-CoV-2 and who have not had a known recent exposure to a person infected with SARS-CoV-2 and: • are at the highest risk of an adverse COVID-19 outcome, namely hospitalisation and death, or • for whom COVID-19 vaccination is not recommended	The target population represents a subgroup of the licenced indication since it focuses on the highest risk patients within those who are unlikely to mount an adequate immune response to COVID-19 vaccination. An independent report commissioned by the UK Department of Health and Social Care (DHSC) identified patient subgroups, as defined by their underlying health conditions, who are deemed to be at the highest risk of adverse clinical outcomes due to COVID-19.(1) These patients predominately comprise of those who are immunocompromised and therefore often do not mount a sufficient immune response to COVID-19 vaccinations. AstraZeneca has consulted with 60 clinical experts across 19 specialities who consistently advised that the populations identified in the DHSC report represents those at highest risk

			of adverse clinical outcomes and are at the greatest need for prophylaxis. Therefore, UK clinical experts advised that the anticipated positioning of Evusheld should be in this clearly defined highest risk subgroup, as well as for adults for whom COVID-19 vaccination is not recommended – and as such inadequate protection is provided. See Section B1.3 for further details.
Intervention	Tixagevimab and cilgavimab (Evusheld)	As per scope	NA
Comparator(s)	No prophylaxis	As per scope	NA
Outcomes	The outcome measures to be considered include: • incidence of symptomatic COVID-19 • mortality • requirement for respiratory support • hospitalisation (requirement and duration) • symptoms of post COVID-19 syndrome • anxiety and depression • time to return to normal activities post COVID-19 • adverse effects of treatment • health-related quality of life	As per scope	NA

Economic analysis	The reference case stipulates that the cost-effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost-effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator, and subsequent treatment technologies will be taken into account.	As per scope	NA
Subgroups to be considered	If the evidence allows the following subgroups will be considered: • adults at highest risk of adverse COVID-19 outcomes	Captured as part of the target population for this submission.	See Section B1.3.5.
Special considerations including issues related to equity or equality	Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the	As per scope	NA

	marketing authorisation granted by the regulator. The impact of vaccination status or SARS-CoV-2 seropositivity on the clinical evidence base of each intervention, generalisability to clinical practice and interaction with other risk factors will be considered in the context of the appraisal. The impact of different variants of concern of COVID-19 on the clinical evidence base of each intervention will be considered in the context of the appraisal.		

Abbreviations: DHSC – Department of Health and Social Care; NA – Not applicable; NHS – National health service; NICE – National Institute for Health and Care Excellence; SARS-CoV-2 – severe acute respiratory syndrome coronavirus 2

B1.2 Description of the technology being evaluated

Table 2: Description of the technology being appraised

UK-approved name and brand name	Evusheld (tixagevimab and cilgavimab)
Mechanism of action	Evusheld is a combination of tixagevimab and cilgavimab, two recombinant human IgG1k monoclonal antibodies, with amino acid substitutions in the Fc regions to extend antibody half-life (YTE) and to reduce antibody effector function and potential risk of antibody-dependent enhancement of disease (TM). Tixagevimab and cilgavimab can simultaneously bind to non-overlapping regions of the spike protein receptor binding domain of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). This unique combination works synergistically to create a more durable mechanism of action and makes it less susceptible to loss of neutralising activity with respect to emerging variants.
Marketing authorisation/CE mark status	Evusheld received conditional marketing authorisation from the Medicines and Healthcare products Regulatory Authority (MHRA) on 17th March 2022. Evusheld is indicated for the pre-exposure prophylaxis (PrEP) of coronavirus disease 2019 (COVID-19) in adults who are not currently infected with SARS-CoV-2 and who have not had a known recent exposure to an individual infected with SARS-CoV-2 and: • who are unlikely to mount an adequate immune response to COVID-19 vaccination, or • for whom COVID-19 vaccination is not recommended. Evusheld is approved at a 300 mg and 600 mg dose depending on the dominant SARS-CoV-2 variant in circulation. [redacted] 300 mg [redacted] the [redacted] the [redacted] of [redacted]. These updated dose recommendations are based on the totality of the available data including clinical pharmacology, pharmacokinetics, antiviral activity, and clinical trial data(2).

<table>
<tr><td></td><td></td></tr>
<tr><td>Indications and any restriction(s) as described in the summary of product characteristics (SmPC)</td><td>Evusheld is indicated for the PrEP of coronavirus disease 2019 (COVID-19) in adults who are not currently infected with SARS-CoV-2 and who have not had a known recent exposure to an individual infected with SARS-CoV-2 and:
who are unlikely to mount an adequate immune response to COVID-19 vaccination, or
for whom COVID-19 vaccination is not recommended.</td></tr>
<tr><td>Method of administration and dosage</td><td>The expected dose of 600 mg of Evusheld is administered as 300 mg of tixagevimab and 300 mg of cilgavimab, given as separate sequential IM injections, at different injection sites in two different muscles, preferably the gluteals.<table><tr><th>Evusheld dose (tixagevimab + cilgavimab)</th><th>Antibody dose</th><th>Number of vials needed</th><th>Volume to withdraw from vials</th></tr><tr><td rowspan="2">300 mg + 300 mg</td><td>tixagevimab 300 mg</td><td>2 vials</td><td>3 mL</td></tr><tr><td>cilgavimab 300 mg</td><td>2 vials</td><td>3 mL</td></tr></table>The 300 mg of Evusheld is administered as 150 mg of tixagevimab and 150 mg of cilgavimab, given as separate sequential IM injections, at different injection sites in two different muscles, preferably the gluteals.<table><tr><th>Evusheld dose

(tixagevimab + cilgavimab)</th><th>Antibody dose</th><th>Number of vials needed</th><th>Volume to withdraw from vial</th></tr><tr><td rowspan="2">150 mg + 150 mg</td><td>tixagevimab 150 mg</td><td>1 vial</td><td>1.5 mL</td></tr><tr><td>cilgavimab 150 mg</td><td>1 vial</td><td>1.5 mL</td></tr></table></td></tr>
<tr><td>Additional tests or investigations</td><td>No</td></tr>
<tr><td>List price and average cost of a course of treatment</td><td>£800 per 300 mg dose
£1,600 per 600 mg dose</td></tr>
</table>

Patient access scheme (if applicable)	At the time of submission, an application to PASLU has been made for a simple PAS, resulting in an estimated net price of [redacted] per 600 mg dose.

Abbreviations: ACE2 – Angiotensin-Converting Enzyme 2; CHMP – Committee for Medicinal Products for Human Use; COVID-19 – Coronavirus disease 2019; EMA – European medicines agency; Fc – Fragment crystallisable; IgG1κ – Immunoglobulin G, subclass 1, κ light chain; IM – intramuscular; KD – Dissociation constant; mg – Milligrams; MHRA – Medicines and Healthcare products Regulatory Agency; ml – millilitre; ng – Nanograms; nM – Nanomolar; pM – Picomolar; RBD – Receptor binding domain; PASLU - Patient Access Schemes Liaison Unit; PrEP – Pre-exposure prophylaxis; SARS-CoV-2 – Severe acute respiratory syndrome coronavirus 2; SmPC – Summary of product characteristics.

B1.3 Health condition and position of the technology in the treatment pathway

B1.3.1 Disease overview

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a highly contagious novel coronavirus, caused a worldwide outbreak of symptomatic and potentially fatal respiratory disease, known as COVID-19.(3)

In December 2019, the first case of COVID-19 was recorded in China, and by March 2020, COVID-19 was declared by the World Health Organization (WHO) as a pandemic(3). This resulted in unprecedented life-limiting restrictions being put in place by governments across the world to prevent the spread of the virus.

Despite a highly effective global vaccine rollout, the development of effective treatments for COVID-19 (Section B1.3.6), and the lifting of UK restrictions in March 2022(4), COVID-19 remains a considerable public health issue in the UK:

- In 2022 the weekly rate of people in England estimated to be infected with COVID-19 has fluctuated, with a highest rate of 7.6% in March and a lowest rate of 1.29% in September(5). A total of 177,977 deaths within 28 days of a positive test have been recorded in the UK.(6,7)

- The Office of National Statistics (ONS) has estimated that 2.0 million people in the UK (2.9% of the UK population) have reported long COVID symptoms (see Section B1.3.7), which have a significant detrimental impact on quality of life.(8)

- The burden of COVID-19 on the UK healthcare system is still substantial. In 2020 and 2021, there were approximately 240,000 and 300,000 COVID-19 related admissions, respectively and since January 2022, there has been a similar number of COVID-19-related admission to those seen over the whole of 2021 by September 2022.. These data demonstrate the ongoing burden that COVID-19 continues to place on health services in England.(9)

COVID-19 continues to pose an unprecedented challenge to the UK healthcare systems, e.g., through substantial increases in hospitalisations and intensive care admissions. This is further exacerbated by the continuous emergence of new variants, which can significantly impact how easily the virus spreads and the severity of disease.(10)

B1.3.2 Clinical presentation and diagnosis

SARS-CoV-2 is transmitted via aerosolised airborne respiratory droplets, e.g., through sneezing and coughing.(11) The contagious nature of COVID-19 renders virus exposure periodically extremely difficult to avoid, an issue is exacerbated by the fact that many cases are asymptomatic. (11)

Clinical presentation of COVID-19 can vary, but symptoms often include a high temperature, a new continuous cough, and a loss or change to taste and/or smell. In addition, other flu-like symptoms can be present such as shortness of breath, fatigue, aches, headache, a sore throat, congestion, loss of appetite, diarrhoea, and feeling or being sick.(3,12)

SARS-CoV-2 viral presence is confirmed by Polymerase chain reaction (PCR). Previously, testing for SARS-CoV-2 infection was mandatory under UK COVID-19 guidelines. However, with UK restrictions uplifted, testing is no longer enforced(13) and as such, many people with SARS-CoV-2 infection remain unidentified and continue to spread the disease unknowingly.(14)

B1.3.3 Disease severity

COVID-19 has a spectrum of disease severity and has been well-defined by the WHO clinical progression scale on a score of 0-10 (Table 3).

The majority of people infected with COVID-19 present with mild ambulatory disease, which may be self-limiting and result in a requirement for additional assistance from family or carers. However, some people experience severe disease, which can result in hospitalisation and death.

Table 3: WHO clinical progression scale

Patient state	Descriptor	Score
Uninfected	Uninfected; no viral RNA detected	0
Ambulatory mild disease	Asymptomatic; viral RNA detected	1
	Symptomatic; independent	2
	Symptomatic; assistance needed	3
Hospitalised: moderate disease	Hospitalised; no oxygen therapy	4
	Hospitalised; oxygen by mask or nasal prongs	5
Hospitalised: severe disease	Hospitalised; oxygen by NIV or high-flow	6
	Intubation and mechanical ventilation, pO2/FiO2 ≥150 or SpO2/FiO2 ≥200	7
	Mechanical ventilation pO2 /FIO2 <150 (SpO2 /FiO2 <200) or vasopressors	8
	Mechanical ventilation pO2 /FiO2 <150 and vasopressors, dialysis, or ECMO	9
Dead	Dead	10

Abbreviations: FiO2 – Fraction of inspired oxygen; pO2 – Partial pressure of oxygen; RNA – Ribonucleic acid; SpO2 – Peripheral capillary oxygen saturation; NIV – Non-invasive ventilation.

While most people who survive COVID-19 recover within 21 days,(15) many do not clear the virus during this time. A large proportion of patients harbour infection for longer than 28 days and prolonged infection can place individuals at higher risk of recurrent acute COVID-19 Company evidence submission template for Tixagevimab–cilgavimab for preventing COVID-19 [ID6136]

episodes, increasing their risk for adverse outcomes, including hospitalisation and death. In addition, this increases their risk for developing long-term clinical sequalae and new comorbidities; clinically defined as long COVID.(16)

Symptoms of long COVID have been reported across many studies as affecting the ability to carry out day-to-day activities compared to the time before COVID-19. (17–20)

These symptoms, include fatigue, shortness of breath, chest pain, heart palpitations, joint pain, depression, anxiety and changes to smell and taste and can be debilitating.(17–20)

B1.3.4 Epidemiology

The infection rate is currently low, with an estimated 1.29% of people in England believed to be infected in the week ending 5th of September 2022. Rates of infection fluctuate significantly and were as high as 7.6% in the week ending 30th of March 2022.(5) A total of 177,977 deaths within 28 days of a positive test have been recorded in the UK.(6,7)

Prolonged infection with SARS-CoV-2 virus risks the development of viral evolution and the emergence of new mutated viral variants that could be introduced into circulation – which may include variants of concern.(21) There are several variants currently circulating in the UK. Omicron (B.1.1.529) sub-lineage BA.5 is currently the predominant circulating variant of concern in the UK.(22) Other variants of concerns detected in the UK are Omicron (B.1.1.529) sub-lineages BA.1, BA.2 and BA.4.(22)

B1.3.5 High-risk populations

There are a number of risk factors for poor COVID-19 outcomes, including being elderly, certain underlying health conditions, and being immunocompromised.(11,23–27)

Immunocompromised individuals often suffer with an increased period of infection and are at an increased risk of severe outcomes from COVID-19 such as hospitalisation, intensive care unit (ICU) admission and death, due to their reduced rate of antibody development produced after infection and vaccination.(28)

In May 2022, the UK government recognised the need to identify highest risk individuals. The Department of Health and Social Care (DHSC) commissioned a report from an independent advisory group, chaired by Professor Iain McInnes and supported by the NHS England RAPID-C19 team, to identify “highest risk clinical subgroups upon community infection with SARS-CoV-2”, defined as those whose immune system means they are at higher risk of serious illness from COVID-19.(1)

The purpose of the report was to determine who should be eligible to receive approved medications for COVID-19 treatment or prophylaxis, to complement the insufficient protection offered by currently available vaccines. Identified individuals were offered antivirals and neutralising monoclonal antibody (nMAB) treatment in the event of a positive test (see Section B1.3.6).(1)

The report identified a population of approximately 1.8 million people(29) in England, including certain patients from within the clinical subgroups listed in Table 4.

Table 4: Highest risk clinical subgroups

Subgroup
Down's syndrome and other genetic disorders
Solid cancer
Haematological diseases and HSCT recipients
Renal disease
Liver diseases
SOT recipients
Immune-mediated inflammatory disorders
Immune deficiencies
HIV/AIDS
Rare neurological and severe complex life-limiting neuro-disability conditions

Abbreviations: AIDS – Acquired immune deficiency syndrome; HIV – Human immunodeficiency virus; HSCT – Haematopoietic stem-cell transplantation; SOT – Solid organ transplant

B1.3.6 Current NHS care pathway for the management of COVID-19

There are a number of interventional strategies used in the current NHS care pathway for the management of COVID-19.

Strategies to prevent COVID-19 infection

Vaccination

Six COVID-19 vaccines are currently approved and available in the UK[1]; 93.4% of the UK population (aged >12 years) have received a first dose, 87.6% are fully vaccinated (2 doses) and 69.8% have received a booster (as of 14th of July 2022) (30,31) The immune response, safety, and efficacy of the vaccines have been rigorously explored in clinical trials, and monitoring of vaccine effectiveness and population impact is ongoing.

The detrimental impact of COVID-19 for the general UK population health have been substantially reduced due to the successful rollout of the COVID-19 vaccination programme. Most people infected with COVID-19, who do not have an underlying health condition, will experience mild to moderate disease symptoms and make a full recovery, following a period of rest.

However, despite vaccine rollout, individuals who are clinically vulnerable (Table 4) for whom COVID-19 vaccination is less effective remain at the high risk of an adverse COVID-19 outcomes.

Furthermore, 0.00067% of the UK population are not able to be fully vaccinated with any available COVID-19 vaccines due to a documented history of severe adverse reactions to a COVID-19 vaccine or any of its components and as such are considered high-risk.(32) As such, these individuals remain unprotected compared to the rest of society.

[1] Moderna (Spikevax), Oxford/AstraZeneca (Vaxzevria), Pfizer/BioNTech (Comirnaty), Janssen (Jcovden), Novavax (Nuvaxovid) and Valnea

Lifestyle modifications

Despite the lifting of UK government enforced restrictions, some people continue to take precautions by making lifestyle modifications to prevent COVID-19 infection, including wearing face masks, reducing social interaction, and shielding whereby individuals do not leave their homes and minimise all face-to-face contact.(33)

In the absence of adequate protection from vaccination, a considerable proportion of high-risk individuals in the UK make fear-induced lifestyle modifications. Such life-restricting measures include staying at home more, avoiding social gatherings and limiting travel, in particular avoiding public transport.(20)

Strategies to treat COVID-19 infection

Oxygen therapy and ventilation

Hospitalised patients receive oxygen therapy, non-invasive or invasive ventilation aligned with the WHO clinical progression scale (Table 3). Length of stay in hospital depends on the severity of disease; Beigal et al. reported that an average 5, 7, 15 and 29 days for no oxygen, low-flow oxygen, high-flow oxygen, and invasive mechanical ventilation, respectively(34). Such interventions and length of stay in hospital substantially affects quality of life and more severe hospitalisations are known predictors of mortality(35).

Therapies

High-risk individuals identified by the DHSC (detailed in Section B1.3.5) may receive the following acute therapies to manage symptoms and reduce the risk of serious illness(36):

- Antivirals: Paxlovid (nirmatrelvir and ritonavir), Veklury (remdesivir), and Lagevrio (molnupiravir)

- Neutralising monoclonal antibody (nMAB): Xevudy (sotrovimab)

While their use in clinical practice acknowledges the extremely exposed position of high-risk populations, limitations remain as some individuals cannot take these treatments due to interaction with other medications or because of the fear and risks attributed to accessing medical care: (37)

- There is a short period in which patients are eligible for treatment following symptom development and confirmed infection, rendering access difficult. A recent study demonstrated that only 18% of eligible high-risk patients with COVID-19 were actually treated with an antiviral or nMAb in England between December 21 and April 22.(38)

- UK Clinical commissioning guidelines acknowledge several limitations with available treatments:

    - Paxlovid is contraindicated in severe liver disease, has multiple drug-to-drug interactions, and is not recommended for use in pregnancy (39,40)

    - Remdesivir is administrated intravenously with one infusion every day for three days, causing significant inconvenience and pain to patients; it is not

recommended in individuals with severe liver disease (ALT>5 times upper limit of normal) and impaired renal function (39,40)

- Sotrovimab has limited efficacy against Omicron subvariants, is administered intravenously – with significant time and resource expenditure as well as associated discomfort to the patient(39,40)

Furthermore, these treatments are currently undergoing a NICE Multiple technology appraisal (MTA) [TA10936](41) and are not currently routinely commissioned in England and Wales.

B1.3.7 Burden of COVID-19 in high-risk populations

The clinical, humanistic, and economic burden for high-risk, immunocompromised people is substantial and disproportionate compared to the general UK population.

Clinical burden

As discussed in Section B1.3.5, high-risk populations have an increased risk of suffering poor outcomes such as hospitalisation and death from COVID-19.

In particular, immunocompromised individuals make up a disproportionately high number of hospitalisations and deaths due to breakthrough COVID-19 (defined as infection despite vaccination). Despite only accounting for approximately 1-3%(29,42) of the general UK population, the immunocompromised represent:

- Over 40% of all UK vaccine breakthrough COVID-19 hospitalisations (43,44)
- 14.0 to 27.7% of all breakthrough UK ICU admissions(45)
- 13.1 to 17.7% % of breakthrough deaths in England (43,44)

According to a report published by the UK intensive care national audit and research centre (ICNARC), vaccine dose exposure seemed to correlate positively with hospital admissions among immunocompromised individuals – i.e., the more vaccine doses individuals received, the higher the proportion admitted to hospital (Figure 1). This could be an indication that multiple booster vaccinations may not sufficiently reduce hospitalisations in these populations compared to the general population and that further interventions may be warranted.(45)

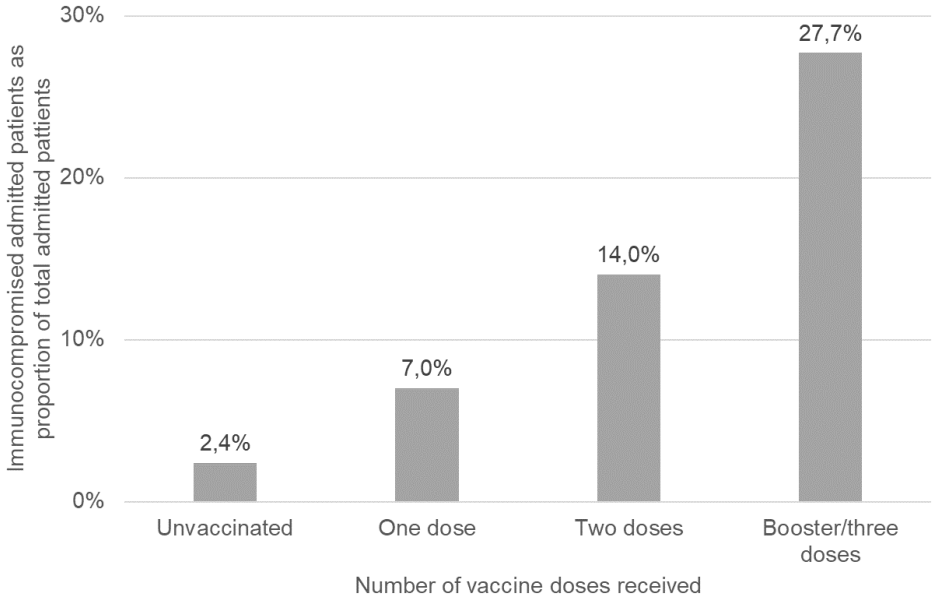
These results are consistent with a recent analysis of Hospital Episode Statistics data looking at hospital admissions in England for a 12-month period ending May 30, 2022, which demonstrated that immunocompromised people that had received three or more COVID-19 vaccinations were disproportionally affected by COVID-19 compared to non-immunocompromised people that had also received three or more COVID-19 vaccinations. (47)

This analysis also demonstrated that in-hospital mortality was approximately 50% higher in the highest risk population compared to the general population. Patients who survived and were discharged had a longer mean length of stay, especially those who received respiratory support.(47)

A recent retrospective cohort study conducted on behalf of NHS England analysed over 18 million adults in England and demonstrated that COVID-19 death rates generally decreased

over the first three pandemic waves. However, groups more likely to experience impaired vaccine effectiveness did not see the same benefit in COVID-19 mortality reduction. Only small decreases in death rates were observed in patients with kidney disease, haematological malignancies or conditions associated with immunosuppression, all groups represented in the highest risk clinical subgroups.(48)

Figure 1: Proportion of critically ill patients with confirmed COVID-19 who are immunocompromised, by vaccination status



Patients admitted from 1 May 2021 to 28 February 2022. Source: (45)

Humanistic burden

The protective measures discussed in Section B1.3.6 and anxiety of being under constant threat of severe illness have a profound negative impact on quality of life in high-risk populations and their close ones.

Lifestyle changes

A considerable proportion of high-risk individuals in the UK make fear-induced lifestyle modifications to protect themselves in the absence of adequate protection from vaccination.

A recent ONS survey on the impact of COVID-19 in clinically extremely vulnerable individuals found that the vast majority (82%) take extra precautions to protect themselves. As many as 13% resort to the extreme of completely shielding, and still do to this day despite no longer being recommended to do so (Figure 2).(20) These outputs are consistent with another recent ONS survey published in July 2022 which similarly reported that 82% of individuals who are at the highest-risk of COVID-19 adverse outcomes continue to take extra precautions and 13% still continue to shield entirely.(49)

When asked about additional measures to keep themselves safe from COVID-19(20):

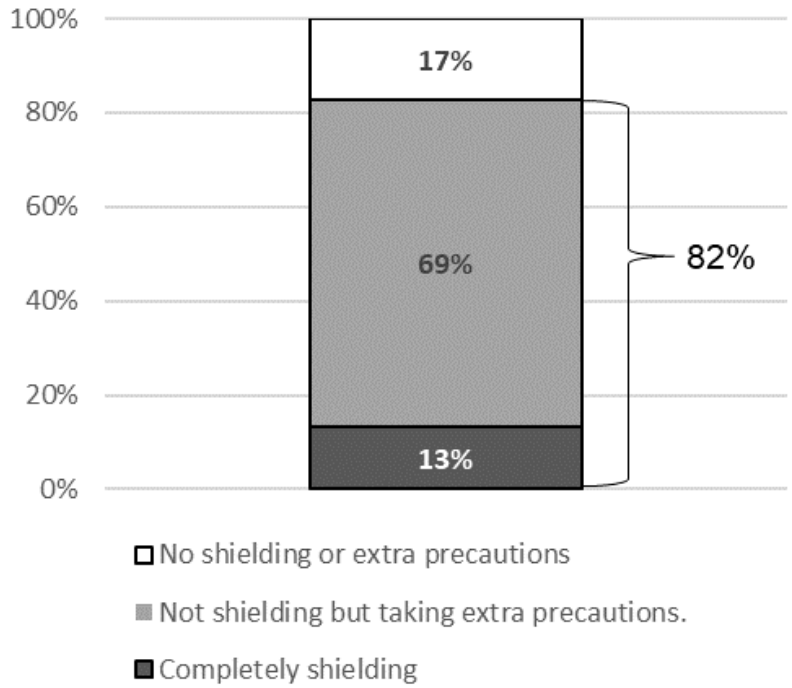
- almost one third (31%) indicated that they are shielding or staying at home more

- 37% avoid social gatherings
- 15% avoid the use of public transport

Such activity limits daily activities, often to an extreme extent, and reduces interaction with family and friends, resulting in social isolation.

Shielding has been shown to have detrimental impact on employment, mental health, health-related quality of life (HRQoL) and access to healthcare.(17,20,50–53) Within mental health alone, individuals have reported emotional distress, mood disorders, depressive symptoms, worsening or emergence of neuropsychiatric symptoms, acute stress disorder, insomnia, frustration, boredom, and loneliness.(50)

Figure 2: Proportion of clinically extremely vulnerable individuals taking additional precautions against COVID-19



Source: (20)

Fear and anxiety

In addition to the life-limiting steps taken to feel safer, the burden of fear and anxiety itself weighs heavily on high-risk individuals.

Although most of the UK population is vaccinated and boosted, COVID-19 continues to be highly prevalent in society and remains an omnipresent threat to the less protected. Fear and uncertainty are further exacerbated by a number of asymptomatic transmissions(11) and the continuous emergence of new and highly transmissible variants.

In a cross-sectional study conducted in the UK throughout the second wave of the pandemic, those shielding demonstrated significantly higher rates of health anxiety and fear of infection in comparison to other groups. Rates of anxiety were higher compared to at the start of the pandemic (March 2020).(54)

A longitudinal, web-based, survey completed by members of general population aged ≥18 years (of whom only 20% had previously been infected with COVID-19) across 13 countries between November and December 2020 quantified the impact of the COVID-19 pandemic on HRQoL as measured by the EQ-5D-5L instrument and its domains. A [redacted] was reported ([redacted]), representing an [redacted] in HRQoL. Those with chronic diseases were more likely to report HRQoL decreases, and notably the psychosocial impact (anxiety and depression) was the domain most impacted for all respondents as shown in Figure 3.(55)

Figure 3: Association between worsened health and clinical characteristics of participants

Source: (55). Abbreviations: PCHC – Paretian classification of health change.

COVID-19 infection

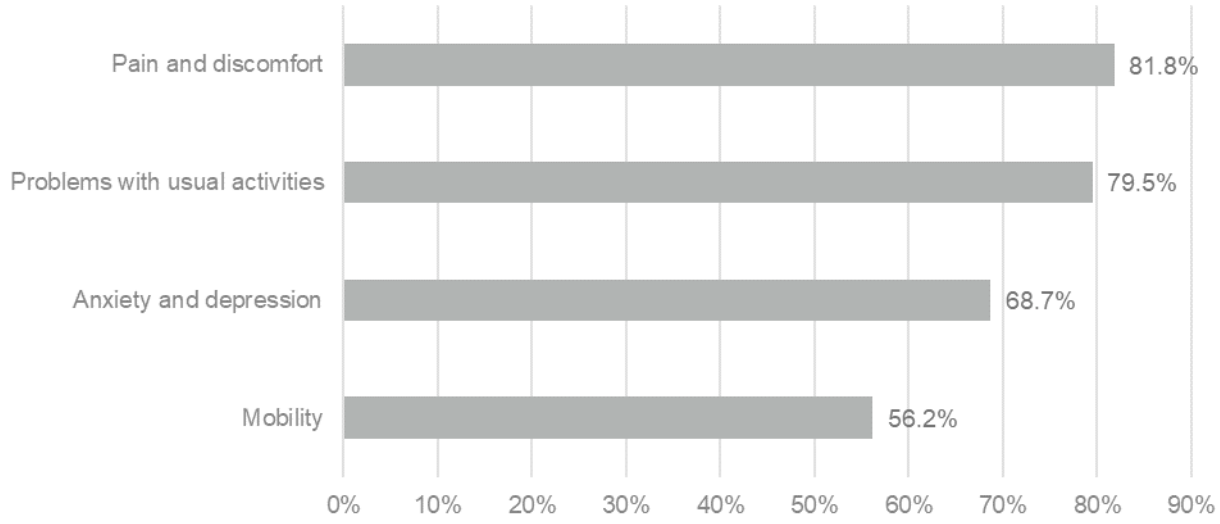
An acute infection with COVID-19 can substantially impact quality of life over a number of weeks, with EQ-5D disutility estimates ranging from -0.19 to -0.79 depending on severity on the WHO prognosis classification scale (Table 3).(56) Specifically, for hospitalised patients, EQ-5D scores range from 0.581 to 0.693 in those admitted to the ICU, compared to 0.613 to 0.724 in the general ward (see Appendix H).(57)

Furthermore, for a proportion of people in the UK who are infected with COVID-19 and survive, the acute infection can result in long COVID; the ONS has estimated that 2.0 million people in the UK (2.9% of the UK population) have reported long COVID symptoms.

Long COVID considerably reduces well-being in the affected. A large (N=1,077), multi-centre, long-term follow-up study of adults discharged from UK hospitals with a clinical diagnosis of COVID-19(58) found the following:

- The vast majority of survivors (91.1%) experienced persistent symptoms
- As many as 20% suffered from new disability at an average follow-up of 5.9 months
- A 2021 global survey study measuring the HRQoL impact of COVID-19 in survivors, their partners and family members also found a major and persisting impact on HRQoL.(59) At 12.8 weeks after diagnosis, the majority of survivors reported pain and discomfort, problems with usual activities, anxiety and depression, and problems with mobility (Figure 4).

Figure 4: Proportion of COVID-19 survivors reporting issues 12.8 weeks after diagnosis



Source: (59)

Caregiver burden

Lifestyle changes due to the fear of contracting COVID-19 has a considerable impact not only on the directly affected, but also on supporting individuals.

Many high-risk individuals rely heavily on support from carers, friends, or family.(60) Those who are close to vulnerable individuals must often take precautions themselves, in order to not put their loved one at risk. Additionally, they may need to support with everyday tasks, and care for vulnerable people.

- A Europe-wide caregiver study demonstrated an increased prevalence of informal caregiving outside the household during the first wave of the pandemic.(61)

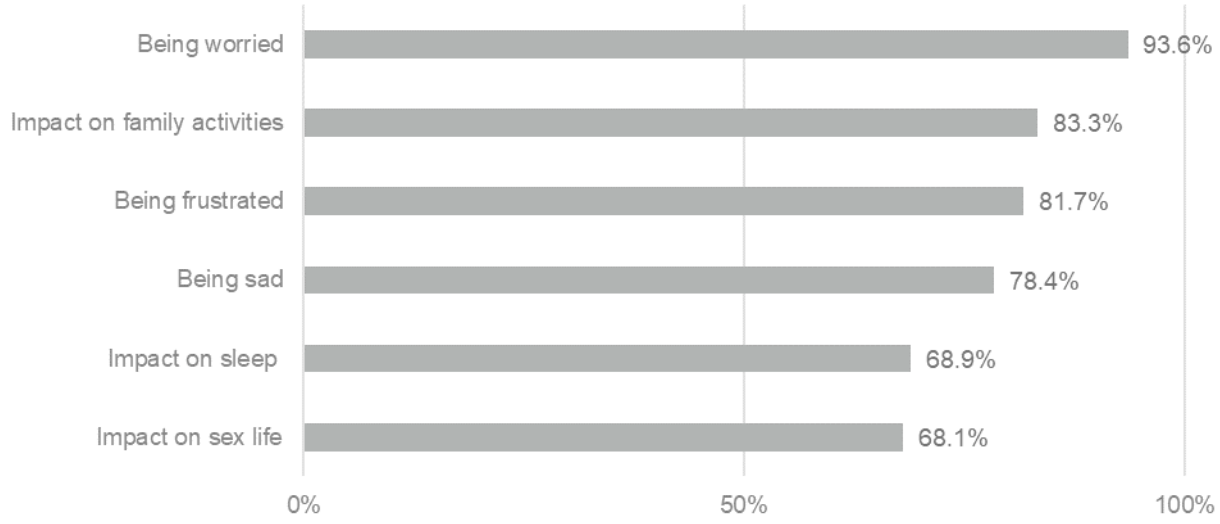
- Increased provision of informal care has been associated with an increased mental health burden for carers, including a significantly higher proportion of caregivers reporting sadness/depression and anxiousness/nervousness than non-caregivers.(54)

- Increased time spent caring for parents was also associated with a significant increase in feelings of sadness/depression and anxiousness/nervousness compared with those who maintained or reduced their time caring for parents.(54)

- More than half of participants who were shielding with others experienced high levels of empathetic health anxiety regarding the health of their loved one.(54)

- Furthermore, long COVID can have a long-term impact on partners and family members of the survivors, with almost everyone indicating being worried (Figure 5).

Figure 5: Proportion of partners and family members of COVID-19 survivors reporting issues 12.8 weeks after COVID-19 survivor diagnosis



Source: (59)

Economic burden

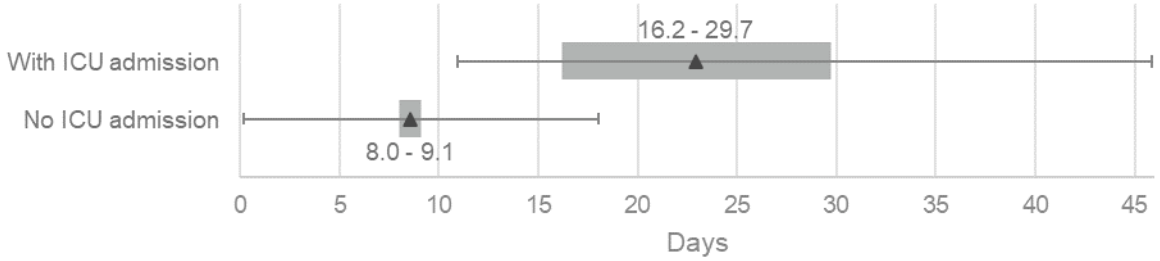
While the majority of COVID-19 infections do not require healthcare intervention, more severe cases incur substantial direct and indirect costs.

Direct costs

Severe disease and resulting hospitalisations and ICU admissions are key drivers of the direct economic costs of COVID-19.

As discussed in Section B1.3.5, a disproportionate number of immunocompromised individuals require hospitalisation and ICU admission. As shown in Figure 6, the length of COVID-19 hospital stay in the UK varies considerably, ranging from a mean of 8.0 (SD: 8.4) to 9.1 (SD: 9.5) days for non-ICU admissions, and from 16.2 (SD: 12.0) to 29.7 (SD: 22.9) days for hospitalisations with ICU admission.(62)

Figure 6: Average range of length of COVID-19 hospitalisation with and without ICU admission in the UK



Abbreviations: ICU – Intensive care unit. Grey area indicates range, error bars represent standard deviation.

Non-urgent routine care has been widely paused to provide care for people with COVID-19, resulting in a growing backlog and reduced healthcare delivery capacity. It has been estimated that clearing this backlog over three years would require treating 1.5 million more patients a year beyond the long-term plan assumptions, at an additional cost of £1.9 billion per year (63). Reducing hospitalisations will be important in clearing this backlog.

Indirect costs

Indirect costs represent a considerable component of the economic burden of COVID-19, both to the affected individuals and society at large. Shielding among immunocompromised individuals negatively impacts their ability to engage in daily activities and return to work.(17,19,64) Among 623,000 vulnerable individuals who were in employment prior to shielding, approximately one in two reported that they were unemployed, furloughed or enrolled in the Self-Employment Income Support scheme following shielding.(64) In the follow-up analysis, 76% said they lost income, of which 62% stated that the loss was greater than expected prior to shielding.(64)

In a study by the ONS in those who have experienced long COVID, 40% reported that it was negatively affecting their work, with an even higher proportion in the age group 30-49 years (51%).(65) Economic inactivity (defined as neither working or looking for work) has increased by over 300,000 people in the age group 16 to 64 years during the pandemic. A main driver of this increase is long-term illness in people of working age, with long COVID considered one of the causes.(66) A report from the Resolution Foundation found that 600,000 adults in the UK reported working less as a consequence of either COVID-19 or fear of the virus.(67)

B1.3.8 Conclusions

There is a substantial medical unmet need for an effective prophylaxis in high-risk populations in which vaccines do not provide adequate protection, that can reduce the risk of COVID-19 infection and poor COVID-19 outcomes (hospitalisation or death).

However, there are currently no prophylaxis available in the UK that could adequately prevent COVID-19 infection and improve COVID-19 outcomes in the high-risk populations.

An ONS survey of people classed as “extremely clinically vulnerable” during the pandemic found that 68% expressed the desire for a prophylaxis. The survey found that almost half (46%) of respondents were “very” or “somewhat” worried about the effect the pandemic has had on their life. When asked about the cause of worry, 24% indicated concerns over whether

vaccination gives adequate protection, and even in the group of respondents who had received four vaccine doses, 25% expressed concern about inadequate protection.(20)

According to UK clinical experts, awareness is increasing among high-risk individuals, and many are intimately familiar with the consequences of their condition in terms of immune response, antibody production and associated lack of protection from vaccination.(68)

UK clinical experts advised that the availability of a prophylaxis would not only reduce the risk of symptomatic infection and poor outcomes, but also improve patient HRQoL by reducing their fear and anxiety and allowing them to return to more normal levels of social functioning.

Consequentially, patients, organisations, and the clinical community(68) identify a substantial unmet need for prophylactic options.

This need has been voiced in a recent consensus statement from the UK All-Party Parliamentary Group (APPG) on vulnerable groups co-signed by 18 charities and 125 physicians, calling for the use of treatments like Evusheld as a vaccine adjunct in immunocompromised populations.(28)

"The number of people being admitted to hospital with coronavirus remains high. As we learn to live with coronavirus, we must also learn to protect immunocompromised people. Protective antibody treatments like Evusheld could offer this solution and it is really important that the voice of patients and clinicians is heard."

- **Bob Blackman,**
  Member of Parliament and co-chair of the APPG on vulnerable groups

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B1.4 Positioning of Evusheld in the management of COVID-19

Evusheld is the only COVID-19 PrEP authorised in the UK.

Aligned with its anticipated use in clinical practice, and for where the highest medical unmet need exists for patients, we propose that Evusheld should be positioned in a subgroup of its licenced indication:

Adults who are not currently infected with SARS-CoV-2 and who have not had a known recent exposure to a person infected with SARS-CoV-2 and:

- are at the highest risk of an adverse COVID-19 outcome, namely hospitalisation and death, or
- for whom COVID-19 vaccination is not recommended

The definition of individuals with the highest risk of an adverse COVID-19 outcomes aligns with the highest risk clinical subgroups identified by the UK DHSC (Table 4).

B1.5 Equality considerations

We do not expect assessment of this technology to raise any equality issues.

B2 Clinical effectiveness

B2.1 Identification and selection of relevant studies

Full details of the process and methods used to identify and select the clinical evidence relevant to the technology being appraised are provided in Appendix D.

B2.1.1 Systematic literature review

A systematic literature review (SLR) was conducted to identify randomised clinical trial (RCT) and non-RCT evidence reporting on the efficacy and safety of Evusheld and other relevant prophylaxes for COVID-19.

Searches of Embase, Medline, and Cochrane databases using Ovid were conducted in October 2021. Supplementary hand searching of recent relevant congresses and health technology assessment (HTA) agency websites focussed on the time-period 2020 to October 2021.

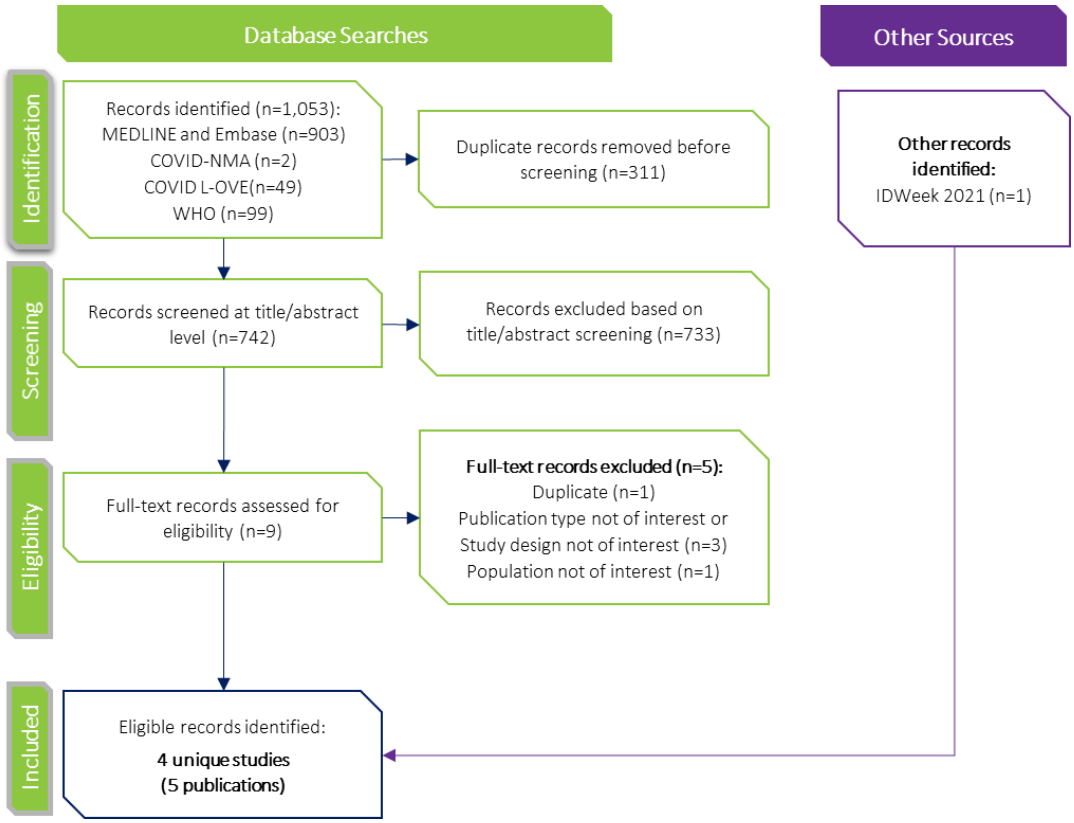
Studies of interest included RCTs and non-RCTs investigating relevant PrEP treatments for COVID-19 which enrolled adult patients (≥18 years).

The aim of the SLR was to identify and synthesise evidence on the efficacy and safety of relevant preventative/prophylaxes for COVID-19 among:

- Healthy people who had not been exposed to coronavirus (PrEP; where healthy is defined as a negative PCR test and no symptoms of COVID-19)
- Healthy people who had been exposed but did not have a positive PCR test, and who had no symptoms (post-exposure prophylaxis [PEP])
- People with positive PCR test but without symptoms (pre-emptive treatment [PET])

A Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram detailing studies that were included and excluded at each stage of screening is provided in Figure 7. Full lists of included and excluded studies are provided in Appendix D.

Figure 7: PRISMA diagram



Abbreviations: n – Number; NMA – Network meta-analysis; WHO – World Health Organization

B2.1.1.1 Selection of relevant studies (SLR)

Of the four unique studies identified, only one included Evusheld as comparator: a Phase III randomised, triple-blinded, placebo-controlled, multi-centre PrEP study (PROVENT).(70,71)

B2.1.2 Targeted literature review

PROVENT included the relevant treatment and comparators as defined in the NICE scope. However, the trial was conducted in the early stages of the pandemic when:

- enrolled subjects were unvaccinated
- earlier COVID-19 variants (Alpha and Delta) were dominant
- individuals were treated with the 300 mg dose of Evusheld

To address these considerations, targeted updates to the SLR were conducted bi-monthly since October 2021 to identify additional sources of data on the clinical effectiveness of Evusheld. Additional identified studies may be considered more generalisable to the current environment, including populations who were:

- Predominantly vaccinated
- Infected during periods of COVID-19 when Omicron was dominant

- Receiving prophylaxis with 600 mg of Evusheld

As of 30th May 2022, five comparative real-world evidence (RWE) studies of Evusheld were identified(2,72–75) These studies evaluated prophylaxis in immunocompromised populations who were predominantly vaccinated, during a period when Omicron sub-lineages were dominant.

B2.1.2.1 Selection of relevant studies (TLR)

The five additional studies are summarised below:

- Young-Xu et al. 2022 (2): a propensity-score-matched analysis in 8,087 immunocompromised veterans in the United States (US) during the Omicron wave, including the 300 mg and 600 mg dose of Evusheld; 87% of the investigated cohort were dosed at 600 mg.
    - Using electronic health records from US Department of Veterans Affairs, one of the largest integrated healthcare systems in the US, the study was able to demonstrate the clinical effectiveness of Evusheld in reducing the incidence of COVID-19 infections, COVID-19 hospitalisations, and all-cause mortality in the overall cohort - comprising of immunocompromised (92%) and patients at high-risk for COVID-19 (8%).
    - Among immunocompromised and severely immunocompromised cohorts, patients that received Evusheld had lower incidence of a composite of COVID-19 outcomes compared to matched controls. In addition, the study also showed that Evusheld augmented the protection against COVID-19 infection in fully vaccinated individuals in the overall cohort akin to a fully vaccinated and boosted non-immunocompromised adult.
- Kertes et al. 2022 (72): an unmatched control study in 5,124 immunocompromised individuals evaluating the association between Evusheld 300 mg administration, SARS-CoV-2 infection and severe disease (COVID-19 hospitalisation and all-cause mortality), during a fifth Omicron-dominated wave of COVID-19 in Israel.
    - The study demonstrated that highly immunosuppressed individuals receiving Evusheld were half as likely to become infected with COVID-19 compared to the non-administered group. They were also 92% less likely to be hospitalised or die than the non-administered group.
    - Among the highly immunosuppressed individuals, those in the Evusheld group that received either anti-cluster of differentiate 20 (CD20) treatment in the last 6 months or those that were solid organ transplant recipients, reported lower rates of COVID-19 infection compared to those that did not receive Evusheld.
- Al-Jurdi et al 2022 (73): a retrospective matched control study comparing 222 solid organ transplant recipients (SOTRs) who had received Evusheld to 222 1:1 vaccine matched SOTRs who did not receive Evusheld (59% received 600 mg dose) in the US.
    - The primary outcome included breakthrough SARS-CoV-2 infection as defined by positive PCR or antigen test, whether performed for symptoms or for another indication. Secondary outcomes included hospitalisation or death from SARS-

CoV-2 infection, changes in allograft function, and adverse events after receiving Evusheld.

  - At a mean follow-up of 87±30 days after Evusheld administration, breakthrough infections occurred in 11 (5%) of Evusheld recipients vs 32 (14%) in the non-administered group. Only one individual from the Evusheld group was hospitalised vs 6 from the non-administered group, while no individual from the Evusheld group died vs 3 from the non-administered group.

  - Sustained protection was observed at an Evusheld 600 mg dose against BA.1, BA.2, and BA.2.12.1, over a prolonged period (up to 120 days).

- Bertrand et al 2022 (74): a retrospective case-control study among 860 kidney transplant recipients (KTRs) vaccinated with ≥3 SARS-CoV-2 vaccine doses, comparing primary outcomes of symptomatic COVID-19, hospitalisations, and deaths between KTRs who did not mount an immune response (non-responders) and received Evusheld 300 mg to those who received either casirivimab-imdevimab or no monoclonal antibody in France.

  - The study demonstrated that non-responders who received Evusheld (n=412) had a significantly lower incidence of symptomatic COVID-19, hospitalisations, and deaths than non-responders who received either casirivimab-imdevimab or no monoclonal antibody

- Kaminski et al 2022 (75): a retrospective case-control study investigating the association between adverse clinical outcomes (symptomatic SARS-CoV-2 infection, COVID-19 related hospitalisation, ICU admission and death) among 333 KTRs who mounted no/low serological response following 3 mRNA vaccinations against SARS-CoV-2 in France

  - Among Evusheld recipients, significant reductions were reported across all primary outcomes (symptomatic SARS-CoV-2 infection, COVID-19 related hospitalisation, ICU admission and mortality) compared to those individuals that did not receive Evusheld

Of the five studies that included Evusheld as a comparator, Young-Xu et al and Kertes et al were considered to be the most appropriate for informing both (i) the clinical effectiveness of Evusheld in a real-world setting and (ii) have been deemed suitable for economic modelling. This is due to the large sample size, generalisability to the population in whom are likely to received treatment in UK clinical practice, and the reporting of clinical outcomes which can be used to inform the inputs of the economic evaluation of Evusheld. Further details on the rationale for inclusion and exclusion in the economic model is outlined in Table 5.

The TLR also identified a Phase III randomised, double-blind, placebo-controlled, multi-centre study for the treatment of COVID-19 in outpatient adults (TACKLE), which collected evidence for the higher Evusheld dose (600 mg). However, as the study considers treatment rather than PrEP for Evusheld, only safety evidence will be presented in this submission.

Table 5: Selection of relevant studies from TLR (reasons for exclusion)

Reason for exclusion	Number of studies	Study reference
Studies included in SLR[2]	1	Levin et al. 2022(76)
Intervention not Evusheld	1	Isa et al. 2021(77)
Population (sample size, outcomes unable to inform economic evaluation*, limited to SOTR)	3	Al-Jurdi et al. 2022(73); Bertrand et al. 2022(74); Kaminski et al. 2022(75)

*Risk reduction of symptomatic infection and risk reduction of hospitalisation. Abbreviations: SLR – Systematic literature review; SOTR – Solid organ transplant recipients; TLR – Targeted literature review.

B2.1.3 Additional effectiveness evidence for variants of concern

Multiple independent in vitro studies have shown that Evusheld neutralises all current variants of concern. The neutralisation of antibodies is a known surrogate marker for clinical effectiveness(78), which supports the conclusion that Evusheld is effective versus all variants of concern, as observed in the clinical evidence base for this submission. A summary of the neutralisation effect of Evusheld and the link between in vitro neutralisation and clinical outcomes can be found in Appendix D.

B2.2 List of relevant clinical effectiveness evidence

B2.2.1 Summaries of relevant clinical effectiveness evidence

Based on the studies identified in Section B2.1, the relevant clinical effectiveness evidence for the submission were:

- **PROVENT:** The primary RCT to inform the clinical efficacy and safety data for Evusheld
- **Young-Xu et al. 2022**(2) and **Kertes et al. 2022**(72): Two key studies informing the clinical effectiveness of Evusheld in a real-world setting
- **TACKLE:** A key study informing the safety of the 600 mg dose of Evusheld

Summaries of the relevant clinical effectiveness studies and the safety study are found below (Table 6 – Table 9)

[2] Levin et al. 2022 had not been published at the time of the original SLR, but PROVENT efficacy results were available to AstraZeneca and already included in the analysis.

Table 6: Summary of PROVENT

Study	PROVENT (NCT04625725)(71)				
Study design	Phase III, randomised, triple-blind, placebo-controlled, multi-centre trial. • **Parent study:** timeframe of 183 days to estimate the efficacy of a single 300 mg dose of Evusheld for the prevention of symptomatic COVID-19 • **Sub-study:** timeframe of 457 days (group 1) and 639 days (group 2), to assess the safety and tolerability of Evusheld[3].				
Population	Participants were adults, ≥18 years of age, who were expected to benefit from receiving monoclonal antibodies (mAbs), defined as: • having an increased risk for inadequate response to active immunisation (predicted poor responders to vaccines or intolerant of vaccine), or; • having an increased risk for SARS-CoV-2 infection, defined as those whose locations or circumstances put them at appreciable risk of exposure to SARS-CoV-2 and COVID-19, based on available risk assessment at time of enrolment.				
Intervention(s)	**Evusheld 300 mg** Single dose (2 x 150 mg IM injections of tixagevimab and cilgavimab) on parent study day 1, sub-study day one and sub-study day 183.				
Comparator(s)	**Placebo** Single dose (2 x 150 mg IM injections of saline placebo) on parent study day 1.				
Indicate if study supports application for marketing authorisation	**Yes**	X	**Indicate if trial used in the economic model**	**Yes**	X
	No			**No**	
Rationale if study not used in model	NA (study used in key scenarios).				
Reported outcomes specified in the decision problem	• **PCR-positive symptomatic illness within first 183 days:** first episode of symptomatic COVID-19, confirmed by positive results on RT-PCR testing, with an onset after the				

[3] The sub-study is still ongoing and therefore is not included as part of the clinical evidence in this submission.

	administration of Evusheld or placebo on or before day 183. • **Adverse effects of treatment:** incidence of AEs, SAEs, MAAEs, and AESIs. • **Mortality:** all-cause mortality during follow-up. • **Hospitalisation:** hospitalisation due to COVID-19.
All other reported outcomes	• **Incidence of post-treatment response:** The incidence of participants who have a post-treatment response (negative at baseline to positive at any time post-baseline) for SARS-CoV-2 nucleocapsid antibodies. • **Incidence of severe or critical illness:** The incidence of SARS-CoV-2 RT-PCR-positive severe or critical symptomatic illness occurring after dosing with intramuscular. • **Emergency department visits:** The incidence of COVID-19-related emergency department visits occurring after dosing with intramuscular. • **Incidence of symptomatic illness (Day 366):** The incidence of the first case of SARS-CoV-2 RT-PCR-positive symptomatic illness occurring after dosing with intramuscular Evusheld through Day 366.

Abbreviations: AE – Adverse event; AESI – Adverse event of special interest; COVID-19 – Coronavirus disease 2019; IM – intramuscular; mAbs – Monoclonal antibodies; MAAEs – Medically attended adverse events; mg – milligrams; NA – Not applicable; RT-PCR – Reverse transcription polymerase chain reaction; SAEs – Serious adverse events; SARS-CoV-2 – Severe acute respiratory syndrome coronavirus 2; TEAEs – Treatment-emergent adverse events.

Table 7: Summary of Young-Xu study

Study	Young-Xu et al. 2022(2)				
Study design	Retrospective observational study.				
Population	US veterans, aged ≥18 years, receiving Veteran Affairs healthcare with at least one dose of intramuscular Evusheld were compared to matched controls selected from patients who were immunocompromised or otherwise at high-risk for COVID-19. In the both arms, 95% had received a COVID-19 vaccination.				
Intervention(s)	**Evusheld 600 mg and 300 mg** Initially, patients were administered 300 mg as a single dose (2 x 150 mg IM injections of tixagevimab and cilgavimab). Following the FDA's EUA revision to a 600 mg dose, patients who received the lower dose were advised to receive an additional dose. A total of 83% of patients in the treatment arm received the higher dose of 600 mg.				
Comparator(s)	Propensity matched controls (no Evusheld).				
Indicate if trial supports application for marketing authorisation	**Yes**	X*	**Indicate if trial used in the economic model**	**Yes**	X
	No			**No**	
Rationale if trial not used in model	NA (used as base case).				
Reported outcomes specified in the decision problem	• **Incidence of COVID-19:** infections confirmed by the presence of COVID-19 virus detected by RT-PCR or antigen testing. • **Hospitalisation:** having both an admission and discharge diagnosis for COVID-19 from a hospital or within 30 days of positive COVID-19 RT-PCR result or antigen test. • **Mortality:** all-cause death during follow-up.				
All other reported outcomes	NA				

*Supports marketing authorisation for Evusheld as acute treatment and is [redacted] Abbreviations: COVID-19 – Coronavirus disease 2019; DoD – date of death; EUA – Emergency use authorisation; FDA – US Food and Drug administration; mRNA – messenger ribonucleic acid; NA – Not applicable; RT-PCR – Reverse transcription polymerase chain reaction

Table 8: Summary of Kertes study

Study	**Kertes, J et al. 2022(72)**				
Study design	Retrospective observational study				
Population	Members of the Maccabi HealthCare Services in Israel, aged 12 and over, with a minimum weight of 40 kg, that did not have a positive test result (PCR or antigen) in the last month, were not vaccinated against COVID-19 in the last two weeks, and had evidence of a severe immunosuppression, as defined by the Israel Ministry of Health. In the treatment arm, 98.8% had received COVID-19 vaccination				
Intervention(s)	**Evusheld 300 mg** Single dose (2 x 150 mg IM injections of tixagevimab and cilgavimab)				
Comparator(s)	Unmatched controls (no Evusheld)				
Indicate if trial supports application for marketing authorisation	**Yes**		**Indicate if trial used in the economic model**	**Yes**	X
	No	X		**No**	
Rationale if trial not used in model	NA (used as a key scenario)				
Reported outcomes specified in the decision problem	• **Incidence of COVID-19:** any person with a recorded positive PCR or positive antigen test result in the follow-up period. • **Hospitalisation:** COVID-19 related hospitalisation during the follow-up period. • **Mortality:** all-cause mortality during the follow-up				
All other reported outcomes	NA				

Abbreviations: COVID-19 – Coronavirus disease 2019; IM – intramuscular; PCR – polymerase chain reaction

Table 9: Summary of TACKLE (safety of 600 mg dose)

Study	**TACKLE (NCT04723394)**(79)				
Study design	Phase III randomised, double-blind, placebo-controlled, multi-centre (110 locations in USA, Latin America, Europe, and Japan) study for the treatment of COVID-19 in outpatient adults.				
Population	Non-hospitalised adults (≥18 years) with laboratory-confirmed (RT-PCR or antigen test) COVID-19 infection and who had not received a COVID-19 vaccination. WHO clinical progression scale score ≥1 to <4.				
Intervention(s)	**Evusheld 600 mg** Single dose (2 x 300 mg IM injections of tixagevimab and cilgavimab) on day 1.				
Comparator(s)	**Placebo** Single dose (2 x 300 mg IM injections of saline placebo) on day 1.				
Indicate if study supports application for marketing authorisation	**Yes**		**Indicate if trial used in the economic model**	**Yes**	
	No	X*		**No**	X
Rationale if study not used in model	Study focuses on treatment/post-exposure, whereas the decision problem is PrEP. This study is included as it provides evidence on the safety of receiving the currently recommended, higher dose (600 mg).				
Reported outcomes specified in the decision problem	• Adverse effects of treatment (AEs, AESIs, SAEs). • Composite of either severe COVID-19 or death from any cause through day 29 (primary outcome). • Death from any cause or hospitalisation from COVID-19 complications. • Respiratory failure (requirement for respiratory support). • Time to return to usual health.				
All other reported outcomes	• Symptom severity. • COVID-19 progression.				

	• Detection, levels, and change from baseline of virus (nasal swab) through day 29. • Duration of fever through day 29. • Incidence of ADA. • Pharmacokinetics: serum concentration, maximum serum concentration, time to maximum serum concentration, area under the plasma concentration-time curve (last measurable time point and extrapolated to infinity).

*Supports marketing authorisation for Evusheld as acute treatment and is [redacted] Abbreviations: ADA – Anti-drug antibodies; AEs – Adverse events; AESIs – Adverse events of special interest; COVID-19 – Coronavirus disease 2019; IM – intramuscular; NA – Not applicable; PrEP – Pre-exposure prophylaxis; RT-PCR – Reverse transcription polymerase chain reaction; SAEs – Serious adverse events; USA – United States of America; WHO – World Health Organization

B2.3 Summary of methodology of the relevant clinical effectiveness evidence

B2.3.1 Comparative summary of trial methodology

A comparative summary of the relevant studies is provided below in Table 10 and Table 11. Further details for each of the studies can be found below.

Table 10: Comparative summary of study methodology

Study	Efficacy and effectiveness sources included in economic analysis			Additional safety evidence (600 mg dose)
	PROVENT (NCT04625725)(71)	**Young-Xu et al. 2022**(2)	**Kertes et al. 2022**(72)	**TACKLE (NCT04723394)**(79,80)
Objective	To assess the efficacy and safety of a single dose of 300 mg Evusheld compared to placebo for the prevention of COVID-19.	To assess the effectiveness of Evusheld for prevention of COVID-19 infection and severe disease among immunocompromised and high-risk patients during the Omicron surge.	To test whether Evusheld reduces the risk of COVID-19 infection and severe disease in immunocompromised individuals in a real-world setting during an Omicron-predominant infection outbreak.	To evaluate the safety and efficacy of Evusheld in preventing progression to severe COVID-19 or death in non-hospitalised adults with mild to moderate COVID-19.
Location	At 87 sites in Belgium, France, Spain, United Kingdom, US.	USA; across the VA healthcare system.	Israel; across the MHS health organisation.	95 sites in USA, Latin America, Europe, and Japan.

Trial design	Phase III, randomised, triple-blind, placebo-controlled, multi-centre trial.	Retrospective observational study.	Retrospective observational study.	Phase III randomised, double-blind, placebo-controlled, multi-centre trial.
Duration of study	**Parent study:** timeframe 183 days (efficacy). **Sub-study:** timeframe 457 days (group 1) and 639 days (group 2), (safety and tolerability).	January 13th, 2022, until death or April 30th, 2022 (whichever occurred earlier).	February 23rd, 2022, until death or May 2nd 2022 (whichever occurred earlier).	Monitoring for 456 days after receiving Evusheld (five half-lives); median safety follow-up in Montgomery et al. 2022(79) was 84.0 days.
Eligibility criteria for participants	Adults with an increased risk for inadequate response to active immunisation (predicted poor responders to vaccines or intolerant of vaccine) or having an increased risk for SARS-CoV-2 infection.	Veterans (aged ≥18 years), immunocompromised or otherwise at high-risk for COVID-19.	Immunocompromised individuals (aged ≥12 years) considered at high-risk for COVID-19 infection and complication.	Non-hospitalised adults (≥18 years) with laboratory-confirmed (RT-PCR or antigen test) COVID-19 infection and who had not received a COVID-19 vaccination. WHO clinical progression scale score ≥1 to <4.
Randomisation	Participants were randomised in a 2:1 ratio.	NR	NR	Participants were centrally randomly assigned in a 1:1 ratio, using interactive response technology.
Blinding	Triple blinding (participant, care provider, investigator). Patients were unblinded due to the	NR	NR	Double blinding (participant, care provider, investigator).

	availability of vaccinations (see Section B.2.4).			
Trial drugs (the interventions for each group with sufficient details to allow replication, including how and when they were administered) **Intervention (n=1) and comparator (n=0)** **Permitted and disallowed concomitant medication**	**Intervention (n=3,460):** A single dose of Evusheld 300 mg, administered intramuscularly in the gluteal muscle as two injections of 150 mg each of tixagevimab and cilgavimab) **Placebo (n=1,737):** Saline placebo 0.9% w/v saline solution, single dose (administered twice by injection) No restrictions on concomitant medication, however any prior receipt of investigational or licenced vaccine or other mAb/biologic indicated for the prevention of SARS-CoV-2 or COVID-19 was an exclusion criterion	**Intervention (n=1,733):** Evusheld, dosing based on recommendations; initially 300 mg, patients advised to receive additional dose after FDA revision of Emergency Use Authorisation to increase dose to 600 mg (17% of total study population received the lower dose) **Control (n=251,756 of which 6,354 remained after propensity-score matching):** Propensity-score matched controls who did not receive Evusheld No restrictions on concomitant medication	**Intervention (n=825):** Evusheld. Single dose 300 mg (2 x 150 mg IM injections of tixagevimab and cilgavimab) **Control (n=5,124):** Unmatched controls who did not receive Evusheld treatment No restrictions on concomitant medication	**Intervention (n=452 in primary safety analysis set):** Evusheld 600 mg; single dose (2 x 300 mg IM injections of tixagevimab and cilgavimab) **Placebo (n=451 in primary safety analysis set):** Placebo; single dose (2 x 300 mg IM injections of saline placebo) on parent study day 1 **The following exclusion criteria concerned concomitant medication:** Use of any prohibited medication within 30 days or five half-lives, whichever was longer, prior to study entry Convalescent COVID-19 plasma treatment at any time prior to study entry

				Systemic steroids (eg, prednisone, dexamethasone) or inhaled steroids within 30 days prior to study entry unless a stable dose used for a chronic condition Patients with history of hypersensitivity, infusion-related reaction, or severe adverse reaction following administration of a monoclonal antibody were excluded, or if they had previously received an investigational or licenced vaccine or other mAb or biologic indicated for the prevention of COVID-19 before study entry, or if administration was expected immediately after enrolment
Primary outcomes (including scoring methods and timings of assessments)	**Primary efficacy endpoint:** Incidence of COVID-19 RT-PCR-positive symptomatic illness from injection to day 183. **Primary safety endpoint:** AEs from injection to day 457	**Primary outcome:** Composite of: 1) COVID-19 infection (positive RT-PCR or antigen test). 2) COVID-19 hospitalisation within 30 days of positive test.	**Primary outcome:** COVID-19 infection (positive PCR or antigen test in follow-up period[c]). **Secondary outcome:** Severe COVID-19: COVID-19-related hospitalisation and/or all-	**Primary safety endpoints:** AEs, SAEs, AESIs (including anaphylaxis and other serious hypersensitivity reactions). **Primary efficacy endpoint:** composite of either severe COVID-19 or death from any

		3) all-cause mortality during follow up[b]	cause mortality in follow-up period[c]	cause (until and including day 29)
Other outcomes used in the economic model/ specified in the scope	• Incidence of post-treatment response • Incidence of severe or critical illness • Emergency department visits • Incidence of COVID-19	NR	NR	NR
Safety	To assess the safety and tolerability of a single, 300 mg IM dose of Evusheld compared to placebo AEs, SAEs, MAAEs, and AESIs were monitored (timeframe: day 457)	NR	NR	Safety analysis in all participants receiving Evusheld; AEs, SAEs, AESIs. Monitoring for 456 days after receiving Evusheld (five half-lives); median safety follow-up in Montgomery et al. 2022(79) was 84.0 days
Pre-planned subgroups	Subgroup analyses were conducted in pre-specified subgroups that included age, sex, race, ethnicity, COVID-19 co-morbidities at baseline, COVID-19 status at baseline, high-risk for severe COVID-19 at baseline, and various	NR	NR	Subgroup analyses were conducted in pre-specified subgroups that included age, sex, race, ethnicity, region, risk group, COVID-19 comorbidity, baseline vitamin D, baseline zinc, SoC, baseline serum antibody, administration time after onset

	individual risk factors for COVID-19			

[a]Investigational products indicated for the treatment or prevention of SARS-CoV-2 or COVID-19, hydroxychloroquine, chloroquine, ivermectin, HIV protease inhibitors, COVID-19 vaccine, contraceptive methods, blood/plasma donation, ova/sperm donation; [b]Follow-up period: date of Evusheld administration (intervention group) or date of pseudo-administration (control group) until 30th April 2022 or death (whichever occurred first); [c]Follow-up period: date of Evusheld administration (intervention group) or date of first contact (control group) until end of study period (26th of May 2022). Abbreviations: AE – adverse event; AESIs – Adverse events of special interest; COVID-19 – Coronavirus disease 2019; FDA – US Food and Drug Administration; IM – Intramuscular; MAAEs – Medically attended adverse events; mAb – Monoclonal antibody; mg – Milligram; MHS – Maccabi HealthCare Services; ml – Millilitre; NR – Not reported; RT-PCR – Reverse transcription polymerase chain reaction; ; SAEs – Serious adverse events; SARS-CoV-2 – Severe acute respiratory syndrome coronavirus 2; SoC – Standard of care; w/v – Weight per volume; VA – Veterans Affairs; USA – United States of America; WHO – World Health Organization

Table 11: Characteristics of participants in the studies across treatment groups

PROVENT		**Treatment group (n=3,460)**	**Placebo (n=1,737)**	**Total (n=5,197)**
Age in years, mean (SD)		53.6 (15.0)	53.3 (14.9)	53.5 (15.0)
Female sex, n (%)		1,595 (46.1)	802 (46.2)	2,397 (46.1)
High-risk, n (%)[a]		2,666 (77.1)	1,362 (78.4)	4,028 (77.5)
Young-Xu et al. 2022		**Treatment group (n=1,733)[d]**	**Controls (n=6,354)[d]**	**SMD**
Age in years, mean (SD)		67.4 (11.0)	68.1 (11.5)	-5.7
Female sex, n (%)		558 (8.8)	154 (8.9%)	-0.4
Immunocompromised, n (%)[b]		1,595 (92.0)	5,863 (92.0)	NA
Kertes et al. 2022		**Treatment group (n=825)**	**Placebo (n=4,299)**	**Total (n=5,124)**
Age group, %	**12-39**	4.1	13.9	12.3
	40-59	29.9	32.4	32.0
	60-69	28.6	22.6	23.6
	70-79	30.5	21.3	22.8
	80+	6.8	9.9	9.4

Female sex, N (%)	313 (37.9)	2,008 (46.7)	2,320 (45.3%)
TACKLE	**Treatment group (n=452)**	**Placebo (n=451)**	**Total (N=903)**
Age in years, mean (SD)	46.3 (15.4)	45.9 (15.0)	46.1 (15.2)
Female sex, n (%)	239 (53%)	216 (48%)	455 (50%)
Immunocompromised state, n (%)	22 (5%)	23 (5%)	45 (5%)

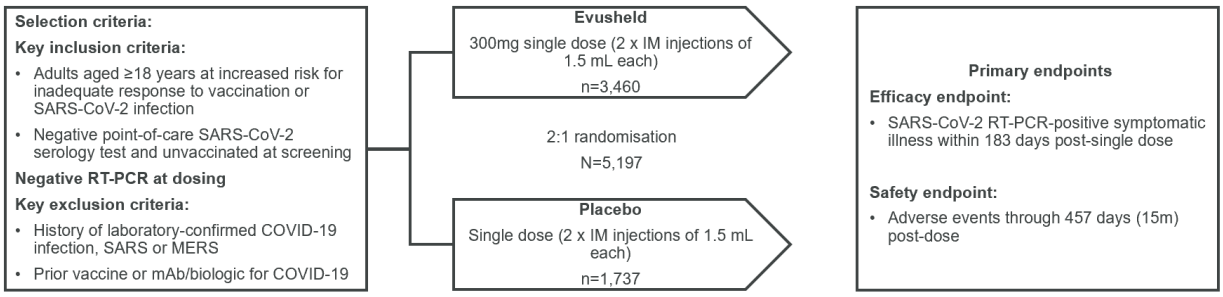
[a]Defined as any high-risk, refer to Table 12; [b]Based on diagnosis or use of immunosuppressants, refer to section 0; [c]As defined by the Israeli Ministry of Health, refer to section B2.5; [d]After propensity-score matching. Abbreviations: SD – Standard deviation; SMD – Standardised mean difference

B2.4 PROVENT study design

The efficacy and safety of Evusheld (150 mg each of tixagevimab and cilgavimab) compared to placebo for the PrEP of COVID-19 in high-risk adults with negative point of care SARS-CoV-2 serology tests was assessed in the Phase III, randomised, multi-centre, triple-blind clinical trial PROVENT.(81)

Figure 8 provides an overview of PROVENT inclusion criteria, randomisation and primary endpoints.(71)

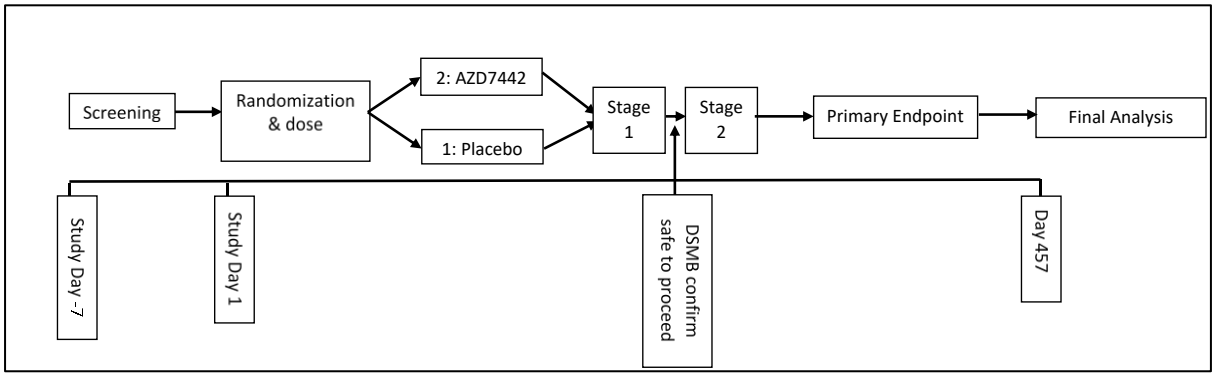
Figure 8: PROVENT trial design



Source: Levin et al. 2021(70); Abbreviations: COVID-19 – Coronavirus disease 2019; IM – Intramuscular; mAb – Monoclonal antibody; MERS – Middle East respiratory syndrome; mo – Month; RT-PCR – Reverse transcription polymerase chain reaction; SARS – severe acute respiratory syndrome; SARS-CoV-2 – Severe acute respiratory syndrome coronavirus 2; TIXA/CILGA – Tixagevimab/cilgavimab.

Following up to seven days of screening, participants were randomised in a 2:1 ratio to receive either Evusheld or placebo and were subsequently followed up to 15 months (until day 457). Figure 9 shows the sequence of treatment periods. Given the extreme vulnerability of this population, it was important that PROVENT did not delay or obstruct vaccine access to those who were eligible to receive vaccination. Participants ongoing in the trial were advised that once they became eligible for vaccines, they should become unblinded. Those who had received Evusheld were asked to wait for six months prior to receiving their COVID-19 vaccine, those who received placebo were advised to get vaccinated as per their local health authority guidance.

Figure 9: Trial design flow chart



Abbreviations: AZD7442 – Evusheld; DSMB – Data and safety monitoring board

Enrolment occurred in two stages, to ensure the safety of participants:

Stage 1 enrolled approximately 300 patients (200 to Evusheld, 100 to placebo), which included a sentinel cohort of 15 patients.

Stage 2 was initiated after an independent Data Safety Monitoring Board (DSMB) had evaluated 7-day safety data from Stage 1 participants. In stage 2, all remaining patients were enrolled, ultimately reaching a total sample size of 5,197.

B2.4.1 Eligibility criteria

PROVENT was conducted in adults considered at risk of inadequate immune response to vaccination and/or severe COVID-19 due to living situation, occupation, or comorbidities. Participants were excluded if they had previously received a COVID-19 vaccine or had known prior or current SARS-CoV-2 infection. (71) Inclusion and exclusion criteria are summarised in (71) Inclusion and exclusion criteria are summarised in Table 12.

Table 12: PROVENT inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Patients were eligible to be included if all the following criteria applied: • Age ≥18 years • Candidate for benefit from passive immunisation with antibodies, defined as either: **1)** At increased risk of an inadequate response to active immunisation (patients considered to be poor responders): o Aged ≥60 years o BMI ≥30 o Congestive heart failure o Chronic obstructive pulmonary disease o Chronic kidney disease (GFR <30 ml/min/1.73 m²) o Chronic liver disease o Immunosuppression following solid organ blood or bone marrow transplantation o Immune deficiency o HIV infection o Use of corticosteroids or other immunosuppressive drugs o Intolerant to vaccines	Patients were excluded if any of the following criteria applied: • Acute infection or illness, including fever >37.8°C (100°F) on the day before, or day of, randomisation • History of virologically confirmed infection or any other results attesting to infection with SARS-CoV-2 during enrolment • History of infection with SARS or MERS • Known history of allergy or reaction to any component of the study drug formulation • History of hypersensitivity, infusion-related reaction, or SAE following administration of a mAb • Previous or planned vaccination or treatment with another mAb/biologic for prevention of infections with SARS-CoV-2/COVID-19 • Clinically significant bleeding disorders[a] or history of significant bleeding or bruising following intramuscular injections or venipunctures • Any other significant disease or disorder that may significantly increase risk during study

2) Presenting an increased risk of infection with SARS-CoV-2 due to places or circumstances: ○ Healthcare professionals ○ Long-term care facility staff ○ Industrial workers at high-risk of transmission ○ Military personnel ○ Students in collective establishments ○ Other people living in high-density proximity environments • Medically stable (disease not requiring significant change in therapy or hospitalisation for worsening during one month prior to enrolment) • Negative result from point of care SARS-CoV-2 serology testing at screening • Use of contraception	participation, affect ability to participate, or interfere with interpreting trial data • Administration of any investigational drug within 90 days, planned administration of an investigational drug during trial follow-up, or concurrent participation in another interventional trial • For women: Confirmed pregnancy or breastfeeding • Blood sample of more than 450 mL, for any reason, within 30 days of randomisation

Source: Levin et al. 2021 (Supplementary appendix)(70); [a]Clinically significant bleeding disorders (e.g., factor deficiency, coagulopathy, or platelet disorder), or history of significant bleeding or bruising following intramuscular injections or venipunctures. Abbreviations: COVID-19 – Coronavirus disease 2019; BMI – Body mass index; GFR – Glomerular filtration rate; HIV – Human immunodeficiency viruses; mAb – Monoclonal antibody; MERS – Middle east respiratory syndrome; SAE – Serious adverse event; SARS – severe acute respiratory syndrome; SARS-CoV-2 – Severe acute respiratory syndrome coronavirus 2.

B2.4.2 Setting and location where data was collected

PROVENT was conducted in 87 sites in five countries (US, UK, Belgium, France and Spain).(71)

B2.4.3 Outcome measures

The primary efficacy endpoint was the incidence of symptomatic, virologically confirmed COVID-19 infection (positive nasopharyngeal RT-PCR test) within the period from injection to day 183. The primary safety endpoint was adverse events (AEs) occurring during the period from injection to day 457. PROVENT objectives and endpoints are summarised in Table 13. Further details can be found in the clinical study report.(81)

Table 13: Objectives and outcome endpoints

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
Primary	**Efficacy**	To estimate the efficacy of a single IM dose of Evusheld compared to placebo for the prevention of COVID-19 prior to Day 183	Incidence of COVID-19 RT-PCR-positive symptomatic illness from injection to day 183. This considered the first case of illness, with data censored at unblinding or receipt of vaccination
Primary	**Safety**	To assess the safety and tolerability of a single IM dose of Evusheld compared to placebo	AEs, SAEs, MAAEs, AESIs from injection to day 457
Key Secondary	**Efficacy**	To estimate the efficacy of a single IM dose of Evusheld compared to placebo for the prevention of SARS-CoV-2 infection	The incidence of participants who have a post-treatment response (negative at baseline to positive at any time post-baseline) for SARS-CoV-2 nucleocapsid antibodies
Secondary	**Efficacy**	To estimate the efficacy of a single IM dose of Evusheld compared to placebo for the prevention of severe or critical symptomatic COVID-19	The incidence of SARS-CoV-2 RT-PCR-positive severe or critical symptomatic illness occurring after dosing with Evusheld
Secondary	**Efficacy**	To estimate the efficacy of a single IM dose of Evusheld compared to placebo for the prevention of COVID-19-related emergency department visits	The incidence of COVID-19-related emergency department visits occurring after dosing with Evusheld

Abbreviations: AE – Adverse event; AESI – Adverse event of special interest; COVID-19 – Coronavirus disease 2019; IM – Intramuscular; RT-PCR – Reverse transcription polymerase chain reaction; SAE – Serious adverse event; SARS-CoV-2 – Severe acute respiratory syndrome coronavirus-2.

B2.4.4 Patient characteristics

In general, baseline patient characteristics were balanced between the Evusheld and placebo arms (Table 14 and Table 15). Most patients in the Evusheld and placebo arms were white (73.6% and 71.9%, respectively), male (53.9% and 53.8%, respectively), and had a negative

PCR (96.4% and 96.3%, respectively). Approximately 30% of participants had chosen to be unblinded at the time of the primary analysis (29.3% and 31.2%, respectively).(81)

Over double the number of participants in the placebo arm chose to be vaccinated compared to those in the Evusheld arm (31.0% vs 12.3%, respectively).(71) Demographics and baseline characteristics for the PROVENT population are presented in Table 14.

Table 14: Demographics and baseline characteristics (81)

Characteristic	Evusheld, n (%) (n=3,460)	Placebo, n (%) (n=1,737)	Total, n (%) (n=5,197)
Age (years)			
≥18 to <60	1,960 (56.6)	980 (56.4)	2,940 (56.6)
≥60	1,500 (43.4)	757 (43.6)	2,257 (43.4)
≥65	817 (23.6)	409 (23.5)	1,226 (23.6)
≥75	148 (4.3)	70 (4.0)	218 (4.2)
Sex			
Male	1,865 (53.9)	935 (53.8)	2,800 (53.9)
Female	1,595 (46.1)	802 (46.2)	2,397 (46.1)
Ethnicity			
Hispanic/Latino	539 (15.6)	215 (12.4)	754 (14.5)
Not Hispanic/Latino	2,731 (78.9)	1,412 (81.3)	4,143 (79.7)
Not Reported	116 (3.4)	72 (4.1)	188 (3.6)
Unknown	74 (2.1)	38 (2.2)	112 (2.2)
Race			
White	2,545 (73.6)	1,249 (71.9)	3,794 (73.0)
Black or African American	597 (17.3)	302 (17.4)	899 (17.3)
Asian	110 (3.2)	60 (3.5)	170 (3.3)
American Indian or Alaska Native	19 (0.5)	10 (0.6)	29 (0.6)
Native Hawaiian or Other Pacific Islander	4 (0.1)	4 (0.2)	8 (0.2)
Not reported	89 (2.6)	56 (3.2)	145 (2.8)
Unknown	79 (2.3)	42 (2.4)	121 (2.3)
Other[a]	15 (0.4)	12 (0.7)	27 (0.5)
Missing	2 (0.1)	2 (0.1)	4 (0.1)
BMI			
<18.5	43 (1.2)	18 (1.0)	61 (1.2)
≥18.5 - <25	885 (25.6)	460 (26.5)	1,345 (25.9)
≥25 - <30	1,067 (30.8)	538 (31.0)	1,605 (30.9)
≥30 - <40	1,187 (34.3)	571 (32.9)	1,758 (33.8)

≥40	269 (7.8)	141 (8.1)	410 (7.9)
Missing	9 (0.3)	9 (0.5)	18 (0.3)
COVID-19 RT-PCR status			
Positive	19 (0.5)	6 (0.3)	25 (0.5)
Negative	3,334 (96.4)	1,672 (96.3)	5,006 (96.3)
Missing	107 (3.1)	59 (3.4)	166 (3.2)
COVID-19 variant in positive patients (n (% of total))			
	Evusheld (n=11)	**Placebo (n=31)**	**Total (n=42)**
B.1.1.7_1 (Alpha[†])	0	5 (11.9)	5 (11.9)
B.1.351 (Beta[†])	1 (2.4)	0	1 (2.4)
B.1.617.2[‡] (Delta[§])	0	5 (11.9)	5 (11.9)
A_1	1 (2.4)	0	1 (2.4)
A_22	1 (2.4)	2 (4.8)	3 (7.1)
AY.3.1	1 (2.4)	0	1 (2.4)
B.1.1.315_1	1 (2.4)	0	1 (2.4)
B.1.429[‖]	2 (4.8)	0	2 (4.8)
B.1.526[¶]	0	1 (2.4)	1 (2.4)
RNA insufficient for sequencing	4 (9.5)	18 (42.8)	22 (52.4)

Source: Levin et al. 2021 (Supplementary appendix)(70). Lineage nomenclature from WHO. The Omicron variant (currently circulating VoC), Gamma variant (previously circulating VoC), and the Zeta, Eta, Theta, Kappa, Lambda, and Mu variants (previously circulating VoIs) were not identified in the PROVENT study population. [†]The Alpha and Beta variants were designated as currently circulating VoCs during the PROVENT study and were redesignated as previously circulating VoCs as of March 9, 2022. [‡]Includes subvariants B.1.617.2_1, _2, _3, and _4 [§]The Delta variant was designated as a current circulating VoC on May 11, 2021. [‖]Former VoI Epsilon; designated as previously circulating VOI as of July 6, 2021. [¶]Former VoI Iota; designated as previously circulating VOI as of September 20, 2021. [a]Includes all other participants (e.g., those who reported more than one race are reported under 'Multiple'). Abbreviations: BMI – Body mass index; COVID-19 – Coronavirus disease 2019; RNA – Ribonucleic acid; RT-PCR – Reverse transcription polymerase chain reaction; SARS-CoV-2 – Severe acute respiratory syndrome coronavirus 2

The comorbidities of participants in PROVENT are shown in Table 15.

Table 15: Comorbidities in PROVENT participants at baseline (primary analysis) (81)

Comorbidities	**Evusheld, n (%) (n=3,460)**	**Placebo, n (%) (n=1,737)**	**Total, n (%) (n=5,197)**
Any high-risk	2,666 (77.1)	1,362 (78.4)	4,028 (77.5)
Obesity (BMI ≥30 kg/m^2)	1,456 (42.1)	712 (41.0)	2,168 (41.7)
Morbid obesity (BMI ≥40 kg/m^2)	[redacted]	[redacted]	[redacted]
Chronic kidney disease	184 (5.3)	86 (5.0)	270 (5.2)
Diabetes	492 (14.2)	242 (13.9)	734 (14.1)
Immunosuppressive disease	15 (0.4)	9 (0.5)	24 (0.5)

Immunosuppressive treatment	109 (3.2)	63 (3.6)	172 (3.3)
CV disease	272 (7.9)	151 (8.7)	423 (8.1)
COPD	179 (5.2)	95 (5.5)	274 (5.3)
Chronic liver disease	149 (4.3)	91 (5.2)	240 (4.6)
Hypertension	1,229 (35.5)	637 (36.7)	1,866 (35.9)
Asthma	378 (10.9)	198 (11.4)	576 (11.1)
Cancer	250 (7.2)	133 (7.7)	383 (7.4)
Smoking	720 (20.8)	370 (21.3)	1,090 (21.0)
Sickle cell disease	1 (0.0)	1 (0.1)	2 (0.0)

Abbreviations: BMI - body mass index; COPD - chronic obstructive pulmonary disease; CV - cardiovascular. Young-Xu et al. 2022 study design(82)

This retrospective observational study analysed Veterans Affairs (VA) healthcare electronic health records of veterans who were immunocompromised or otherwise at high-risk of COVID-19. The study coincided with the Omicron BA.1 surge in the US, and the early BA.2 and BA.2.12.1 surge, assessing clinical effectiveness predominantly with the 600 mg dose.

Evusheld patients were identified based on prescriptions in the VA Pharmacy Benefits Management Emergency Use Authorisation prescription dashboard. The dashboard contains information on recipients, date, and dosage of medication administered in VA facilities. The first identified administration of Evusheld (150 mg each of tixagevimab and cilgavimab) was January 13, 2022.

After the US FDA's revision of Evusheld's Emergency Use Authorization (EUA) dose to 600 mg (tixagevimab 300 mg/ cilgavimab 300 mg) on February 24, 2022, patients who received the previously authorised lower dose were advised to receive an additional dose. The analysis included any patient receiving at least one dose of Evusheld. Overall, a total of 83% of study participants in the treatment arm received the 600 mg dose.

The trial population included two groups:

- **Evusheld patients** (defined as any patient who received at least one dose of Evusheld during the observation period)
- **Propensity-score matched controls** (immunocompromised or other high-risk patients who did not receive Evusheld)

Control group patients were assigned pseudo-administration dates matching the real Evusheld administration dates of the Evusheld group (index date). Baseline characteristics were assessed up to two years prior to index date, and follow-up was until 30 April 2022 or until the patient died (whichever occurred first).

B2.4.5 Eligibility criteria

The study enrolled veterans, aged ≥18 years and who were immunocompromised or otherwise at high-risk of COVID-19.

Immunocompromised status was defined based on either receiving immunosuppressive medication during the 30 days before index date, or presence of ≥1 qualifying International Classification of Diseases 10th Revision (ICD-10) diagnosis within two years before the index date. Severe immunocompromise was defined as having had solid organ transplant or received anti-rejection medication for transplant or chemotherapy for cancer treatment in the month before the index date.(83)

B2.4.6 Outcome measures

The primary endpoint was a composite of any of the below occurring during the follow-up period:

- **COVID-19 infection** (confirmed by positive SARS-CoV-2 RT-PCR or antigen test)
- **COVID-19 hospitalisation,** defined as having both an admission and discharge diagnosis for COVID-19 from a hospital or within 30 days of positive SARS-CoV-2 RT-PCR result or antigen test
- **All-cause mortality**

B2.4.7 Setting and location where data was collected

US Department of Veterans Affairs healthcare system provides care to almost 9 million veterans at 171 US medical centres and 1,112 outpatient clinics.(84,85) The VA data source used (VA Corporate Data Warehouse) contains information in all visits in VA medical facilities.

B2.4.8 Patient characteristics

Baseline characteristics measured included demographics, significant comorbidities, and healthcare utilisation. Comorbidities were based on diagnosis codes recorded in VA electronic data for healthcare visits two years before the index date. Significant comorbidities were defined according to an adaptation of Deyo-Charlson comorbidity index (DCCI).(86)

After propensity-score matching, the treatment group (n=1,733) and control group (n=6,354) were well balanced across baseline characteristics, as shown in Table 16.

Table 16: Selected baseline characteristics (Young-Xu et al. 2022)

	Before matching			**After matching**		
	Controls (N= 251,756)	**Evusheld (N= 1,848)**	**SMD**	**Controls (N= 6,354)**	**Evusheld (N= 1,733)**	**SMD**
Sex						
Male	222,642 (88%)	1,688 (91%)	9.7	5,796 (91%)	1,579 (91%)	-0.4
Age at 31 Dec 2021						
Mean (SD)	64.6 (14.7)	67.5 (10.9)	22.6	68.1 (11.5)	67.4 (11.0)	-5.7

Age category						
18-49	41,873 (17%)	131 (7%)	-29.8	493 (8%)	126 (7%)	-1.9
50-64	63,835 (25%)	448 (24%)	-2.6	1,378 (22%)	420 (24%)	6.1
65-69	31,171 (12%)	291 (16%)	9.7	952 (15%)	268 (15%)	1.3
70-74	52,227 (21%)	531 (29%)	18.6	1,861 (29%)	491 (28%)	-2.1
75-79	34,498 (14%)	300 (16%)	7.1	1,125 (18%)	284 (16%)	-3.5
>79	28,152 (11%)	147 (8%)	-11	545 (9%)	144 (8%)	-1
Race / ethnicity						
Black: non-Hispanic Black	49,021 (19%)	285 (15%)	-10.7	804 (13%)	277 (16%)	9.5
Hispanic any race	15,899 (6%)	79 (4%)	-9.1	237 (4%)	76 (4%)	3.3
Other	18,802 (7%)	139 (8%)	0.2	452 (7%)	130 (8%)	1.5
White: non-Hispanic White	168,034 (67%)	1,345 (73%)	13.2	4,861 (77%)	1,250 (72%)	-10
Number of vaccinations						
0 dose vaccine	67,753 (27%)	98 (5%)	-61.5	286 (5%)	88 (5%)	2.7
1 dose mRNA vaccine	0	0	0	0	0	
Two dose vaccine (includes one dose of Janssen)	108,134 (43%)	386 (21%)	61.5	1,377 (21%)	385 (22%)	-2.7
3rd dose of vaccine	75,869 (30%)	1,364 (74%)	97.2	4,691 (74%)	1,260 (73%)	-2.5
BMI category						

Missing	11,478 (5%)	55 (3%)	-8.3	239 (4%)	52 (3%)	-4.2
Normal	56,600 (22%)	530 (29%)	14.2	1,703 (27%)	493 (28%)	3.7
Overweight / obese	183,678 (73%)	1,263 (68%)	-10.1	4,412 (69%)	1,188 (69%)	-1.9
Deyo-Charlson Comorbidity Index (DCCI)						
Mean St Dev	1.6 (2.1)	2.7 (2.3)	52.1	2.4 (2.3)	2.6 (2.3)	9.7
High-risk comorbidities						
Asthma	41,011 (16%)	313 (17%)	1.7	958 (15%)	289 (17%)	4.4
Cancer	30,842 (12%)	670 (36%)	58.3	1,844 (29%)	597 (34%)	11.7
Coronary Artery Disease	35,504 (14%)	312 (17%)	7.7	1,041 (16%)	286 (17%)	0.3
Cancer Metastatic	7,327 (3%)	49 (3%)	-1.6	325 (5%)	49 (3%)	-11.7
Congestive Heart Failure	17,451 (7%)	190 (10%)	12	485 (8%)	173 (10%)	8.3
Chronic Kidney Disease	26,551 (11%)	442 (24%)	36	1,125 (18%)	391 (23%)	12.1
Chronic Obstructive Pulmonary Disease	44,214 (18%)	347 (19%)	3.2	1,056 (17%)	321 (19%)	5
Cardiovascular disease	11,256 (4%)	86 (5%)	0.9	318 (5%)	74 (4%)	-3.5
Dementia	4,057 (2%)	NR	NR	89 (1%)	NR	S
Diabetes Mellitus w/ complications	26,865 (11%)	293 (16%)	15.3	815 (13%)	268 (15%)	7.6
Diabetes Mellitus w/o complications	41,315 (16%)	291 (16%)	-1.8	1,021 (16%)	275 (16%)	-0.5

Hypertension	130,311 (52%)	1,111 (60%)	16.9	3,694 (58%)	1,029 (59%)	2.5
Liver disease, mild	12,834 (5%)	167 (9%)	15.4	455 (7%)	160 (9%)	7.6
Liver disease, severe	1,367 (1%)	32 (2%)	11.2	60 (1%)	27 (2%)	5.5
Renal disease	28,839 (11%)	488 (26%)	38.9	1,312 (21%)	429 (25%)	9.8
Immunocompromised						
Based on diagnoses	81,540 (32%)	1,336 (72%)	87.2	4,225 (66%)	1,226 (71%)	9.2
Based on diagnoses or use of immunosuppressants	211,390 (84%)	1,707 (92%)	26.2	5,863 (92%)	1,595 (92%)	-0.9

Abbreviations: DCCI – Deyo-Charlson Comorbidity Index; mRNA – Messenger ribonucleic acid; NR – Not reported; SD – Standard deviation; SMD – Standardised mean difference

B2.5 Kertes et al. 2022 study design

This retrospective observational study included immunocompromised individuals identified in the MHS (Maccabi HealthCare Services) database in Israel. The MHS is the second largest health management organisation in Israel, with six regional centres including 150 branches and clinics.

Immunocompromised individuals aged 12 and over identified in the MHS database were invited by SMS/email to receive Evusheld. Demographic information, comorbidities, coronavirus vaccination and prior SARS-CoV-2 infection and COVID-19 outcome data (infection, severe disease), were extracted from the database. The index date for the group that received Evusheld was the date of Evusheld administration, and they were followed until the end of the study period.

For the non-administered group, the index date was the date of the first SMS/email that they received notifying that they are eligible for Evusheld and were followed up until the end of the study period. Rates of infection and severe disease were compared between those administered Evusheld and those who did not respond to the invitation, over a three-month period.

The dominating variant during the study period was Omicron (predominantly BA1 between February and March 2022, and BA2 from April 2022).

B2.5.1 Eligibility criteria

Evusheld 300 mg (150 mg each of tixagevimab and cilgavimab) was offered free of charge from February 2022 to MHS members who fulfilled all the following criteria:

- ≥12 years of age,
- weight ≥40 kg,
- no positive COVID-19 test result in the past month,
- no vaccination against COVID-19 in the last two weeks,
- evidence of a severe immunosuppression (Table 17).

Table 17: Definition of conditions/treatments for Evusheld eligibility (Kertes et al. 2022)

Condition/treatment	Definition
Hypogammaglobulinemia	Diagnosis of chronic hypogammaglobulinemia AND purchase of intravenous immunoglobulin treatment in the past three months
Chronic lymphocytic leukaemia	Diagnosis of chronic lymphocytic leukaemia AND purchase of immunosuppressant antineoplastic medications in the last three months OR purchase of anti-CD20 medications in the last six months
Anti-CD20 monoclonal antibody-mediated B cell depletion therapy	Purchase OR record of anti-CD20 treatment in last six months
Bone marrow transplant	Record of allogeneic bone marrow transplant in last year OR record of autologous bone marrow transplant in last six months
Chimeric antigen receptor T-cell therapy	Record of Chimeric antigen receptor T-cell treatment in last six months
Solid organ transplant	Record (ever) of solid organ transplant procedure
Aggressive lymphoma	Diagnosis of aggressive lymphoma
Multiple myeloma	Diagnosis of multiple myeloma undergoing active treatment

Eligible MHS members were recorded in a daily updated database and contacted by SMS and Email with information on Evusheld eligibility, and a link to further information on Evusheld effectiveness, target population and contraindications. The message also encouraged the recipient to make an appointment.

Study population

The study population included all who had been contacted between February 23, 2022, and May 02, 2022. The population was grouped as follows:

- Contacted and had Evusheld administered
- Contacted but did not have Evusheld administered

Both groups were followed up between the date of first SMS/email and May 26, 2022.

B2.5.2 Outcome measures

- **The primary endpoint** was COVID-19 infection, defined as a recorded positive PCR or antigen test result in the follow-up period.
- **The secondary study outcome** was severe COVID-19 disease, defined as either COVID-19 related hospitalisation and/or all-cause mortality.

B2.5.3 Setting and location where data was collected

MHS is the second largest health maintenance organisation in Israel.

B2.5.4 Patient characteristics

Table 18 shows the baseline characteristics of the study population. The study population included severely immunocompromised patients, the majority had been fully vaccinated and one fourth had prior COVID-19 infection.
A total of 825 patients (16.1% of the total population) were administered Evusheld. No matching was performed and differences between the intervention and the control arm were observed, including:

- The Evusheld administered group were younger, with a larger proportion of males and from higher socioeconomic levels than those not administered Evusheld.
- The Evusheld patients were also more likely to have certain comorbidities, and more likely to have been fully vaccinated (at least three doses).
- Evusheld patients were less likely to have had prior COVID-19 infection compared to those not administered Evusheld.

Based on this, the authors speculate a potential underestimation of the effect of Evusheld, if unvaccinated individuals and those in lower socioeconomic groups were less inclined to test. In this case, more untested, positive COVID-19 cases would have been among the non-administered group.

Table 18: Demographics and health characteristics of the study population by Evusheld administration status, MHS, Feb-May 2022 (Kertes et al. 2022)

Characteristic	Category	Administered Evusheld (N=825)	Not administered Evusheld (N=4,299)	p-value
Age group	12-39	4.1	13.9	<0.001
	40-59	29.9	32.4	
	60-69	28.6	22.6	
	70-79	30.5	21.3	
	80+	6.8	9.9	
Gender	% Male	62.1	53.3	<0.001
Socioeconomic status	Low	8.6	18.8	<0.001
	Middle	44.4	48.8	
	High	47	32.4	
Population group	General	95.8	89.6	<0.001
	Orthodox religious	2.5	3.6	
	Arab	1.7	6.8	
Health factors:				
Cardiovascular disease	% in registry	32.6	28.1	0.008
Diabetes	% in registry	29.2	25.8	0.040
HTN	% in registry	58.8	49.4	<0.001
Cancer	% in registry	64.1	65.4	0.493
CKD	% in registry	61.9	49.4	<0.001
Obesity (BMI ≥30)	% in registry	26.1	25.2	0.589
Number COVID-19 vaccine:	None	1.2	12	<0.001
	One-two	7.5	11.7	
	Three-four	91.3	76.3	
Prior COVID-19 episode	% with prior episode	20.7	25.9	0.002
Immunity compromised condition/treatment (Rx):				
Hypogammaglobulinemia	% with condition	0.7	0.4	0.153
CLL	% with condition	4.8	2.2	<0.001

Anti-CD20 Rx in last 6 months	% with condition	26.2	17.7	<0.001
Bone marrow transplant	% with condition	3.4	2.1	0.026
CAR-T Rx	% with condition	0.5	0.1	0.062
Solid organ transplant	% with condition	40.5	31.5	<0.001
Lymphoma	% with condition	24.6	42.4	<0.001
Multiple myeloma	% with condition	16.8	12.6	0.001

Abbreviations: BMI – Body mass index; CAR-T – Chimeric antigen receptor T cells; CKD – Chronic kidney disease; CLL – Chronic lymphocytic leukaemia; HTN – Hypertension; Rx – Prescription

B2.6 Statistical analysis and definition of study groups in the relevant clinical trials

Further details on each study, including a summary of the statistical analyses, are detailed in Table 19.

Table 19: Summary of statistical analyses

Study	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
PROVENT(71)	Evusheld reduces symptomatic COVID-19 in patients who have an increased risk of an inadequate response to vaccination against COVID-19 or are at higher risk for exposure to COVID-19 compared to SoC	Further details on statistical requirements found below (Section B2.6.1)	The sample size calculations were based on the primary efficacy endpoint and were derived following a modified Poisson regression approach. The sample size necessary to achieve the power for the primary endpoint was calculated based on various assumed attack rates in the placebo group and an assumed true efficacy of 80% using Poisson regression model with robust variance	Participants were free to withdraw from the study at any time. Specific reasons for withdrawal of a participant from this study and procedures were followed for data inclusion.
Young-Xu et al. 2022(2)	Evusheld reduces COVID-19 infection, COVID-19-related hospitalisation and all-cause mortality compared to those who do not receive Evusheld	Propensity-score matching was used to account for observable baseline differences. Prior event rate ratio (a type of difference-in-difference analysis) was used	NR	NR

		to adjust for residual confounding. To address immortal time bias, pseudo-administration dates were assigned to the controls. Cox proportional hazards modelling was used to estimate the hazard ratios and 95%CI for the association between administration of Evusheld and the outcomes		
Kertes et al. 2022(72)	Evusheld reduces COVID-19 infection and severe disease amongst severely immunocompromised patients compared to those who do not receive Evusheld	Patient characteristics were compared using Chi Square statistic or Fisher exact test. Kaplan-Meier was used to assess relationship between Evusheld administration status and outcomes over time. Variables associated with outcome variables were included in a logistic regression model	NR	NR

Abbreviations: CI – Confidence Interval; COVID-19 – Coronavirus disease 2019; NR – Not reported; SoC – Standard of care

B2.6.1 PROVENT statistical analysis

The primary efficacy outcome was calculated as a relative risk reduction (RRR), which is the incidence of symptomatic infection in the Evusheld group relative to the incidence of symptomatic infection in the placebo group, expressed as a percentage (i.e., 100% × relative risk).

Efficacy summaries were presented with a two-sided 95% Confidence interval (CI) and statistical significance was achieved if the two-sided p-value was <0.05.

B2.6.1.1 Sample size calculations (Intention to treat population)

Approximately 5,150 participants were planned to be randomised in a 2:1 ratio to receive a single IM dose of Evusheld (divided in two sequential injections, one for each mAb component) (the active group, n=approximately 3,433) or saline placebo (the control group, n=approximately 1,717) on day 1.

The sample size calculations were based on the primary efficacy endpoint and were derived following a modified Poisson regression approach.(87) The sample size necessary to achieve the power for the primary endpoint was calculated based on various assumed attack rates in the placebo group and an assumed true efficacy of 80% using Poisson regression model with robust variance, as shown in Table 20.

Table 20: Simulated power by number of events

λ Placebo	λ Evusheld	Events	Simulated Power
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

Simulated power is based upon 10,000 simulations of trials assuming 80% efficacy $\left(1 - {\lambda_{AZD7442}}/{\lambda_{Placebo}}\right)$, using Poisson regression model with robust variance, with no participants lost follow-up. Power is the proportion of trials with p-value < 0.05.

B2.6.1.2 Statistical considerations

During the trial, highly efficacious vaccines against COVID-19 were being deployed on a mass scale. Top priority target populations for vaccine administration in the UK were similar to the population being recruited for this trial, including the elderly, those with a chronic condition that increased their risk of developing severe COVID-19, as well as workers whose location or circumstances put them at increased risk of exposure to COVID-19. However, many people who are immunocompromised fail to adequately respond to vaccination and therefore remain at high-risk of adverse clinical outcomes due to COVID-19.

Given the extreme vulnerability of this population, it was important that PROVENT did not delay or obstruct vaccine access to those who were eligible to receive vaccination. Participants ongoing in the trial were advised that once they became eligible for vaccines, they should become unblinded. Those who had received Evusheld were asked to wait for six months prior

to receiving their COVID-19 vaccine, those who received placebo were advised to get vaccinated as per their local health authority guidance.

A protocol amendment was used for the primary analysis to reduce the potential impact of unblinding and/or COVID-19 vaccination on the trial's ability to robustly quantify placebo-controlled efficacy. The primary analysis was originally scheduled to occur after 183 days but was amended to take place either after 24 events or when the trial reached an unblinding rate of 30%. This resulted in a reduced follow-up time; median follow-up was 83 days for the primary analysis, and 196 days for the 6-month follow-up. All changes relevant to the primary analysis were made before unblinding the trial.

B2.6.2 Young-Xu et al. 2022 statistical analysis

B2.6.2.1 Propensity-score matching

The study used propensity-score models to account for observable baseline differences between intervention and controls. The propensity score covariates were measured before treatment initiation to avoid adjustment for potential mediators.

Missing or unknown values for the matching criteria were captured using indicator variables to retain patients in the study. The propensity-score matching used greedy nearest neighbour matching (calliper of 0.2 and ratio of 1:4 with replacement).(88)

The robustness of the matching was assessed by standardised mean difference (SMD). A match was deemed successful when at least 90% of covariates included in the propensity-score model had SMD ≤10.(89)

Control group patients were assigned pseudo-administration dates matching the actual Evusheld administration dates of the Evusheld group, to address immortal time bias. The generated pseudo-dates followed the same distribution as the actual administration dates for Evusheld recipients.(90,91)

Finally, Evusheld patients were matched to eligible controls based on date (or pseudo-date) and the facility where Evusheld was administered. To ensure focusing on new infections, any patient who had a positive RT-PCR or antigen result within 3 months of the date or pseudo-date were excluded.

Cox proportional hazards regression was used to compare patients who received Evusheld and their matched controls.

B2.6.2.2 Difference-in-difference analysis

Difference-in-difference analysis was used to assess outcomes. A person-time denominator was calculated for Evusheld patients and controls by counting the number of days patients were enrolled during an extended study period (September 1, 2021 to April 30, 2022).

A per-period numerator was calculated as total number of outcomes (including multiple outcomes for a single patient). Outcome rates were then calculated during the baseline (September–December 2021) and observation periods.

Following the propensity-score matching, residual confounding was adjusted for using the prior event rate ratio (PERR) approach. The PERR approach accounts for two distinct time

periods (before the intervention – e.g., administration date and pseudo-date – and after the intervention). The rates of each outcome were calculated for each cohort and compared before and after the intervention within the extended study period.

The incidence rate ratio (RR), defined as the rate of the outcome among Evusheld recipients divided by the rate of the outcome in the control arm, was calculated for each study outcome in the observation period (RR_o) and the baseline period (RR_b). The RR of the post-treatment period was divided by the RR of the pre-treatment period. The PERR was calculated per the following formula:

$$PERR = \frac{(RR_{O)}}{(RR_b)}$$

The relative effectiveness of Evusheld to SPM (rE) is defined as:

$$(1 - PERR) * 100\%$$

Falsification analysis was conducted using urinary tract infection (UTI) as outcome as healthcare encounters with UTI as primary diagnosis was unlikely to be associated with Evusheld. Propensity-score matched analysis showed similar effectiveness of Evusheld and control (hazard ratio [HR] 1.05; 95% CI: 0.68-1.62).

This lack of association between UTI and Evusheld supports that the protective effects associated with the treatment of Evusheld were unlikely to be due to bias or other major methodological flaws.

B2.6.3 Kertes et al. 2022 statistical analysis

Chi Square statistic or Fisher exact test were used to assess demographics and patient characteristics between the two study groups and compare the relationship between group and study outcomes.

The relationship between Evusheld administration (or non-administration) and outcome variables over time was analysed using Kaplan-Meier methodology. Variables associated with outcome variables were included in a logistic regression model.

Although no matching was undertaken between the individuals administered Evusheld and those that did not receive Evusheld, potential confounding variables (age, sex, socioeconomic status, comorbidities, prior COVID-19 infection) were adjusted for in the analysis of primary and secondary outcomes (COVID-19 infection & COVID-19 hospitalisation or all-cause mortality).

B2.7 Quality assessment of the relevant clinical effectiveness evidence

Table 21 and Table 22 show the quality assessment results for the relevant trials.

Table 21: Quality assessment results for RCTs (PROVENT)

	Grade (Yes/ No/ Not clear/NA)	How is the question addressed?
Was randomisation carried out appropriately?	Yes	
Was the concealment of treatment allocation adequate?	Yes	The dose of intramuscular for administration was prepared by the unblinded IMP Manager or other qualified professional and labels were attached to the IM syringes to maintain blinding during administration
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	The demographic and other baseline characteristics of the trial population were well balanced between treatment groups
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes	Triple blinding (participant, care provider, investigator) was used. Patients were unblinded due to the availability of vaccinations (see Section B.2.4)
Were there any unexpected imbalances in drop-outs between groups?	No	No notable imbalances between Evusheld and placebo in drop-outs; 12.1% of total discontinuations were lost to follow-up in the Evusheld group compared to 14.8% of total discontinuations in the placebo group
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	All measured outcomes were reported in the CSR
Did the analysis include an intention to treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	Participants were analysed according to their randomised treatment irrespective of whether they had prematurely discontinued, according to the Intention to treat (ITT) principle

Adapted from systematic reviews: Centre for Reviews and Dissemination guidance for undertaking reviews in health care (University of York Centre for Reviews and Dissemination). Abbreviations: CSR – Clinical study report; IMP – Investigational medicinal product; ITT – Intention to treat; RCT – Randomised controlled trial

Table 22: Quality assessment results for non-RCTs (Young-Xu et al. 2022 and Kertes et al. 2022)

Study Name	Young-Xu et al. 2022 (2)	Kertes et al. 2022 (72)
Was the cohort recruited in an acceptable way	Yes - cohort was representative of a defined population	Yes - cohort was representative of a defined population
Was the exposure accurately measured to minimise bias	Exposure to COVID-19 was not measured, outcomes were based on PCR test Evusheld use was identified through prescription data from the VA pharmacy Benefits Management, and it links records of recipients, date, and dosage of Evusheld administered at the facilities.	Exposure to COVID-19 was not measured, outcomes were based on PCR test or antigen test Evusheld use was recorded in the MHS database which is updated daily.
Was the outcome accurately measured to minimise bias?	Yes - outcome measure was an objective measure and cases were detected through reliable system.	Yes- outcome measure was an objective measure and cases were detected through reliable system.
Have the authors identified all confounding factors?	Yes - propensity-score matching and difference-in-difference analysis were used to adjust for measured and unmeasured confounding variables.	Yes- no statistical analyses were undertaken to identify or measure the confounding variables in the study.
Have the authors taken account of the confounding factors in the design and/or analysis?	Yes - large sample size allowed for propensity-score matching to adjust for confounding.	No- potential confounding factors were included in the study and adjusted for when analysing the odds of COVID-19 infection and severe disease between patients that received Evusheld and those that did not.
Was the follow-up of patients complete?	Yes - similar follow-up periods between recipients and matched controls were reached with immortal time	Evusheld administered patients were followed up from administration to end of study period (May 2022), while non-administered

	bias accounted for through pseudo-administration dates.	patients were followed up from their first email/SMS sent to them to the end of study period. Median follow-up days for those receiving Evusheld was shorter than those not receiving Evusheld.
How precise (for example, in terms of confidence and p-values) are the results?	95% confidence intervals were reported alongside hazard ratios for the composite outcome. p-values were not provided throughout.	95% confidence intervals and p-values provided to two decimal places throughout.

Adapted from Critical Appraisal Skills Programme (CASP): Making sense of evidence 12 questions to help you make sense of a cohort study. Abbreviations: COVID-19 – Coronavirus disease 2019; PCR – Polymerase chain reaction; RCT – Randomised controlled trial

B2.8 Clinical effectiveness results of the relevant trials

B2.8.1 PROVENT

B2.8.1.1 Primary outcome (incidence of COVID-19 positive symptomatic illness)

The primary endpoint (incidence of COVID-19 RT-PCR-positive symptomatic illness from administration to day 183) was met (Table 23). There was a statistically significant reduction in incidence of COVID-19 RT-PCR-positive symptomatic illness for participants who had received Evusheld compared to placebo (RRR 76.7%, 95% CI: 46.1-90.0%, p <0.001). The median (range) duration from dose of Evusheld to primary analysis data cut-off (5 May, 2021) was 83.0 (3–166) days.

At the median 6-month follow-up the magnitude of effect increased for participants who had received Evusheld compared to placebo (RRR 82.8%, 95% CI: 65.8-91.4% [11 (0.3%) compared to 31 (1.8%)]). The median duration from dose of Evusheld to 6-month follow-up was 196 days.

Additional pre-specified analyses were conducted to assess both the impact of unblinding and/or vaccination on the primary result as well as on all-cause mortality. The primary analysis was conducted after 30% of trial participants had become unblinded. All primary endpoint events (25 events) accrued up until the data cut-off (5 May, 2021) were included in the primary analysis. Participants who were unblinded to Evusheld assignment/took vaccine prior to experiencing a primary endpoint event were censored at the earlier time of unblinding/vaccine.

In the full pre-exposure analysis set, 1,008 (29.3%) Evusheld participants were unblinded compared with 540 (31.2%) placebo participants. COVID-19 vaccinations were received by 424 (12.3%) Evusheld participants compared to 537 (31.0%) placebo participants.

Both analyses were consistent with the primary result indicating that neither the high unblinding and vaccination rates nor the non-COVID-19 related deaths affected the analysis of this endpoint. symptoms that qualified for the primary endpoint are summarised in Table 24. The events presented here are not censored at time of unblinding and/or COVID-19 vaccination so more participants with COVID-19 positive symptomatic illness are included in this table.

Table 23: Primary outcome of PROVENT*

First case of SARS-CoV-2 RT-PCR-positive symptomatic illness	Primary analysis				Median 6-Mo Follow-up†		
	Evusheld (n = 3,441)	Placebo (n=1,731)	Relative risk reduction % (95% CI)	P-value	Evusheld (n = 3,441)	Placebo (n=1,731)	Relative risk reduction % (95% CI)
Primary endpoint: first case of illness, with data censored at unblinding or receipt of COVID-19 vaccine	8 (0.2)	17 (1.0)	76.7 (46.0-90.0)	<0.001	11 (0.3)	31 (1.8)	82.8 (65.8-91.4)
Key supportive analyses							
First case of illness, regardless of unblinding or receipt of COVID-19 vaccine	10 (0.3)	22 (1.3)	77.3 (52.0-89.3)	<0.001	20 (0.6)	44 (2.5)	77.4 (61.7-86.7)
First case of illness, including all deaths, with data censored at unblinding or receipt of COVID-19 vaccine	12 (0.3)	19 (1.1)	68.8 (35.6-84.9)	0.002	18 (0.5)	36 (2.1)	75.8 (57.3-86.2)

*The full pre-exposure analysis set consisted of all the participants who had undergone randomisation, received at least one injection of Evusheld or placebo, and did not have RT-PCR– confirmed SARS-CoV-2 infection at baseline. Estimates were based on a Poisson regression with robust variance. The model included trial group (Evusheld or placebo) and age at informed consent (≥60 years or <60 years), with the log of the follow-up time as an offset. Unadjusted RRRs (95% CI) for the primary end point were the same as the adjusted RRRs for both the primary analysis and the median 6-month follow-up. An estimated relative risk reduction greater than zero favoured Evusheld, with a p-value of less than 0.05 indicating statistical significance. †This analysis was not pre-specified in the trial protocol, so p-values were not calculated. Abbreviations: CI – Confidence intervals; COVID-19 – Coronavirus disease 2019; PCR – Polymerase chain reaction; SARS-CoV-2 – severe acute respiratory syndrome coronavirus 2

Table 24: Summary of qualifying symptoms for definition of primary efficacy endpoint, full pre-exposure analysis set, primary analysis data cut-off

Events occurring post dose	Number (%) of participants	
	Evusheld 300 mg (n=3,441)	Placebo (N=1,731)
All participants with COVID-19 RT-PCR-positive symptomatic illness	10 (0.3)	20 (1.2)
Events with no minimum duration		
Fever	0	9 (45.0)
Shortness of breath	2 (20.0)	6 (30.0)
Difficulty breathing	0	3 (15.0)
Present for ≥2 days		
Chills	2 (20.0)	9 (45.0)
Cough	4 (40.0)	15 (75.0)
Fatigue	5 (50.0)	16 (80.0)
Muscle aches	3 (30.0)	9 (45.0)
Body aches	1 (10.0)	7 (35.0)
Headache	4 (40.0)	9 (45.0)
New loss of taste	1 (10.0)	6 (30.0)
New loss of smell	1 (10.0)	8 (40.0)
Sore throat	5 (50.0)	4 (20.0)
Congestion	7 (70.0)	7 (35.0)
Runny nose	3 (30.0)	11 (55.0)
Nausea	3 (30.0)	3 (15.0)
Vomiting	0	1 (5.0)
Diarrhoea	0	3 (15.0)

Events presented are not censored at time of unblinding and/or COVID-19 vaccination. Percentages are based on the total number of participants with SARS-CoV-2 RT-PCR-positive symptomatic illness. Presented event categories are mutually exclusive and participants are only counted once across the event categories. Abbreviations: COVID-19 – Coronavirus disease 2019; DCO – Data cut-off; IM – Intramuscular; N – Number of participants in the full pre-exposure analysis set; SARSCoV2 – Severe acute respiratory syndrome coronavirus 2; RT-PCR – Reverse transcription polymerase chain reaction

B2.8.1.2 Time to first COVID-19 RT-PCR-positive symptomatic illness

A Kaplan-Meier plot and Cox Proportional Hazards analysis of the time to first COVID-19 RT-PCR-positive symptomatic illness is presented in Figure 10. Time to first COVID-19 RT-PCR-positive symptomatic illness was longer in the Evusheld arm compared to placebo: HR 0.23 (95% CI: 0.10-0.53); p-value <0.001.

Figure 10: Time to first COVID-19 RT-PCR-positive symptomatic illness occurring post dose of IMP KM curves by arm; Primary analysis (5 May 2021)

HR is from the PH model with Efron method. The 95% CI for the HR is obtained by taking 95% profile likelihood CI of the hazard ratio from the PH model with treatment group as a covariate, stratified by age at informed consent (≥ 60 years versus < 60 years). P-value is obtained from log-rank test, stratified by age at informed consent (≥60 years versus <60 years). Abbreviations: CI – Confidence interval; DCO – Data cut-off; HR – Hazard ratio; IMP – Investigational medicinal product; KM – Kaplan-Meier; PH – Proportional hazard; RT-PCR – Reverse transcription polymerase chain reaction; SARSCoV2– Severe acute respiratory syndrome coronavirus 2; + indicates a censored observation.

B2.8.1.3 Sensitivity analysis of the primary endpoint

As a sensitivity analysis to handle missing follow-up time in the analysis of the primary efficacy endpoint, the primary analysis of the primary efficacy endpoint was repeated with multiple imputation for intercurrent events. The results were consistent with the primary analysis: RRR 77.29 (95% CI: 48.28-90.03); p < 0.001.

B2.8.1.4 Key secondary outcomes

B2.8.1.4.a Incidence of participants who had a post-treatment response for SARS-CoV-2 Nucleocapsid antibodies

The incidence of a post-treatment response (negative at baseline to positive at any time post-baseline) for COVID-19 nucleocapsid antibodies (produced in response to a natural infection and therefore a measure of symptomatic and asymptomatic COVID-19 infection), was statistically significantly lower for participants who had received Evusheld compared to placebo, with an RRR of 51.1% (95% CI: 10.6-73.2%); p-value 0.020 (Table 25).

Table 25: Incidence of participants who had a post-treatment response for SARS-CoV-2 nucleocapsid antibodies, full pre-exposure analysis set, primary analysis data cut-off

Endpoint	Evusheld 300 mg IM (N = 3,123)	Placebo (N = 1,564)
Secondary endpoint – SARS-CoV-2 Nucleocapsid Antibodies		
n (%)	21 (0.7)	21 (1.3)
RRR (95% CI; p-value)	51.1 (10.5-73.2; p=0.020)	

Post-treatment response is defined as negative at baseline and positive at any time post-baseline. Estimates are based on a Poisson regression with robust variance. The model includes covariate for treatment (Evusheld versus placebo), and age at informed consent (≥60 years versus <60 years), with the log of the follow-up time as an offset. Estimated RRR greater than 0% provides evidence in favour of Evusheld with p-values less than 0.05 indicating statistical significance. Percentages are based on the number of participants in the analysis by arm (N). Abbreviations: CI – Confidence interval; IM – Intramuscular; N – Number of participants in the full pre-exposure analysis set; n – Number of participants with event; RRR – Relative risk ratio; SARSCoV2 – Severe acute respiratory syndrome coronavirus 2

Furthermore, the time from baseline to first positive nucleocapsid antibody test was significantly longer in the Evusheld arm compared to placebo: HR 0.48 (95% CI: 0.26-0.89), p = 0.018.

B2.8.1.4.b Incidence of SARS-CoV-2 RT-PCR-positive severe or critical symptomatic illness after dosing with Evusheld

There were no participants with COVID-19 RT-PCR-positive severe or critical symptomatic illness in the Evusheld arm, compared with one participant in the placebo arm. An additional two participants in the placebo group had COVID-19 RT-PCR-positive severe or critical symptomatic illness but these were censored due to unblinding.

Too few events occurred to be able to calculate the time to first severe or critical COVID-19 RT-PCR-positive severe or critical symptomatic illness after dosing with IMP.

B2.8.1.4.c Incidence of COVID-19 related emergency department visits occurring after dosing with Evusheld

Emergency department visits are distinct from hospitalisations and were captured on the emergency room visit electronic case report form where the primary reason for emergency room visit was selected as COVID-19 symptoms.

The participant was not required to have a positive PCR test and the COVID-19 symptoms were determined by the investigator and did not need to meet the qualifying symptoms or duration of symptoms that were applied to the primary endpoint.

The RRR of Evusheld compared with placebo for COVID-19-related emergency department visits could not be estimated due to low numbers: 6 participants in the Evusheld group compared with zero in the placebo arm.

Three of the six participants had PCR-positive symptomatic illness (and therefore also met the primary endpoint), however three participants tested negative by PCR for COVID-19 within 8 days of the emergency room visit. In addition, in the safety update, which was conducted at the June 2021 data cut-off, the proportion of participants who had COVID-19 emergency room visits was the same between the treatment groups (0.2%).

B2.8.1.5 Subgroup analyses

B2.8.1.5.a Primary endpoint

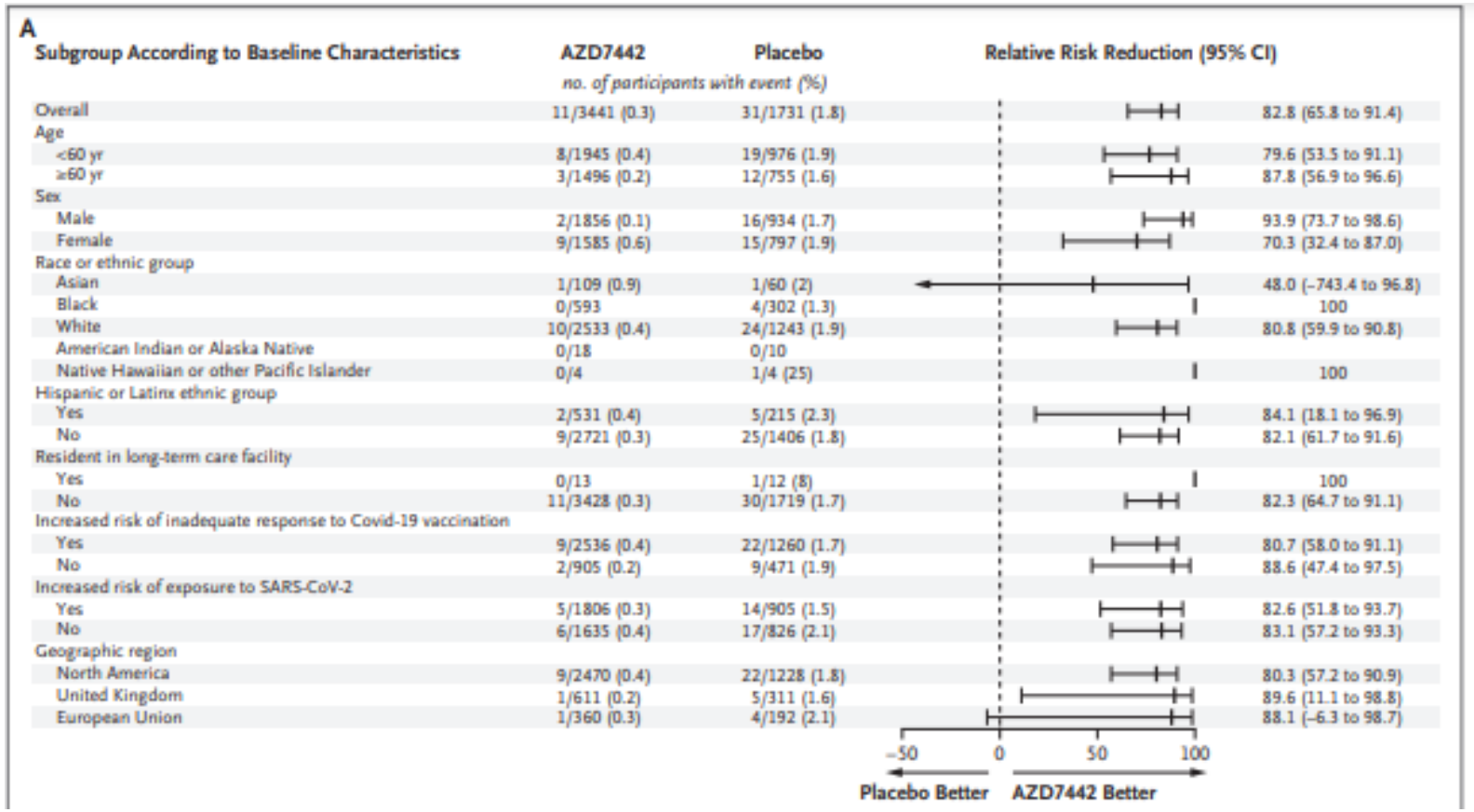
The PROVENT study included a subset population categorised as being immunocompromised (defined as at increased risk for inadequate response to active immunisation i.e., history of chronic kidney disease, immunosuppressed disease, immunosuppressive treatment, chronic liver disease, cancer, or solid organ transplant). In the full pre-exposure analysis set, [redacted] of participants were immunocompromised.

For the primary endpoint in PROVENT through a data cut-off of 5 May 2021, the efficacy results in the immunocompromised subgroup are in line with the results observed in the overall population [redacted] Note that the study was not designed to detect treatment differences within subgroups with high statistical power.

Subgroup analyses were conducted in pre-specified subgroups that included age, sex, race, ethnicity, COVID-19 co-morbidities at baseline, COVID-19 status at baseline, high-risk for severe COVID-19 at baseline, and various individual risk factors for COVID-19.

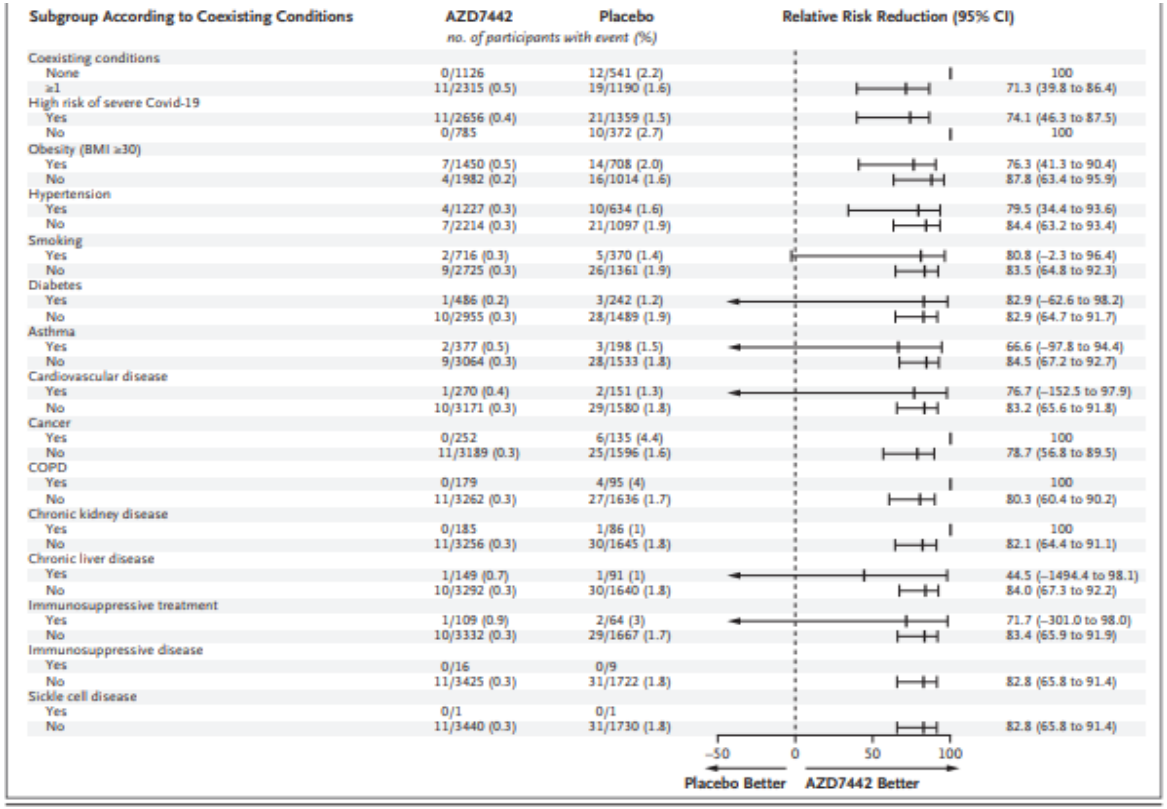
For the primary endpoint, the efficacy of Evusheld versus placebo was consistent across pre-defined subgroups (Figure 11 and Figure 12).

Figure 11: Forest plot for efficacy for incidence of first SARS-CoV-2 RT-PCR-positive symptomatic illness by subgroup, full pre-exposure analysis set, primary analysis data cut-off(76)



Abbreviations: AZD7442 – Evusheld; CI – Confidence interval; NE – Not estimable; RRR – Relative risk reduction; RT-PCR – Reverse transcription polymerase chain reaction; SARSCoV2 – Severe acute respiratory syndrome coronavirus 2

Figure 12: Forest plot for efficacy for incidence of first SARS-CoV-2 RT-PCR-positive symptomatic illness by subgroup, full pre-exposure analysis set, primary analysis



Estimates are based on Poisson regression with robust variance using full model or reduced model. The full model includes covariates for treatment group, age at informed consent (≥ 60 years versus < 60 years), subgroup and treatment*subgroup interaction, and the log of the follow-up time as an offset. If it is not converged, a reduced model by excluding age at informed consent will be applied. P-values are for the treatment*subgroup interaction. Within each level of a subgroup, same approach is utilised. Estimated RRR greater than zero provides evidence in favour of Evusheld. Percentages are based on the number of participants in the subgroup (if applicable) in the analysis set by arm.
Abbreviations: CI – Confidence interval; COPD – Chronic obstructive pulmonary disorder; COVID-19 – Coronavirus disease 2019; CV – Cardiovascular; NE – Not estimable; RT-PCR – Reverse transcription polymerase chain reaction; RRR – Relative risk reduction; SARSCoV2 – Severe acute respiratory syndrome coronavirus 2; + indicates a censored observation

B2.8.1.5.b Key secondary endpoint

Subgroup analyses for the key secondary endpoint were conducted in pre-specified subgroups that included age, sex, race, ethnicity, COVID-19 comorbidities at baseline, COVID-19 status at baseline, high-risk for severe COVID-19 at baseline, and various individual risk factors for COVID-19. For the key secondary endpoint, the efficacy of Evusheld compared with placebo was consistent across pre-defined subgroups (see Appendix E for further details).

B2.8.2 Young-Xu et al. 2022

B2.8.2.1 Primary outcomes

Results from the propensity-score matched analysis show that Evusheld recipients had a lower incidence of the composite of COVID-19 outcomes versus control patients in the overall cohort (HR 0.31; 95% CI: 0.18-0.53 [17/1733 [1.0%] vs 206/6354 [3.2%]]) (Table 26, Figure 13). Results were similar within the immunocompromised (HR 0.32; 95% CI: 0.18-0.62, severely immunocompromised (HR 0.44; 95% CI: 0.21-0.93), and age 65 or older (HR 0.33; 95% CI: 0.18-0.61).

Each of the disaggregated COVID-19 outcomes showed significant benefits in favour of Evusheld, including test-confirmed COVID-19 infection (HR 0.34; 95% CI: 0.13-0.87), COVID-19 hospitalisation (HR 0.13; 95% CI: 0.02-0.99), and all-cause mortality (HR 0.36; 95% CI: 0.18-0.73).

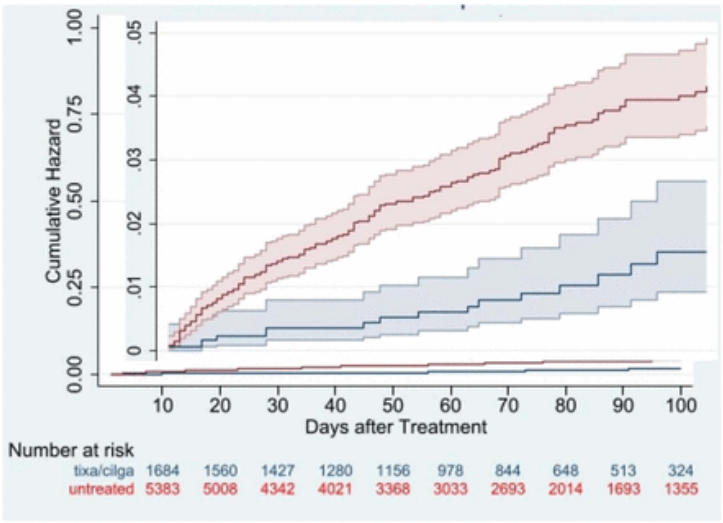
Table 26: Relative effectiveness of Evusheld versus untreated controls using propensity-score matched analysis and difference-in-difference (Young-Xu et al. 2022)

	Matched Controls N=6,354	**Evusheld recipients N=1,733**	**Propensity-score survival analysis**	**Difference in Difference Analysis***
	Number of Events (%)	**Number of events (%)**	**Hazard Ratio (95% CI)**	**Incidence Rate Ratio (95% CI)**
Composite outcome (COVID-19 infection, COVID-19 hospitalisation, and all-cause mortality)				
Overall cohort	206 (3.2%)	17 (1.0%)	0.31 (0.18-0.53)	
Immunocompromised	147 (3.5%)	12 (1.0%)	0.32 (0.18-0.62)	
Severely immunocompromised	87 (3.7%)	11 (1.4%)	0.44 (0.21-0.93)	
Not immunocompromised [**] **but at high-risk**	59 (2.8%)	(<1%)	0.27 (0.13-0.56)	
Individual outcome (overall cohort)				
COVID-19 Infection	69 (1%)	(<0.5%)[†]	0.34 (0.13-0.87)	0.32 (0.24-0.44)

COVID-19 related hospitalisation	38 (0.5%)	(<0.5%)†	0.13 (0.02-0.99)	0.10 (0.05-0.22)
All-cause mortality	99 (2%)	(<0.5%)†	0.36 (0.18-0.73)	

*DiD analysis was not performed on outcomes involving mortality data because matched cohorts were all alive at index dates; **Electronic data regarding immunocompromised conditions or immunosuppressant use were found; †Numbers not shown to protect patient information. Abbreviations: CI – confidence interval; COVID-19 – Coronavirus disease 2019

Figure 13: Cumulative risk of composite COVID-19 outcomes for Evusheld recipients compared to untreated controls (Young-Xu et al. 2022)



Abbreviations: tixa/cilg – tixagevimab and cilgavimab (Evusheld)

B2.8.2.2 Sensitivity (difference-in-difference) analysis

The matched, PERR-adjusted effectiveness, as measured by incidence rate ratio was 0.32 (95% CI: 0.24-0.44%) against COVID-19 infection verified by a positive test, and 0.10 (95% CI: 0.05-0.22) against COVID-19-related hospitalisation, almost identical to the point estimates from propensity-score matched survival analysis (Table 26). This consistency across findings shows that the results are robust and the observed benefit of Evusheld is unlikely to be due to any confounding. Because both actual and pseudo-Evusheld use required the subjects to be alive, PERR analysis was not able to be performed on mortality, including the composite outcome.

This approach removes biases in post-intervention period comparisons between the treatment and control group possibly originating from permanent differences between the groups, as well as biases from comparisons over time in the treatment group that could be the result of trends due to other causes of the outcome.

This consistency across findings shows that the results are robust and the observed benefit of Evusheld is unlikely to be due to any confounding. Because both actual and pseudo-Evusheld use required the subjects to be alive, PERR analysis was not able to be performed on mortality, including the composite outcome.

B2.8.2.3 Falsification analysis

Healthcare encounters with UTI as the primary discharge diagnosis were unlikely to be associated with Evusheld; therefore, served as a falsification test. 163 UTI visits were observed during the follow-up period. Propensity scores matched analysis demonstrated a similar effectiveness of Evusheld versus control against UTI (HR 1.05; 95% CI: 0.68-1.62) (Table 26). This lack of association between UTI and the treatment is reassuring and provides evidence that the protective effects associated with the treatment of Evusheld were unlikely due to bias or other major methodological flaws.

B2.8.2.4 Summary

Using electronic health records from US Department of Veterans Affairs, one the largest integrated healthcare systems in US, the study was able to demonstrate the clinical effectiveness of Evusheld in reducing the incidence in COVID-19 infections, COVID-19 hospitalisations, and all-cause mortality in the overall cohort (comprising of immunocompromised (92%) and patients at high-risk for COVID-19 (8%)).

Among Immunocompromised and severely immunocompromised cohorts, patients that received Evusheld had lower incidence of a composite of COVID-19 outcomes compared to matched controls. In addition, the study also showed that Evusheld augmented the protection against COVID-19 infection in fully vaccinated individuals in the overall cohort akin to a fully vaccinated and boosted non-immunocompromised adult.

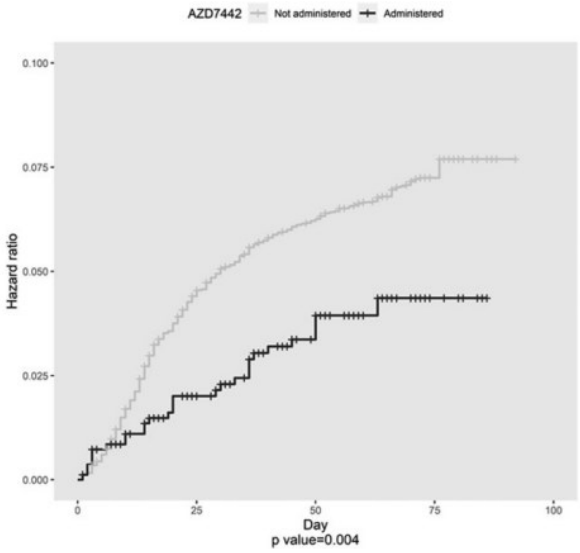
One of the key strengths of this study is its large sample size with 1,486 patient-years of observation. The study also utilises various approaches to adequately adjust for measured and unmeasured confounders. The study controls for confounding through propensity-score matching, while unmeasured residual confounders (time-varying factors) are adjusted using difference-in-difference analysis. More importantly, it is one of the few studies that includes patients that received the 600 mg dose of Evusheld (83% of the population).

B2.8.3 Kertes et al. 2022

B2.8.3.1 Primary outcomes

A total of 29 patients (3.5%) in the Evusheld administered population, were infected with COVID-19 compared to 308 (7.2%) of the non-Evusheld administered population (p<0.001). This finding was consistent over time (Figure 14). The odds of infection for the Evusheld administered group compared to the non-administered Evusheld group was significantly reduced by almost 50% (OR: 0.51, 95% CI: 0.30-0.84) (Table 27).

Figure 14: COVID-19 infection rates over time by AZD7442 administration status, Kaplan-Meier hazards ratios, MHS, Feb-May 2022 (Kertes et al. 2022)



Abbreviations: AZD7442 – Evusheld; COVID-19 – Coronavirus disease 2019; MHS – Maccabi HealthCare Services;

Univariate analysis identified that age, number of COVID-19 vaccines, prior COVID-19 illness, socioeconomic status, and CKD as presenting higher risk of COVID-19 infection (Table 27).

Table 27: Factors associated with COVID-19 infection among selected Immunocompromised individuals (ICIs), logistic regression model, MHS, Feb-May 2022 (Kertes et al. 2022)

Characteristic	Category	N	OR	95% CI
Evusheld	Not administered	4,299	-	
	Administered	825	0.51	0.30 – 0.84
Prior COVID-19 episode	No	3840	-	
	Yes	1,284	0.17	0.11 – 0.28
Age group	12-79	4,643	2.43	1.50 – 3.93
	80+	481	-	

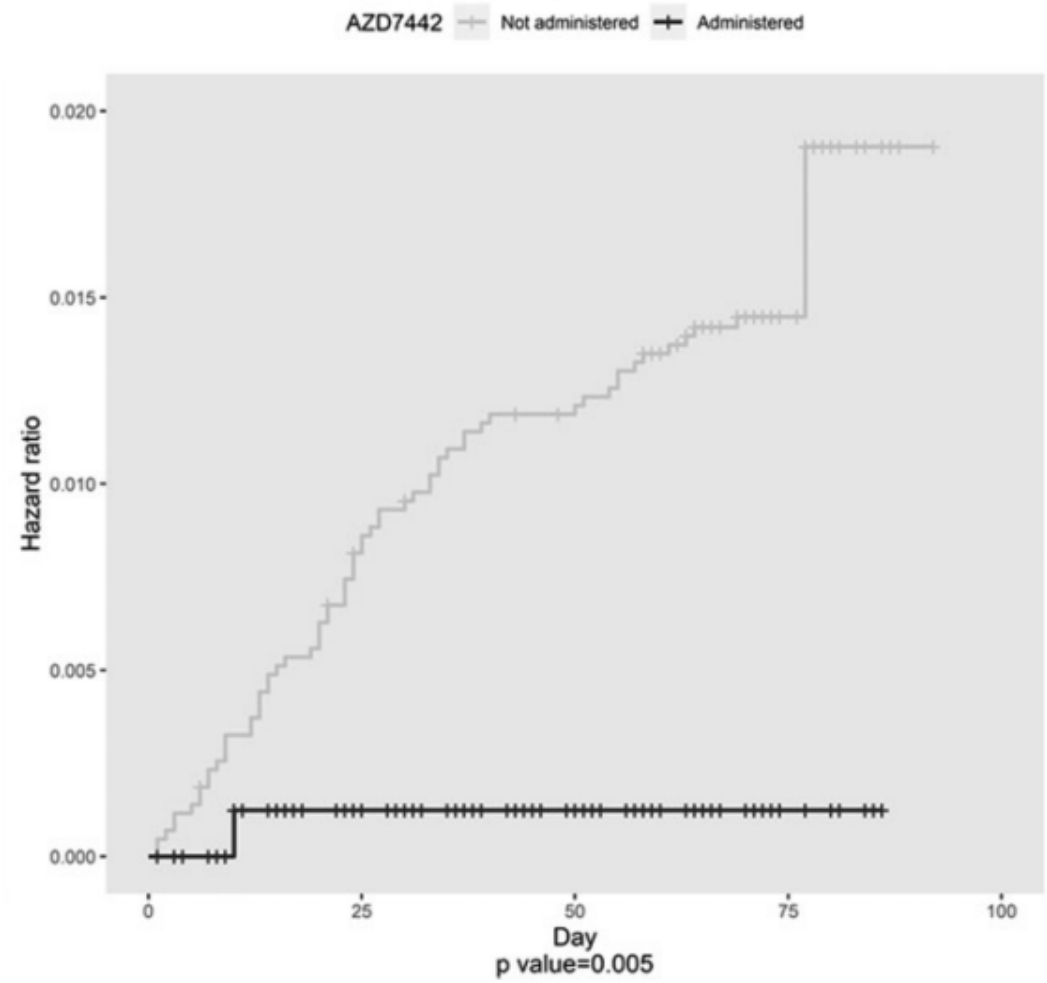
Socioeconomic status	Low	879	-	
	Middle	2,463	1.78	1.20 – 2.64
	High	1,782	2.45	1.65 – 3.66
CKD	No	2488	-	
	Yes	2,636	1.42	1.13- 1.79
Number coronavirus vaccine doses	None	526	0.60	0.37- 0.95
	One-two	564	0.79	0.49 –1.24
	Three-four	4034	-	
Number of follow-up days		5,124	1.02	1.0-1.04

Abbreviations: CI – Confidence interval; COVID-19 – Coronavirus disease 2019; CKD – Chronic kidney disease; ICIs – Immunocompromised individuals; MHS – Maccabi HealthCare Services; OR – odds ratio

B2.8.3.2 Key secondary outcomes: Severe COVID-19 disease

Only 0.1% (n=1/825) in the Evusheld administered group was hospitalised for COVID-19 compared to 0.6% (n=27/4299) in the non-Evusheld administered group (p=0.07). No deaths occurred in the Evusheld administered group during the follow-up period, compared to 40 deaths (0.9%) in the non-Evusheld administered group (p-0.005). Only 0.1% of the Evusheld administered group had evidence of severe disease compared to 1.5% of the non-administered group (p-0.001). This finding was consistent over time (Figure 15).

Figure 15: COVID-19 hospitalisation or death – Severe disease rates over time by Evusheld administration status, Kaplan-Meier hazards ratios, MHS, Feb-May 2022 (Kertes et al. 2022)



Abbreviations: COVID-19 – Coronavirus disease 2019; MHS – Maccabi HealthCare Services

Age and all comorbidities (except for obesity) were associated with severe disease outcomes in the univariate analysis. Vaccination status, socioeconomic status and prior COVID-19 illness were not associated with a severe disease outcome.

Due to the small number of patients with severe disease (n=64), a logistic regression was conducted, including age group and cardiovascular disease. After adjustment, the Evusheld group odds of having severe disease were 0.08 (95% CI: 0.01-0.54).

B2.8.3.3 Summary

This study demonstrated that highly immunosuppressed individuals receiving Evusheld were nearly 50% as likely to become infected with COVID-19 compared to the non-administered group (OR: 0.51, 95% CI: 0.30-0.84). They were also 92% less likely to be hospitalised or die than non-administered group (OR: 0.08, 95% CI: 0.01- 0.54).

Among the highly immunosuppressed patients, patients in the Evusheld group that received anti-CD20 treatment in the last 6 months and solid organ transplant recipients reported lower

rates of COVID-19 infection compared to those that did not. While a similar trend was observed in other conditions (lymphoma, multiple myeloma and all other), due to the low sample size, the infections rates were not significantly different between those that received Evusheld and those that did not. The factors associated with higher rates of COVID-19 infection include age, socioeconomic status, number of prior doses of vaccine, prior COVID-19 infection and CKD.

A key strength of the study is that it investigated a heterogeneous population of immunocompromised individuals (hypogammaglobulinemia, bone marrow transplant patients, patients who received anti-CD20 and CAR-T therapy, solid organ transplant recipients, patients with CLL, aggressive lymphoma and multiple myeloma).

Although no matching was undertaken between the individuals that were administered Evusheld and those that did not receive Evusheld, potential confounding variables (age, sex, socioeconomic status, comorbidities, prior COVID-19 infection) were adjusted for the analysis of primary and secondary outcomes (COVID-19 infection & COVID-19 hospitalisation or all-cause mortality).

B2.9 Meta-analysis

The NICE scope of no prophylaxis is representative of the placebo arm in the PROVENT study. Since PROVENT is the only RCT identified evaluating Evusheld compared to no prophylaxis, no meta-analysis or indirect treatment comparison is required.

B2.10 Adverse reactions

B2.10.1.1 PROVENT

The co-primary endpoint of PROVENT was to assess the safety and tolerability of a single IM dose of Evusheld compared to placebo by assessing AEs, serious adverse events (SAEs), adverse events of special interest (AESIs), and medically attended adverse events (MAAEs).

Note that the occurrence of COVID-19 as an AE in this section does not align with the number of COVID-19 events in the efficacy analysis. AEs reported as COVID-19 without a corresponding positive lab result are not counted as primary endpoint events.

Efficacy was based on protocol pre-specified qualifying symptoms collected separately from AEs in the case report form with a corresponding RT-PCR-positive test. Furthermore, some COVID-19 symptoms may have been reported as separate AEs rather than as AEs related to COVID-19.

B2.10.1.2 Categories of AEs

The AE categories are presented for Evusheld versus placebo in Table 28. Approximately 45% of participants had at least one AE in the trial and there were no notable differences in the proportion of AEs in each category between the treatment groups.

Table 28: Overall summary of AEs in any category, safety analysis set, June 2021 data cut-off

Participants with at least one event, n (%)*	AZD7442 (n=3461) †	Placebo (n=1736)†	Total (N=5197)
AEs	1579 (45.6)	790 (45.5)	2369 (45.6)
Mild AEs	835 (24.1)	419 (24.1)	1254 (24.1)
Moderate AEs	596 (17.2)	295 (17.0)	891 (17.1)
Severe AEs	128 (3.7)	65 (3.7)	193 (3.7)
SAEs	130 (3.8)	58 (3.3)	188 (3.6)
Intervention-related‡ SAEs	1 (<0.1)	0	1 (<0.1)
AEs leading to study discontinuation	2 (0.1)	1 (0.1)	3 (0.1)
Medically attended AEs	641 (18.5)	280 (16.1)	921 (17.7)
AEs of special interest	92 (2.7)	37 (2.1)	129 (2.5)
Injection site reaction	82 (2.4)	36 (2.1)	118 (2.3)
Anaphylaxis	1 (<0.1)	0	1 (<0.1)
Immune complex disease§	0	0	0
Other	9 (0.3)	2 (0.1)	11 (0.2)
Intervention-related‡ AEs of special interest	87 (2.5)	36 (2.1)	123 (2.4)
All AEs with outcome of death‖	9 (0.3)	7 (0.4)	16 (0.3)
Illicit drug overdose	2 (0.1)	1 (0.1)	3 (0.1)
Narcotic toxicity¶	0	1 (0.1)	1 (<0.1)
Covid-19**	0	1 (0.1)	1 (<0.1)
Covid-19 ARDS**	0	1 (0.1)	1 (<0.1)
Septic shock	1 (<0.1)	0	1 (<0.1)
Arrhythmia	1 (<0.1)	0	1 (<0.1)
Cardio-respiratory arrest	1 (<0.1)	0	1 (<0.1)
Congestive cardiac failure	1 (<0.1)	0	1 (<0.1)
Myocardial infarction	1 (<0.1)	0	1 (<0.1)
End-stage renal disease	1 (<0.1)	0	1 (<0.1)
Renal failure	1 (<0.1)	0	1 (<0.1)
Hepatic cirrhosis	0	1 (0.1)	1 (<0.1)
Malignant neoplasm (unknown primary site)	0	1 (0.1)	1 (<0.1)
Dementia (Alzheimer's type)	0	1 (0.1)	1 (<0.1)

*Participants may have had more than one event. †One participant was randomized to placebo and incorrectly received AZD7442; per study protocol this participant was assessed in the AZD7442 group for the SAS. ‡Events were determined to be intervention-related by investigators based on their judgment. Page 41 of 49 §Immune complex disease was removed as an AEs of special interest following adjudication. ‖All deaths were determined by the investigator to not be related to the study drug received. ¶Participant died as a result of accidental exposure to two substances controlled under Schedule I of the 1961 United Nations Single Convention on Narcotic Drugs. 12 **Cases were adjudicated to be Covid-19 related by the independent and external Morbidity Adjudication Committee. AEs were coded using the Medical Dictionary for Regulatory Activities, version 24.0. Abbreviations: AE–adverse event; ARDS – acute respiratory distress syndrome; COVID-19 – coronavirus disease 2019; SAE – serious adverse event; SAS – safety analysis set.

The most frequently reported AEs (≥1% of participants) are presented for Evusheld versus placebo in Table 29. The most common adverse event of special interest was an injection site reaction, which occurred in 2.4% of the participants in the Evusheld group and in 2.1% of those in the placebo group. The incidence of serious adverse events was similar in the two groups.

Evusheld is administered as two sequential injections, therefore, a participant could potentially discontinue between injections. There were no participants with an AE leading to permanent discontinuation of Evusheld. Two participants in the Evusheld arm and one in the placebo arm discontinued treatment as part of the study. For missing data, participants who discontinued early from the study or were lost to follow-up before experiencing a primary endpoint event were censored in the Kaplan-Meier and Poisson regression analyses.

Table 29: Most frequently reported (≥1%) AEs by preferred term, safety analysis set, June 2021 data cut-off (76)

	Evusheld (N=3461)	Placebo (N=1736)	Total
Any adverse event	1221 (35.3)	593 (34.2)	1814 (34.9)
Mild	761 (22.0)	369 (21.3)	1130 (21.7)
Moderate	387 (11.2)	191 (11.0)	578 (11.1)
Severe	64 (1.8)	27 (1.6)	91 (1.8)
Serious adverse events			
Any serious adverse event	50 (1.4)	23 (1.3)	73 (1.4)
Related to Evusheld or placebo	1 (<0.1)	0	1 (<0.1)
Adverse events leading to trial discontinuation	1 (<0.1)	0	1 (<0.1)
Medically attended adverse events	360 (10.4)	157 (9.0)	517 (9.9)
Adverse events of special interest			
Any adverse event of special interest	93 (2.7)	37 (2.1)	130 (2.5)
Injection-site reaction	82 (2.4)	36 (2.1)	118 (2.3)
Anaphylaxis	1 (<0.1)	0	1 (<0.1)
Immune complex disease	1 (<0.1)	0	1 (<0.1)
Other	9 (0.3)	2 (0.1)	11 (0.2)
Related to Evusheld or placebo	87 (2.5)	36 (2.1)	123 (2.4)
Adverse events leading to outcome of death			
All adverse events	4 (0.1)	4 (0.2)	8 (0.2)
Illicit-drug overdose	2 (0.1)	2 (0.1)	4 (0.1)
Myocardial infarction	1 (<0.1)	0	1 (<0.1)
Renal failure	1 (<0.1)	0	1 (<0.1)

COVID-19	0	1 (0.1)	1 (<0.1)
COVID-19–related ARDS	0	1 (0.1)	1 (<0.1)

AEs are defined as any AE that started or worsened in severity on or after the first dose of Evusheld through to the data cut-off. Percentages are based on the number of participants in the analysis set by treatment group. Preferred terms are sorted by decreasing order of total frequency. Participants with more than one event within a preferred term are counted only once. Percentages are based on the number of participants in the analysis set by treatment group. Abbreviations: AE – Adverse event; ARDS – Acute respiratory distress syndrome; COVID-19 – Coronavirus disease 2019; IM – Intramuscular; N – Number of participants in the safety analysis set

B2.10.1.3 Deaths

Deaths, and AEs with an outcome of death, are summarised by organ class and term in Table 30.The causes of death were adjudicated by an independent committee to determine whether deaths could be COVID-19 related. Overall, the number of deaths was low (n = 16 across both arms).

There were no cases of severe COVID-19- or COVID-19-related deaths in those treated with Evusheld. In the placebo arm, 2 (0.1%) participants died due to COVID-19 (preferred terms: COVID-19 pneumonia and acute respiratory distress syndrome).(76) Note that COVID-19 related deaths were excluded from the primary analysis as they occurred after unblinding. At the time of the June 2021 data cut-off, no participants receiving Evusheld had died.

Table 30: Deaths and AEs with an outcome of death by system organ class and preferred term, safety analysis set, June 2021 data cut-off (76)

Participants with at least one SAE, n (%)	Evusheld (n=3461)	Evusheld (n=1736)	Total (N=5197)
Any SAE	50 (1.4)	23 (1.3)	73 (1.4)
Infections and infestations	8 (0.2)	5 (0.3)	13 (0.3)
Injury, poisoning, and procedural complications	4 (0.1)	8 (0.5)	12 (0.2)
Nervous system disorders	9 (0.3)	0	9 (0.2)
Cardiac disorders	6 (0.2)	1 (0.1)	7 (0.1)
Gastrointestinal disorders	6 (0.2)	1 (0.1)	7 (0.1)
Renal and urinary disorders	6 (0.2)	1 (0.1)	7 (0.1)
Musculoskeletal and connective tissue disorders	4 (0.1)	1 (0.1)	5 (0.1)
Hepatobiliary disorders	3 (0.1)	1 (0.1)	4 (0.1)
Metabolism and nutrition disorders	3 (0.1)	0	3 (0.1)
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	0	3 (0.2)	3 (0.1)
Respiratory, thoracic, and mediastinal disorders	1 (<0.1)	2 (0.1)	3 (0.1)
Vascular disorders	2 (0.1)	1 (0.1)	3 (0.1)
Blood and lymphatic system disorders	2 (0.1)	0	2 (<0.1)
Clinical laboratory tests	1 (<0.1)	1 (0.1)	2 (<0.1)
Pregnancy, puerperium, and perinatal conditions	1 (<0.1)	0	1 (<0.1)
Psychiatric disorders	1 (<0.1)	0	1 (<0.1)

Reproductive system and breast disorders	1 (<0.1)	0	1 (<0.1)

Abbreviations: AE – Adverse event; COVID-19 – Coronavirus disease 19; IM – Intramuscular; N – Number of participants in the safety analysis set

B3.1.1 Young-Xu et al. 2022

No data was published on adverse reactions.

B3.1.2 Kertes et al. 2022

No data was published on adverse reactions.

B3.1.3 TACKLE

The overall TACKLE safety results are in line with those reported in PROVENT; current evidence indicates that the safety profile of the higher, 600 mg dose of Evusheld is in line with that of the 300 mg dose.

The primary safety endpoints in the TACKLE study were AEs, SAEs and AESI throughout the study. Final analysis will estimate the endpoints until day 457, published results available as of September 2022 have a median safety follow-up of 84.0 days in both arms (interquartile range: Evusheld 31.0–86.0, placebo 30.0–86.0). AEs were reported by 132 patients (29%) in the Evusheld arm, and 163 (36%) in the placebo arm. SAEs were reported by 33 (7%) in the Evusheld arm, and 54 (12%) in the placebo arm.

The incidence of AEs and AESIs (Table 31), as well as SAEs (Table 32) were similar over both arms, and the majority were of mild or moderate severity. The most common AE was COVID-19 pneumonia in both arms, experienced by 6% of Evusheld patients and 11% of placebo patients. While there were fewer COVID-19 reported deaths in the Evusheld group, all-cause mortality rates were similar (Table 31).(79)

Table 31: Adverse events in the safety analysis set

Participants with an AE (average follow-up 84 days), n (%)	Evusheld (n=452)	Placebo (n=451)
Any adverse event	**132 (29%)**	**163 (36%)**
Mild	67 (15%)	65 (14%)
Moderate	34 (8%)	50 (11%)
Severe	22 (5%)	30 (7%)
Total deaths	**6 (1%)**	**6 (1%)**
Acute myocardial infarction or acute left ventricular failure	1 (<1%)	0
Sudden cardiac death	1 (<1%)	0
COVID-19 pneumonia with outcome of death	2 (<1%)	4 (<1%)
COVID-19 with outcome of death	1 (<1%)	1 (<1%)

COVID-19 pneumonia, superinfection bacterial, or septic shock	0	1 (<1%)
Malignant disease progression	1 (<1%)	0
Any serious adverse event including death	**33 (7%)**	**54 (12%)**
Any treatment-related adverse event	**23 (5%)**	**21 (5%)**
Any adverse event leading to study withdrawal	**5 (1%)**	**7 (2%)**
Common adverse events		
COVID-19 pneumonia	26 (6%)	49 (11%)
Headache	5 (1%)	2 (<1%)
Any adverse event of special interest	**15 (3%)**	**15 (3%)**
Injection site pain	8 (2%)	10 (2%)
Injection site erythema	2 (<1%)	2 (<1%)
Injection site discomfort	2 (<1%)	1 (<1%)
Injection site bruising	1 (<1%)	1 (<1%)
Injection site haematoma	1 (<1%)	1 (<1%)
Injection site induration	1 (<1%)	0
Injection site inflammation	1 (<1%)	0
Injection site nodule	1 (<1%)	0
Injection site warmth	0	1 (<1%)

Source: Montgomery et al. 2022(79)
Abbreviations: AE – Adverse event; COVID-19 – Coronavirus disease 2019

Table 32: Serious adverse events by system organ class and preferred term, safety analysis set

Participants with a SAE (average follow-up 84 days), n (%)	Evusheld (n=452)	Placebo (n=451)
Any SAE	**33 (7.3)**	**54 (12.0)**
Infections and infestations	25 (5.5)	37 (8.2)
COVID-19 pneumonia	23 (5.1)	49 (10.9)
COVID-19	1 (0.2)	9 (2.0)
Vascular disorders	3 (0.7)	0
Cardiac disorders	2 (0.4)	1 (0.2)
Renal and urinary disorders	2 (0.4)	1 (0.2)
Blood and lymphatic system disorders	1 (0.2)	0
General disorders and administration site conditions	1 (0.2)	0
Musculoskeletal and connective tissue disorders	1 (0.2)	0

Neoplasms benign, malignant, and unspecified (including cysts and polyps)	1 (0.2)	0
Nervous system disorders	1 (0.2)	3 (0.7)
Respiratory, thoracic, and mediastinal disorders	1 (0.2)	1 (0.2)

Source: Montgomery et al. 2022, supplementary material(79)
Abbreviations: COVID-19 – Coronavirus disease 2019; SAE – Serious adverse event

B2.11 Innovation

As described in Section B1.3.8, despite a successful vaccine rollout, individuals with the highest risk of an adverse COVID-19 outcome remain clinically vulnerable, and there is a substantial medical unmet need for an effective prophylaxis in high-risk populations that can reduce the risk of COVID-19 infection and poor COVID-19 outcomes (hospitalisation or death).

Currently there are no prophylaxes routinely commissioned in the UK which could prevent COVID-19 infection and improve COVID-19 outcomes in high-risk populations. (28)

There is strong emerging evidence that prophylactic measures using monoclonal antibodies are an effective strategy for immunocompromised individuals, and further research and innovation has been highlighted as important to ensure that immunocompromised patients continue to be adequately safeguarded and protected during the coronavirus pandemic.(92)

Evusheld, a combination of two antibodies, is the first and only COVID-19 PrEP approved by the MHRA, with clinical evidence demonstrating clinically effectiveness and safety across RCT and real-world settings.

We therefore consider Evusheld to be innovative, as its introduction to the NHS would represent a step-change in the treatment pathway for individuals with the highest risk of an adverse COVID-19 outcome, namely hospitalisation and death, or in individuals for whom COVID-19 vaccination is not recommended.

B2.12 Interpretation of clinical effectiveness and safety evidence

B2.12.1.1 Summary of findings from the clinical evidence

Evusheld is the first and only COVID-19 PrEP approved by the MHRA, with clinical evidence demonstrating clinical effectiveness and safety across RCT and real-world settings. A large body of evidence shows that Evusheld PrEP significantly and substantially reduces symptomatic COVID-19 illness among higher risk patients and consequentially results in lower hospitalisation and (all cause) mortality

Clinical efficacy and safety in a randomised setting

The efficacy and safety of Evusheld has been demonstrated in a large (n=5,197), Phase III, randomised, triple-blind, placebo-controlled, multi-centre RCT (PROVENT), which met its primary and key secondary endpoints, demonstrating a consistent effect across all pre-specified subgroups.

The primary efficacy analysis in PROVENT showed that Evusheld administered in a prophylactic setting significantly reduced the risk of developing symptomatic COVID-19

compared with placebo: RRR 76.7% (95% CI: 46.05–89.96, p < 0.001). The magnitude of effect increased by 6-month follow-up: RRR 82.80% (95% CI: 65.79–91.35), and was consistent across all pre-specified subgroups.(76)

Secondary endpoint analyses demonstrated favourable outcomes for Evusheld compared to placebo:

- Time to first COVID-19 RT-PCR-positive symptomatic illness was longer in the Evusheld arm compared to placebo: HR 0.23 (95% CI: 0.10-0.53); p < 0.001.

- The incidence of a post-treatment response for COVID-19 nucleocapsid antibodies was statistically significantly lower for participants who had received Evusheld compared to placebo, with an RRR of 51.1% (95% CI: 10.6-73.2%); p = 0.020.

Safety analyses from the PROVENT study have demonstrated that the Evusheld 300 mg dose is well tolerated. For commonly reported AEs, there were no meaningful differences between the treatment groups except for COVID-19, which was reported by a smaller proportion of Evusheld participants (0%) compared with placebo participants (0.1%). Two participants in the Evusheld arm and one in the placebo arm discontinued treatment as part of the study, with no Evusheld discontinuations due to AEs. There were only 16 deaths (nine in the Evusheld arm and seven deaths in the placebo arm) recorded in the PROVENT study, and the investigator did not consider these to be related to Evusheld or placebo.(76)

Safety analyses from the TACKLE study have demonstrated that the Evusheld 600 mg dose is equally well tolerated. There were fewer AEs reported in the Evusheld arm (29%) compared to the placebo arm (36%), and fewer SAEs reported in the Evusheld arm (7%) compared to the placebo arm (12%).

Clinical effectiveness in a real-world setting

The significance and magnitude of the reduced risk observed in PROVENT has been confirmed in real-world settings, where consistent, significant efficacy was shown in immunocompromised populations, predominantly vaccinated, during surges dominated by Omicron variants.

Young-Xu et al. 2022(2): A large retrospective study (n=8,037) in US veterans, aged ≥18 years, receiving VA healthcare, compared individuals with at least one dose of intramuscular Evusheld with matched controls, selected from patients who were immunocompromised or otherwise at high-risk for COVID-19.

- The study aligned to the current UK environment, with 95% of patients having received COVID-19 vaccination and the analysis period was during high prevalence of Omicron BA.1 and the early BA.2 and BA.2.12.1 surge.

- Furthermore, 83% of patients received 600 mg dose of Evusheld.

- Results from the propensity-score matched analysis showed that Evusheld recipients had a lower incidence of the composite of COVID-19 outcomes versus control patients (HR 0.31; 95% CI: 0.18-0.53 [17/1733 [1.0%] vs 206/6354 [3.2%]]).

- Each of the COVID-19 outcomes showed similar Evusheld benefits, including test-confirmed COVID-19 infection (HR 0.34; 95% CI: 0.13-0.87), COVID-19 hospitalisation (HR 0.13; 95% CI: 0.02-0.99), and all-cause mortality (HR 0.36; 95% CI: 0.18-0.73).

Kertes et al. 2022(72): A large retrospective study (n=5,124) in members of the Maccabi HealthCare Services (MHS) in Israel, aged 12 and over, and with evidence of a severe immunosuppression, compared individuals receiving Evusheld with unmatched controls.

- The study aligned to the current UK environment, with 98.8% of patients in the Evusheld group having received COVID-19 vaccinations. The analysis period took place when Omicron BA1 and BA2 were predominant.

- All patients received the 300 mg dose.

- Results from the analysis found that the odds of infection for the Evusheld administered group compared to the non-administered Evusheld group was significantly reduced by almost 50% (OR: 0.51, 95% CI: 0.30-0.84) (Table 27).

- Each of the COVID-19 outcomes showed similar Evusheld benefits, including risk of hospitalisation (0.1% in the Evusheld group compared to 0.6% in the non-Evusheld group [p = 0.07], risk of death (0% in the Evusheld group compared to 0.9% in the non-Evusheld group [p = 0.005], and severe disease (0.1% in the Evusheld group compared to 1.5% in the non-Evusheld group [p = 0.001]).

In addition, sustained protection against COVID-19 was demonstrated through a retrospective matched control study which investigated the efficacy of 600 mg of Evusheld in patients who had previously received an SOT.(73)

Finally, the inference of generalisability across COVID-19 variants is further demonstrated by studies which have shown that Evusheld maintains neutralisation against Omicron subvariants of concern(2) (see Appendix D).

B2.12.1.2 Strengths and limitations

The strengths of the clinical evidence base are:

- Evusheld has been evaluated in both large, randomised trials and real-world settings across 21,608 individuals; 7,167 of which were treated with Evusheld and 14,441 placebo/matched controls.

- Across different settings and populations, Evusheld demonstrates a consistent and significant benefit in preventing infection from COVID-19 and reducing poor outcomes in terms of hospitalisation and mortality.

- The magnitude of benefit across all study types and populations is large and clinically meaningful for patients.

- Evusheld has demonstrated a well tolerated safety profile across the 300 mg and 600 mg doses; in fact, safety data presented in this submission have shown more AEs associated with placebo compared to Evusheld.

The limitations of the clinical evidence base are:

- Only [redacted] of participants in the PROVENT trial were immunocompromised, aligning with the target population for this submission.(70) However, treatment effectiveness was not shown to significantly differ between immunocompromised and immunocompetent participants (see Section B2.8.1.5). Furthermore, RWE studies have shown the clinical effectiveness of Evusheld in immunocompromised populations.

- Due to the evolving nature of COVID-19, PROVENT was not conducted in vaccinated patients or at a time when the Omicron variant was dominant. Nonetheless, RWE studies have demonstrated a consistent treatment effect in real-world settings during periods of Omicron; in different populations, across differing geographies and irrespective of vaccination status.

- The licenced dose for Evusheld is expected to become 600 mg, whilst PROVENT studied the 300 mg dose. However, the safety of a higher 600 mg dose has been confirmed in the TACKLE study (79), with tolerability observed to be consistent across the 300 mg and 600 mg doses. Furthermore, Young-Xu et al. 2022 (2), Al-Jurdi et al. (73) and Kertes et al. 2022(72) have demonstrated the clinical effectiveness of both 600 mg and 300 mg doses.

- It is noted that NICE DSU guidance TSD17(93) provides guidance on methods to identify and adjust for potential biases that may arise due to using non-RCT data for deriving treatment effectiveness. Young-Xu et al. 2022(2) did use a matching technique as advised in TSD17 to avoid the potential of known confounding variables, whilst Kertes et al. 2022(72) did not adjust for known confounding variables. In both studies, the impact of unknown confounding variables is not fully understood as access to the patient level data were not available at the time of submission. Nonetheless, NICE recently published their RWE framework which outlines their commitment to utilising RWE for decision making and a consistent treatment effect has been observed in RCT and RWE settings.(94)

In summary, the clinical evidence base demonstrates that PrEP treatment with Evusheld reduces the risk of developing symptomatic COVID-19 and reduces the risk of poor outcomes including hospitalisation and death. This offers much needed protection for high-risk populations and would represent a step-change in the treatment pathway for individuals with the highest risk of an adverse COVID-19 outcome, or in individuals for whom COVID-19 vaccination is not recommended.

B3 Cost effectiveness

B3.1 Published cost-effectiveness studies

A SLR was undertaken on 6th of May 2022 to identify published cost-effectiveness studies relevant to the decision problem (see Section B1.1)

Please see Appendix G for the methods used to identify all relevant studies, in addition to a description and quality assessment of the cost-effectiveness studies identified.

In line with guidance from the Centre for Reviews and Dissemination(95), the population, interventions, comparators, outcomes and study type (PICOS) principal was used to define the following review question to identify relevant cost-effectiveness studies:

- What are the available economic evaluations on COVID-19 treatments, in any setting or indication (including prophylaxis)?

Overall, 21 publications were included in the SLR: one for PEP, two for outpatient treatments, 17 for inpatient treatments and one for outpatient and inpatient treatments (See Table 33). No economic evaluations evaluated PrEP.

B3.1.1.1 Post-exposure

Flaxman 2022 examined the health outcomes and net cost of implementing PEP with monoclonal antibodies (mAbs) against household exposure to COVID-19. The analysis was conducted from a US payer perspective using a decision tree structure, with a time horizon corresponding to one wave of SARS-CoV-2 transmission (roughly one month). No quality-adjusted life years (QALYs) or incremental cost-effectiveness ratio (ICER) information was published.

B3.1.1.2 Outpatient

Two studies conducted economic evaluations in outpatient treatments for COVID-19.

Jovanoski 2022 estimated the cost-effectiveness of casirivimab/imdevimab in ambulatory individuals with COVID-19. The analysis was conducted from a US payer perspective using a decision tree followed by a Markov model. A lifetime horizon with a cycle length of one year was considered, with both costs and outcomes discounted at 3%. Treatment with casirivimab/imdevimab was a cost-effective option for most outpatients with COVID-19 compared to usual care. In the base case, at a willingness to pay (WTP) threshold of $100,000, compared to usual care, treatment with casirivimab/imdevimab was found to be cost-effective in most patients, compared to usual care.

Marjiam 2022 evaluated the cost-effectiveness of sotrovimab versus SoC in a cohort of 1,000 outpatients with mild to moderate COVID-19 at high-risk of progression (the authors did not define high-risk). The analysis was conducted from a third-party US payer perspective using a Markov model structure over a lifetime horizon. Costs and outcomes were discounted at 3%. Sotrovimab was cost-effective compared to usual care, assuming a WTP threshold of $50,000 per QALY. Increased direct healthcare costs with sotrovimab for the 1,000-patient cohort were $1,355,765. The 1000-patient cohort receiving sotrovimab gained 122.19 QALY over their lifetime, resulting in an ICER of $11,096/QALY gained.

Company evidence submission template for Tixagevimab–cilgavimab for preventing COVID-19 [ID6136]

B3.1.1.3 Inpatient

Seventeen studies conducted economic evaluations in inpatient treatments for COVID-19, three of which were UK studies and are summarised below (remaining studies are reported in Appendix G).

Kilcoyne 2022 assessed the clinical and economic benefits of lenzilumab plus SoC compared with SoC alone in the treatment of hospitalised patients with COVID-19 from the UK NHS England perspective. The analysis used a cost calculator to estimate the clinical benefits and costs of adding lenzilumab to SoC in newly hospitalised patients with COVID-19 over a period of 28 days. No discounting was applied due to this short time horizon. Overall, the findings supported the clinical and economic benefits of adding lenzilumab to SoC. In a base case population, adding lenzilumab to SoC was estimated to result in 2.40 bed days saved, 2.73 ICU days saved, and 3.33 mechanical ventilation (MV) days saved, and it led to inpatient cost savings of £1,162 per patient. In a weekly cohort of 4,754 newly hospitalised patients, adding lenzilumab to SoC resulted in 599 invasive mechanical ventilation (IMV) uses avoided, 352 additional lives saved, and more than £5,524,952 in cost savings.

Aguas 2021(96) evaluated the health and economic impact of dexamethasone in patients with COVID-19 from a UK healthcare provider perspective. The analysis used a decision tree structure over a 6-month time horizon. Dexamethasone was a cost-effective option, estimated to save an additional 12,000 lives and result in 102,000 life years (LY) gained compared with SoC, leading to a total incremental cost of £85,000,000.

Rafia 2022 (97) explored the cost-effectiveness of remdesivir in hospitalised patients with COVID-19 in England and Wales. The study was conducted from an NHS/Personal Social Services perspective using a decision analytic model considering an area under the curve approach. A lifetime horizon with a daily cycle length was used up to 70 days, followed by a weekly cycle for the remainder. Costs and health outcomes were discounted at 3.5%. The incremental QALY of 0.64 and costs of £3,332 translated into the cost-effectiveness ratio for remdesivir at £11,881/QALY gained compared with SoC.

B3.1.1.4 Outpatient / inpatient

Mulligan 2020 estimated the health-related benefits of two hypothetical treatments for COVID-19: one that is effective in mild disease (outpatient setting), and one that benefits hospitalised patients with more severe disease (inpatient setting) in a US population. The study used decision tree over a lifetime horizon, and both cost and health outcomes were discounted at 3%. Compared to no treatment, the hypothetical treatment for COVID-19 resulted in health benefits and cost savings. Treatments for both mild and serious disease resulted in a significant cost savings, assuming 20% of the population was infected with COVID-19 by the end of 2021.

Table 33: Summary list of published cost-effectiveness studies

Study	Year	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
Flaxman, 2022(98)	NR	**Evaluation Type:** Cost-Effectiveness Analysis **Currency**: USD **Model structure:** Decision Tree **Perspective:** Payer **Time horizon:** 1 month **Health States:** A single choice node for PEP with mAbs for each individual household contact, followed by a series of chance nodes for secondary infection, hospitalisation, and mortality, leading eventually to	General US population between 20 and 80 years	NR	Incremental costs <u>PEP with mAbs vs no monoclonal antibodies prophylaxis</u> **Low transmission scenario** • ≥20 y: 50% PEP Coverage= $145M; 75% PEP Coverage= $218M; 100% PEP Coverage= $291M • ≥50 y: 50% PEP Coverage= $34M; 75% PEP Coverage= $51M; 100% PEP Coverage= $68M • ≥80 y: 50% PEP Coverage= - $1M; 75% PEP Coverage= - $1M; 100% PEP Coverage= - $2M	NR

		terminal nodes for recovery or death. **Discounting:** Not considered due to short time horizon			**High transmission scenario** • ≥20 y: 50% PEP Coverage= $52M; 75% PEP Coverage= $78M; 100% PEP Coverage= $105M • ≥50 y: 50% PEP Coverage= - $30M; 75% PEP Coverage= - $45M; 100% PEP Coverage= - $60M • ≥80 y: 50% PEP Coverage= - $9M; 75% PEP Coverage= - $14M; 100% PEP Coverage= - $18M	
Jovanoski, 2022(99)	NR	**Evaluation Type:** Cost-Utility Analysis **Currency:** USD **Model Structure:** decision tree (short-term) and Markov model (long-term) **Perspective:** Payer	Ambulatory patients with mild to moderate COVID-19 between 20 and 80 years	NR	NR	<u>Casirivimab + imdevimab vs usual care</u> • **Base case (hospitalisation risk, and age, respectively):** Dominant (10%, regardless of age) • ICER WTP $100,000-$150,000/QALY: $142,955/QALY (3%, 20 years)

		Time horizon: Lifetime with a cycle length of one year **Health States:** Decision tree: recovered and dead. Markov model: no new health issues, moderate new health issues, severe new health issues. **Discounting:** 3%				• ICER WTP >$150,000/ QALY: $150,191/QALY (2%, 30 years) • ICER WTP >$200,000/ QALY: $222,671/QALY (2%, 20 years)
Marijam, 2022(100)	2021	**Evaluation Type:** Cost-Effectiveness Analysis/ Cost-Utility Analysis **Currency:** USD **Model Structure:** Markov model **Perspective:** Payer	Patients with mild to moderate COVID-19 at high-risk of progression	Incremental QALYs <u>Sotrovimab vs SoC</u> • QALYs total lifetime: 122.19 per 1,000 patients • QALYs acute outpatient and inpatient: 0.54 (2.1%) per 1,000 patients	Incremental costs <u>Sotrovimab vs SoC</u> • Total: $1,355,765 (95%) per 1,000 patients, discounted • Total outpatient: $2,485,750 per 1,000 patients, discounted ○ Acquisition = $2,100,000	<u>Sotrovimab vs SoC</u> • ICER=$8,673.06/LY • ICER=$11,095.56/QALY

		Time horizon: Lifetime **Health States:** NR **Discounting:** 3%			○ Administration = $309,600 ○ Primary care management = $76,150 • Total inpatient = -$1,129,985 (-79%) per 1,000 patients, discounted ○ Ever in ICU = -$584,363 (-79%) ○ General ward only = -$489,374 (-79%) ○ Emergency department = -$56,247 (-79%)	
Kilcoyne, 2022(101)	2020	**Evaluation Type:** Cost-effectiveness Analysis Study **Currency:** GBP **Model Structure:** Cost calculator **Perspective:** Healthcare payer	Newly hospitalised patients with COVID-19 pneumonia, with SpO2 ≤94% on room air and/or requiring supplemental oxygen, but not on IMV, aged <85 years with CRP <150 mg/L	NR	Incremental costs <u>Lenzilumab vs SoC</u> **Per treated patient:** • **Base case:** aged <85 years with CRP <150 mg/L cost (£):–£1162 Weekly Cohort: • **Base case:** aged <85 years with CRP	NR

		Time horizon: 28 days with a cycle length of 1 week **Health states:** NR Discounting: Not considered due to short time horizon			<150 mg/L cost (£): –£5,524,952	
Aguas, 2021(96)	2020	**Evaluation Type:** Cost-effectiveness Analysis **Currency:** GBP **Model Structure:** Decision tree **Perspective:** Healthcare provide **Time horizon:** 6 months **Health States:** Patients requiring oxygen, patients requiring ventilation, patients not receiving oxygen or ventilation, patients	Hospitalised patients who needs supplemental oxygen	NR	Incremental costs <u>Dexamethasone vs SoC:</u> • £85 million	NR

		receiving oxygen, patients receiving ventilation alive post-hospitalisation, death **Discounting:** Not considered due to short time horizon				
Rafia, 2022(97)	2020	**Evaluation Type:** Cost-utility Analysis **Currency:** GBP **Model Structure:** Decision-analytical model using a partitioned survival/area under the curve approach **Perspective:** NHS/Personal Social Services perspective **Time horizon:** Lifetime **Health States:** Discharged from	Hospitalised patients in England and Wales with COVID-19 and requiring supplemental oxygen (LFO, HFO or NV) at the start of treatment	Incremental QALYs <u>Remdesivir vs SoC:</u> • 0.28 QALYs (undiscounted)	Incremental costs <u>Remdesivir vs SoC:</u> • £3,332 (undiscounted)	<u>Remdesivir vs SoC=</u> • ICER = £11,881/QALY

		hospital and alive, hospitalised with or without COVID-19, death from any cause (COVID-19 or because of other causes) **Discounting:** 3.5%				

Mulligan, 2020(102)	2020	**Evaluation Type:** Cost-Effectiveness Analysis
		
		Currency: USD
		
		Model Structure: Decision Tree
		
		Perspective: NR
		
		Time horizon: Lifetime
		
		Health States: Healthy, infected, asymptomatic, symptomatic, not hospitalised, hospitalised and recovers,
			US population among which 35% are asymptomatic and assumed a 20% attack rate for 2020-2021	NR	Incremental costs
					
					<u>COVID-19 treatment (hypothetical) vs no treatment</u>
					
					Mild mortality:
					• Scenario 1 (outpatient)
					  ○ Hospitalisations cost savings ($) = 10.9B
					  ○ Cost savings from mortality ($) = 46.1B
					  ○ Total cost savings ($) = 56.9B.
					• Scenario 2 (inpatient)
						NR

		hospitalised and dead **Discounting:** 3%			○ Hospitalisations cost savings ($) = 13.1B ○ Cost savings from mortality ($) = 55.3B ○ Total cost savings ($) = 68.4B **High mortality:** • Scenario 1 (outpatient) ○ Hospitalisations cost savings ($) = 0.9B ○ Cost savings from mortality ($) = 77.1B ○ Total cost savings ($) = 87.9B. • Scenario 2 (inpatient) ○ Hospitalisations cost savings ($) = 13.1B ○ Cost savings from mortality ($) = 92.5B	

					Total cost savings ($) =105.6B	

Abbreviations: COVID-19 – Coronavirus disease 2019; CRP – C-reactive protein; GBP – Pound sterling; HFO – High-flow oxygen; HR – Hazard ratio; ICER – Incremental cost-effectiveness ratio; ICU – Intensive care unit; IMV – Invasive mechanical ventilation; LFO – Low-flow oxygen; LY – Life year; MOD – Multiorgan dysfunction; NHS – National Health Service; NNT – Number needed to treat; NR – Not reported; NV – Non-invasive ventilation; ONS – Office for National Statistics; OS – Overall survival; QALY – Quality-adjusted life years; SoC – Standard of care; SpO2 – Oxygen saturation; SWOV – Survival without ventilation; UK – United Kingdom

B3.2 Economic analysis

Models identified through the SLR mainly considered decision tree and Markov model structures based on whether short or long-term time horizons were being considered. However, there were a couple exceptions including a decision analytic area under the curve approach and cost calculator.

A subsequent targeted literature search identified an Assessment Report for an economic evaluation of therapeutics for people with COVID-19 associated with TA10936, which was published by the School of Health and Related Research (ScHARR) on 30 June 2022 after the SLR searches were completed. The analysis adapted the structure by Rafia 2022 for hospitalised patients and considered a decision tree structure for non-hospitalised patients.

Unfortunately, while evidence synthesised as part of the SLR was informative for this decision problem, no model structures considered treatments for the PrEP of COVID-19, and therefore a *de novo* model structure was considered, using a decision tree to capture the costs and outcomes during an acute infection period phase followed by a Markov model to capture the longer-term costs and outcomes.

Short-term acute decision tree phases followed by long-term Markov models with lifetime horizons for outcomes have also been used in other published models for COVID-19, including economic modelling reports produced by the US Institute for Clinical and Economic Review (ICER)(56), Sheinson 2021(35) and Jovanoski 2022(99).

B3.2.1 Patient population

Aligned with the population with highest medical unmet and Evusheld's anticipated use in clinical practice (see Section B1.3.8), the economic analysis models a subgroup of the licenced indication:

Adults who are not currently infected with SARS-CoV-2 and who have not had a known recent exposure to a person infected with SARS-CoV-2 and:

- are at the highest risk of an adverse COVID-19 outcome, namely hospitalisation and death, or
- for whom COVID-19 vaccination is not recommended

This aligns with the proposed positioning of Evusheld in the management of COVID-19 (see Section B1.4)

For the purposes of modelling, the vast majority of this patient population (>99%) are patients deemed to be at the highest risk of adverse COVID-19 outcomes due to underlying health conditions compromising their immunity (see Section B1.3.5). The remaining <1% of the population are patients for whom COVID-19 vaccination is not recommended (see Section B1.3.6).

B3.2.2 Intervention technology and comparators

The intervention (Evusheld) and comparator (no prophylaxis) are aligned with the NICE scope.

Furthermore, as agreed with NICE and the Evidence Assessment Group (EAG) during the decision problem meeting on the 17th of August 2022, treatments under evaluation in TA10936 are not included as comparators nor as subsequent treatments in the model, since these treatments are not in routine commissioning.

The model considers a 1-year treatment duration for Evusheld (600 mg dose administered at time zero and at 6 months as per Section B1.2), based on the following rationale:

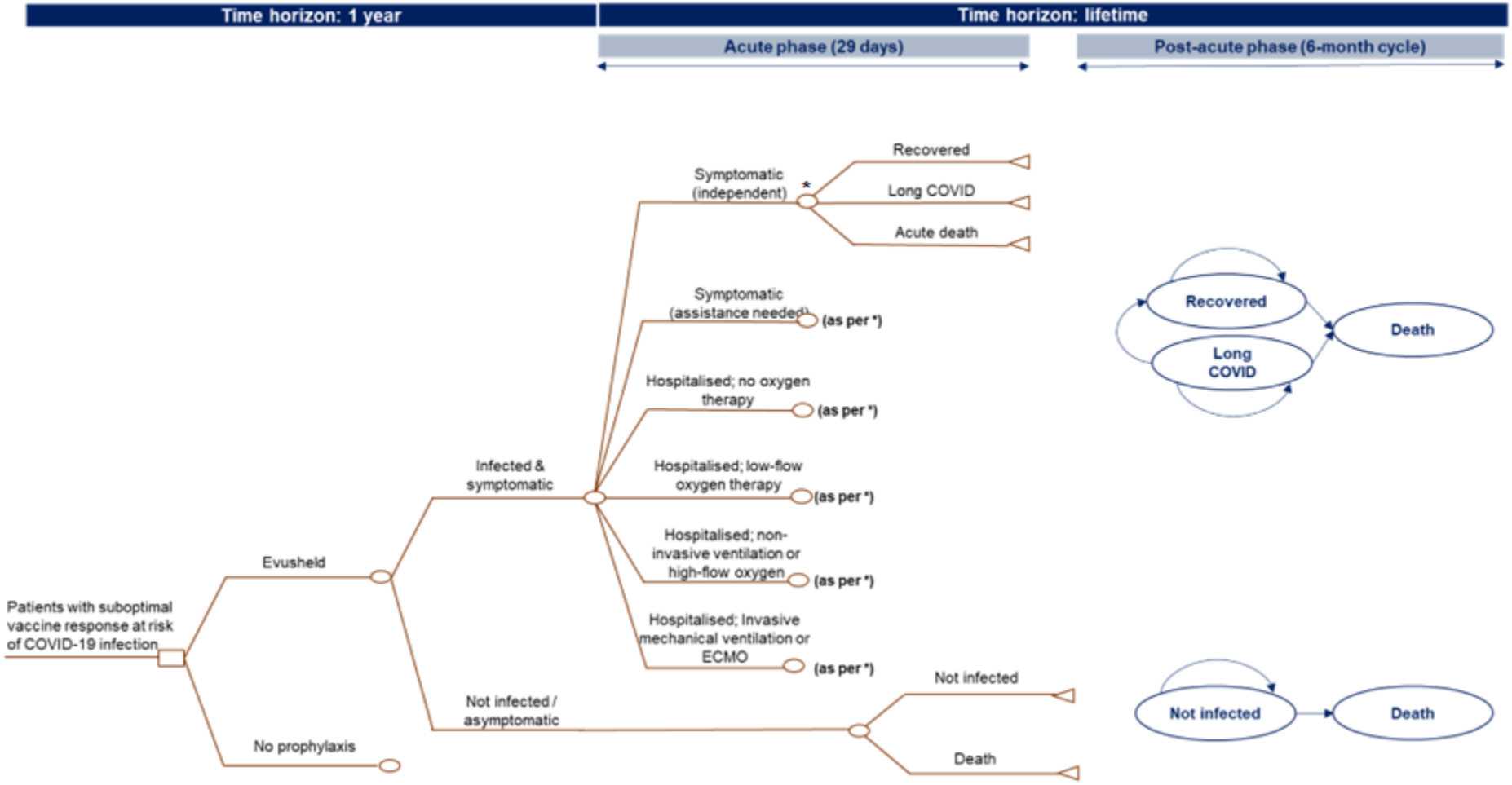
- Firstly, the environment for COVID-19 is constantly changing and it is unclear how long Evusheld will be prescribed as the risk of COVID-19 infection and associated adverse outcomes changes over time. As highlighted by APPG consensus statement, co-signed by 125 physicians treating people who are immunocompromised, prophylaxis treatments should only be delivered when the drug is effective and for those that still need protection.(28,103)
    - Mutations in the virus make it difficult to estimate what infection risk, attack rate, hospitalisation risk, and mortality risk may be within the timeframe of, for example, a typical influenza season, leading to even further uncertainty when extrapolating for longer time horizons.
    - How the management of COVID-19 will evolve over time is unknown due to the uncertainty in predicting COVID-19 variants and epidemiology parameters. As such, the long-term clinical effectiveness of any treatment strategy for COVID-19 is uncertain.
- Secondly, while some clinicians may want to protect certain patients in the target population for more than 1-year, some clinical subgroups in the target population will only be treated until a certain date due to the management of an acute condition or future-dated procedure (e.g. patients with resected solid organ cancer, patients undergoing HSCT, patients with HIV/AIDs).
- It is therefore highly unlikely that all patients will require continuous prophylaxis over their lifetime (which equates to 50 or more years); in clinical practice treatment duration will likely vary from person to person.
- Therefore, in the base case we have assumed a 1-year treatment duration such that NICE can have some degree of certainty in interpreting the cost-effectiveness results. While we acknowledge that in clinical practice, some patients may be treated for longer, we are confident that the results are an accurate reflection of cost-effectiveness assuming this treatment duration.
- This challenging situation was acknowledged by NICE and the EAG during the decision problem meeting on the 17 August 2022. The EAG advised to explore alternative treatment durations, which would require structural changes to the model. We will look at possible routes to explore the long treatment duration scenarios during the appraisal process following submission.

Redosing was chosen at 6-months to align with the medial follow-up duration from the PROVENT study, where clinical efficacy and safety has been demonstrated.

B3.2.3 Model structure

A *de novo* model structure considering a decision tree to capture the costs and outcomes during an acute infection period phase followed by a Markov model to capture the longer-term costs and outcomes was selected (Figure 16).

Figure 16: Model structure



B3.2.3.1 Acute phase (decision tree):

The decision tree time horizon is 29 days in line with the longest modelled duration of stay taken from Beigel, et al. 2020.(34)

Prior to entering the acute phase, patients either receive Evusheld or no prophylaxis and are at risk of COVID-19 infection for 1-year, they then enter the acute phase, transitioning to the "infected & symptomatic" or "not infected/asymptomatic" health states.

Patients in the "not infected/asymptomatic" health state transition to either the "not infected" or "death" health states at the end of the decision tree, and subsequently enter the post-acute phase (Markov model).

Patients in the "infected & symptomatic" health state are assigned to one of six health states based on the severity of infection. These were aligned to WHO clinical progression scale, the efficacy endpoints used in clinical studies of Evusheld, and was validated with three UK clinical experts (Table 34). (104)

Table 34: Description of acute modelled health states

Model health states classifying infection severity	WHO clinical progression scale (104)
Not hospitalised – no assistance needed	Symptomatic; independent (2)
Not hospitalised – assistance needed	Symptomatic; assistance needed (3)
Hospitalised; no oxygen therapy	Hospitalised: no oxygen therapy (4) Hospitalised: oxygen by mask or nasal prongs (5)
Hospitalised; low-flow oxygen therapy	NA
Hospitalised; non-invasive ventilation or high-flow oxygen	Hospitalised; oxygen by NIV or high-flow (6)
Hospitalised; Invasive mechanical ventilation or extracorporeal membrane oxygenation	Intubation and MV, pO_2/FiO_2 ≥ 150 or SpO_2/FiO_2 ≥200 (7) MV pO_2/FiO_2 <150 or SpO_2/FiO_2 <200 or vasopressors (8) MV pO_2/FiO_2 <150 and vasopressors, dialysis or ECMO (9)

Abbreviations: FiO2 – Fraction of inspired oxygen; MV – Mechanical ventilation; NA – not applicable for the WHO clinical progression scale NIV – Non-invasive ventilation; pO2 – Partial pressure of oxygen; SpO2 – Peripheral capillary oxygen saturation; WHO – World Health Organization

B3.2.3.2 Post-acute phase (Markov model):

Following the acute phase (decision tree), patients transition to the post-acute phase (Markov model), whereby patients enter one of four health states: "not infected", "recovered", "long COVID", or "death":

- Patients in the “not infected” health state either remain in this state or transition to the “death” state.

- Patients in the “recovered” health state either remain in this state or transition to the “death” state.

- Patients in the “long COVID" health state develop long-term sequelae that result in utility losses, reduced life expectancy, and costs associated with treating long COVID. These patients either remain in this state, transition to the “recovered” health state or transition to the “death” health state.

The possibility for COVID-19 infection risk after year 1 is considered by adjusting the total cost and QALY results derived from the structure described above. The adjustment considers a decrement to total QALYs and an increase in total costs for both arms based on the possibility for reinfection after year 1. This was included based on advice from the (EAG) during the decision problem meeting on the 17th of August 2022. For more details on methodology, see section B.3.3. (Reinfection after year 1).

The cycle length during the post-acute phase is 6 months, and a half cycle correction is applied.

B3.2.4 Time horizon

The model incorporates three distinct forms of time horizon for the analysis: one for the period over which COVID-19 infections are captured (1-year), short-term outcomes following this infection period captured by a decision tree (29 days) and long-term outcomes for patients with or without COVID-19 captured by a Markov model (lifetime).

The rationale for choosing an infection period of 1-year is based on the treatment duration of Evusheld (see Section B3.2.2). The rationale for then considering a 29-day decision tree is based on duration of stay in hospital taken from Beigel 2020.

The rationale for a lifetime horizon is to ensure the time horizon is sufficiently long to reflect all important differences in costs or outcomes between the technologies being compared are captured in line with the NICE reference case. Such benefits from treatment as improved survival and reductions in long COVID would be underestimated with any shorter time horizon.

The use of a 1-year time horizon for infections and lifetime horizon for outcomes is consistent with previously published COVID vaccine models (Kohli 2021). Short-term acute decision tree phases followed by long-term Markov models with lifetime horizons for outcomes have also been used in other published models for COVID, including economic modelling reports produced by ICER(56), Sheinson 2021(35) and Jovanoski 2022(99). This type of time horizon approach is also used in static seasonal influenza models (such as Chit 2015(105), Ruiz-Aragón 2022(106)).

B3.2.5 Perspective

An NHS and personal social services (PSS) perspective was chosen, in line with the NICE reference case.(107)

B3.2.6 Discounting

Costs and utilities are discounted at 3.5% per annum, in line with the NICE reference case.(107)

B3.2.7 Features of the economic analysis

Table 35 describes the features of the economic analysis, compared to the ScHARR Assessment Report in TA10936.

It should be noted that the ScHARR Assessment Report in TA10936 did not consider prophylaxis and built separate models for hospitalised and non-hospitalised patients to evaluate a broad range of alternative COVID-19 treatments. Therefore, though the disease area of COVID-19 might be similar, the decision problem is considerably different between this submission and TA10936.

Table 35: Features of the economic analysis

Factor	Ongoing evaluations	This evaluation	
	ScHARR assessment report in TA10936 (108)	**Chosen values**	**Justification**
Time horizon	Lifetime	Lifetime	Same methodology applied
Treatment waning	Not applied	Not applied	Treatment effect lasts for 6 months until redosing, reflecting the duration of the pivotal study (PROVENT) (70)
Outcomes: Risk of hospitalisation	• 0.9%, Nyberg et al.(109)	• 17.1%, Shields et al. 2022 (46)	The UK PIN data (46) set is more reflective of the high-risk immunocompromised population, whereas Nyberg et al. is reflective of general population data
Outcomes: Distribution of hospitalised patients	• Recalibrated Beigel et al. data from the ACTT-1 study (34) o Not requiring supplemental oxygen – OS 3, 5-7 (day 0): 0% – OS 4 (day 0): 100% – OS 3 (day 14): 21% – OS 4 (day 14): 36% – OS 5 (day 14): 26% – OS 6 (day 14): 14% – OS 7 (day 14): 3% o Requiring supplemental oxygen – OS 3-4 (day 0): 0% – OS 5 (day 0): 56% – OS 6 (day 0): 43% – OS 7 (day 0): 1% – OS 3 (day 14): 4% – OS 4 (day 14): 15%	• Cusinato et al. 2022(110) o No oxygen therapy, 26.1% o Low-flow oxygen therapy, 40.7% o Non-invasive ventilation or high-flow oxygen, 17.8% o Invasive mechanical ventilation or ECMO, 15.4%	• Beigel et al. (34) data was recalibrated to reflect current UK estimates o ACTT-1 was early in the pandemic: February 2020-April 2020 o ACTT-1 only included 5 out of 60 centres and therefore is less representative of UK clinical practice o Data reported do not reflect the health states of the model structure chosen for this evaluation • Cusinato et al. (110) was chosen as: o A more recent study – reviewed hospital admissions across the

	– OS 5 (day 14): 28% – OS 6 (day 14): 46% – OS 7 (day 14): 7%		first/second wave of the pandemic: January 2020 – March 2021 ○ A UK only study ○ Data captured reflected the model structure chosen in the evaluation
Outcomes: Risk of long COVID	All patients hospitalised due to COVID-19 would suffer long COVID	All patients hospitalised due to COVID-19 would suffer long COVID	Same methodology applied
Outcomes: Duration of and recovery from long COVID	Lognormal parametric model	Adapted lognormal parametric model	The lognormal parametric model used by in the ScHARR Assessment Report (108) was updated with more recent data from Evans 2022 (111) to improve the external validity of the extrapolation
Long COVID costs	• Annual cost £1,013, Vos-Vromans et al. 2017 (112)	• Annual cost of £1,128 (inflated), Vos-Vromans et al. 2017(112)	Same methodology applied
HRQoL (acute)	• Wilcox et al. 2017,(113) Hollman et al. 2013,(114) and assumption • Hospitalised (not requiring supplemental oxygen): -0.36 • Hospitalised (LFO): -0.58 • Hospitalised (HFO/NIV): -0.58 • Hospitalised (IMV/ECMO): 0	• Barbut et al. 2019,(115) ICER 2020 (56) • Symptomatic (no assistance needed): -0.19 • Symptomatic (assistance needed): -0.19 • Hospitalised (No oxygen): -0.49 • Hospitalised (low-flow oxygen): -0.49 • Hospitalised (NIV/HF oxygen): -0.69 • Hospitalised (IMV or ECMO): -0.79	• ICER 2020 provides a more up to date source for utility decrements in the health states of interest (56) • However, values used for the ScHARR Assessment Report in TA10936 are broadly in line with those in this evaluation and have been explored in scenario analysis. (108)
HRQoL (post-acute)	• Evans et al. 2021(58) ○ Ambulatory: -0.13	• Adjusted Evans et al. 2021 (58) • Evans et al. 2022 (111)	Evans et al. 2021 (58) utility values include patients irrespective of

	○ No oxygen: -0.13 ○ LF oxygen: -0.13 ○ NIV/HF oxygen: -0.13 ○ IMV or ECMO: -0.13	○ Ambulatory: -0.154 ○ No oxygen: -0.154 ○ LF oxygen: -0.154 ○ NIV/HF oxygen: -0.188 IMV or ECMO: -0.360	recovery status at follow-up and therefore will underestimate the disutility of patients with long COVID. Follow-up data from Evans et al. 2022,(111) which looked at utility of recovered patients, was used to adjust the utility values.

Abbreviations: ACTT – Amlodipine Cardiovascular Community Trial; COVID-19 – Coronavirus disease 2019; ECMO – Extracorporeal membrane oxygenation; HFO – High-flow oxygen; HRQoL – Health-related quality of life; ICER – Institute for clinical and economic review; IMV – Intermittent mandatory ventilation; LFO – Low-flow oxygen; NIV – Non-invasive ventilation; OS – Ordinal scale; PIN – Primary Immunodeficiency Network; ScHARR – School of Health and Related Research; UK – United Kingdom

B3.3 Clinical parameters and variables

B3.3.1 Population characteristics

Population characteristics for age, sex and weight are sourced from the PROVENT trial population (Table 36), since the selection criteria for PROVENT aligns closely with the population for Evusheld's proposed use in terms of age, sex, and weight.

Table 36. Patient Characteristics at Baseline

Parameter	Value
Baseline mean age (years)	53.5
% Male	53.9%
Weight (kgs)	85.7

Abbreviations: Kg – kilogram

No prophylaxis decision tree

B3.3.1.1 Risk of symptomatic infection

Symptomatic infection risk for no prophylaxis in the model over the initial 1-year period is calculated as 22.58% based on UK government data.(116)

It was calculated by averaging the 7- day attack rate (initial and subsequent attack rates) over the period August 2021 – August 2022 (accessed 11th August). The average 7-day attack rate was re-calculated to a 1-year attack rate using the following formulae:

$$1\,year\ infection\ rate = 1 - EXP(-7 day rate * 52)$$

B3.3.1.2 Hospitalisation

The proportion of patients with symptomatic infection who were hospitalised for no prophylaxis was taken from a recent study by Shields et al. 2022.(46)

Shields et al. 2022 assessed the impact of vaccination on hospitalisation and mortality from COVID-19 in patients with primary and secondary immunodeficiency in the UK, which aligns closely with the target population for the submission.

The study included a cohort of 140 patients infected between January 2021 and March 2022. Study participants represent patients infected after the deployment of vaccination and the routine use of antiviral and monoclonaly antibody treatments in inpatient and outpatient settings. Furthermore, the majority of infections occurred later in the pandemic, after patients had received at least two vaccine doses, after the more transmissible B.1.1.529 (Omicron) SARS-CoV-2 variant became dominant, and after legal restrictions on social interactions had been lifted (16). Results from the study showed that 16.8% of patients with primary immunodeficiency and 18.2% of patients with secondary immunodeficiency required hospitalisation. A weighted average of 17.13% is used in the base case analysis.

B3.3.1.3 Severity of hospitalisation

The severity of hospitalisation was defined based on the four hospitalisation health states: (no oxygen, low-flow oxygen, high-flow oxygen or non-invasive ventilation (NIV), or intermittent mandatory ventilation (IMV) or extracorporeal membrane oxygenation (ECMO)).

The proportions of patients in each of the health states were based on hospitalisation data from a South London hospital (Table 37); these data were not specific to immunocompromised patients and thus may underestimate the true severity of hospitalisation associated with COVID-19 infection in this high-risk cohort.

Table 37. Distribution of Hospitalised Patients

	No oxygen therapy	Low-flow oxygen therapy	NIV or high-flow oxygen therapy	IMV or ECMO	Source
No prophylaxis	26.1%	40.7%	17.8%	15.4%	Cusinato et al. 2022(110)

Abbreviations: ECMO – Extracorporeal membrane oxygenation; IMV – Invasive mechanical ventilation; NIV – Non-invasive ventilation

B3.3.1.4 Non-hospitalised patients

The proportion of symptomatic patients who were not hospitalised was calculated as 1 minus the percentage hospitalised. The split between the 'not hospitalised – no assistance needed' and 'not hospitalised – assistance needed' health states was assumed to be 50/50% in the base case. The model was built with the flexibility to incorporate health-state-specific data however, in the absence of such data, clinical, cost and QALY data between the two health states is assumed equal. As such, amendments to the percentage split between health states does not impact the ICER.

Table 38 summarises the distribution of patients between hospitalised and non-hospitalised states in the no prophylaxis arm.

Table 38. Overall distribution of hospitalised and non-hospitalised patients

	Not hospitalised- NAN	Not hospitalised- AN	No oxygen therapy	Low-flow oxygen therapy	NIV or High-flow oxygen therapy	IMV or ECMO
No prophylaxis	41.4%	41.4%	4.5%	7.0%	3%	2.6%

Abbreviations: AN – Assistance needed; ECMO – Extracorporeal membrane oxygenation; IMV – Invasive mechanical ventilation; NAN – No assistance needed; NIV – Non-invasive ventilation.

B3.3.2 Evusheld decision tree

The clinical effectiveness of Evusheld is captured in two ways in the economic model

- A percent reduction in symptomatic infection, applied as a RRR to the no prophylaxis 1-year symptomatic infection rate

- A percent reduction in severity, if symptomatic, applied as a RRR to the hospitalisation rate of no prophylaxis

With no data to inform how Evusheld would affect the distribution of severity in hospitalised patients, the proportion of patients transitioning within hospitalised health states was assumed the same between arms (see Table 37). This is deemed conservative as UK clinicians advised it would be reasonable to assume reduced hospitalisation severity, given Evusheld's mechanism of action and known benefits in reducing symptomatic infection and hospitalisation risk.

Three data sources exist that could inform the clinical effectiveness of Evusheld:

- PROVENT
- Young-Xu et al 2022
- Kertes et al. 2022

These three studies are described in Section B2.

B3.3.2.1 PROVENT

The primary source of randomised clinical effectiveness data for Evusheld is the PROVENT trial as described in Section B2.8.1. Results from the study showed a RRR in symptomatic COVID-19 of 82.8% (95% CI: 65.8–91.4% [11 (0.3%) compared to 31 (1.8%)]) at the median 6-month follow-up.

Although results from PROVENT are derived using the optimal RCT design, there are limitations in the application of this data to the economic model:

- [redacted] of participants in the PROVENT trial were immunocompromised, though treatment effectiveness was not shown to significantly differ between immunocompromised and immunocompetent participants (Section B2.8.1.5).
- Per the PROVENT exclusion criteria, all participants were COVID-19 vaccine naïve at enrolment and only earlier variants of COVID-19 (Beta and Delta) were prevalent. This does not necessarily reflect the current UK environment, which would include individuals who are vaccinated and may be infected with Omicron sub-lineages predominantly circulating the UK.
- A 300 mg dose was used in the PROVENT study, whilst the licenced indication is anticipated to be updated to a 600 mg dose only (see Table 2).

B3.3.2.2 Real-world evidence

As described in Section B2.1.2.1, two RWE studies were identified during a period when Omicron sub-lineages were circulating. Both studies informed the clinical effectiveness of Evusheld in a real-world setting and could be used for the purposes of economic modelling.

Young-Xu et al. 2022(2) provided the most robust source of evidence. The large retrospective study (n=8,037) was conducted in US veterans, aged ≥18 years, receiving Veteran's Affairs (VA) healthcare. It compared individuals with at least one dose of intramuscular Evusheld with

matched controls, selected from patients who were immunocompromised or otherwise at high-risk for COVID-19.

- The study aligned to the current UK environment, with 95% of patients having received COVID-19 vaccination and the analysis period was during high prevalence of Omicron (BA.1 and the early BA.2 and BA.2.12.1 surge).
- Furthermore, 83% of patients received 600 mg dose of Evusheld.
- Results from the propensity-score matched analysis showed that Evusheld recipients had a lower incidence of the composite of COVID-19 outcomes versus control patients (HR 0.31; 95% CI: 0.18-0.53 [17/1733 [1.0%] vs 206/6354 [3.2%]])
- Each of the COVID-19 outcomes showed similar Evusheld benefits, including test-confirmed COVID-19 infection (HR 0.34; 95% CI: 0.13-0.87), COVID-19 hospitalisation (HR 0.13; 95%CI, 0.02-0.99), and all-cause mortality (HR 0.36; 95% CI: 0.18-0.73).

Kertes et al. 2022(72) provided a secondary source of evidence. The large retrospective study (n=5,124) was conducted in members of the Maccabi HealthCare Services in Israel, aged 12 and over with evidence of a severe immunosuppression, and compared individuals receiving Evusheld with unmatched controls.

- The study aligned to the current UK environment, with 98.8% of patients having received at least one COVID-19 vaccination. The analysis period took place when Omicron BA1 and BA2 were predominant.
- All patients received the 300 mg dose.
- Results from the analysis found that the odds of infection for the Evusheld administered group compared to the controls was significantly reduced by almost 50% (OR: 0.51, 95% CI: 0.30-0.84) (Table 27).

B3.3.2.3 Clinical effectiveness source used for the base case

Young-Xu et al. 2022(2) was used in the base case as it represented the most generalisable population to the decision problem, with a study design and statistical methods that minimised the risk of bias in a non-randomised setting. PROVENT and Kertes et al. were used in scenario analyses to explore the impact of randomised evidence and alternative data sources.

Young-Xu et al. 2022(2) was selected as a stronger source of evidence compared to Kertes et al. 2022(72) as:

- Young-Xu et al. 2022(2) had a larger sample size (n=8,037) compared with Kertes et al. 2022(72) (n=5,124).
- Young-Xu et al. 2022(2) used the 600 mg dose in 83% of patients, whereas Kertes et al. 2022(72) used the 300 mg dose in all patients.
- Young-Xu et al. 2022(2) conducted a matching exercise to mitigate the risk of imbalances that may confound results (see Section B2.6.2.1), whereas Kertes et al. 2022(72) did not, which may confound results.(72)

- It is noted that NICE Decision Support Unit TSD17(93) provides methods to identify and adjust for potential biases that may arise due to using non-RCT data for deriving treatment effectiveness. Young-Xu et al. 2022(2) did use a matching technique as advised by TSD17 to avoid the potential of known confounding variables. However, the impact of unknown confounding variables is not fully understood as access to the patient level data is not currently available.

Table 39 and Table 40 summarise the RRRs applied to the no prophylaxis risk of symptomatic infection and risk of hospitalisation, to derive the distribution of patients across health states in patients receiving Evusheld.

To calculate the RRR of symptomatic infection with Evusheld, a 66% reduction is applied to the risk of symptomatic infection with no prophylaxis, based on the HR reported in Young-Xu et al. 2022 (2).

The RRR of hospitalisation with Evusheld, given symptomatic infection was calculated as 1 minus the HR for hospitalisation reported in Young-Xu et al. 2022(2) divided by the HR for symptomatic infection reported for in Young-Xu et al. 2022(2) (1-0.13/0.34 = 61.8%).

Table 39: Clinical effectiveness inputs for Evusheld

Source	**RRR symptomatic infections vs no prophylaxis:**	**RRR hospitalisation given symptomatic infection vs no prophylaxis**
Base case: Young-Xu et al. 2022**(2)**	66%	61.8%
Scenario: PROVENT study**(76)**	82.8%	100%*
Scenario: Kertes et al. 2022**(72)**	49%	62.3%**

*No additional benefit assumed due to low hospitalisation numbers as only three patients (0 with Evusheld and three with placebo) were hospitalised at the time of primary data cut (regardless of prior vaccination status or unblinding).
**RRR of hospitalisation in Kertes et al. was estimated as *1 – the risk of being hospitalised given infection*. The risk of being hospitalised given infection was calculated as the HR of hospitalisation (0.19) divided by the HR of infection (0.51). Abbreviations: HR – Hazard ratio; RRR – Relative risk reduction

Table 40. Overall distribution of hospitalised and non-hospitalised patients (Evusheld)

	Young-Xu et al. 2022 (base case)	PROVENT (scenario)	Kertes et al. 2022 (scenario)
Not infected	92.34%	96.13%	88.52%
Not hospitalised – no assistance needed	3.42%	1.88%	5.37%
Not hospitalised – assistance needed	3.42%	1.88%	5.37%
No oxygen therapy	0.21%	0.03%	0.19%
Low-flow oxygen therapy	0.33%	0.05%	0.30%
NIV or high-flow oxygen	0.14%	0.02%	0.13%
IMV or ECMO	0.12%	0.02%	0.11%

Abbreviations: AN – Assistance needed; ECMO – Extracorporeal membrane oxygenation; IMV = Invasive mechanical ventilation; NAN – No assistance needed; NIV = Non-invasive ventilation.

B3.3.3 Distribution of patients at the end of acute period

At the end of the acute period, patients were assigned to one of three health states; “recovered”, “long COVID” or “death”.

B3.3.3.1 Recovered

Patients who did not transition to “long COVID” or “death”, transitioned to the “recovered” health state.

B3.3.3.2 *Long COVID*

In the base case it was assumed that all hospitalised patients had long COVID at discharge and transitioned to the “long COVID” health state. This assumption is in line with the ScHARR Assessment Report in TA10936.(108)

Augustin et al. 2021 conducted a longitudinal study with 958 non-hospitalised patients and found that 34.5% had a least one COVID-19 symptom at 7 months; this percentage was used to derive the proportion transitioning to long COVID in the non-hospitalised health states.(117)

Scenario analyses considered using estimates from the literature for hospitalised health states. Evans et al. 2021(58) looked at the Physical, cognitive, and mental health impacts of COVID-19 in 1,077 patient as part of the Post-hospitalisation COVID-19 study (PHOSP-COVID) study. Results for COVID-19 status at 5 months post discharge when asked “Do you

feel fully recovered?" are shown in Table 41. It was assumed that the 50% of patients answering 'not sure' were recovered.

Findings from Evans et al. 2020 (20–30% recovery at 6 months after hospitalisation for COVID-19) are consistent with previous reports.(118,119) However, it is important to note that these estimates are for the general population and likely overestimate recovery rates in the high-risk patient population.

The distributions of patients at the end of the acute period for the base case and scenario analysis are summarised in Table 42 and Table 43.

Table 41: Proportion of patients with long COVID/ recovered (Evans et al. 2021(58))

	WHO Class 3-4	WHO class 5	WHO class 6	WHO class 7-9
Recovered	30.9%	36.3%	28.5	18.8%
Not recovered	45.5%	44.8%	45.1%	67.9%
Not sure	23.6%	18.9%	26.4%	13.9%
Model health state application	No oxygen therapy	Low-flow oxygen	NIV or high-flow oxygen	IMV or ECMO

Abbreviations: COVID-19 – Coronavirus disease 2019; ECMO – Extracorporeal membrane oxygenation; IMV – Invasive mechanical ventilation; NIV – Non-invasive ventilation; WHO – World Health Organization

Table 42. Distribution of patients at end of acute period – base case

	Not hospitalised- NAN	Not hospitalised- AN	No oxygen therapy	Low-flow oxygen therapy	NIV or high-flow oxygen therapy	IMV or ECMO
Recovered	65.5%	65.5%	0.00%	0.00%	0.00%	0.00%
Long COVID	34.5%	34.5%	95.43%	92.36%	86.10%	53.00%
Dead	0.00%	0.00%	4.57%	7.64%	13.90%	47.00%

Abbreviations: AN – Assistance needed; ECMO – Extracorporeal membrane oxygenation; IMV – Invasive mechanical ventilation; NAN – No assistance needed; NIV – Non-invasive ventilation

Table 43. Distribution of patients at end of acute period – scenario analysis

	Not hospitalised- NAN	Not hospitalised- AN	No oxygen therapy	Low-flow oxygen therapy	NIV or high-flow oxygen therapy	IMV or ECMO
Recovered	54.55%	54.55%	52.05%	50.94%	47.24%	17.00%
Long COVID	45.45%	45.45%	43.38%	41.41%	38.86%	36.00%
Dead	0.00%	0.00%	4.57%	7.64%	13.90%	47.00%

Abbreviations: AN – Assistance needed; ECMO – Extracorporeal membrane oxygenation; IMV – Invasive mechanical ventilation; NAN – No assistance needed; NIV – Non-invasive ventilation

B3.3.3.3 COVID-related mortality

Patients in hospitalisation health states could die in the decision tree due to COVID-related mortality and would transition to the "death" health state, while non-hospitalised patients were assumed not to die during this acute phase. Other cause mortality was captured through general population statistics in the Markov model (see Section B3.3.1).

As shown in Table 44, data informing COVID-19 mortality for the no-oxygen and low-oxygen health states were taken from Ohsfeldt et al. 2021 (35), which reported the hospital discharge status by the Adaptive COVID-19 Treatment Trial Ordinal Scale (ACTT OS) for COVID-19 patients in the US. ACTT OS level 3-4 was used for the no oxygen health state and ACTT OS level 5 was used for the low-flow oxygen health state. Data for the NIV/high-flow health and IMV/ECMO health states was taken from an ICNARC (45) report on COVID-19 in critical care for England, Wales and Northern Ireland.

Table 44. COVID-related mortality

	No oxygen therapy	Low-flow oxygen therapy	NIV or high-flow oxygen therapy	IMV or ECMO
COVID-related mortality	4.6%	7.6%	13.9%	47.0%

Abbreviations: COVID-19 – Coronavirus disease 2019; ECMO – Extracorporeal membrane oxygenation; IMV – Invasive mechanical ventilation; NIV – Non-invasive ventilation

B3.3.4 Markov model

B3.3.4.1 Recovered

As per the decision tree, patients who did not transition to "long COVID" or "death", transitioned to the "recovered" health state in the Markov model.

B3.3.4.2 Long COVID

Patients remained in the "long COVID" health state in the Markov model based on the proportion of patients with long COVID over time.

The proportion of patients with long COVID over time was estimated using parametric modelling conducting by ScHARR, as reported in the Assessment Report for TA10936(41), which considered published estimates at the time from self-reported[4] ONS data.

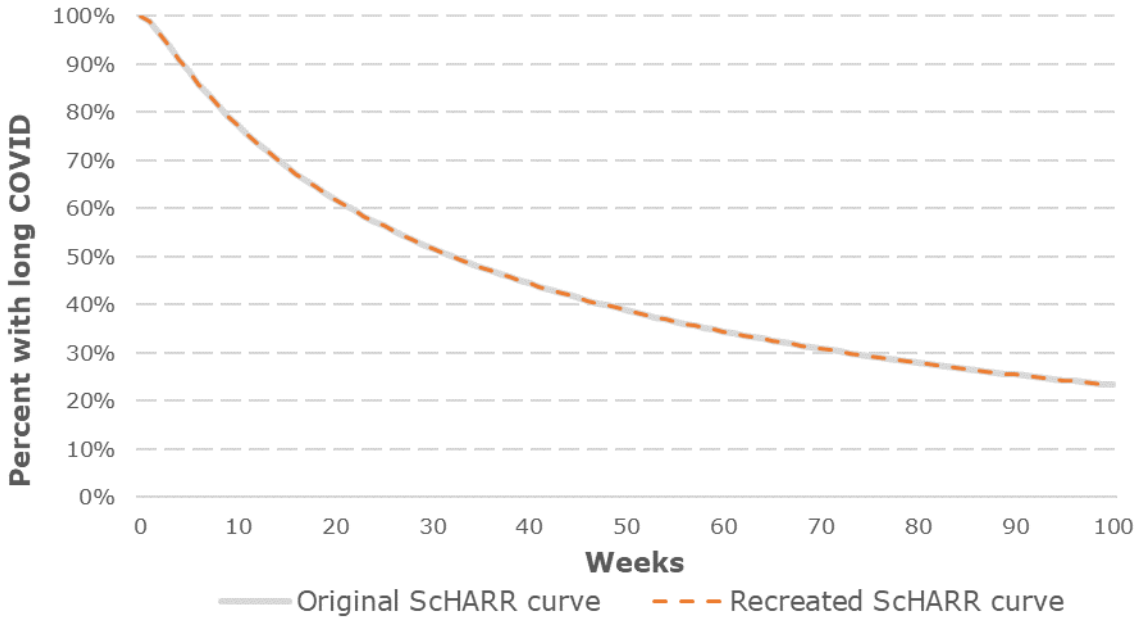
Simple parametric modelling fitted reported estimates of at least 12 weeks (72% with long COVID at 12 weeks, 42% at 1 year, and 22% at 2 years). The EAG report of TA1096 (ScHARR, ID4038(41)) selected the lognormal in the base case, with a mean time of 108.6 weeks, as it was noted that the mean duration of COVID-19 had increased compared to

[4] Long COVID, defined as "symptoms continuing for more than four weeks after the first suspected coronavirus (COVID-19) infection that were not explained by something else"

previous ONS reports and the data on long COVID is relatively immature and may be administratively censored.

Shapes and scales reported in the ScHARR ID4038 were used to recreate their time-to-recovery curve for patient with long COVID (lognormal distribution, mean 3.468, standard deviation 1.562) (Figure 17).

Figure 17: Recreated ScHARR curve



Abbreviations: COVID-19 – Coronavirus disease 2019; ScHARR – School of Health and Related Research

However, it was noted that these estimates are based on the general population rather than a high-risk immunocompromised or hospitalised population, and as such likely underestimates the duration of long COVID in the target population for Evusheld, since “hospitalisation is associated with a lower likelihood of recovery” (Evans 2021)(58).

Furthermore, the EAG report of TA10936 compared estimates from the lognormal curve to data from Evans et al. 2021(58), which estimated that at 5 months, 51.7% of hospitalised patients had not recovered from COVID-19 (corresponding estimate from lognormal 55.3%).

However, more recent follow-up data from Evans et al. 2022(111) showed that 50% of patients are still not recovered at 1 year follow-up which is much higher than the predicted ~37% in the using the lognormal curve.

Therefore, data from Evans 2022 was used to adjust the lognormal curve to reflect the newer long COVID estimate for patients at 1 year. A limitation with the Evans information is that it only provides estimates at two time-points (5 months and 1 year). In contrast, the ONS evidence is based on three time-points (12 weeks, 1 year and 2 years). Therefore, the ONS data were used to inform the shape and scale of the survival function (aligned with the ScHARR Assessment Report in TA10936), whilst Evans 2022 was used to adjust the survival function.

Evans 2021(58) and 2022(111) both report the proportion of patients who state they are 'recovered' and those who are 'not sure'. The EQ-5D value reported in Evans 2022 for patients in the 'unsure' category is approximately half-way between the EQ-5D values of the 'recovered' and 'not recovered' categories (Table S3 of Evans 2022). Therefore, it was assumed that half of the unsure category had not recovered, which provided the estimates of 64.70% and 59.95% at 5 months and 1 year respectively for the proportion of patients who have not recovered.

Calculations are shown in Table 45. Hence, from a baseline of five months, the proportion of patients who still had long COVID seven months later was equal to 92.65% (59.95% / 64.70%). Note that as this value is a ratio, it is unlikely to be overly influenced by the assumption of how many unsure patients have not recovered.

Table 45: Proportion of patients with long COVID – Evans et al. 2022

	Not recovered	Not sure	Total N	Calculation
5 months	1,079	385	1965	(1079 + 385/2)/(1079 + 385 + 501) = 64.70%
1 year	392	180	804	(392 + 180/2)/(392 + 180 + 232)= 59.95%

Abbreviations: COVID-19 – Coronavirus disease 2019

To perform the adjustment to the survival function using Evans 2022, the model was re-written as a linear model using the methodology described in Kearns et al. 2019(120). Parameters of the linear model were found using Solver in Excel to ensure that model predictions over time matched those from the recreated model and verified visually.

The rationale for representing the lognormal as a linear model is that the slope (trend) may be interpreted as the shape, whilst the intercept controls the absolute value. Hence, the slope parameter was kept fixed, whilst the intercept was adjusted (using Solver in Excel) so that the proportion still with long COVID at 12-months was 92.65%. The slope and intercept parameters of the resulting linear curve were 0.64021 and -3.62754 respectively.

The adjusted lognormal curve was used to derive the proportions of patients who remained in the "long COVID" health state. The adjusted lognormal curve did not include deaths as both the ONS survey and Evans 2022(111) are retrospective studies i.e. patients had to have long COVID and still be alive to enter the study, with duration of long COVID assessed retrospectively (hence people who had long COVID but died prior to the study were not included).

Figure 18 and Figure **19** illustrate the proportion of patients with long COVID using the ScHARR curve from the Assessment Report in TA10936, and the adjusted ScHARR curve used in this submission; the adjusted ScHARR curve hits the ratio calculated from Evans 2022 (0.92) as well as the two data points derived from the publication (0.647 at month 5, and 0.595 and 1 year). On the other hand, the ScHARR curve from the Assessment Report underestimates the data reported by Evans 2022.

Figure 18: Proportion of patients with long COVID, who remain in long COVID over time

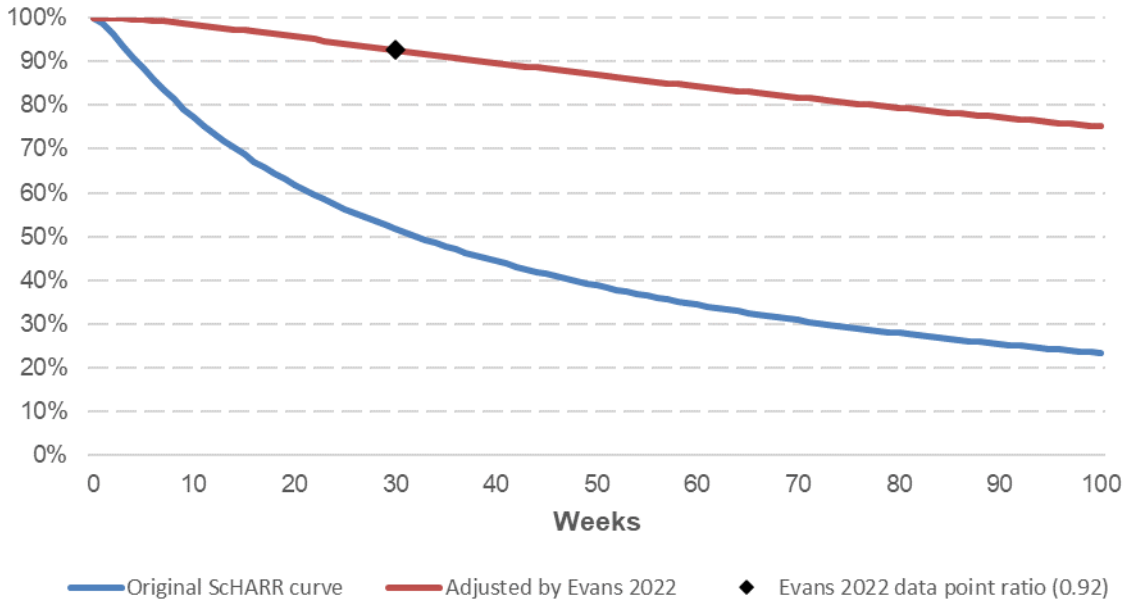
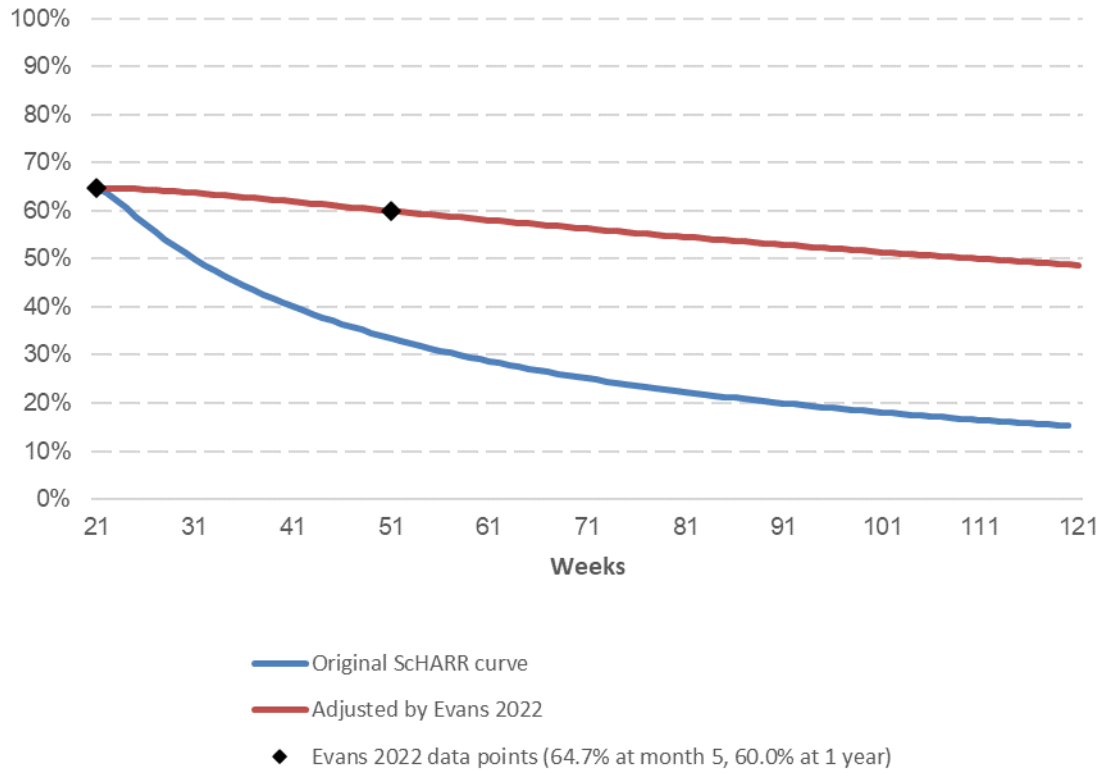


Figure 19: Proportion of all patients, who have long COVID over time



B3.3.4.3 Mortality

Transition probabilities to the “death” health state from both the “recovered” and “long COVID” health states were defined by applying mortality HR to age and sex specific UK life table data.(121)

An underlying mortality HR for all immunocompromised patients compared to the general population of 1.7 estimated from the standardised mortality ratio for COVID-19 patients compared with the general European population was applied to the UK life table data.(122)

Furthermore, additional HRs were applied on top of the underlying mortality HR based on the acute phase health state, with more severe health states having an increased probability of death (Table 46). In the absence of current mortality estimates for recovered and long COVID patients, mortality HRs for both recovered and long COVID patients were based on Sheinson 2021(35). No additional mortality was assumed for not hospitalised or non-ICU hospitalised states. It was assumed that patients in the “NIV or high-flow oxygen” and “IMV or ECMO” health states were treated in the ICU setting.

In line with Sheinson 2021(35), 5-year mortality among ICU- versus non-ICU-admitted hospital patients post discharge was estimated at HR of 1.33; these HRs were applied for a 5-year period after hospital discharge, after which patients were assumed to have the same mortality risk as the general population.

Table 46. Hazard Ratios for mortality for recovered and long COVID patients

Acute health state	HR	Source
Not hospitalised – NAN	1.00	Assumption
Not hospitalised – AN	1.00	Assumption
No oxygen therapy	1.00	Assumption
Low-flow oxygen therapy	1.00	Assumption
NIV or high-flow oxygen	1.33	Sheinson 2021(35)
IMV or ECMO	1.33	Sheinson 2021(35)

Abbreviations: AN – assistance needed; COVID-19 – Coronavirus disease 2019; ECMO – extracorporeal membrane oxygenation; IMV – invasive mechanical ventilation; NAN – no assistance needed; NIV – non-invasive ventilation

B3.3.5 Post year one infection rate

As described in Section B3.2.3, the possibility for COVID-19 infection risk after year 1 was considered by adjusting the total cost and QALY results, as follows:

- The post year one infection rate was estimated using the no prophylaxis infection rate at year 1 (22.58%) and was adjusted to a 6-month rate of 12.00%.
- Post year one infection rate was assumed constant over time and applied to all patients remaining alive in each cycle.

- The risk of hospitalisation associated with post year one infection for Evusheld and no prophylaxis was calculated from the no prophylaxis decision tree (17.13%).(46)

- Surviving patients who were infected after year one incurred a cost and utility decrement as described in Sections B3.4 and B3.5. This is a utility decrement of -0.0023 and cost increase of £347.15.

- Patients who were infected after year one were also set to have a mortality of 2.4%, calculated as the weighted average of the acute mortality associated with each health state in Table 38 and Table 44. A post-hoc adjustment was made to total QALYs in each cycle such that 0.29% (2.4% x 12%) of patients were set to have a utility of 0 (applied as QALYs decrement to total QALYS).

B3.4 Measurement and valuation of health effects

B3.4.1 Health-related quality of life data from clinical trials

No HRQoL data was collected from the PROVENT or RWE studies. Section B3.4.3 includes HRQoL values identified from the SLR.

B3.4.2 Mapping

No mapping was conducted as part of this study.

B3.4.3 Health-related quality of life studies

A HRQoL SLR was undertaken in June 2022 to identify existing studies investigating HRQoL associated with preventative treatment/prophylaxis of COVID-19. Please see Appendix G and H for the methods used to identify all relevant studies, and description of the HRQoL studies identified.

The review question in the HRQoL SLR was:

- What are the utility values for health states experienced by pre- and post-exposure COVID-19 patients?

In total, 47 studies were included in the review, see Appendix H for a tabular view of the HRQoL results. A summary of the SLR findings is provided below.

B3.4.3.1 Disutility of acute COVID-19 infection

The SLR did not identify any studies that measured utility decrements associated with COVID-19 infection.

B3.4.3.2 Utility values

The SLR identified studies reporting utility values in COVID-19, as summarised in Table 47.

Two studies Vlake et al. and Demoule et al. reported HRQoL results following ICU admission for COVID-19.

- Vlake et al. found that mental and overall HRQoL were lower in COVID-19 ICU survivors than in the general population where the study was situated. The study reported an overall mean EQ-5D utility score of 0.69 (SD: 0.24) for COVID-19 ICU survivors six weeks after hospital discharge.

- Demoule et al concluded that significant number of patients reported changes in HRQoL, dyspnoea, and symptoms that were not evident prior to admission 12 months following ICU hospitalisation for COVID-19. The study found that median EQ-5D-3L time trade-off was 0.80 (Inter-quartile range (IQR), 0.36–0.91) at 2 months and 0.91 (0.52–1.00) at 12 months (P = 0.12).

Nakshbandi et al. reported results of lung function, symptoms, and quality of life after admission with COVID-19 infection. The mean baseline EQ-5D-5L utility score was 0.71 (95% CI: 0.65–0.74).

Han et al. also reported HRQoL values for mild acute COVID-19. The study demonstrated the burden of persistent symptoms was significantly associated with poorer long-term health status, poorer quality of life, and psychological distress, and at long-term follow-up, the median (IQR) score for EQ-VAS was 78 (69, 89), for EQ-5D-5L was 0.90 (0.79, 1.00).

B3.4.3.3 QALYS

Two studies reported QALY values: Crawford et al and Sandmann et al. Of those, only the Sandmann et al. study calculated the HRQoL impact of non-hospitalised laboratory-confirmed COVID-19 cases in England before the national vaccination programme commenced. With a mean follow-up duration of 77.9 days (weighted mean: 84.5 days), the unadjusted health loss due to COVID-19 ranged between 0.179 and 0.192 QALYs with the EQ-5D value sets of different countries. Results weighted by age and sex of the population in England showed adjusted health loss due to COVID-19 ranging between 0.024 and 0.038 QALY (see Appendix H for further details).

B3.4.3.4 Targeted literature searches

Due to the paucity of utility estimates identified in the SLR that were derived from patients with COVID-19 infection – additional targeted literature searches were undertaken to identify utility estimates in proxy disease areas and published health economic evaluations of treatments for COVID-19. These studies are presented in Table 48.

Table 47: Summary of studies reporting utility values identified through SLR

Study name	Patient group/ Intervention	n	Scale used to calculate utilities	QoL values					
				Mean	Median	SD	95% CI	IQR	P-value
Nakshbandi, 2022	All subjects at baseline (at hospital discharge)	117	EQ-5D-5L	0.71	-		0.65-0.74	-	-
	All subjects during study (6 months after hospitalisation)		EQ-5D-5L	0.83	-	-	-	-	p < 0.001
Demoule, 2022	2 months after ICU admission	77	EQ-5DL-3L TTO	-	0.8	-	-	0.36-0.91	p = 0.012
	12 months after ICU admission	86		-	0.91	-	-	0.52-1.00	p = 0.012
Vlake, 2021	COVID-19 patients at 6 weeks post ICU discharge	118	EQ-5D	0.69	-	0.24	-	-	-
Han, 2022	All subjects (patients with symptomatic COVID-19 at the time of positive SARS-COV-2 test and reporting patient-important outcomes at long-term follow-up)	213	EQ-5D-5L	-	0.9	-	-	0.79-1	-

Abbreviations: COVID-19 – Coronavirus 2019 disease; EQ-5D-3L – Euroqol 5 dimensions 3 levels; EQ-5D-5L –Euroqol 5 dimensions 5 level; ICU – intensive care unit; IQR – Interquartile range; QoL – Quality of life; SARS-COV-2 – Severe acute respiratory syndrome coronavirus 2; SD – Standard deviation; SLR – Systematic literature review

Table 48: Summary of studies reporting utility values identified through TLR

Study name	Value type	Population measured	Value	Calculation details	Publications used within calculation			
					Source Number	Title	Author and year of publication	Source population
Rafia, 2022	Utility loss	Increased comorbidities at entry	-0.116	Calculation from [1,2,3,4]. Utility values are age-adjusted as patients get older based on Ara and Brazier, with the baseline utility value pre-COVID-19 estimated from the mean age at entry, adjusted by a decrement in utility taken from Ara and Brazier to reflect increased comorbidities for patients with COVID-19 compared with the general population. During the hospitalisation episode, decrements in utility values are applied (subtracted) to the baseline, taken from the published literature. As with the assignment of costs, these utility decrements align with the degree of care required	***[1]***	*Populating an Economic Model with Health State Utility Values: Moving toward Better Practice*	*Ara and Brazier. 2010*	*Cardiovascular patients, UK*

				while in the hospital as indicated by the ordinal scale. Following hospital discharge patients with COVID-19 have a reduced QoL, with QoL returning to pre-COVID-19 baseline after 52 weeks				
		COVID-19 patients discharged from hospital (first 52 weeks)	-0.097		***[2]***	*Post discharge symptoms and rehabilitation needs in survivors of COVID-19 infection: A cross-sectional evaluation*	*Halpin et al. 2020*	*COVID-19 patients, UK*
		Hospitalised COVID-19 patients, not on oxygen	-0.36		***[3]***	*Impact of recurrent Clostridium difficile infection: hospitalisation and patient quality of life*	*Wilcox et al. 2017*	*Clostridium difficile infection patients, UK*

		Hospitalised COVID-19 patients, on LFO, or HFO or NIV	-0.58		***[4]***	*Impact of Influenza on Health-Related Quality of Life among Confirmed (H1N1)2009 Patients*	*Malen et al. 2013*	*H1N1 infection patients, Spain*
Martin, 2021	Utility loss	COVID-19 patients left with permanent injury post COVID	0.318	Calculated from the utility loss at 1-year post ICU discharge for ARDS [1] and the population norm for England [2]	***[1]***	*One year resource utilisation, costs, and quality of life in patients with ARDS: Secondary analysis of a randomised controlled trial*	*Marti et al. 2016*	*UK ICU admission in patients who required MV for ARDS (non-COVID-19)*
			0.856		***[2]***	*Population norms for the EQ-5D-3L: a cross-country analysis of population surveys for 20 countries.*	*Janssen et al. 2019*	*General population , UK*
		All symptomatic cases (COVID-19 symptomatic patients on	0.103	Derived from weighting the average utility loss for symptomatic ward and ITU survivors at 6 weeks [3].	***[3]***	*Post discharge symptoms and rehabilitation needs in survivors of COVID-19*	*Halpin et al. 2020*	*COVID-19 patients, UK*

		average 48 days post discharge)		Symptomatic non-hospitalised patients are assumed to have similar utility loss as symptomatic ward patients		*infection: A cross-sectional evaluation*		
Sinha and Linas, 2021	QALY	COVID-19 patients treated with tocilizumab and dexamethasone	9.36	Years of life saved were projected using the mortality data from the RECOVERY trial [1-2]. Of participants who received combination therapy, 457 of 1664 (27.4%) died. Of those who received corticosteroids alone, 565 of 1721 (32.8%) died. Finally, 127 of 367 (34.6%) of individuals who only received supportive care died. Age specific life expectancy was estimated from the Social Security actuarial table [3]. Subsequently, life expectancy was discounted using the following formula: Years of Life Saved = (1*1-(1 + Discount Rate)-Life expectancy at age)/Discount Rate. To adjust years of life gained for quality of life lost due to chronic lung disease, the	***[1]***	*Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial*	*Abani et al. 2021*	*COVID-19 patients, Global*
		COVID-19 patients treated with dexamethasone alone	8.66		***[2]***	*Investigators R–C. Interleukin-6 receptor antagonists in critically ill patients with COVID-19*	*REMAP-CAP Investigators, 2021*	*COVID-19 patients, Global*
		COVID-19 patients treated with supportive care alone	8.43		***[3]***	*Social Security Administration. Actuarial life table.*	-	*General population, US*
		-	-		***[4]***	*Respiratory function in patients' post-infection by COVID-19: a systematic review and meta-analysis.*	*Torres-Castro et al. 2021*	*COVID-19 patients, Global*

				n-weighted mean of post COVID-19 forced vital capacity (FVC) reported in a systematic review [4] was calculated. QALYs were estimated by multiplying years of life saved by the QALY weight corresponding to the FVC of survivors as listed in the Tufts cost-effectiveness analysis registry [5]				
					[5]	*Skills of the trade: the Tufts Cost-Effectiveness Analysis Registry.*	*Thorat et al. 2021*	*-*
Padula, 2021	QALY (deterministic value)	Utility of emergency department treatment of COVID-19 patients	0.5	QALY values for health states involving infection with COVID-19 (i.e., ED, home monitoring, hospitalisation, and critical car) were assumed to be equal to the lower bound QALY estimates for SARS as estimated from a Canadian study using the Health Utilities Index-3 [1]. QALY values for recovery health state are based on EQ-5D score for chronic conditions in the US [2]	***[1]***	*Managing febrile respiratory illnesses during a hypothetical SARS outbreak*	*Khan et al. 2005*	*SARS patients, Canada*

		Utility of at home monitoring of COVID-19 patients	0.5		***[2]***	*Preference-Based EQ-5D index scores for chronic conditions in the United States.*	*Sullivan et al. 2006*	*Chronic disease patients, US*
		Utility of hospitalisation of COVID-19 patients	0.25		**-**	-	-	-
		Utility of critical care treatment of COVID-19 patients	0.05					
		Utility of recovery of COVID-19 patients	0.76					
Li, 2021	QALY (for 100,000 people)	Full vaccination with BNT162b2	48908.4	Health utility scores for patients with COVID-19 were derived from the disutility weights of severe lower respiratory tract infection [1,2]	***[1]***	*Global. regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017*	*GBD 2017*	*Disease patients, Global*
		Full vaccination with BNT162b2 + booster	48912.1		***[2]***	*Cost-effectiveness of intensive care for hospitalised COVID-19 patients: experience from South Africa*	*Cleary et al. 2021*	*COVID-19 patients, South Africa*

Ohsfeldt, 2021	QALY gain (vs SoC alone)	Baricitinib + SoC	0.6703	Age-adjusted health utilities for the US general population were used to represent overall quality of life absent the effects of COVID-19. These utilities were adjusted to account for the greater prevalence of comorbidities in the modelled population [1,2]	***[1]***	*Alternative Pricing Models for Remdesivir and Other Potential Treatments for COVID-19*	*Campbell et al. 2020*	-
	Utility	COVID-19 patients without severe comorbidities, aged 18-29	0.922		***[2]***	*Preference-Based EQ-5D index scores for chronic conditions in the United States*	*Sullivan et al. 2006*	*General population , US*
		COVID-19 patients without severe comorbidities, aged 30-39	0.901					
		COVID-19 patients without severe comorbidities, aged 40-49	0.871					
		COVID-19 patients without severe comorbidities, aged 50-59	0.842					
		COVID-19 patients without severe	0.823					

		comorbidities, aged 60-69						
		COVID-19 patients without severe comorbidities, aged 70-79	0.79					
		COVID-19 patients without severe comorbidities, aged 80+	0.736					
Basu and Gandhay 2021	QALY loss per day	Symptomatic infection with COVID-19	-0.43	Disutility for symptomatic infection [1], hospital admission and receipt of critical care [1,2] were obtained from literature estimates of quality of life losses. These quality of life losses were divided by 365 to calculate QALYs lost per day that a patient remains in a particular health state. For example, the quality of life loss for symptomatic no hospitalised COVID-19 health state was estimated to be –0.43 based on the experiences of patients with H1N1. Therefore, the	***[1]***	*Impact of influenza on health-related quality of life among confirmed (H1N1) 2009 patients*	*Hollmann et al. 2013*	*H1N1 infection patients, Spain*
		Patient admitted to hospital for COVID-19	-0.5		***[2]***	*Quality of life and utility decrement associated with Clostridium difficile infection in a French hospital setting.*	*Barbut, et al. 2019*	*Clostridium difficile infection patients, France*
		Patient receiving critical care for COVID-19	-0.6		**-**	-	-	-

				disutility per day would be –0.0012 QALYs				
Jovanoski, 2022	Utility	General population age-adjusted utility	0.9442–0.0027× age	The model uses data on age-adjusted general population utility values from Sullivan and Ghushchyan [1] and	***[1]***	*Preference-Based EQ-5D index scores for chronic conditions in the United States*	*Sullivan et al. 2006*	*Chronic disease patients, US*
					[2]	*Alternative Pricing Models for Remdesivir and Other Potential Treatments for COVID-19*	*Campbell et al. 2020*	*-*
					[3]	*Remdesivir for the treatment of COVID-19 - Final report*	*Beigel et al. 2020*	*COVID-19 patients, Global*
	Disutility	COVID-19 symptoms	0.19	Calculated from [1]	***[1]***	*Cost-effectiveness of newer treatment strategies for influenza*	*Smith, 2002*	*Influenza patients, Global*
		COVID-19 in hospital setting (weighted average)	0.61	Calculated from [2]	***[2]***	*Quality of life and utility decrement associated with Clostridium difficile infection in a French hospital setting.*	*Barbut et al. 2019*	*Clostridium difficile infection patients, France*
Kelton, 2021	Utility	COVID-19 patients without severe comorbidities, aged 18-29	0.922	Utility scores obtained through panel survey: EQ-5D index Scores of US Adults by age in Medical Expenditure Panel Survey	***[1]***	*Preference-Based EQ-5D index scores for chronic conditions in the United States*	*Sullivan et al. 2016*	*General population, US*
		COVID-19 patients without severe	0.901					

		comorbidities, aged 30-39						
		COVID-19 patients without severe comorbidities, aged 40-49	0.871					
		COVID-19 patients without severe comorbidities, aged 50-59	0.842					
		COVID-19 patients without severe comorbidities, aged 60-69	0.823					
		COVID-19 patients without severe comorbidities, aged 70-79	0.79					
		COVID-19 patients without severe comorbidities, aged 80+	0.736					
	Disutility	COVID-19 symptoms	-0.19	Calculated from [2]	*[2]*	*Cost-effectiveness of newer treatment strategies for influenza.*	*Smith et al. 2002*	*Influenza patients, Global*

		Mechanical ventilation	-0.6	Calculated from [3]	*[3]*	*Alternative pricing models for remdesivir and other potential treatments for COVID-19.*	*Whittington et al. 2020*	-
		Non-invasive ventilation	-0.5	Calculated from [3]				
		Supplemental oxygen	-0.4	Average of non-invasive ventilation and medical care without oxygen non-invasive ventilation				
		Medical care without oxygen non-invasive ventilation	-0.3	Calculated from [3]				
Whittington, 2022	Disutility	COVID-19 symptoms	-0.19	Calculated from [1]	*[1]*	*Cost-effectiveness of newer treatment strategies for influenza.*	*Smith et al. 2002*	*Influenza patients, Global*
		Mechanical ventilation	-0.6	Calculated from [2]	*[2]*	*Alternative pricing models for remdesivir and other potential treatments for COVID-19. Institute for Clinical and Economic Review Report*	*Whittington et al. 2020*	*Influenza patients, Global*
		Non-invasive ventilation	-0.5	Calculated from [2]				
		Supplemental oxygen	-0.4	Average of non-invasive ventilation and medical care without oxygen non-invasive ventilation				
		Medical care without oxygen	-0.3	Calculated from [2]				

		non-invasive ventilation						
Congly, 2021	Utility	Severe COVID-19	0.23	Calculated based on utility during the influenza episode; EQ-5D index [1]	*[1]*	*Impact of influenza on health-related quality of life among confirmed (H1N1) 2009 patients*	*Malen et al. 2013*	*Influenza population ; Spain*
		Moderate COVID-19	0.5616	Calculated based on health utility of influenza inpatient (Weighted) [2]	*[2]*	*The impact of influenza on the health-related quality of life in China: An EQ-5D survey*	*Yang et al. 2017*	*Influenza inpatient; China*
		-	-	Utilities were based on previous experiences with H1N1 and influenza; patients were assumed to have these utilities for 28 days based on their initial degree of disease severity and would not change during this period and then return to the US average utility of 0.815 [3]	*[3]*	*US population norms for the EQ-5D-5L and comparison of norms from face-to-face and online samples*	*Jiang et al. 2021*	*General population , US*
Wouterse, 2022	QALYs lost	Women with COVID-19 (naïve estimate)	6.85	Calculated from [1,2,3,4]. Searched the literature for review articles reporting on utilities for diabetes, heart failure, and COPD. The resulting values are 0.80 for diabetes, 0.73 for COPD Gold, and 0.64 for heart failure. QoL in nursing homes was set at	*[1]*	*Review of utility values for economic modelling in type 2 diabetes.*	*Beaudet, 2014*	*Population with type 2 diabetes; UK*
		Men with COVID-19 (naïve estimate)	7.35		*[2]*	*Catalogue of EQ-5D scores for the United Kingdom*	*Sullivan et al. 2011*	*Population with chronic conditions ; UK*

		Women with COVID-19 (adjusted estimate)	3.52	0.49, which represents EQ-5D-3L based average QoL in a Dutch nursing home sample using the Dutch value set. the utility for adjusted figures considering individual with previous health problems	*[3]*	*Do model-based studies in chronic obstructive pulmonary disease measure correct values of utility? A Meta-Analysis*	*Moayeri et al. 2016*	*-*
		Men with COVID-19 (adjusted estimate)	3.94		*[4]*	*Cost-effectiveness of Sacubitril-Valsartan combination therapy compared with enalapril for the treatment of heart failure with Heart Failure and Reduced Ejection Fraction*	*King et al. 2016*	*Population with heart failure; US*
Carta and Conversano, 2021	Disutility	Patients hospitalised with COVID-19, not requiring supplemental oxygen	0.581	Calculated from [1]	*[1]*	*The impact of influenza on the health-related quality of life in China: an EQ-5D survey*	*Yang et al. 2017*	*Influenza inpatients; China*
		Patients hospitalised with COVID-19, requiring supplemental oxygen	0.5					
		Patients hospitalised with COVID-19, receiving non-invasive ventilation or	0.23	Calculated from [2]	*[2]*	*The Impact of influenza on health-related quality of life among confirmed (H1N1) 2009 patients.*	*Hollmann et al. 2013*	*Influenza patients, Spain*

		high-flow oxygen devices						
		Patients hospitalised with COVID-19, receiving IMV or Extracorporeal Membrane Oxygenation	0.05	Calculated from [3]	*[3]*	*Cost-utility evaluation of extracorporeal membrane oxygenation as a bridge to transplant for children with end-stage heart failure due to dilated cardiomyopathy*	*Brown et al. 2009*	-
	Utility	Base Utility	0.851	Calculated from [4]	*[4]*	*Preference-Based EQ-5D Index Scores for Chronic Conditions in the United States*	*Sullivan et al. 2006*	*US healthy patients*

Abbreviations: ARDS – Acute respiratory distress syndrome; COPD – Chronic obstructive pulmonary disease; COVID-19 – Coronavirus disease 2019; EQ-5D-5L – Euro Qol-5 dimension-5 level; EQ-5D-3L – Euro Qol-5 dimension-3 level; HFO – High-flow oxygen; ICER – Institute for Clinical & Economic Review; ICU – Intensive care unit; LFO – Low-flow oxygen; NIV – Non-invasive ventilation; QALY – Quality-adjusted life year; QoL – Quality of life; SARS – Severe acute respiratory syndrome; SARS-CoV-2 – Severe acute respiratory syndrome coronavirus 2; SLR – Systematic literature review; UK – United Kingdom; US – United States; WHO– World Health Organisation

B3.4.4 Adverse reactions

Incidence of key SAEs are shown in Table 49, based on PROVENT trial data(70). Given the relatively low incidence of SAEs observed in the PROVENT trial, particularly treatment-related SAEs, a conservative approach was applied whereby treatment-emergent SAEs were included in the model if ≥5 events occurred in either treatment arm.

Disutility values for the key serious AEs were sourced from a targeted review and applied for Evusheld and no prophylaxis arms based on published models and/or utility studies. These decrements were included in the base case analysis and are shown in Table 50.

In the absence of available SAE duration data from the PROVENT trial, SAE durations were based on the weighted average length of stay estimates for the health resource group (HRG) codes used to cost the SAEs (Table 50) from NHS reference costs 2017/18 (the latest set of NHS reference costs with length of stay estimates) and converted to months.

Table 49. Prophylaxis related AE Incidence (Over 12 months)

Adverse event	No prophylaxis	Evusheld	Source
Infections and Infestations	0.58%	0.46%	PROVENT (Levin et al. 2022(76))
Injury, Poisoning or Procedural Complications	0.92%	0.23%	
Nervous System Disorders	0.00%	0.52%	
Cardiac Disorders	0.12%	0.35%	
Gastrointestinal Disorders	0.12%	0.35%	
Renal and Urinary Disorders	0.12%	0.35%	

Abbreviations: AE – Adverse event

Table 50. SAE Disutility

SAE	Disutility (annual)	Source	Duration (months)	Source
Infections and Infestations	0.1710	Cornely et al. 2018(123) NICE TA370(124)	0.17	NHS reference costs 2017-18(125)
Injury, Poisoning or Procedural Complications	0.1100	Svedbom et al. 2018(126)	0.13	

Nervous System Disorders	0.0700	Kansal et al. 2019(127) Sullivan et al. 2016(128)	0.20	
Cardiac Disorders	0.1080	Cornely et al. 2018(123) Clarke et al. 2002(129)	0.20	
Gastrointestinal Disorders	0.1350	Akehurst et al. 2002(130)	0.16	
Renal and Urinary Disorders	0.2500	Javanbakht et al. 2020(131) Shepherd et al. 2010(132)	0.14	

Abbreviations: NHS – National health service; SAE – serious adverse event

B3.4.5 Health-related quality of life data used in the cost-effectiveness analysis

B3.4.5.1 General population utility

Age specific utilities are modelled using general population utilities from Ara & Brazier 2010(133). Health states utilities are calculated by applying health-state-specific disutilities to the general population utilities by age.

B3.4.5.2 Disutility associated with immunocompromised comorbidities

The population of interest for Evusheld are high-risk immunocompromised patients who have additional comorbidities associated with their underlying conditions. A baseline disutility of 0.1160 was applied to all patients to reflect baseline comorbidities in line with the utility value applied in Rafia 2022(97) (Table 48), which assessed the cost effectiveness of Remdesivir in Wales. This disutility was used to reflect the comorbidities of patients hospitalised with COVID-19 at study entry and is based on UK tariff EQ-5D-3L data.

B3.4.5.3 Decision tree – COVID-19 infection disutilities

A disutility for initial COVID-19 symptoms of 0.19 was applied in the base case in line with values used in Kelton et al. 2021(134) and Whittington et al. 2022(135). (Table 48) This value was sourced from an influenza modelling study (Smith et al. 2002(136)), identified as part of the HRQoL TLR.

Additional health-state-specific disutilities were then applied to each of the hospitalised health states based on Whittington et al. 2022(135) identified in the TLR, which sourced EQ-5D-3L disutility estimates from a French study of hospitalised patients with clostridium difficile (Barbut 2019(115)).

Total disutility values applied in the acute phase of the model were calculated using time to symptom resolution (TTSR) reported in the base case analysis from the ICER Modelling Analysis Plan(137) identified in the TLR (Table 51).

Utility values from the ScHARR Assessment Report in TA10936 were based on Rafia et al.(97) identified through the TLR. These values were not used in the base case as they did not differentiate between the NIV/high-flow oxygen health states and low-flow oxygen health states. Furthermore, it was deemed that the assumption of zero utility for IMV/ECMO was inappropriate as it means that the health state utility value remains the same regardless of age – while every health state utility value for every other acute health state would decrease with increasing age (after disutility value is applied to general population norms). However, a scenario analysis was considered to measure the impact on the cost-effectiveness results (Table 52).

Table 51: Disutility associated with acute COVID-19 & hospitalisation

	Hospitalisation disutility (115,137)	Total health state disutility (annual)	TTSR (days)(137)	Total health state disutility applied in CEM
Not hospitalised – NAN	-0.00	-0.19	11.0	0.0057
Not hospitalised – AN	-0.00	-0.19	11.0	0.0057
No oxygen therapy	-0.30	-0.49	17.0	0.0228
Low-flow oxygen therapy	-0.30	-0.49	19.0	0.0255
NIV or high-flow oxygen	-0.50	-0.69	21.0	0.0397
IMV or ECMO	-0.60	-0.79	28.0	0.0627

Abbreviations: AN – Assistance needed; COVID-19 – Coronavirus disease 2019; ECMO – Extracorporeal membrane oxygenation; HF – High-flow; IMV - Invasive mechanical ventilation; LF – Low-flow; NAN – No assistance needed; NIV – Non-invasive ventilation

Table 52: Disutility hospitalisation from ScHARR Assessment Report in TA10936 – Scenario analysis

Therapy	Hospitalisation disutility	Source
No oxygen therapy	-0.36	Wilcox et al. 2017(113)
Low-flow oxygen	-0.58	Hollmann et al. 2013(114)
NIV or High-flow oxygen	-0.58	

Abbreviations: NIV – Non-invasive ventilation

B3.4.5.4 Markov model – Recovered utility

The utility of patients in the recovered health state was assumed to be equal to the adjusted general population utility values in the absence of data.

B3.4.5.5 Markov model – Long COVID disutility

No utility values were obtained through the SLR or targeted literature search for long COVID.

In the absence of available disutility data specific to long COVID patients, long-term post discharge disutility values were calculated from Evans et al. 2021(58) (Table 47) and Evans et al. 2022 identified in TLR, and applied to the adjusted general population utility values. Both studies reported quality of life data from the PHOSP-COVID study.

Evans et al. 2021 reported utility values for patients following hospital discharge from COVID-19 at 5 months follow-up (EQ-5D-5L). The weighted average utility loss at 5 months was -0.13 and was utilised for long COVID disutility in the ScHARR Assessment Report in TA10936 (41). However, these utility values recorded patient quality of life irrespective of recovery status at follow-up (28.85% recovered and 19.5% not sure) and therefore underestimate the utility of patients with long COVID.

Follow-up data from Evans et al. 2022 reported EQ-5D-5L utility values for patients based on recovery status for the whole population (not split by severity) as shown in Table 53. The average disutility for patients who had not recovered compared with pre-COVID-19 from Evans et al. 2022 was -0.22 compared with the average discharge disutility (-0.13) reported in Evans 2021.

Given this, the distribution by severity was utilised from Evans et al. 2021 assuming a higher average utility of -0.22 (distribution of patients by WHO class similar between studies). Values reported in Evans 2021 were uplifted by a factor of 1.71 (-013/-0.22) and are given in Table 54. For patients who were not hospitalised, the disutility was assumed equal to the no oxygen therapy health state. A scenario analysis considers the Evans 2021 results without adjustment, as per the ScHARR Assessment Report in TA10936.(41)

Table 53: EQ-5D-5L disutility values post discharge (5 months) – Evans et al. 2021

	WHO class 3-4	WHO class 5	WHO class 6	WHO class 7-9	Total
Pre-COVID-19	0.82	0.84	0.82	0.87	0.84
Post – COVID-19	0.72	0.76	0.69	0.67	0.71
Change	-0.09	-0.09	-0.11	-0.21	-0.13

Abbreviations: COVID-19 – Coronavirus disease 2019; EQ-5D – Euroqol 5 dimensions 5 level; WHO – World Health Organization

Table 54: EQ-5D-5L disutility values applied in the base case

	Disutility value reported in Evans et al. 2021	Disutility values applied in the base case
Not hospitalised – NAN	-0.09 (Assumption)	-0.154
Not hospitalised – AN	-0.09 (Assumption)	-0.154
No oxygen therapy	-0.09	-0.154
Low-flow oxygen therapy	-0.09	-0.154

NIV or high-flow oxygen	-0.11	-0.188
IMV or ECMO	-0.21	-0.360

Abbreviations: AN – Assistance needed; ECMO – Extracorporeal membrane oxygenation; EQ-5D – Euroqol 5 dimensions 5 level; IMV – Invasive mechanical ventilation; NAN – No assistance needed; NIV – Non-invasive ventilation

B3.4.5.6 Markov model – Evusheld utility gain associated with reduced anxiety and improved social functioning

Lifestyle changes due to the fear of contracting COVID-19 severely impacts life and well-being, and as discussed in Section B.1.3.7 is more common in high-risk, immunocompromised populations.

There is an associated level of anxiety with living 'normal life' in the knowledge that the measures they have taken (such as vaccinations) do not provide adequate protection against COVID-19 and that the consequences of inadequate protection may be catastrophic given their clinical status. The constant stress of potential life-threatening consequences can have a substantial negative impact on quality of life (QoL) and lead to substantial restrictions to daily activities as detail in Section B1.3.7.

Anxiety and reduced social functioning is associated with a perceived risk of poor quality of life and potentially death, as has previously been seen in NICE TAs (TA246(138) and TA769(139)). In these TAs, patients were provided a treatment they perceived to reduce their risk, which in doing so conferred improved quality of life due to reduced anxiety and improved social functioning. This improvement was accepted by NICE for both TAs.

Many non-high-risk vaccinated individuals will recall the sense of relief felt when receiving their vaccination and changes to their own behaviours which improved their quality of life. Similarly, 68% of extremely clinically vulnerable patients would welcome a prophylaxis were it made available(20). Evusheld is targeted for these patients specifically, where the level unmet need is high and where prophylaxis desired.

Indeed, UK clinicians advised that the availability of Evusheld would cause an instant improvement in high-risk immunocompromised patients (as has been seen for vaccines in non-high-risk patients) as they believed the perceived protection patients feel knowing they have received an efficacious treatment (Evusheld) will allow them to feel less anxious and depressed, socialise and resume normal activities.

To estimate the utility improvement Evusheld would confer, in a similar way to treatments in TA246 and TA769, a study conducted by the CANDOUR study group (publication by Violato et al. 2022(55)) was leveraged. This study found a HRQoL loss of [redacted] associated with lockdown in >150,000 patients. This value is in line with the magnitude of that used in TA246 for the improvement in anxiety/social function with Pharmalgen (-0.072), which was also leveraged in calculating similar disutility magnitudes in TA769 (138).

Therefore, a utility gain associated with Evusheld of [redacted] was used in the base case and applied to all patients for the duration of treatment (1-year). A scenario analysis to test the impact of the utility gain on the results was considered by reducing the proportion of patients receiving this utility gain to 82% based on a recent ONS survey on the proportion of extremely clinically vulnerable individuals taking extra precautions to protect themselves(20). This is deemed conservative since Evusheld would only be made available to patients who would

want to receive a prophylactic in the first place, and the knowledge of additional protection following vaccination would confer an instant utility benefit to all such patients.

B3.4.5.7 Post year one infection utility decrement after year 1

The utility decrement associated with post year one infection was calculated as the total acute utility loss in the 29 days following infection, calculated from the decision tree of the no prophylaxis arm to give a value of -0.0023.

B3.4.5.8 Summary of utility values for the cost-effectiveness analysis

Table 55 summarises the utility values used in the cost-effectiveness analysis.

Table 55: Summary of utility values for cost-effectiveness analysis

State	Utility value: mean (standard error)	95% confidence interval	Reference in submission (section and page number)	Justification
Recovered	General population	NA		Assumption
No symptomatic infection	General population	NA		Assumption
Not hospitalised – NAN	-0.19 (0.019)	0.1542-0.2286)		Non-hospitalised infected patients used utility values from Rafia et al. in base case. Values were EQ-5D-3L in line with NICE reference case
Not hospitalised – AN	-0.19 (0.019)	0.1542-0.2286)		
Hospitalisation disutilities – applied in addition to -0.19 associated with COVID-19 infection				
No oxygen therapy*	-0.30 (0.03)	(0.2429-0.2604)		Base case values are in line with published literature from Whittington et al. 2022 and Kelton et al. 2022. Sourced values use EQ-5D-3L disutility estimates from a French study of hospitalised patients with clostridium difficile (Barbut 2019 [40]) based on the French EQ-5D-3L value set.
Low-flow oxygen Therapy*	-0.30 (0.03)	(0.2429-0.2604)		
NIV or high-flow oxygen therapy*	-0.50 (0.045)	(0.4118-0.5882)		
IMV or ECMO*	-0.60 (0.084)	(0.4299-0.7585)		
Long COVID disutility following discharge from acute health states:				
Not hospitalised – NAN	-0.1542 (0.0308)	(0.0988-0.2191)		Base case values use data from Evans et al. 2021 reporting EQ-5D-5L utilities for patients post
Not hospitalised – AN	-0.1542 (0.0308)	(0.0988-0.2191)		

No oxygen therapy	-0.1542 (0.0308)	(0.0988-0.2191)		discharge (recovered and non-recovered) for COVID-19 by WHO classification. Utilities were adjusted using Evans et al. 2022 to estimate utility for patients with long COVID only
Low-flow oxygen Therapy	-0.1542 (0.0308)	(0.0988-0.2191)		
NIV or high-flow oxygen therapy	-0.1884 (0.0377)	(0.1204-0.2675)		
IMV or ECMO	-0.3597 (0.0719)	(0.2256-0.5060)		
Adverse events				
Infections and infestations	0.171 (0.0342)	(0.1094 – 0.2429)		Cornely et al. 2018(123) NICE TA370(124)
Injury, poisoning or procedural complications	0.1100 (0.022)	(0.0707 – 0.1566)		Svedbom et al. 2018(126)
Nervous system disorders	0.0700 (0.0314)	(0.0219 – 0.1428)		Kansal et al. 2019(127) Sullivan et al. 2016(128)
Cardiac disorders	0.1080 (0.0309)	(0.0553 – 0.1754)		Cornely et al. 2018(123) Clarke et al. 2002(129)
Gastrointestinal disorders	0.1350 (0.027)	(0.0866 – 0.1921)		Akehurst et al. 2002(130)
Renal and urinary disorders	0.2500 (0.03)	(0.1936 – 0.3110)		Javanbakht et al. 2020(131) Shepherd et al. 2010(132)

Abbreviations: AN – Assistance needed; COVID-19 – Coronavirus disease 2019; ECMO – Extracorporeal membrane oxygenation; EQ-5D-3L – EuroQol-5 dimensions 3 levels; EQ-5D-5L – EuroQol-5 dimensions 5 levels; IMV – Intermittent mandatory ventilation; NA – Not applicable; NAN – No assistance needed; NICE – National institute of Health and Care Excellence; NIV – Non-invasive ventilation; WHO – World Health Organization

B3.5 Cost and healthcare resource use identification, measurement and valuation

A cost/resource use SLR was undertaken in August 2022 to identify existing studies reporting costs/resource use associated with preventative treatment/prophylaxis of COVID-19. Please see Appendix I for the methods used to identify all relevant studies, and description of the costs/resource use studies identified. The SLR alongside more targeted searches was used to inform the cost and resource use used in the model.

B3.5.1 Intervention and comparators' costs and resource use

B3.5.1.1 Treatment acquisition costs

Drug acquisition costs considered the cost of Evusheld, set at list price of £1,600 per 600 mg dose and a price of [redacted] per 600 mg dose after applying a confidential PAS. As noted in section B.3.2, only 1-year of treatment with Evusheld is modelled. Evusheld dosing is 1 x 600 mg dose at start of the model, followed by another 600 mg dose at 6 months giving a total drug acquisition cost of £3,200 (list) and [redacted] (with PAS) in year 1 (Table 56).

Table 56: Input Related to Treatment Acquisition Costs of Evusheld

Treatment	Presentation	List price (per dose)	Price with PAS (per dose)
Evusheld	Dose (600 mg)	£1,600	[redacted]

Abbreviations: PAS – Patient access scheme

No treatment acquisition costs are assumed for no prophylactic.

B3.5.1.2 Administration

Each administration for Evusheld is assumed to take 30 minutes with an additional hour of monitoring based on the Evusheld UK patient information leaflet. The cost is calculated based on the hourly cost for a GP nurse from PSSRU data (Table 57) .(140) Two administrations are costed in the model in line with the dosing regimen of Evusheld, giving a total cost of administration of £126.19 in year 1.

Table 57: Evusheld administration costs

Administration cost	Cost per administration	Source
Intramuscular	£63.10	Assumed to require 1.5 hours of nurse time for administration, including 30 minutes for preparation/administration + 1 hour for monitoring (based on Evusheld patient information leaflet) PSSRU 2021(140); Evusheld Fact Sheet(141)

Abbreviations: PSSRU – Personal Social Services Research Unit

No administration costs are assumed for no prophylactic.

B3.5.1.3 Monitoring

All hospitalised patients were assumed to have two chest x-rays and six GP consultations post discharge, with monitoring costs applied at the point of discharge in the model (i.e. captured within the acute disease phase). This is in line with the ScHARR Assessment Report in TA10936, which used the same assumptions based on Rafia 2022(97) (Table 58).

Table 58: Monitoring costs

Monitoring costs	Cost	Frequency	Source
X-rays	£32.65	2	NHS reference costs (20/21)(142)
GP visit	£33.00	6	PSSRU 2021(140)

Abbreviations: GP – General Practitioner; NHS – National Health Service; PSSRU – Personal Social Services Research Unit

B3.5.1.4 Unit costs summary

Table 59 summarises the unit costs associated with technologies used in the model.

Table 59: Summary of unit costs associated with the technology in the economic model

Item	Evusheld (confidence interval)	Reference in submission	No prophylaxis	Reference in submission
Technology cost	[redacted](with PAS) per 600 mg dose	NA	NA	NA
Mean cost of technology treatment	[redacted](with PAS) in year 1	NA	NA	NA
Administration cost	£63.10	PSSRU 2021(140)	NA	NA
Monitoring cost	GP visits - £33.00	PSSRU 2021(140)	GP visits - £33.00	PSSRU 2021(140)
Tests	X-rays - £32.65	NHS reference costs (20/21) (142)	X-rays - £32.65	NHS reference costs (20/21) (142)

Abbreviations: GP – General Practitioner; NHS – National Health Service; PAS – Patient Access Scheme; PSSRU – Personal Social Services Research Unit

B3.5.2 Health state unit costs and resource use

B3.5.2.1 Long COVID

The management of long COVID was assumed to be similar to chronic fatigue syndrome and a study from the Netherlands assessing rehabilitation treatment versus cognitive behavioural therapy for patients with chronic fatigue syndrome was utilised (Metry et al. 2022).(41) This is in line with the ScHARR Assessment Report in TA10936.(108)

Resource use included GP care, mental healthcare specialist, paramedical care, medical specialist care, hospital care, medications, alternative healers, and the evaluated interventions. An annual cost of £1,128.02 per health state was calculated after applying current conversion rates from EUR to GBP.(143)

B3.5.2.2 Resource use

The resource use cost associated with each health state was calculated from Rafia et al. 2022(97) and Beigel 2020(34) as shown in Table 60, taking into account both the cost per day and the total inpatient stay.

There are no costs associated with patients who are asymptomatic/not infected in the acute and long-term model phases.

In the absence of data split by level of oxygen support, patients with no or low-flow oxygen therapy only received care in the general ward, while NIV or high-flow patients received care in the ICU, and IMV or ECMO patients received MV support in addition to care in the ICU.

Table 60: Calculation of MRU costs in acute phase

Maximum level of care	Cost per day per care setting (Rafia 2022)(97)	Total inpatient stay (Beigel 2020) (34)	Inpatient stay by care setting				Total Inpatient MRU cost
			No oxygen	Low-flow oxygen	NIV/ High-flow oxygen	IMV/ ECMO	
No oxygen	£346.89	5	5	0	0	0	£1,734.45
Low-flow oxygen	£615.91	7	5	2	-	-	£2,966.27
NIV/high-flow oxygen	£933.19	15	4.5	4.5	6	-	£9,931.74
IMV/ ECMO	£1,518.46	29	3	3	6	17	£34,301.36

Abbreviations: ECMO – Extracorporeal membrane oxygenation; IMV – Invasive mechanical ventilation; MRU – Medical resource use; NIV – Non-invasive ventilation

B3.5.2.3 Adverse reaction unit costs and resource use

Six AEs were identified to be included in the base case analysis. Unit costs for AEs, shown in Table 61, are taken from NHS Costs. Following application of the incidence estimates, the total adverse event costs for no prophylaxis and Evusheld were £26.32 and £35.13, respectively.

Table 61: Prophylaxis related AE incidence and Unit Costs

Adverse event	No prophylaxis incidence	Evusheld incidence	Unit costs	Source	Notes
Infections and Infestations	0.58%	0.46%	£1,872.20	NHS reference costs	Weighted average of WH07A-G HRG codes
Injury, Poisoning or Procedural Complications	0.92%	0.23%	£1,138.31		Weighted average of WH04A-E and WH07A-G HRG codes
Nervous System Disorders	0.00%	0.52%	£1,649.98		Weighted average of AA25C-G and AA29C-F HRG codes

Cardiac Disorders	0.12%	0.35%	£1,556.36		Weighted average of AA35A-F, EB02A-7E and EB10A-15C HRG codes
Gastrointestinal Disorders	0.12%	0.35%	£1,446.16		Weighted average of FD10A-M HRG codes
Renal and Urinary Disorders	0.12%	0.35%	£1,408.75		Weighted average of LA09J-Q and LB19C-G HRG codes
Total AE cost	**£26.32**	**£35.13**			

Abbreviations: AE – Adverse event; HRG – Healthcare resource group; NHS – National Health Service

B3.5.2.4 Post year one infection cost after year 1

The cost associated with post year one infection was calculated as the total acute cost in the 29 days following infection, calculated from the decision tree of the no prophylaxis arm: £347.15.

B3.6 Severity

This is not applicable to this submission.

B3.7 Uncertainty

There is inherent uncertainty associated with the ever-evolving landscape of COVID-19, which can impact model parameters when considering re-treatment with Evusheld over an extended period of time past 1-year. Please see Section B3.2.2 for further details.

B3.8 Managed access proposal

This is not applicable to this submission. A confidential PAS has been submitted resulting in a net price of [redacted] per 600 mg dose.

B3.9 Summary of base case analysis inputs and assumptions

B3.9.1 Summary of base case analysis inputs

A summary of variables applied in the economic analysis is presented in Table 62.

Table 62: Summary of variables applied in the economic model

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to section in submission
General Settings			
Infection Risk Time Horizon (Months)	12.00	NA	B3.2.4

Long-term Time Horizon	46.50	NA	B3.2.4
Discount Rate (Costs)	3.50%	NA	B3.2.6
Discount Rate (Health Outcomes)	3.50%	NA	B3.2.6
Acute Phase Duration (Days)	29.00	NA	B3.2.4
Population Characteristics			
Age (years): PROVENT	53.50	53.09 to 53.91 (Normal)	B3.2.1, B1.3.8
Proportion of Males: PROVENT	53.88%	52.52% to 55.23% (Beta)	B3.2.1, B1.3.8
Weight (kg): PROVENT	85.72	85.13 to 86.31 (Normal)	B3.2.1, B1.3.8
Symptomatic Infection Risk: PROVENT	22.58%	22.57% to 22.59% (Beta)	B3.2.1, B1.3.8
Case Distribution			
% of symptomatic cases requiring hospital admission: Shields et al. 2022	17.13%	13.15% to 21.51% (Beta)	B3.3.1.2
% of non-hospitalised patients requiring no assistance	50.00%	50.00% to 50.00% (Beta)	B3.3.1.4
Distribution of Hospitalisation			
PROVENT: Not Hosp - assistance needed	26.10%	24.46% to 27.77% (Dirichlet)	B3.3.1.3
PROVENT: No Oxygen Therapy	40.70%	38.85% to 42.56% (Dirichlet)	B3.3.1.3
PROVENT: Low-flow Oxygen Therapy	17.80%	16.38% to 19.26% (Dirichlet)	B3.3.1.3
PROVENT: Non-invasive Ventilation or High-flow Oxygen	15.40%	14.06% to 16.78% (Dirichlet)	B3.3.1.3
Case Distribution			
Case Distribution: Not hospitalised - no assistance needed	41.44%	41.44% to 41.44% (Beta)	B3.3.1.4
Case Distribution: Not Hospitalised - assistance needed	41.44%	41.44% to 41.44% (Beta)	B3.3.1.4
Case Distribution: Hospitalised: No Oxygen Therapy	4.47%	4.47% to 4.47% (Beta)	B3.3.1.4
Case Distribution: Hospitalised: Low-flow Oxygen Therapy	6.97%	6.97% to 6.97% (Beta)	B3.3.1.4

Case Distribution: Hospitalised: Non-invasive Ventilation or High-flow Oxygen	3.05%	3.05% to 3.05% (Beta)	B3.3.1.4
Case Distribution: Hospitalised: Invasive Mechanical Ventilation or ECMO	2.64%	2.64% to 2.64% (Beta)	B3.3.1.4
Efficacy			
Overall Symptomatic Infections - Evusheld (AstraZeneca)	66.00%	64.96% to 67.03% (Beta)	B3.3.2.3
% Reduction in hospitalisation (Evusheld vs. No prophylaxis) - Hospitalised: No Oxygen Therapy	61.76%	60.70% to 62.82% (Beta)	B3.3.2.3
% Reduction in hospitalisation (Evusheld vs. No prophylaxis) - Hospitalised: Low-flow Oxygen Therapy	61.76%	60.70% to 62.82% (Beta)	B3.3.2.3
% Reduction in hospitalisation (Evusheld vs. No prophylaxis) - Hospitalised: Non-invasive Ventilation or High-flow Oxygen	61.76%	60.70% to 62.82% (Beta)	B3.3.2.3
% Reduction in hospitalisation (Evusheld vs. No prophylaxis) - Hospitalised: Invasive Mechanical Ventilation or ECMO	61.76%	60.70% to 62.82% (Beta)	B3.3.2.3
% of Patients alive with long covid at discharge (before death)			
Not hospitalised - no assistance needed	34.50%	21.68% to 48.58% (Beta)	B3.3.3.2
Not Hospitalised - assistance needed	34.50%	21.68% to 48.58% (Beta)	B3.3.3.2
Hospitalised: No Oxygen Therapy	100.00%	100.00% to 100.00% (Beta)	B3.3.3.2
Hospitalised: Low-flow Oxygen Therapy	100.00%	100.00% to 100.00% (Beta)	B3.3.3.2
Hospitalised: Non-invasive Ventilation or High-flow Oxygen	100.00%	100.00% to 100.00% (Beta)	B3.3.3.2

Hospitalised: Invasive Mechanical Ventilation or ECMO	100.00%	100.00% to 100.00% (Beta)	B3.3.3.2
Mortality			
HR for Immunocompromised Mortality	1.70	1.70 to 1.70 (Lognormal)	B3.3.4.3
HR vs General Population: Not Hospitalised (No assistance needed)	1.00	1.00 to 1.00 (Lognormal)	B3.3.4.3
HR vs General Population: Not hospitalised (Assistance needed)	1.00	1.00 to 1.00 (Lognormal)	B3.3.4.3
HR vs General Population: No Oxygen Therapy	1.00	1.00 to 1.00 (Lognormal)	B3.3.4.3
HR vs General Population: Low-flow Oxygen Therapy	1.00	1.00 to 1.00 (Lognormal)	B3.3.4.3
HR vs General Population: Non-invasive Ventilation or High-flow Oxygen	1.33	1.09 to 1.60 (Lognormal)	B3.3.4.3
HR vs General Population: Invasive Mechanical Ventilation or ECMO	1.33	1.09 to 1.60 (Lognormal)	B3.3.4.3
Markov			
Evans proportion with long covid at five months	64.71%	62.58% to 66.81% (Beta)	B3.3.4.2
Log-normal curve: intercept	-3.6275	-3.6275 to -3.6275 (Normal)	B3.3.4.2
Log-normal curve: slope	0.64	0.64 to 0.64 (Normal)	B3.3.4.2
Infection post year 1 parameters			
6 month infection post year 1 rate SoC	12.01%	7.72% to 17.10% (Beta)	B3.3.5
6 month infection post year 1 rate Evusheld	12.01%	7.72% to 17.10% (Beta)	B3.3.5
Cost of infection post year 1 SoC	£ 347.15	£ 347.15 to £ 347.15 (Gamma)	B3.5.2.4
Cost of infection post year 1 Evusheld	£ 347.15	£ 347.15 to £ 347.15 (Gamma)	B3.5.2.4
Utility decrement associated with infection post year 1: SoC	-0.0023	-0.002 to -0.002 (Beta)	B3.4.5.7
Utility decrement associated with infection post year 1: Evusheld	-0.0023	0.00 to 0.00 (Beta)	B3.4.5.7
Mortality associated with infection post year 1	2.40%	1.55% to 3.43% (Beta)	B3.5.2.4

Quality of Life			
Comorbid patients' disutility	0.116	0.05 to 0.20 (Beta)	B3.4.5.2
Disutility from Initial COVID Symptoms	0.190	0.15 to 0.23 (Beta)	B3.4.5.3
Hospitalisation disutility - No Oxygen Therapy	0.300	0.24 to 0.36 (Beta)	B3.4.5.3
Hospitalisation disutility - Low-flow Oxygen Therapy	0.300	0.24 to 0.36 (Beta)	B3.4.5.3
Hospitalisation disutility - Non-invasive Ventilation or High-flow Oxygen	0.500	0.50 to 0.50 (Beta)	B3.4.5.3
Hospitalisation disutility - Invasive Mechanical Ventilation or ECMO	0.600	0.43 to 0.76 (Beta)	B3.4.5.3
Time Spent (Acute Phase) being Not Hospitalised (Assistance needed)	11.000	7.12 to 15.71 (Gamma)	B3.4.5.3
Time Spent (Acute Phase) being Not Hospitalised (No assistance needed)	11.000	7.12 to 15.71 (Gamma)	B3.4.5.3
Time Spent (Acute Phase) being No Oxygen Therapy	17.000	11.00 to 24.28 (Gamma)	B3.4.5.3
Time Spent (Acute Phase) being Low-flow Oxygen Therapy	19.000	12.30 to 27.14 (Gamma)	B3.4.5.3
Time Spent (Acute Phase) being Non-invasive Ventilation or High-flow Oxygen	21.000	13.59 to 30.00 (Gamma)	B3.4.5.3
Time Spent (Acute Phase) being Invasive Mechanical Ventilation or ECMO	29.000	- to - (Gamma)	B3.4.5.3
Long COVID disutility (Not hospitalised - assistance needed)	0.154	0.10 to 0.22 (Beta)	B3.4.5.5
Long COVID disutility (Not hospitalised - No assistance needed)	0.154	0.10 to 0.22 (Beta)	B3.4.5.5
Long COVID disutility (No Oxygen Therapy)	0.154	0.10 to 0.22 (Beta)	B3.4.5.5
Long COVID disutility (Low-flow Oxygen Therapy)	0.154	0.10 to 0.22 (Beta)	B3.4.5.5
Long COVID disutility (Non-invasive Ventilation or High-flow Oxygen)	0.188	0.12 to 0.27 (Beta)	B3.4.5.5

Long COVID disutility (Invasive Mechanical Ventilation or ECMO)	0.360	0.23 to 0.51 (Beta)	B3.4.5.5
Utility gain Evusheld	[redacted]	[redacted]	B3.4.5.6
Acquisition, Administration and Logistics			
Evusheld 600 mg dose	[redacted]	NA	B3.5.1.1
Administration Cost: Intramuscular	63.10	40.83 to 90.13 (Gamma)	B3.5.1.2
Number of Initial Administrations: Evusheld (AstraZeneca)	1.00	1.00 to 1.00 (Gamma)	B3.5.1.2
Number of Subsequent Administrations: Evusheld (AstraZeneca)	1.00	1.00 to 1.00 (Gamma)	B3.5.1.2
Monitoring			
Unit Cost - X-rays	£ 32.65	£ 21.13 to £ 46.64 (Gamma)	B3.5.1.3
Unit Cost - GP Visit	£ 33.00	£ 21.36 to £ 47.14 (Gamma)	B3.5.1.3
Tests required: X-rays	£ 2.00	£ 1.29 to £ 2.86 (Gamma)	B3.5.1.3
Tests required: GP Visit	£ 6.00	£ 3.88 to £ 8.57 (Gamma)	B3.5.1.3
Long COVID			
Long COVID costs	£ 1.128.02	£ 729.99 to £ 1611.26 (Gamma)	B3.5.2.1
Resource Use			
Aggregated Costs - No Oxygen Therapy	£ 1.734.45	£ 1,122 to £ 2,477 (Gamma)	B3.5.2.2
Aggregated Costs - Low-flow Oxygen Therapy	£ 2.966.27	£ 1,920 to £ 4,237 (Gamma)	B3.5.2.2
Aggregated Costs - Non-invasive Ventilation or High-flow Oxygen	£ 9.931.74	£ 6,427 to £ 14,187 (Gamma)	B3.5.2.2
Aggregated Costs - Invasive Mechanical Ventilation or ECMO	£ 34.301.36	£ 22,198 to £ 48,996 (Gamma)	B3.5.2.2
Adverse Events			
AE Cost: Infections and Infestations	£ 1.872.20	£ 1,212 to £ 2,674 (Gamma)	B3.5.2.3
AE Cost: Injury, Poisoning or Procedural Complications	£ 1.138.31	£ 737 to £ 1,626 (Gamma)	B3.5.2.3

AE Cost: Nervous System Disorders	£	1.649.98	£ 1,068 to £ 2,357 (Gamma)	B3.5.2.3
AE Cost: Cardiac Disorders	£	1.556.36	£ 1,007 to £ 2,223 (Gamma)	B3.5.2.3
AE Cost: Gastrointestinal Disorders	£	1.446.16	£ 936 to £ 2,066 (Gamma)	B3.5.2.3
AE Cost: Renal and Urinary Disorders	£	1.408.75	£ 912 to £ 2,012 (Gamma)	B3.5.2.3

B3.9.2 Assumptions

A summary of the model assumptions is provided in Table 63.

Table 63: Assumptions underpinning the cost-effectiveness analysis

Variable	Assumed value	Justification
Proportional split between 'not hospitalised – no assistance needed' and 'not hospitalised – assistance needed' health states	50%/50%	No data to inform proportional split, and does not affect cost-effectiveness results.
Proportional split within hospitalisation health states	Equal for Evusheld and no prophylaxis: No oxygen therapy – 26.1% LF oxygen therapy – 40.7% NIV of HF oxygen therapy – 17.8% IMV or ECMO – 15.4%	Though UK clinicians advised it would be reasonable to assume a benefit in reducing hospitalisation severity with Evusheld, no data were available to inform this expected benefit. Therefore, these values may be deemed conservative estimates, and the cost-effectiveness of Evusheld may be underestimated.
Long COVID health state transitions	All hospitalised patients had long COVID at discharge and transitioned to the "long COVID" health state	In line with the ScHARR Assessment Report in TA10936
Long COVID health state transitions	Half of patients who reported as "unsure" to the question "Do you feel fully recovered?" from Evans 2021(58) were assumed to be recovered, with the	No data to inform alternative estimate.

	other half assumed to have long COVID	
Mortality	Mortality for not hospitalised or non-ICU hospitalised states assumed equal to general population	• No data to inform alternative estimate • This is a conservative approach as any additional mortality would only result in more favourable ICERs for Evusheld.
Mortality	Patients in the "NIV or high-flow oxygen" and "IMV or ECMO" health states were treated in the ICU setting Excess mortality for ICU hospitalised states assumed to return to general population after 5-years	• No data to inform alternative estimate • Aligned to the study length of Sheinson 2021 • This is a conservative approach as any additional mortality would only result in more favourable ICERs for Evusheld.
Post year one infection	Constant over time and year 1 parameter values applied to all patients remaining alive in each cycle	• No data to inform alternative estimate • The variable has a negligible impact on the cost-effectiveness results as demonstrated by scenario analysis (Section B3.11.3)
Recovered utility	Equal to the age-gender matched adjusted general population utility values	No data to inform alternative estimate.
Long COVID disutility	Evans 2021 values uplifted by a factor of 1.71	Informed by more recent data from Evans 2022
Long COVID disutility	For patients who were not hospitalised, the disutility was assumed equal to the no oxygen therapy health state	In line with the ScHARR Assessment Report in TA10936
Evusheld utility gain	[redacted]	In line with Violato 2022 Evusheld utility gain 2022 (using data from the CANDOUR study), which measured HRQoL loss in patients during lockdown. Value also aligns with

		disutilities associated with fear/anxiety in other conditions, accepted by NICE in TA246 and TA769.
Carer disutility	0	No data to inform an estimate, despite the fact that carer disutility is reported in the literature for COVID-19. Therefore, the cost-effectiveness of Evusheld may be underestimated.
Technology costs for no prophylaxis	£0	The introduction of Evusheld will be given on top of existing SoC with no prophylaxis, administration of vaccination will be equal between arms. Furthermore, as agreed with NICE and the EAG during the decision problem meeting on the 17th of August 2022, treatments under evaluation in TA10936 are not included as comparators nor as subsequent treatments in the model, since these treatments are not in routine commissioning.
Monitoring costs	Resource use: 2 X-rays and 6 GP visits	In line with the ScHARR Assessment Report in TA10936.
Long COVID costs	Similar to chronic fatigue syndrome such that Metry et al. 2022 can be utilised	In line with the ScHARR Assessment Report in TA10936.

B3.10 Base case results

B3.10.1 Base case incremental cost-effectiveness analysis results

Evusheld generates [redacted] incremental QALYs and £[redacted] incremental costs over a lifetime horizon compared with no prophylaxis, resulting in an ICER of £12,290 per QALY gained. Disaggregated base case results are presented in Appendix J.

Table 64: Base case results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
No prophylaxis	[redacted]	[redacted]	[redacted]					
Evusheld	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	12,290	12,290

Abbreviations: ICER – Incremental cost-effectiveness ratio; LYG – Life years gained; QALYs – Quality-adjusted life years

B3.11 Exploring uncertainty

Sensitivity analyses have been conducted to explore structural and parameter uncertainty.

With regards to Evusheld's effectiveness, uncertainty has been explored by considering both RWE studies and the RCT, to ensure that limitations in one design of the other does not unduly influence the cost-effectiveness results.

B3.11.1 Probabilistic sensitivity analysis

A probabilistic sensitive analysis (PSA) was conducted to explore the impact of model parameters uncertainty on the results. PSA involves drawing a value at random for each variable from its uncertainty distribution. This is performed for each parameter simultaneously and the resulting incremental results are recorded. This constitutes one 'simulation'. 1,000 simulations were performed, which each gave a distribution of incremental results and an assessment of the robustness of the cost-effectiveness results.

For event rates and utilities, a beta distribution was used to restrict draws to between 0 and 1. For costs and resource use estimates, and hazard ratios a gamma distribution was fitted to prevent values less than zero. Treatment costs remained fixed. An incremental cost-effectiveness plane (ICEP) scatter plot and cost-effectiveness acceptability curve (CEAC) were produced to graphically illustrate the level of variability and uncertainty in the results.

The mean values for total costs, LYs, QALYs, and incremental cost per QALY gained for Evusheld versus no prophylaxis through 1,000 simulations of the PSA are presented in Table 65. In the PSA, Evusheld generates [redacted] incremental QALYs and [redacted] incremental costs over a lifetime horizon compared with no prophylaxis, resulting in an ICER of £11,916 per QALY gained (similar to the base case).

The corresponding ICEP and CEAC are presented in Figure 20 and Figure 21, respectively.

Table 65: PSA results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
No prophylaxis	[redacted]	[redacted]	[redacted]					
Evusheld	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	11,916	11,916

Abbreviations: ICER – Incremental cost-effectiveness ratio; LYG – Life years gained; QALYs – Quality-adjusted life years

Figure 20: Incremental cost- effectiveness plane

Abbreviations: PSA – Probabilistic sensitivity analysis

Figure 21: Cost-effectiveness acceptability curve

Abbreviations: NMB – Net medical benefit

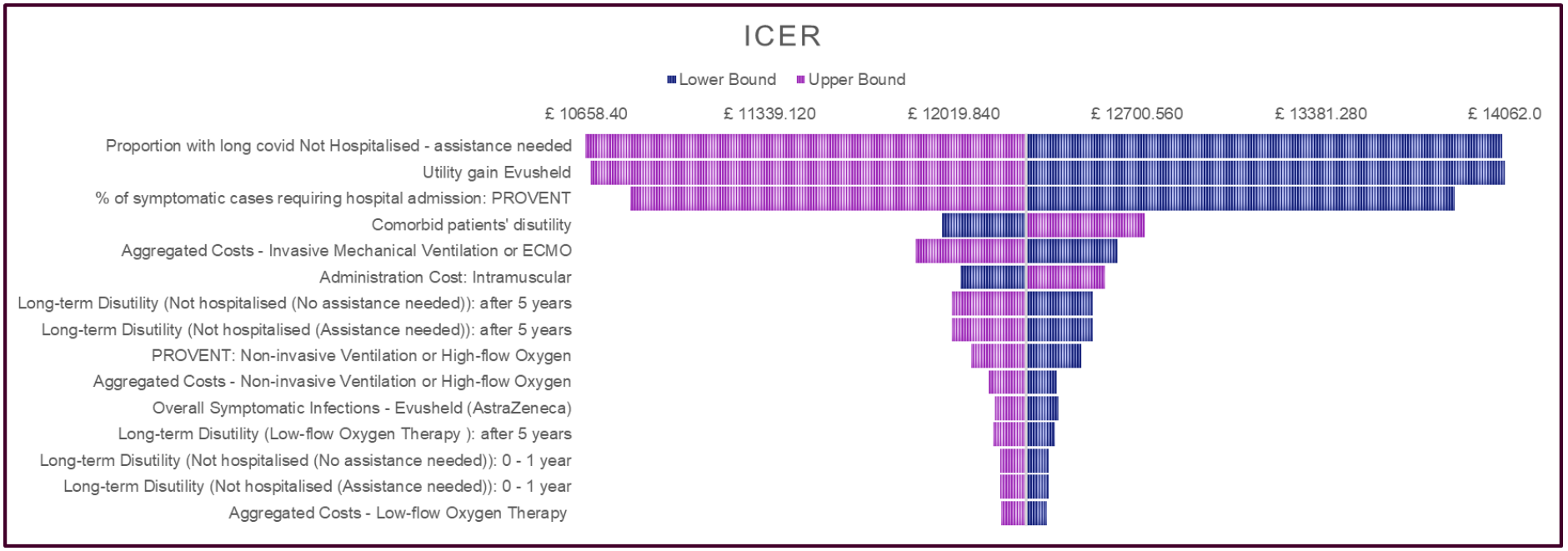
B3.11.2 Deterministic sensitivity analysis

A deterministic one-way sensitivity analysis (OWSA) was conducted to explore the level of uncertainty in the model results. The OWSA involved varying one parameter at a time and assessing the subsequent impact on the incremental QALYs and incremental costs. By adjusting each parameter individually, the sensitivity of the model results to that parameter can be assessed.

The OWSA was conducted by allocating a 'low' value and a 'high' value to each parameter; the low value is the lower bound of the 95% CI, the high value is the upper bound of the 95% CI. The variable will be altered by +/- 20% in the absence of CI data. A tornado diagram was developed to graphically present the parameters which have the greatest effect on the ICER.

The OWSA tornado diagram presenting the 15 most sensitive parameters for the sub-population of interest is presented in Figure 22. Table 66 presents the OWSA results for these 15 parameters. The model was most to the proportion of patients with long COVID in the non-hospitalised- assistance needed health state. All scenarios resulted in ICERs below £20,000 per QALY.

Figure 22: Tornado diagram



Abbreviations: ECMO – Extracorporeal membrane oxygenation; ICER – Incremental cost-effectiveness ratio

Table 66: DSA results

ICER		
Proportion with long covid- Not Hospitalised - assistance needed	£14,055	£10,658
Utility gain Evusheld	£14,062	£10,678
% of symptomatic cases requiring hospital admission: PROVENT	£13,877	£10,823
Comorbid patients' disutility	£11,978	£12,729
Aggregated costs - invasive mechanical ventilation or ECMO	£12,627	£11,881
Administration cost: Intramuscular	£12,048	£12,584
Long-term Disutility (Not hospitalised (No assistance needed)): after 5 years	£12,536	£12,014
Long-term Disutility (Not hospitalised (Assistance needed)): after 5 years	£12,536	£12,014
PROVENT: Non-invasive ventilation or high-flow oxygen	£12,493	£12,085
Aggregated costs - non-invasive ventilation or high-flow oxygen	£12,403	£12,153
Overall symptomatic infections - Evusheld (AstraZeneca)	£12,409	£12,173
Long-term Disutility (Low-flow Oxygen Therapy): after 5 years	£12,397	£12,167
Long-term Disutility (Not hospitalised (No assistance needed)): 0 - 1 year	£12,373	£12,194
Long-term Disutility (Not hospitalised (Assistance needed)): 0 - 1 year	£12,373	£12,194
Aggregated costs - low-flow oxygen therapy	£12,367	£12,196

Abbreviations: DSA – Deterministic sensitivity analysis; ICER – Incremental cost-effectiveness ratio

B3.11.3 Scenario analysis

Table 67 details scenario analyses results for Evusheld versus no prophylaxis. Results were most sensitive to discount rates for costs and outcomes, efficacy sources, and post-acute HRQoL. Results were least sensitive to removing post year one infection. All scenarios resulted in ICERs below £20,000 per QALY.

Table 67: Scenario analysis results

Description	Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	ICER versus baseline (£/QALY)
Base case	**No prophylaxis**	[redacted]	[redacted]	[redacted]				
	Evusheld	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	12,290
Discount rate: 0%	**No prophylaxis**	[redacted]	[redacted]	[redacted]				
	Evusheld	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	9,059
Discount rate: 6%	**No prophylaxis**	[redacted]	[redacted]	[redacted]				
	Evusheld	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	14,315
Reinfection: Not applied	**No prophylaxis**	[redacted]	[redacted]	[redacted]				
	Evusheld	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	12,223
Efficacy source: PROVENT	**No prophylaxis**	[redacted]	[redacted]	[redacted]				
	Evusheld	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	10,335
Efficacy source: Kertes et al. 2022	**No prophylaxis**	[redacted]	[redacted]	[redacted]				

	Evusheld	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	14,422
% with long COVID at discharge: Evans et al. 2021	**No prophylaxis**	[redacted]	[redacted]	[redacted]				
	Evusheld	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	12,685
Apply utility benefit associated with Evusheld treatment: 82%	**No prophylaxis**	[redacted]	[redacted]	[redacted]				
	Evusheld	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	13,128
Hospitalisation disutility: ScHARR report	**No prophylaxis**	[redacted]	[redacted]	[redacted]				
	Evusheld	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	12,275
Post-acute HRQoL: Evans 2021	**No prophylaxis**	[redacted]	[redacted]	[redacted]				
	Evusheld	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	14,410

Abbreviations: COVID – Coronavirus disease; HRQoL – Health-related quality of life; ICER – Incremental cost-effectiveness ratio; LYG – Life years gained; QALYs – Quality-adjusted life years; ScHARR – School of health and related research

B3.12 Subgroup analysis

No subgroup analyses were conducted, as Evusheld is positioned in this submission within a subgroup of its licenced indication, which encapsulates the subgroup of interest identified in the NICE scope (Section B1.1).

B3.13 Benefits not captured in the QALY calculation

Carer disutility was known to be present in patients during an acute infection and for those suffering from long COVID (see Section B1.3.7), however no data were available to populate this estimate at the time of submission. Since Evusheld has been shown to prevent infection and consequent long COVID, the ICER results can be deemed conservative.

B3.14 Validation

B3.14.1 Validation of cost-effectiveness analysis

The inputs and methodologies used within the economic analysis were validated, specifically:

- The anticipated positioning and key clinical assumptions were validated by UK clinicians during telephone interviews.
- All key modelling assumptions were validated by independent UK health economics experts.

B3.15 Interpretation and conclusions of economic evidence

The results of the base case analysis, probabilistic sensitivity analysis, DSA, and scenario analyses indicate that Evusheld is a cost-effective use of NHS resources. All ICERs are below £20,000 per QALY, which is considered the lower bound of willingness to pay by NICE. The results show that the introduction of Evusheld into the treatment paradigm will significantly improve patient outcomes for high-risk immunocompromised or vaccine-contraindicated patients and provide a cost-effective use of NHS resources.

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National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

Additional Evidence Report – amended redaction

Tixagevimab–cilgavimab for preventing COVID-19 [ID6136]

On 29th November 2022, NICE communicated to stakeholders that the Committee meeting for this appraisal has been brought forward from 14th March 2022 to 24th January 2022. As a result of this, NICE has removed the Technical Engagement step from the appraisal process.

AstraZeneca recognises the need to accelerate the appraisal to facilitate timely decision making on enabling access to Evusheld for people in the UK. Following receipt of the EAG report, NICE agreed that it would be helpful for AstraZeneca to submit additional evidence to address a number of key issues identified by the EAG. Therefore, as agreed with NICE this document contains the following:

- Further evidence that directly addresses some of the key issues identified by the EAG. Specifically, the additional evidence relates to addressing the following scenarios explored in the EAG report
    - **EA1: Reducing the proportion of Evusheld patients experiencing a direct utility gain with Evusheld from 100% to 13% of the target population (reflecting shielding patients only).** Evidence from a recent utility study reported a utility gain of [redacted] for prophylaxis in high-risk immunocompromised patients who do not fully shield but take preventative measures from contracting COVID-19 (e.g. mask wearing or avoiding busy places). This utility gain increased dramatically in patients who fully shield to [redacted]. This implies that the utility gain associated with prophylaxis should be applied to all Evusheld patients who feel anxious and depressed, make lifestyle modifications, and desire prophylaxis treatment. The value of

[redacted] should be included in the base case economic model in place of the initial estimate of [redacted] based on this latest evidence.

- **EA4: Assuming a cost of administration for Evusheld of £410 based on COVID Medicine Delivery Units (CMDU) costing exercise.** As previously noted by the company, AstraZeneca will be providing Evusheld in a secondary care setting as part of a patient's routine care, through secondary care led community services, [redacted]. As such, the administration costs proposed by the EAG do not reflect the administration routes for which Evusheld will be used; particularly as the provision of new, large-scale services will not need to be set up by the NHS to deploy Evusheld. [redacted]
- **EA6: Using the long COVID annual costs of £1128 assuming chronic fatigue as a proxy.** It is not appropriate to use the annual cost of £1,128 based on a cost for chronic fatigue, as this proxy will not capture the full manifestations of long COVID-19 such as organ damage. Instead, a cost of £2,500 should be applied which is more reflective of the cost burden of this stage of the disease, as recognised by stakeholders in response to the ongoing MTA.

[redacted]

In the 'factual accuracy check' document provided by the company on 7th December 2022, AstraZeneca recreated and amended the ICER table contained in the EAG report Section 1.7, page 23, to remove the scenarios or amendments implemented by the EAG that are factually inaccurate/implausible to arrive at a revised EAG base case. This 'Additional Evidence Report' document reproduces the same table from the 'factual accuracy check', to include further revisions, based on the new evidence related to scenarios EA1, EA4 and EA6, to arrive at an updated revised EAG base case (Table 1).This document also presents the company's preferred base case, where errors and more appropriate sources/assumptions have been acknowledged and updated by AstraZeneca accordingly (

Table **2**). [redacted]

For reference, the updated revised EAG base case ICER [redacted] whilst the revised company's base case ICER [redacted]

Company response to draft EAG report

Table 1. Company's revised "EAG report Table 2" (EAG base case) (PAS price)

Scenario	Implemented	**Incremental cost**	**Incremental QALYs**	**ICER (change from company base case)**
Company base case (Deterministic)	-	[redacted]	[redacted]	£ 8,111
EAG's corrected company base case: correcting implementation errors in the company's economic model [included in all subsequent rows]	Partly – the EAG implementation was factually inaccurate	[redacted]	[redacted]	£ 8,729 (+£618)
EA1: Varying size of direct utility gain or size of group it is applied for to 13%	No – factually inaccurate – new evidence included to update utility gain to [redacted] for 100% of target population	[redacted]	[redacted]	£ 7,453 (-£658)
EA2 Halving the duration of direct utility gain for those infected while on Evusheld	Included	[redacted]	[redacted]	£ 8,843 (+732)
EA3: Assuming 12.7% of the non-hospitalised cohort would develop long COVID	Included	[redacted]	[redacted]	£ 12,657 (+£4,546)
EA4: Assuming cost of administration for Evusheld of £410 based on CMDU costing exercise	No – new evidence included to update to £41.00 per administration	[redacted]	[redacted]	£ 8,948 (+837)
EA5: Using the October 2022 update of the ONS data to estimate the duration for long COVID without the Evans 2022 adjustment	Included	[redacted]	[redacted]	£ 16,827 (+£8,716)

EA6: Using the long COVID annual costs of £1128 assuming chronic fatigue as proxy	No – new evidence included to update to £2,500 per administration	-	-	-
EA7: Recalculating disutility values due to long COVID and assuming linear HRQoL improvement by time for 5 years	Partly – waning over 5 years removed	[redacted]	[redacted]	£ 9,169 (+£1,058)
EA8: Using 9.9% as the risk estimate of hospitalisation for infected patients.	Partly - Included at 15.9%	[redacted]	[redacted]	£ 9,336 (+£1,225)
EA9: Updating hospitalisation reference costs associated with acute admissions	Included	[redacted]	[redacted]	£ 8,371 (+£260)
EA10: Reducing proportion of hospitalised patients requiring invasive mechanical ventilation (IMV)	Included	[redacted]	[redacted]	£ 9,768 (+£1,657)
EA11: Applying long COVID to new infections after 1 year	Partly – the EAG implementation was factually inaccurate	[redacted]	[redacted]	£ 11,856 (+£3,745)
EA12: Assuming reduction in relative efficacy by one-third	Included	[redacted]	[redacted]	£ 13,119 (+£5,008)
EAG's preferred base case applying analyses EA1 to EA11 (minus factual inaccuracies and new evidence noted in this response) – deterministic	-	[redacted]	[redacted]	£ 18,263 (+£10,152)

Table 2. Revised company base case (PAS price)

Scenario	Implemented	Incremental cost	Incremental QALYs	ICER (change from company base case)
Company base case (Deterministic)	-	[redacted]	[redacted]	£8,111
EAG's corrected company base case: correcting implementation errors in the company's economic model [included in all subsequent rows]	Partly – the EAG implementation was factually inaccurate	[redacted]	[redacted]	£8,729 (+£618)
EA1: Varying size of direct utility gain or size of group it is applied for to 13%	No – factually inaccurate – new evidence included to update utility gain to [redacted] for 100% of target population	[redacted]	[redacted]	£7,453 (-£658)
EA2 Halving the duration of direct utility gain for those infected while on Evusheld	Included	[redacted]	[redacted]	£8,843 (+£732)
EA3: Assuming 12.7% of the non-hospitalised cohort would develop long COVID	Not included – as per Company base case	-	-	-
EA4: Assuming cost of administration for Evusheld of £410 based on CMDU costing exercise	No – new evidence included to update to £41.00 per administration	[redacted]	[redacted]	£ 8,948 (+837)
EA5: Using the October 2022 update of the ONS data to estimate the duration for long COVID without the Evans 2022 adjustment	Not included – as per Company base case	-	-	-
EA6: Using the long COVID annual costs of £1128 assuming chronic fatigue as proxy	No – new evidence included to update to	-	-	-

Scenario	Implemented	Incremental cost	Incremental QALYs	ICER (change from company base case)
	£2,500 per administration			
EA7: Recalculating disutility values due to long COVID and assuming linear HRQoL improvement by time for 5 years	Not included – as per Company base case	-	-	-
EA8: Using 9.9% as the risk estimate of hospitalisation for infected patients	Partly - Included at 15.9%	[redacted]	[redacted]	£9,336 (+£1,225)
EA9: Updating hospitalisation reference costs associated with acute admissions	Included	[redacted]	[redacted]	£8,371 (+£260)
EA10: Reducing proportion of hospitalised patients requiring invasive mechanical ventialiation (IMV)	Not included – as per company base case	-	-	-
EA11: Applying long COVID to new infections after 1 year	Partly – the EAG implementation was factually inaccurate	[redacted]	[redacted]	£11,856 (+£3,745)
EA12: Assuming reduction in relative efficacy by one-third	Not included – as per Company base case	-	-	-
Company's preferred base case also applying appropriate corrections and analyses EA1, EA2, EA4, EA8, EA9 and EA11 – deterministic	**-**	[redacted]	[redacted]	£10,606 (+£2,495)

Table 3. Abbreviations

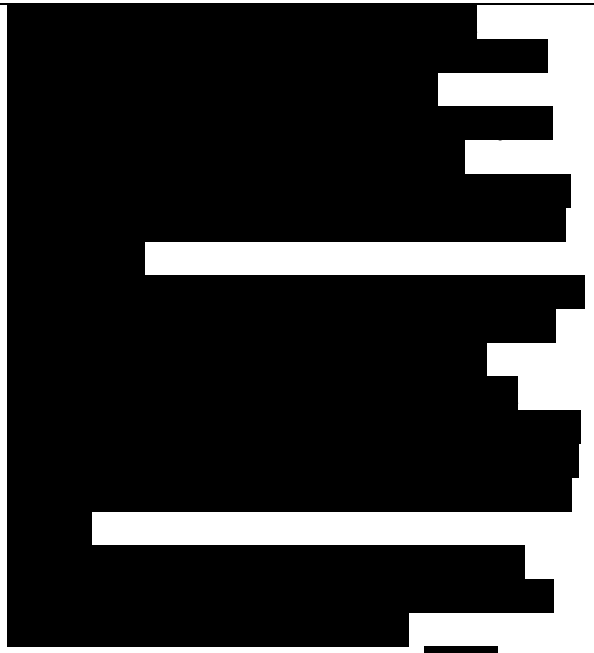
AIC	Academic in confidence
CANDOUR	Covid-19 vAccine preference anD Opinion sURvey
CIC	Commercial in confidence
CMDU	COVID medicines delivery unit
COVID-19	Coronavirus disease 2019
EA	Exploratory analyses
EAG	Evidence assessment group
ECMO	Extracorporeal membrane oxygenation
EQ-5D	European Quality of Life Five Dimension
HRQoL	Health related quality of life
HTA	Health technology assessment
IC	Immunocompromised
ICER	Incremental cost-effectiveness ratio
IMID	Immune-mediated inflammatory disorders
IMV	Intermittent mandatory ventilation
MTA	Multiple technology assessment
NICE	National Institute for Health and Care Excellence
ONS	Office for National Statistics

PAS	Patient access scheme
PASLU	Patient access scheme liaison unit
PSSRU	Personal social services research unit
QALY	Quality adjusted life year
QoL	Quality of life
SARS-Cov 2	Severe acute respiratory syndrome coronavirus 2
ScHARR	School of Health and Related Research
SoC	Standard of Care
SPC	Summary of product characteristics
TTO	Time trade-off

Company Issue 1 EA1: The direct utility gain associated with Evusheld should be increased to reflect recent findings from patient interviews and applied to 100% of patients in the target population.

Description of problem	Description of proposed amendment	Justification for amendment
Section 1.3, Page 13: *"The EAG suggests that the direct utility gain should only apply to the 13% of patients in the target population who are currently continuing to follow shielding advice."* **Section 4.4.2.2, Page 142:** *"a utility gain of [redacted] is applied to all patients receiving Evusheld in the model. The company describes this utility gain as being applied to all patients receiving Evusheld for the duration of treatment (i.e., 1 year)."*	Update the proportion of patients the utility gain is applied to 100% and update the utility gain to [redacted] in line with the recent utility study	In the initial factual accuracy check provided by AstraZeneca on the 7th December 2022, robust argumentation was presented which evidenced why applying the utility gain to only a proportion of patients (i.e. 13%) and not 100% of patients treated with Evusheld is inappropriate and contrary to the available evidence. In summary, the factual accuracy check refers to ratification by clinical experts, the outputs from the CANDOUR study (1) and previous health technology assessments (TA246(2) and TA769 (3)), to illustrate this point. Further to this, since the factual accuracy check was completed, AstraZeneca are now in receipt of additional important and relevant data which further enhances the conclusion that the utility gain should be applied to all Evusheld patients, and that the utility gain in the original company economic model of 0.066 is an underestimate. Full details provided in Appendix 2. Specifically, these additional data relate to a utility study which was designed to elicit societal and patient valuations to estimate the HRQoL benefit associated with

Description of problem	Description of proposed amendment	Justification for amendment
		prophylactic treatment through the EQ-5D-5L and time trade-off (TTO) interviews. Objectives of the study included: 1. To develop and validate vignettes describing the health-related quality of life (HRQoL) of immunocompromised (IC) patients included in the highest risk clinical subgroups before and after a prophylactic treatment for COVID-19. 2. To estimate utilities for each health state using two different approaches: a) IC patients completing EQ-5D-5L for their current quality of life (QoL) and 'treated' HRQoL based on a vignette describing prophylactic treatment for COVID-19 [redacted] and b) General population utility estimates from TTO interviews and EQ-5D-5L valuation of vignettes [redacted]

Description of problem	Description of proposed amendment	Justification for amendment
		 • An EQ-5D utility gain of [redacted] was reported between the post-treatment and shielding health states, and • An EQ-5D utility gain of [redacted] was reported between the post-treatment and modified behaviour health states Furthermore, AstraZeneca has received feedback from clinicians who have treated a considerable number of immunocompromised patients with Evusheld

Description of problem	Description of proposed amendment	Justification for amendment
		who have shared comments from their patients which further highlights the positive impact that prophylaxis treatment has had on their wellbeing and quality of life. Further details are provided in Appendix 3. Therefore, based on the latest evidence, the economic analysis has been updated to include a utility gain of [redacted] and applied to all (i.e. 100%) of patients.

Company Issue 2 EA4: The administration cost of Evusheld is not aligned to its deployment in clinical practice

Description of problem	Description of proposed amendment	Justification for amendment
Section 4.2.6.2, Page 97 *"The company applied the unit cost for nursing time in primary care from PSSRU of £42 per hour to estimate an administration cost of £42 over 2 doses in their updated base case analysis.111 The EAG notes that the company's updated approach assumes no resources are allocated for the 1 hour post-administration observation period."* **Section 4.3.4.2, Page 123** *"The SPC states that "administration should be under conditions where management of severe hypersensitivity reactions, such as anaphylaxis, is*	This text should be updated to reflect the updated positioning of Evusheld put forward by AstraZeneca. Specifically, Evusheld should be prescribed upon specialist advice, and is therefore expected to be administered as part of routine specialist care in a hospital, or via secondary care led community services, [redacted] Reference to using the CMDU costings as a proxy is therefore not appropriate, nor needed, and so reference to this should	The approach adopted by AstraZeneca was in response to the EAGs clarification question B2, in which they asked: *"Please explain the rationale for assuming that the costs of administration would be equivalent to 1.5 hours of GP nurse time. This implies that a primary care nurse will spend all of their time during this period administering the drug to and monitoring a single patient and assumes that the space required to monitor the patient is available within the GP practice for this duration. These assumptions do not allow for any efficiencies to be gained from multiple patients being monitored simultaneously…".* The EAGs question implies that there would likely be efficiencies within the system rather than a 1:1 nurse-to-patient ratio needed for observation post injection. It is unclear why the EAG has since applied an unreasonable cost of £410 using the CMDU costs for administering oral anti-virals as a proxy. The CMDUs are an acute service in which a patient needs to quickly attend a local community centre to receive timely treatment for COVID-19 infection; typically within 5 days. Therefore, there needs to be multiple centres requiring significant NHS resource and co-ordination beyond the existing infrastructure to facilitate this service. AstraZeneca has been engaging with NICE and NHS England on how it can best support the NHS with the deployment of Evusheld in those patients at greatest risk. Following this engagement, AstraZeneca would seek to position the use of Evusheld upon specialist advice only, since specialists would be best placed to make

Description of problem	Description of proposed amendment	Justification for amendment
possible".17 This implies the availability of other members of the GP team to deal with the immediate management and transfer to secondary care of any patient experiencing anaphylaxis" *"The EAG would argue that the logistical resource required to administer Evusheld to the estimated 1.8 million eligible patients identified by the company as being within the target population (CS, B1.3.5, page 20) would be substantial and may be better estimated by considering the cost for administering COVID-19 therapeutics in the community through COVID Medicine Delivery Units (CMDUs)."*	<u>be removed. The EAG should update their model to incorporate the revised costs provided by AstraZeneca, which are likely to overestimate the administration costs.</u>	prescribing decisions for Evusheld and would be able to make informed decisions on the basis of the evolving COVID-19 landscape and changing variants. Furthermore, as those who are at greatest risk either have primary or secondary immunodeficiencies, patients should receive treatment in a hospital setting, or in specialist-led community services where a sterile environment can be maintained to reduce the risk of infection in these high-risk individuals. Therefore, it is more appropriate for Evusheld to be prescribed upon specialist advice and that people would receive treatment as part of their routine outpatient appointments, or via secondary care led community services[redacted]. [redacted] As such, unlike for the case of large-scale, time-sensitive treatment using COVID-19 therapeutics, prophylaxis use of Evusheld will not require significant logistical resources for implementation at cost to the NHS. Therefore, as per AstraZeneca's response to clarification question B2, the economic case should consider a 1-hour cost for a Band 5 nurse per patient, per dose; equating to £41 per dose.(4) This likely overestimates the administration cost for patients for the following reasons: 1) Patients will visit their specialists as part of routine care and these appointments may already last for 45 minutes.

Description of problem	Description of proposed amendment	Justification for amendment
"In reality, the EAG expects that some form of coordinated provision would need to be set up for the administration of Evusheld, to the 1.8 million patients that the company estimate would be eligible, and this would fall outside of any existing agreements for routine care by primary care providers, or routine vaccinations within primary care. Therefore, the incorporation of administration costs from CMDUs is explored in the EAG's exploratory analysis (see Section 4.4.2.5) as a proxy for the provision likely to be required to administer Evusheld." **Section 4.4.2.5, Page 142**		2) As suggested by the EAG in Clarification question B2, there's likely efficiencies meaning a 1:1 nurse-to-patient ratio is unlikely. [redacted]

Description of problem	Description of proposed amendment	Justification for amendment
"Therefore, the EAG applied a cost of £410 per dose administered in their base case analysis."		

Company Issue 3 EA6: using an annual long COVID cost of £1128, assuming chronic fatigue as proxy, is an underestimate and the cost of £2,500 used in the sensitivity analysis from the ongoing multiple technology assessment (MTA) is more appropriate

Description of problem	Description of proposed amendment	Justification for amendment
Section 1.5, Page 17 *"The EAG's preference is to use the estimate for the cost of chronic fatigue (£1128) as a proxy for the cost of long COVID, as assumed in the ScHARR COVID-19 MTA base case analysis. [EA6]"* **Section 4.3.4.16, Page 137** *"Therefore, the EAG's preference is to use the estimate for chronic fatigue (£1128) employed in the ScHARR COVID-19 MTA base case analysis"*	The cost applied in the EAG preferred base case reflected the cost of chronic fatigue as a proxy for long COVID-19, which is an underestimate since this would not capture the range of clinical outcomes, such as organ damage, which manifest with this stage of the disease. A more appropriate cost of £2,500 referenced in the Appraisal Committee meeting slides should be used.(5)	The EAG state that the preferred cost for long COVID-19 aligns with the cost applied in the ScHARR base case from the ongoing NICE MTA of therapeutics for people with COVID-19 [TA10936], (6). However it is important to note that as part of the MTA consultation, consultee comments highlighted that the EAG's preferred cost was a considerable underestimate and would not be generalisable to long COVID-19. One commentator noted: *"We consider this to be huge underestimate – the authors have not considered thrombosis and other conditions more serious than chronic fatigue"*(6) This commentator has rightly and appropriately highlighted that the EAG preferred cost does not capture all of the relevant and serious implications of long COVID-19 which would extend beyond chronic fatigue. In addition, it is also worth noting that this long COVID-19 cost was

Description of problem	Description of proposed amendment	Justification for amendment
		considered underestimated at the MTA committee meeting. (5) The company appreciates that there is uncertainty and a paucity of data for estimating the true impact of long COVID-19 at present. The company also note the clarification in the EAG report that the cost of £2,500 from the MTA was not informed by specific evidence. However, persisting with using chronic fatigue as a proxy which severely underestimates the cost of long COVID-19 is fundamentally flawed. Therefore, the higher cost of £2,500, referenced in the NICE committee slides should be used in the base case, as this is more reflective of the entire cost burden of long COVID-19.

References

1. Violato et al. The impact of the COVID-19 pandemic on health-related quality of life: a cross-sectional survey of 13 high and low-middle income countries (In press). In press. 2022;

2. National Institute for Health and Care Excellence. Evidence | Pharmalgen for the treatment of bee and wasp venom allergy | Guidance | NICE [Internet]. NICE; [cited 2022 Aug 9]. Available from: https://www.nice.org.uk/guidance/ta246/evidence

3. National Institute for Health and Care Excellence. NICE TA769: Palforzia for treating peanut allergy in children and young people [Internet]. 2022. Available from: https://www.nice.org.uk/guidance/ta769

4. UK Government. Summary of Product Characteristics for Evusheld [Internet]. 2022 [cited 2022 Jul 29]. Available from: https://www.gov.uk/government/publications/regulatory-approval-of-evusheld-tixagevimabcilgavimab/summary-of-product-characteristics-for-evusheld

5. NICE (Technology appraisal committee C). ID4038 COVID PART 1- MTA slides to PM for public observers [redacted]. Therapeutics for people with COVID 19 Multiple Technology Appraisal. 2022 Oct 18.

6. National Institute for Health and Care Excellence. Multiple Technology Appraisal | Therapeutics for people with COVID-19 [ID4038] |Committee Papers [Internet]. Available from: https://www.nice.org.uk/guidance/gid-ta10936/documents/committee-papers

Appendix 1: ICERs without the PAS

Table 4: Company's revised "EAG report Table 2" (EAG base case) (list price)

Scenario	Implemented	Incremental cost	Incremental QALYs	ICER (change from company base case)
Company base case (Deterministic)	-	[redacted]	[redacted]	[redacted]
EAG's corrected company base case: correcting implementation errors in the company's economic model [included in all subsequent rows]	Partly – the EAG implementation was factually inaccurate	[redacted]	[redacted]	[redacted]
EA1: Varying size of direct utility gain or size of group it is applied for to 13%	No – factually inaccurate – new evidence included to update utility gain to [redacted] for 100% of target population	[redacted]	[redacted]	[redacted]
EA2 Halving the duration of direct utility gain for those infected while on Evusheld	Included	[redacted]	[redacted]	[redacted]
EA3: Assuming 12.7% of the non-hospitalised cohort would develop long COVID	Included	[redacted]	[redacted]	[redacted]
EA4: Assuming cost of administration for Evusheld of £410 based on CMDU costing exercise	No – new evidence included to update to £41.00 per administration	[redacted]	[redacted]	[redacted]
EA5: Using the October 2022 update of the ONS data to estimate the duration for long COVID without the Evans 2022 adjustment	Included	[redacted]	[redacted]	[redacted]
EA6: Using the long COVID annual costs of £1128 assuming chronic fatigue as proxy	No – new evidence included to update to	-	-	-

	£2,500 per administration			
EA7: Recalculating disutility values due to long COVID and assuming linear HRQoL improvement by time for 5 years	Partly – waning over 5 years removed	[redacted]	[redacted]	[redacted]
EA8: Using 9.9% as the risk estimate of hospitalisation for infected patients.	Partly - Included at 15.9%	[redacted]	[redacted]	[redacted]
EA9: Updating hospitalisation reference costs associated with acute admissions	Included	[redacted]	[redacted]	[redacted]
EA10: Reducing proportion of hospitalised patients requiring invasive mechanical ventilation (IMV)	Included	[redacted]	[redacted]	[redacted]
EA11: Applying long COVID to new infections after 1 year	Partly – the EAG implementation was factually inaccurate	[redacted]	[redacted]	[redacted]
EA12: Assuming reduction in relative efficacy by one-third	Included	[redacted]	[redacted]	[redacted]
EAG's preferred base case applying analyses EA1 to EA11 (minus factual inaccuracies and new evidence noted in this response) – deterministic	-	[redacted]	[redacted]	[redacted]

Table 5: Revised company base case

Scenario	Implemented	Incremental cost	Incremental QALYs	ICER (change from company base case)
Company base case (Deterministic)	-	[redacted]	[redacted]	[redacted]

Scenario	Implemented	Incremental cost	Incremental QALYs	ICER (change from company base case)
EAG's corrected company base case: correcting implementation errors in the company's economic model [included in all subsequent rows]	Partly – the EAG implementation was factually inaccurate	[redacted]	[redacted]	[redacted]
EA1: Varying size of direct utility gain or size of group it is applied for to 13%	No – factually inaccurate – new evidence included to update utility gain to [redacted] for 100% of target population	[redacted]	[redacted]	[redacted]
EA2 Halving the duration of direct utility gain for those infected while on Evusheld	Included	[redacted]	[redacted]	[redacted]
EA3: Assuming 12.7% of the non-hospitalised cohort would develop long COVID	Not included – as per company base case	-	-	-
EA4: Assuming cost of administration for Evusheld of £410 based on CMDU costing exercise	No – new evidence included to update to £41.00 per administration	[redacted]	[redacted]	[redacted]
EA5: Using the October 2022 update of the ONS data to estimate the duration for long COVID without the Evans 2022 adjustment	Not included – as per company base case	-	-	-
EA6: Using the long COVID annual costs of £1128 assuming chronic fatigue as proxy	No – new evidence included to update to £2,500 per administration	-	-	-

Scenario	Implemented	Incremental cost	Incremental QALYs	ICER (change from company base case)
EA7: Recalculating disutility values due to long COVID and assuming linear HRQoL improvement by time for 5 years	Not included – as per company base case	-	-	-
EA8: Using 9.9% as the risk estimate of hospitalisation for infected patients	Partly - Included at 15.9%	[redacted]	[redacted]	[redacted]
EA9: Updating hospitalisation reference costs associated with acute admissions	Included	[redacted]	[redacted]	[redacted]
EA10: Reducing proportion of hospitalised patients requiring invasive mechanical ventialiation (IMV)	Not included – as per company base case	-	-	-
EA11: Applying long COVID to new infections after 1 year	Partly – the EAG implementation was factually inaccurate	[redacted]	[redacted]	[redacted]
EA12: Assuming reduction in relative efficacy by one-third	Not included – as per Company base case	-	-	-
Company's preferred base case also applying appropriate corrections and analyses EA1, EA2, EA4, EA8, EA9 and EA11 – deterministic	**-**	[redacted]	[redacted]	[redacted]

Appendix 2: Utility study protocol

Provided in a separate document.

Appendix 3: HCP feedback following the use of Evusheld as a prophylaxis in the UK

Email received from [redacted] to AstraZeneca on 30th November 2022 which stated:

"… As mentioned my patients are extremely happy with this medication not only because of the fact that they can now take the risk of un-schielding but also because of the quality of life that they can expect now.

It is incredibly rewarding for me to hear stories of mothers and daughters finally being able to meet outside, of whole families being able to reunite 3 generations after years, of friends sharing this experience together and in general the feeling of mental freedom.

Often I think Evusheld is helping prevent Covid as much as it is helping prevent/recover mental health issues…"

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Tixagevimab–cilgavimab for preventing COVID-19 [ID6136]

Clarification questions amended redaction

December 2022

File name	Version	Contains confidential information	Date
[ID6136]_tixa-mab EAG Clarification letter response_[Amended_redaction]	3.0	Yes	22/12/2022

Section A: Clarification on effectiveness data

Dosing schedule for the intervention

A1. PRIORITY The SmPC for tixagevimab–cilgavimab (referred to hereafter as Evusheld) states that there are no safety or efficacy data available for repeat dosing with Evusheld. Please provide results for the sub-study within PROVENT which examined repeated dosing at 6 months and the sub-study which examined repeated dosing at 12 months as described on the trials registry entry for PROVENT (https://clinicaltrials.gov/ct2/show/NCT04625725). If these results are not yet available, please summarise the design of these sub-studies and the outcomes being measured and explain how these results, when available, will relate to the company's proposal that a second 600mg dose is given 6 months after the first.

Response:

The sub-study within PROVENT (https://clinicaltrials.gov/ct2/show/NCT04625725) examines the following:

Evusheld 300 mg redosing at 6-months

Evusheld 300 mg redosing at 12-months

Evusheld 600 mg redosing at 6-months

Data reported at 12-months for the 300 mg dose and 6-months for the 600 mg dose is anticipated to be available [redacted]. Data reported at 6-months for the 300 mg dose pertains to safety and pharmacokinetics (PK) only, and is summarised below.

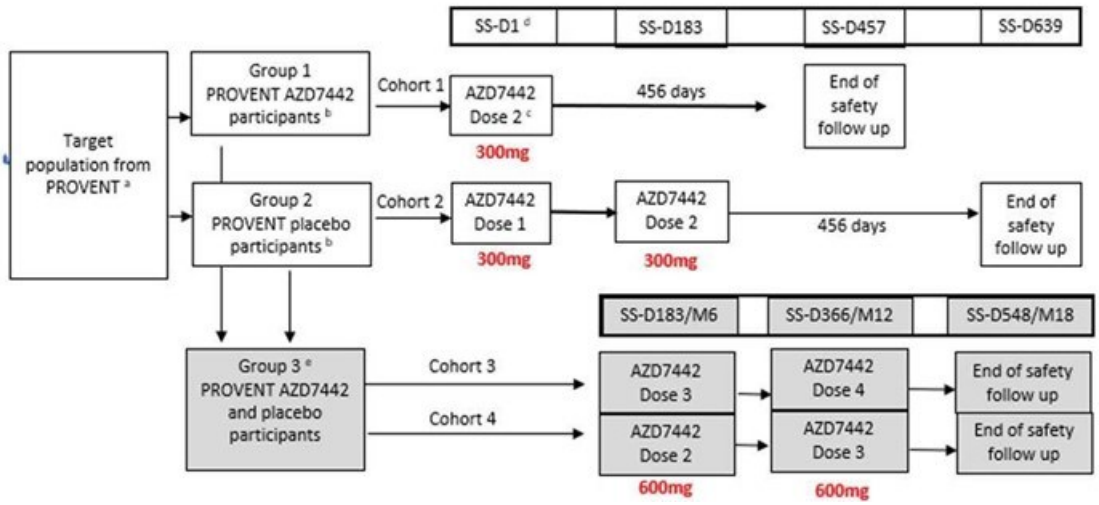
Study design

The study design is shown in Figure 1. A subset of study sites in the US, UK, and Belgium that were active in the PROVENT parent study were invited to enrol adult participants who could benefit from a repeat dose of Evusheld.

The sub study was designed to investigate the safety profile and PK of repeat doses of Evusheld in PROVENT study participants who may benefit from repeat dose of

Evusheld, and whether repeat dosing can maintain serum levels associated with protection against COVID-19.(1)

Figure 1: PROVENT Repeat Dose Sub-study design



Key: [a]Participants from PROVENT parent study who may benefit from a repeat dose of Evusheld; [b]Based on randomization in the parent study; [c]Participants were eligible for the sub-study once they reached 12 ± 2 months post-dose in the double-blind parent study; [d]Therefore, in Group 1, the dosing interval between Dose 1 (parent study) and Dose 2 (SS-D1) is approximately 12 months. For participants who have not undergone a Day 366 visit in the parent study, the Day 366 assessments were performed at SS-D1.
Abbreviations: AZD7442 – Evusheld; D – Day; SS – Sub-study

Results

In the Safety Analysis Set:

- Group 1 participants (n=[redacted]) received their first dose of Evusheld 300 mg in the PROVENT parent study and their second dose in the sub-study.
- Group 2 participants (n=[redacted] received placebo in the PROVENT parent study and their first dose of Evusheld (300 mg IM in the sub-study.

Up to the data cut-off (DCO) of 25 February 2022, the median (min, max) durations of follow-up in the sub-study were similar in Group 1 and Group 2: [redacted] days ([redacted]) and [redacted] days ([redacted]), respectively.(2)

Adverse events

Overall, the type of AEs observed in the sub-study were consistent with the events observed in the PROVENT parent study.

Adverse events (AEs) were reported by [redacted] and [redacted] of participants in Group 1 and Group 2, respectively. The most commonly reported AEs by PT (experienced by > 1% of participants in the total group) were headache[redacted]fatigue[redacted]asymptomatic COVID-19_[redacted]COVID-19 [redacted]cough[redacted]oropharyngeal pain_([redacted]dyspnoea_[redacted]and pain [redacted]. These interim results are generally consistent with those observed in the PROVENT parent study Primary Analysis. (2)

Fatalities and serious adverse events

There [redacted] AEs leading to death. Serious adverse events (SAEs) were reported by [redacted] participants in Group 1 and Group 2, respectively (migraine [considered related to Evusheld], worsening major depression [considered not related], and flank pain [considered not related]). There were too few SAEs to note any trends within or between the groups. However, no differences in SAEs were observed between treatment arms in the main PROVENT study. (2)

Adverse events of *special interest*

AEs of special interest (AESIs) (anaphylaxis/other serious hypersensitivity reactions and injection site reactions) were reported by [redacted] of participants in Group 1 (PTs of injection site pain in_[redacted]) and Group 2 (injection site pruritus, injection site swelling[redacted]injection-related reaction), respectively.

[redacted] had an event of anaphylaxis or any other serious hypersensitivity reaction. There were [redacted] with events in the AESI categories of cardiac ischemia, cardiac failure, and thrombotic events. There were [redacted] participants with emergency room visits[redacted] participants ([redacted]) in Group 1 and [redacted] participants ([redacted]) in Group 2. [redacted] visits were reported as COVID-19-related emergency room visits.

There were no clinically meaningful trends in the shifts from baseline in Group 1 or Group 2 in the clinical chemistry, clinical haematology, coagulation, urinalysis, and cardiac biomarkers parameters. These results were consistent with the clinical laboratory evaluations in the PROVENT parent study. (2)

Serum concentration

In Group 1, at the DCO of 25 February 2022, serum tixagevimab concentration data were available at baseline/Day 1 (pre-dose value) for 50 participants and at Day 29 for 53 participants. (2) Table 1 shows serum tixagevimab, cilgavimab, and Evusheld concentrations in the sub-study Day 29 following a second dose of Evusheld 300 mg in comparison to serum Evusheld concentrations in the PROVENT parent study at Day 29 following the first dose of Evusheld 300 mg. (2)

Among the 53 participants in Group 1 who received their second Evusheld dose on Day 1 in the sub-study, the geometric mean Evusheld drug concentration at Day 29 ([redacted] µg/mL) was similar to the mean drug concentration at Day 29 ([redacted] µg/mL) in the Evusheld group in the PROVENT parent study. (2)

Based on these interim data, with a 12-month dosing interval, there was limited accumulation ([redacted] Day 29 mean concentration after second dose). The sufficient minimum protection level for the original SARS-CoV-2 strain (> 2.2 µg/mL [IQR 1.1 to 5.0 µg/mL]) [redacted]
The minimum protection level for the Omicron BA.2 variant Y
[redacted]

Table 1: Summary of Serum tixagevimab, cilgavimab, and Evusheld, Concentrations on PROVENT Sub-study Day 29 Following Second Dose of Evusheld 300mg in Comparison to Serum Evusheld Concentrations in the PROVENT Parent Study Day 29 Following First Dose of Evusheld (2)

Statistics	PROVENT substudy Group I Day 29 (after second dose)			PROVENT parent study Evusheld group Day 29 (after first dose)
	tixagevimab (N=53)	cilgavimab (N = 53)	Evusheld (N = 53)	Evusheld (N = 1852)
n (n < LLOQ)	[redacted]	[redacted]	[redacted]	1222 (5)
Geometric mean	[redacted]	[redacted]	[redacted]	23.331
Geometric SD	[redacted]	[redacted]	[redacted]	19029
Geometric CV%	[redacted]	[redacted]	[redacted]	71.605
Mean (SD)	[redacted]	[redacted]	[redacted]	26721 (11.2166)
Median	[redacted]	[redacted]	[redacted]	26.595
Min, Max	[redacted]	[redacted]	[redacted]	0.30, 59.83
Accumulation ratio *	[redacted]	[redacted]	[redacted]	1.1310

*Ratio of geometric mean Day 29 concentration of EVUSHELD of substudy to that of the parent study.
Group I = EVUSHELD participants from the parent study. The first tixagevimab/cilgavimab dose for Group I participants occurred in the parent study.
Baseline is defined as the last non-missing measurement taken prior to the first dose oftixagevimab, cilgavimab (including unscheduled measurements, if any).
EVUSHELD is sum of tixagevimab and cilgavimab.
LLOQ • Lower limit of quantification (0.3 pg/ml„).
CV , coefficient ofvariation; 1M, intramuscular; NC, not calculated; Max, maximum; Min, minimum; N, number of participants in the analysis set; n, number of participants, PR, pharmacokinetic; SD, standard deviation.
Derived from: Table 14.2.4.2S in Appendix B and Table 14.2.4.2A in Appendix F of the PROVENT substudy IA Module 5.3.5.1

A2. PRIORITY CS, Section B1.2, Table 2. The company states that the recommendation to increase the dose from 300mg to 600mg was based on the totality of the available data including clinical pharmacology, pharmacokinetics, antiviral activity, and clinical trial data, but the reference cited in support of this statement is a single real world evidence study (Young-Xu 2022). Please clarify what evidence exists to demonstrate that a higher dose of EVUSHELD (600mg) is more effective than the original dose (300mg) against current dominant Omicron variants in the UK. In addition, if the high dose (600mg) becomes less effective against the dominant and future variants, could higher doses be proposed and what evidence does the company have on the safety of doses higher than 600mg?

Response:

In view of the current and future circulating dominant SARS-CoV-2 sub-variants, a dosage for PrEP of 600 mg is anticipated to be more effective in protecting people from symptomatic SARS-CoV-2 than a dose of 300 mg.

This scientific assessment is based on the totality of the available data on Evusheld that is relevant to PrEP against Omicron SARS-CoV-2. This includes data on clinical trial efficacy and real-world clinical effectiveness, pharmacokinetic and pharmacodynamic properties and *in-vitro* anti-viral activity against variants of concern. The clinical safety of 600 mg Evusheld for PrEP use is supported by safety data from TACKLE in patients with mild to moderate COVID-19.

Clinical effectiveness – real-world evidence

The pivotal PROVENT trial demonstrated clinical efficacy of Evusheld at a dose of 300 mg, measured at day 183. However, the study was conducted when the dominant circulating VOCs were Alpha, Beta, Gamma, Delta, and Epsilon.

In February 2022, based on the FDA's modelled assessment of Evusheld's *in-vitro* neutralising activity against BA.1 and BA.1.1 the recommended dose of Evusheld was amended from 300 mg to 600 mg in the US.(3)

Following the updated dose recommendation, RWE from the US has demonstrated consistent protection offered by 600 mg Evusheld with respect to a sustained

reduction in the risk of symptomatic COVID-19, and hospitalisation and/or death due to COVID-19.(4,5)

In particular, data from a retrospective cohort study conducted at Massachusetts General during the BA.1 and BA.2 waves, comparing 222 solid organ transplant recipients (SOTRs) who received Evusheld for pre-exposure prophylaxis and 222 age-matched vaccinated solid organ transplant recipients who did not receive Evusheld. In the Evusheld arm 59% received the 600 mg dose, and 40.5% received the 300 mg dose, allowing for comparison of effectiveness between the 300 mg and 600 mg doses. (5)

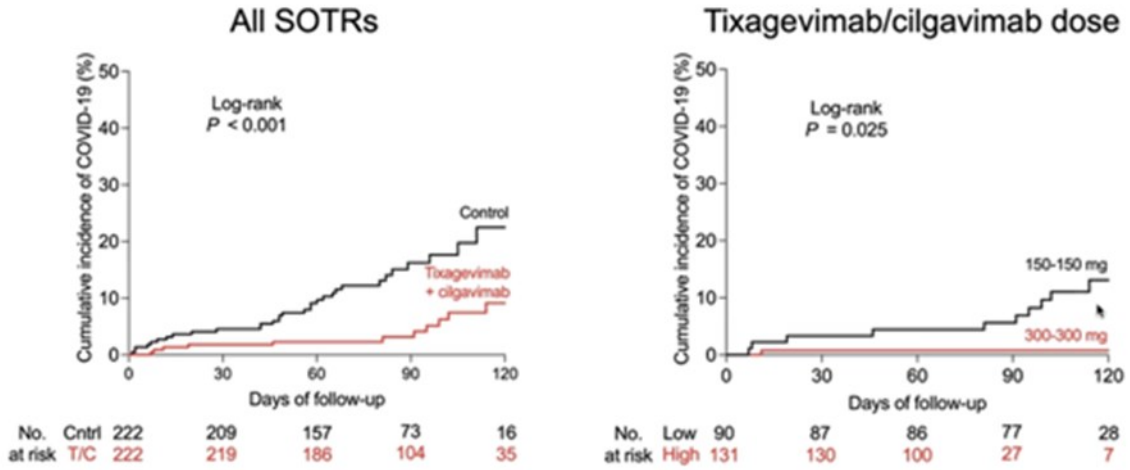
Breakthrough SARS-CoV-2 infections occurred in 11 (5%) of SOTRs who received Evusheld and in 32 (14%) of SOTRs in the control group ($p<0.001$). In the Evusheld group, SOTRs who received the 300 mg dose had a higher incidence of breakthrough infections compared to those who received the 600 mg dose ($p=0.025$) (Table 2). In addition to fewer breakthrough cases, patients who received 600 mg Evusheld had a longer duration of protection compared to those who received 300 mg (Figure 2).

Table 2: Summary of Evusheld recipients with breakthrough infections

	Date of Infection (2022)	Most Common Variant at the Time	SOT	Number of Vaccines	Months Since Last Vaccine	Evusheld dose (mg)	Days Since Evusheld	Hospitalisation	Treatment	Outcome
1	19 Jan	B.1.1.529	Kidney	4	3.9	300	7	No	None	Recovered
2	05 Feb	B.1.1.529	Lung	3	0.9	300	8	Yes	remdesivir	Recovered
3	02 Mar	B.1.1.529	Lung	4	1.1	300	19	No	bamlanivimab	Recovered
4	29 Mar	BA.2	Liver	3	7.4	300	46	No	bebtelovimab	Recovered
5	13 Apr	BA.2	Lung	2	6.1	300	91	No	bebtelovimab	Recovered
6	21 Apr	BA.2	Lung	3	8.1	300	99	No	bebtelovimab	Recovered
7	24 Apr	BA.2	Kidney	4	2.2	600	11	No	bebtelovimab	Recovered
8	06 May	BA2	Lung	3	8.5	300	114	No	mAb at outside institution	Recovered
9	15 May	BA.2	Lung	4	9.0	300	95	No	mAb at outside institution	Recovered
10	15 May	BA.2	Kidney	4	3.4	300	81	No	bebtelovimab	Recovered
11	30 May	BA.2.12.1	Kidney	3	9.5	300	102	No	bebtelovimab	Recovered

Abbreviations: mAb – monoclonal antibody; SOT – solid organ transplant. Source: Al Jurdi et al. 2022 (5)

Figure 2: Summary of COVID-19 breakthrough infections in retrospective study of SOTR patients (Al Jurdi et al. 2022)(5)



Abbreviations: Cntrl – control; COVID-19 – coronavirus disease 2019; SOTR – solid organ transplant recipients; T/C – tixagevimab/cilgavimab. Source: Al Jurdi et al. 2022 (5)

In addition to Al-Jurdi et al, 2022, RWE published by Young-Xu et al, 2022 (which is well described in our submission) demonstrated the effectiveness of 600 mg Evusheld against the composite outcome of SARS-CoV-2 infection, COVID-19-related hospitalisation, and all-cause mortality.(4)

RWE data has therefore demonstrated that the 600 mg dose not only improves the durability of response, but also maintains statistically significant and clinically meaningful protection against developing symptomatic COVID-19 and adverse COVID-19 outcomes irrespective of subvariants of COVID-19, geography, or vaccination status.

600mg Dose Safety Profile

The safety of the 600 mg dose has been demonstrated and reported in the real-world, in a Phase I study which reported the safety of Evusheld in doses up to 3,000 mg across 12 months, and in the pivotal RCT evaluating the efficacy and safety of 600 mg Evusheld for the treatment of COVID-19, TACKLE.(6,7) Specifically, the TACKLE study demonstrated that the number of participants with AEs was lower in the Evusheld group than in that observed in the placebo group. All treatment-emergent AEs occurring in at least 1% of participants were reported at similar or lower incidence rates among participants receiving Evusheld compared to

those receiving placebo. Except for disease under study and injection site pain, all AEs occurred in less than 2% of the participants. Most AEs reported in TACKLE were mild or moderate in severity.(7)

Pharmacodynamics and Pharmacokinetics

PK modelling of predicted Evusheld concentrations in serum, using a target based on *in-vitro* neutralisation (IC80 = IC50 × 4) and a 1.8% partition ratio into the upper respiratory track, demonstrates [redacted] (Figure 3); however, at a dose of [redacted] (

Figure 4). The percent of individuals at or above the modelled MPC for BA.4/5 at 3, 6, 12 months is projected to be [redacted] Evusheld dosed every six months. (Figure 5)

Moreover, using a 6.5% partition ratio assumption for lower respiratory tract distribution, a regimen of [redacted] (Table 3). Prevention of disease in the lower respiratory tract provides an important clinical benefit in reducing the risk of severe disease and death from COVID-19, a priority for all health authorities around the globe.

Table 3: Predicted Percentage of Population Above Serum Target Concentrations to Prevent Symptomatic and Severe Disease, Evusheld 300 mg vs Evusheld 600 mg dose

Percentage of the population above serum target for 300 mg										
	Victoria		Delta		BA.1		BA.2		BA.4/5	
	Symptomatic disease	Severe disease	Symptomatic disease	Severe disease	Symptomatic disease	Severe disease	Symptomatic disease	Severe disease	Symptomatic disease	Severe disease
3 months	[redacted]									
6 months	[redacted]									
Percentage of the population above serum target for 600 mg										
	Symptomatic disease	Severe disease	Symptomatic disease	Severe disease	Symptomatic disease	Severe disease	Symptomatic disease	Severe disease	Symptomatic disease	Severe disease
3 months	[redacted]									
6 months	[redacted]									

The serum target concentration for symptomatic disease is based on IC80 (IC50 x 4) from pseudotyped VLP assay and a partition ratio of 1.8% for the upper respiratory tract. The serum target concentration for severe disease is based on IC80 from pseudotyped VLP assay and a partition ratio of 6.5% for the lower respiratory tract. Abbreviations: IC80 – 80% maximal inhibitory concentration; VLP – virus like particle from pseudotyped VLP assay.

Figure 3 – Figure 5 below are included to illustrate the Evusheld concentration in serum (300 mg and 600 mg) and duration of protection against various VOC, as well as the predicted serum Evusheld concentration over time for the 600 mg initial dose and 600mg maintenance dose every 6 months for BA.4/5 Variants.

Figure 3: Evusheld Concentrations in Serum with 300 mg Dose and Duration of Protection Against VOCs

Key: Solid line = median predicted concentration, ribbon = 80% prediction interval. Key: dashed horizontal lines serum target concentration for Victoria, BA.2, BA.3 and BA.4/5 calculated using IC80 from pseudotyped VLP assay and upper respiratory tract partition ratio of 1.8%. Abbreviations: IC80 – 80% maximal inhibitory concentration; VLP – virus like particle from pseudotyped VLP assay; VOC – variant of concern.

Figure 4: Evusheld Concentrations in Serum with 600 mg Every 6 Months Dose and Duration of Protection Against VOCs

Key: Solid line = median predicted concentration, ribbon = 80% prediction interval; dashed horizontal lines = serum target concentration for BA.2, BA.3 and BA.4/5 calculated using IC80 from pseudotyped VLP assay and upper respiratory tract partition ratio of 1.8%. Abbreviations: IC80 – 80% maximal inhibitory concentration; VLP – virus like particle; VOC – variant of concern.

Figure 5: Predicted Serum Evusheld Concentration over Time for the 600 mg Initial Dose and 600mg Maintenance Dose Every 6 months for BA.4/5 Variants

Key: Solid line = median predicted concentration, ribbon = 80% prediction interval; % number next to blue dashed line represent % subjects predicted to be above serum target level 14.4 µg/mL (using 1.8% upper respiratory partition ratio and IC80 from pseudotyped VLP assay) for BA.4/5.; % number next to purple dashed line represent

% subjects predicted to be above serum target level 4 ug/ml (using 6.5% lower respiratory partition ratio and IC80 from pseudotyped VLP assay) for BA.4/5. Abbreviations: IC80 – 80% maximal inhibitory concentration; VLP – virus like particle from pseudotyped VLP assay.

AstraZeneca position on Evusheld dosing at 600 mg

AstraZeneca maintains its position that the 600 mg dose is the dose supported by the totality of currently available data.

A3. PRIORITY CS Section B1.3.8 The company states on page 30 that "UK clinical experts advised that the availability of a prophylaxis would not only reduce the risk of symptomatic infection and poor outcomes, but also improve patient HRQoL by reducing their fear and anxiety and allowing them to return to more normal levels of social functioning". Please clarify what evidence exists to support this assertion that shielding behaviours are likely to change following Evusheld prophylaxis, given that many immunocompromised individuals have continued to shield following vaccination, and comment on whether any reductions in shielding behaviour are likely to be dependent on the dominant variant of concern prevalent at the time. With respect to this, we draw the company's attention to the recent FDA update asking healthcare providers in the US to warn patients of the risk for COVID-19 due to SARS-CoV-2 viral variants not neutralised by Evusheld. [https://www.fda.gov/media/154701/download]

Response:

It is important to note that Evusheld can improve HRQoL in two ways, and is not simply associated with reduced shielding behaviours:

- Firstly, Evusheld can reduce the fear and anxiety that exists in people who do not feel adequately protected with the current vaccination programme;
- Secondly, Evusheld can improve social functioning in people who make lifestyle modifications, which may include shielding behaviours but also may include avoiding social gatherings, limiting travel, and wearing face masks

The evidence base supporting this assertion comes from parliamentary groups, interviews with clinical experts, and from two Office for National Statistics (ONS) surveys undertaken in high-risk, immunocompromised individuals and in individuals previously considered clinically extremely vulnerable, respectively.

UK All-Party Parliamentary Group (8)

Patients, organisations, and the clinical community have identified a substantial unmet need for prophylactic options.

This need has been voiced in a recent consensus statement from the UK All-Party Parliamentary Group (APPG) on vulnerable groups co-signed by 18 charities and 125 physicians, calling for the use of treatments like Evusheld as a vaccine adjunct in immunocompromised populations.(8) In particular, reference has been made to the expected improvement in quality of life, were Evusheld to be made available.

"The number of people being admitted to hospital with coronavirus remains high. As we learn to live with coronavirus, we must also learn to protect immunocompromised people. Protective antibody treatments like Evusheld could offer this solution and it is really important that the voice of patients and clinicians is heard."(10)

- Bob Blackman,

Member of Parliament and co-chair of the APPG on vulnerable groups

"Clinical care should be designed to maximise uptake of Evusheld amongst eligible immunocompromised individuals whilst simultaneously making effective use of healthcare resources. This will maximise patient mental health, allow a return to normal working environments and ***improve quality of life****."*(8)

Clinical expert interviews

Interviews with three UK clinical experts directly treating high-risk, immunocompromised patients were conducted on the 22nd and 26th of July 2022.

The experts all expressed a substantial demand from their patients for effective prophylactic treatment, and that their patients are increasingly aware of the limited protection conferred by vaccination. A considerable proportion of high-risk people still feel vulnerable and continue to take extra precautions despite vaccination since

they know that vaccinations do not sufficiently protect them. Examples of this awareness highlighted in the interviews included:

- Patients' knowledge of the association between their disease and low antibody response
- Patients asking about their vaccination response at clinics and purchasing test kits
- Participation in MELODY – a study which aims to estimate how many immunosuppressed people in the UK have antibodies that may provide protection against COVID-19 after 3 vaccines, e.g., through sending test kits to immunocompromised people's homes.

All experts expressed that Evusheld availability would provide more reassurance than vaccination, reduce anxiety/depression, and change life-limiting behaviours, resulting in an overall improvement in HRQoL.

ONS surveys in vulnerable and high-risk populations

Patients previously considered extremely vulnerable

The view expressed by clinical experts is further supported by findings in the Office for National statistics (ONS) survey undertaken in clinically extremely vulnerable people.(11) A considerable proportion of these people continue to feel unprotected, take extra precautions, and express a wish to access prophylactic treatment:

- The majority, 68%, wish to access prophylactic COVID-19 treatment.
- Most, 82%, continue to take precautions, of whom 13% go to the extreme of completely shielding.
- Almost half are “very” or “somewhat” worried about the effect that the pandemic is currently having on their life, with 24% indicating concern whether vaccination gives adequate protection.

Immunocompromised, high-risk patients

A recent ONS survey published in July 2022 reported that 82% of individuals who are at the highest-risk of COVID-19 adverse outcomes continue to take extra precautions and 13% still continue to shield entirely.(12)

When asked about additional measures to keep themselves safe from COVID-19:

- almost one third (31%) indicated that they are shielding or staying at home more
- 37% avoid social gatherings
- 15% avoid the use of public transport

Such lifestyle modifications can greatly limit daily activities, sometimes to an extreme extent, and reduce interaction with family and friends, resulting in social isolation.

Variants of concern

Evusheld maintains neutralisation against Omicron sub-lineages and all currently circulating variants of concern (VOC) in the UK. Though the FDA warns that certain variants may not be neutralised by Evusheld, these variants are not VOCs in the UK and the correlation between neutralisation activity and efficacy of treatments in preventing symptomatic and severe infection has yet to be established (see Response to A4).

Conclusions

As evidenced above, lifestyle changes due to the fear of contracting COVID-19 severely impacts life and well-being, and is more common in high-risk, immunocompromised populations.

There is an associated level of anxiety with living ‘normal life’ in the knowledge that the measures they have taken (such as vaccinations) do not provide adequate protection against COVID-19 and that the consequences of inadequate protection may be catastrophic given their clinical status.

The constant stress of potential life-threatening consequences has a substantial negative impact on quality of life (QoL) and leads to substantial restrictions to daily activities.

An appropriate analogy to evidence the expected improvement in quality of life with Evusheld in high-risk populations is to consider the effects of the vaccination programme on the general population. Many non-high-risk vaccinated individuals will recall the sense of relief felt when receiving their vaccination and changes to their own behaviours in re-engaging with society, which resulted in improved quality of life, despite not knowing the specific protection offered to them by the vaccination.

The level of unmet need voiced by clinicians, patients, and governmental organisations demonstrates the desire for additional protection, with 68% of extremely clinically vulnerable patients stating that they would welcome a prophylaxis were it made available(11).

Evusheld is targeted for these patients specifically, where the level unmet need is high and where prophylaxis desired. It is therefore logical to conclude that this population would perceive that treatment with Evusheld would provide additional protection akin to that provided by conventional vaccination in the wider population. The feeling of increased protection would, like vaccination in the general population, result in reduced anxiety/depression and improved social functioning.

This effect was also noted during the first appraisal committee meeting of the ongoing NICE MTA of therapeutics for people with COVID-19 [TA10936](13), in that having access to a quick and safe treatment in the community has been a great relief and gives people more confidence to return to their previous routines and activities. We would expect the same to true for pre-exposure prophylaxis, and indeed for the impact to be much greater as it would offer protection from COVID-19 rather than treatment in the event that they still develop COVID-19.

A4. PRIORITY CS, Appendix D, Figure 6. The plot provided shows Evusheld's neutralising activity across 10 variants of concern including 5 within the Omicron classification. The half maximal inhibitory concentrations (IC50) which are shown on a log scale, and vary from [redacted]ng/mL in original strain COVID-19 to figures [redacted]ng/mL

for Omicron BA.4/5 and higher values of [redacted]ng/mL for BA.1 and BA.1.1. Is there evidence to demonstrate that these measures of neutralising activity correlate with the efficacy of treatments to prevent symptomatic and severe infections in clinical studies and is there an agreed threshold for determining when a treatment is deemed ineffective on the basis of neutralising activity?

Response:

Whilst there is not an agreed or known published correlate for determining when a treatment is deemed ineffective based on neutralising activity, it is known that the higher the IC50 values the more likely that efficacy may be reduced.

Despite this, even in variants with the greatest IC50 values i.e., BA.1 and BA.1.1, RWE has continued to demonstrate a statistically significant and clinically meaningful reduction in the risk of developing symptomatic COVID-19 and hospitalisation and/or death and link to all the RWE studies that support this:

- **Currently available RWE** data covering the BA. 1 / BA 1.1 surge in the US include published results from a retrospective analysis of US Department of Veterans Affairs (Young-Xu et al 2022(4)).
    - For the composite outcome of SARS-CoV-2 infection, COVID-19-related hospitalisation, and all-cause mortality, Evusheld-treated patients had a lower incidence of the composite COVID-19 outcome (17/1733 [1.0%] vs 206/6354 [3.2%]; HR 0.31; 95% CI: 0.18-0.53), and individually SARS-CoV-2 infection (HR 0.34; 95% CI: 0.13-0.87), COVID-19 hospitalisation (HR 0.13; 95% CI, 0.02-0.99), and all-cause mortality (HR 0.36; 95% CI, 0.18-0.73).
- Evusheld had demonstrated clinical effectiveness against BA. 1 and BA. 1.1 and ***in-vitro*** **live virus neutralisation** data, which suggest an IC50 of [redacted]ng/ml and [redacted] ng/ml for BA. 1 and BA. 1.1 respectively. Therefore, Evusheld is expected to be clinically effective against any variant (BA. 1, BA. 2, BA. 4/5) with an IC50 below [redacted] ng/ml (14–16). This however does not suggest clinical ineffectiveness for any IC50 beyond [redacted] ng/ml but conservatively infer real-world efficacy against emerging variants of concern:

those that are neutralised to the same extent as, or even better than, BA.1 and BA. 1.1 (numerically, a lower IC50) would be expected to remain effective.(17)

A5. PRIORITY CS, Appendix D1.5. Please confirm whether a systematic review was undertaken to identify studies reporting the neutralisation effect of Evusheld against all variants of concern, especially for BA4 and BA.5 (the predominant variant of concern in the UK)? If not, please justify and provide details of the validity, robustness and reliability of the review approach taken (e.g. how relevant studies were selected, data extracted [including consistency of definitions], quality assessed and data synthesised) and how the evidence identified supports the statements made on p22 of the Appendices e.g. strong correlation is observed between varying Evusheld potencies; current published real-world data provides strong evidence to confirm that all in vitro analyses to date have been corroborated by clinical effectiveness data from a variety of global settings.

Response:

Regular systematic reviews are conducted by AstraZeneca to identify the most up to date literature reporting both on the neutralising effect of Evusheld as well as on clinical effectiveness, utilising standard systematic literature review methodology. Daily literature searching is completed using PubMed and the following preprint servers: MedRxiv, SSRN and Research square.

Search terms used for the preprint servers include key words from the PubMed search string and AstraZeneca specified criteria. On average, 2–3 relevant articles are flagged weekly. Daily PubMed searches result in around 2,000 hits, which are then manually screened for eligibility from the last result obtained from the previous day. The eligibility criteria are as follows:

I. Evusheld RWE papers

II. Opinion pieces/review articles on Evusheld

III. Novel Omicron neutralisation papers; although papers about in vitro neutralisation of emerging Omicron variants are not considered RWE, they are still of interest and are flagged for review if they contain data on Evusheld

IV. Once a week, the following journals are manually checked for relevant RWE Evusheld papers which have been posted online:

V. The Lancet, The Lancet Infectious Diseases, The Lancet Respiratory Medicine, The Lancet Microbe, eClinicalMed, eBioMed, Science, Cell, Nature, Nature Med

Full details of the search terms used in the SLR are presented in Appendix A

The reviews only include authentic Evusheld, as there are considerable limitations associated with evaluating *in-vitro* neutralisation using *generic Evusheld* – i.e., antibodies generated in a research laboratory.

Multiple laboratories have published *in-vitro* neutralisation results using antibodies referred to as Evusheld or its components. These laboratories have generated the antibodies that make up Evusheld themselves using publicly available sequence information.

It is not possible for the quality and potency of antibodies generated in individual laboratories to be verified for similarity to the genuine Evusheld product and therefore the IC50 values generated from the use of these generic antibodies cannot be assumed to be an accurate representation of what would be observed with Evusheld.

AstraZeneca collaboration with independent laboratories

In addition to the systematic reviews, AstraZeneca collaborates with independent laboratories to continuously generate and evaluate *in-vitro* neutralising data for Evusheld against all key and emerging VOCs.

In these collaborations, Evusheld is provided by AstraZeneca and the results are generated independently to minimise bias and to account for the variability that can occur across multiple assays.

Real world evidence

Evusheld's potency in *in-vitro* neutralisation activity is confirmed by findings in real-world settings, where effectiveness of Evusheld against Omicron and its sub-variants is evidenced.

As referred to in Question A4, clinical effectiveness against BA.1.1 and BA.1 and BA.2 demonstrated in **Young-Xu et al. 2022** and **Al Jurdi et al. 2022** suggest that the IC50 measures of neutralising activity correlate with the efficacy of treatments to prevent symptomatic and severe infections observed in clinical studies.(4,5)

To conclude:

1. Evusheld shows clinical effectiveness against BA.1 and BA.1.1.
2. *In*-vitro live virus neutralisation data suggests an IC50 of [redacted] ng/ml and [redacted] ng/ml for BA. 1 and BA. 1.1 respectively.
3. Therefore, Evusheld is expected to be clinically effective against any variant (e.g., BA. 1, BA. 2, BA. 4/5) with an IC50 below [redacted] ng/ml ((14,15)).

A6. Please clarify what evidence exists to support the synergistic effect of tixagevimab with cilgavimab, especially against BA.5, the predominant variant of concern in the UK. An article by Focosi et al. (Pathogens. 2022 Aug; 11(8): 823.) suggests that neither drug retains efficacy against BA.1 or BA.4/BA.5, and only one of the drugs retains efficacy against BA.2.

Response:

Synergistic effect of Evusheld's component parts

AstraZeneca originally developed Evusheld as a combination of two antibodies capable of acting synergistically *in-vitro* to 3-fold higher potency than individual monoclonal potencies; with a combined dose of 79 ng/mL [16 ng/mL of cilgavimab and 63 ng/mL of tixagevimab] having the same activity as 250 ng/mL of each individual antibody) (Zost, et al., 2021).(18) Each antibody is highly potent on its

own, but in a situation where the activity of one or both is reduced, the potential exists for the antibody combination to be better than either of the two alone.

Support for the concept of the synergy between tixagevimab and cilgavimab can be drawn from the BA.1 and BA.2 variants. Against these variant the IC50 for each antibody is substantially higher than the combination of both, even though the overall activity was reduced compared to the original SARS-CoV-2 strain. Despite the reduction in *in-vitro* neutralising activity, Evusheld has been shown to be effective in preventing symptomatic and severe COVID-19 throughout the BA.1 and BA.2 waves (Young-Xu et al.(4), Al Jurdi et al. (5), Kertes et al.(19)).

In the case of BA.2, BA.4, and BA.5, where one of the antibodies appears to have lost neutralising activity, the other antibody remains able to potently neutralise the virus. This is because the activity of each antibody is not dependent on the other. Each individual antibody works together to increase overall activity of the product against certain variants. This also enables prevention against potential viral evolution in the case where one antibody is less active against a certain variant. These traits along with the long-acting benefit are unique characteristics of Evusheld compared with other monoclonal antibodies, which can help deliver best in-kind prevention for immunocompromised populations.

Comments on Focosi et al. 2022(20)

When interpreting *in-vitro* neutralisation data of antibodies against COVID-19, it is vital to also critically appraise the technical methodologies used to draw any conclusions before inferring the likely impact on efficacy. This comment is particularly evident in the case for the conclusions drawn in Focosi et al., 2022. For example, most laboratories cited by Focosi et al. used techniques with ACE2-overexpressing cells, despite such methods previously showing a clear lack of neutralisation of SARS-CoV-2 by certain classes of monoclonal antibodies, yet clinical efficacy has been retained.(17) At fundamental level, comparison of *in-vitro* data across laboratories is hampered by the use of different cell lines that may be infected by SARS-CoV-2 variants to different extents.

In contrast the techniques employed in the studies critiqued by Focosi et al., a study by Wu et al. 2022 utilised an assay calibrated with the WHO International Standard

for anti-SARS-CoV-2 immunoglobulin and reporting of neutralisation titres in International Units – an assay useful for standardised comparisons of different monoclonal antibodies against various variants.(17,20) Using this assay, the authors calculated IC50 values by fitting a four-parameter dose–response curve to 288 independent data points, generated from three independent repeats of 12 independent titrations, each consisting of two technical replicates of a four-point dilution series against live SARS-CoV-2 variants.

In addition to the more rigorous and internationally recognised methodology utilised by Wu et al, the authors also reported confidence intervals, rather than just point estimates. The reporting of confidence intervals is essential to evaluate the significance of any possible changes in neutralisation; particularly when considering IC90 values, which lie close to the plateau of the dose–response curve and are inherently noisy, both in cell-based assays and in fitting of a dose–response curve (the methodology utilised by the studies appraised by Focosi, et al. 2022).

Furthermore, the study conducted by Wu et al. demonstrated that sotrovimab retained neutralisation activity against some variants in which other non-standardised methodologies reported a lack of neutralisation activity, such as was the case for BA.2. This particular conclusion led to UK health authorities, in contrast to US authorities, deciding not to withdraw sotrovimab from use in treating extremely clinically vulnerable patients who are at risk of progression to severe COVID-19.

Therefore, in conclusion, the studies reported and appraised by Focosi et al. should be reviewed critically and an appropriate QC conducted to ensure the rigor and the scientific methodologies employed are appropriate to inform clinical and policy decision making. This point is made evident with respect to Evusheld in which Focosi et al. reported a loss of neutralisation activity against BA.1 and BA.4/BA.5 and only one antibody retaining activity against BA.2 despite the conclusions from Wu et al, which demonstrated strong neutralisation against all omicron variants tested (all dominant VOC circulating in UK), with IC50s reported for BA.1, BA.2, BA.2.12.1, BA4/5 displayed in Table 4. The conclusions made by Wu et al are also supported by real-world evidence in France, Israel, and the USA in which Evusheld has been shown to be efficacious; reducing both symptomatic COVID-19, and severe COVID-

19 and/or death during variants in which Focosi et al supposedly reports a loss of neutralisation activity.

Table 4: IC50s reported for dominant VOC circulating in the UK

		Ancestral	DG614G	Alpha	Beta	Delta	Omicron				Serum concentration (µg/ml)	
							BA.1	BA.2	BA.2.12.1	BA.4/5	Max.	28 d.p.i.
Evusheld (cilgavimab + tixagevimab)	**EC_{50} (ng/ml)**	17.4	18.4	9.1	31.1	9.6	287.2	75.3	33.5	84.3	NR.	26,700
	95% CI [Lower,	15.6	16.8	8.4	26.4	8.8	250.5	68.4	30.1	72.7		
	Upper]	19.5	20.1	9.8	36.3	10.4	329.4	82.9	37.2	97.8		

Abbreviations: NR– not reported.

A7. CS Appendix D1.5. p21. The CS states that "Two pivotal publications including studies from the University of Oxford (84) and Washington University (77) have been conducted on the neutralisation activity of Evusheld. Data from the Oxford study showed that Evusheld retains in vitro neutralising activity against Omicron BA.4/5 variant.(84)." Please provide full bibliographic details for these two studies as the sources numbered 77 and 84 in the bibliography do not appear to match (one appears to be a news article in Dutch and the other appears to refer to a drug price database). Please also describe the methods and results of these studies in sufficient detail for the EAG to assess their robustness.

Response:

Three pivotal publications including studies from the University of Oxford(21), Washington University(22), and the Francis Crick Institute(17) have been conducted on the neutralisation activity of Evusheld. Data from the Oxford and Francis Crick Institute study showed that Evusheld retains in vitro neutralising activity against Omicron BA.4/5 variant. The latter was published following our initial submission and the methods and results of this study, along with those from the University of Oxford and Washington University are discussed below:

University of Oxford (21) (previously referenced in initial submission: 84)

> *Tuekprakhon, A., Nutalai, R., Dijokaite-Guraliuc, A., Zhou, D., Ginn, H.M., Selvaraj, M., Liu, C., Mentzer, A.J., Supasa, P., Duyvesteyn, H.M. and Das, R., 2022. Antibody escape of SARS-CoV-2 Omicron BA. 4 and BA. 5 from vaccine and BA. 1 serum. Cell, 185(14), pp.2422-2433.*

Summary: this study reports the antigenic characterization of BA.4/5 compared with the other Omicron sub lineages. The authors constructed a panel of pseudotyped lentiviruses (Di Genova et al., 2020) expressing the S gene from the Omicron sub lineages BA.1, BA.1.1, BA.2, BA.3, and BA.4/5 together with the early pandemic Wuhan-related strain, Victoria, used as a control.

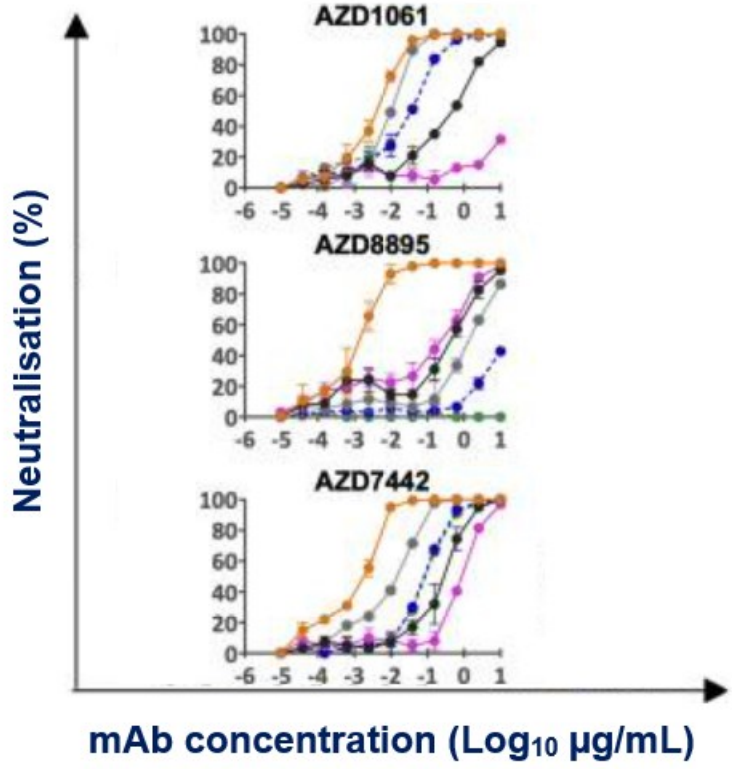
Neutralisation assays were performed using serum obtained 28 days following a third dose of the Oxford-AstraZeneca vaccine AZD1222 (n = 41) (Flaxman et al., 2021)(23) or Pfizer-BioNtech vaccine BNT162b2 (n = 19) (Cele et al., 2022a).(24) Early in the Omicron outbreak when BA.1 predominated, they recruited vaccinated

volunteers who had suffered PCR-confirmed SARS-CoV2 infection—most were sequence-confirmed BA.1 infections or contacts of BA.1 confirmed cases, and all of the infections were mild. Early samples (n = 12, 9F and 3M; median age was 26; and median time since vaccine was 141 days) were taken 17 days from symptom onset (median = 12 days), and later samples (n = 14, 7F and 7M; median age = 23; and median time since vaccine = 111 days) were taken R28 days following symptom onset (median is 45 days). All cases had been vaccinated, all but 2 had received 2 doses, and 3 of the late convalescent cases received a third dose of vaccine following Omicron infection.

Pseudoviral neutralisation assays were performed against the panel of pseudo viruses described above. To confirm that the neutralisation effects observed were directly attributable to alterations in RBD interactions, they also performed binding analyses of selected antibodies to BA.4/5 and BA.2 RBDs by surface plasmon resonance (SPR). The authors tested a panel of antibodies that have been developed for therapeutic / prophylactic use against BA.4/5.

They found that for AZD1061, activity against BA.4/5 was similar to that against BA.2 (<2-fold reduction), while for AZD8895, residual activity against BA.2 was knocked out (the antibodies that combine as Evusheld). Irrespective of this, the activity of the combination of both antibodies for Evusheld continued to show activity against BA.4/5 at ~65 ng/mL, although this was reduced 8.1-fold compared with BA.2 (Figure 6, Table 5).

Figure 6: Pseudoviral neutralisation assays against commercial monoclonal antibodies



Pseudoviral neutralisation assays against commercial monoclonal antibodies, related to Table 5 where IC50 titres are shown

Table 5: IC50 values for Omicron and commercial mAbs

IC50 (µg/mL) Pseudoviruses						
mAbs	**Victoria**	**BA.1**	**BA.1.1**	**BA.2**	**BA.3**	**BA.4/5**
AZD1061	0.002	0.308	10	0.008	0.019	0.015
AZD8895	0.001	0.246	0.1	1.333	10	10
Evusheld	0.001	0.232	0.806	0.008	0.065	0.065

Washington University (22) (previously referenced in initial submission: 77)

Case, J.B., Mackin, S., Errico, J.M., Chong, Z., Madden, E.A., Whitener, B., Guarino, B., Schmid, M.A., Rosenthal, K., Ren, K. and Dang, H.V., 2022. Resilience of S309 and AZD7442 monoclonal antibody treatments against infection by SARS-CoV-2 Omicron lineage strains. Nature communications, 13(1), pp.1-11.

Summary: this pivotal study demonstrates the resilience of Evusheld against emerging SARS-CoV-2 variant strains and provide insight into the relationship between loss of antibody neutralisation potency with ACE2-overexpressing cells and retained protection in vivo. It reports on the protective efficacy against three SARS-CoV-2 Omicron lineage strains (BA.1, BA.1.1, and BA.2) of Evusheld, corresponding to what is used to treat or prevent SARS-CoV-2 infections in humans. Despite losses in neutralisation potency in cell culture, Evusheld treatments reduced BA.1, BA.1.1, and BA.2 lung infection in susceptible mice that express human ACE2 (K18-hACE2) in prophylactic and therapeutic settings.

The authors first analysed the substitutions in the receptor-binding domains (RBDs) of BA.1 (B.1.1.529), BA.1.1 (B.1.1.529 R346K), and BA.2 strains in the context of the structurally defined binding epitopes of tixagevimab and cilgavimab. Across Omicron lineage strains, substitutions at several antibody contact residues have occurred (tixagevimab: K417N, S477N, T478K, E484A, Q493R; cilgavimab: R346K, N440K, E484A, Q493R).

As a result of these sequence changes, the authors assessed the neutralising activity of tixagevimab and cilgavimab, and Evusheld against BA.1, BA.1.1, and BA.2 viruses in Vero-TMPRSS2 cells. For these studies, they used mAbs that correspond to the products in clinical use which have Fc modifications. Compared to the historical WA1/2020 D614G strain (hereafter D614G), antibody incubation with BA.1 was associated with 25-fold (Evusheld), 118-fold (tixagevimab), and 206-fold (cilgavimab) reductions in neutralisation potency, which agree with experiments with authentic or pseudotyped SARS-CoV-2. Some differences were observed with BA.1.1: whereas tixagevimab were only slightly less effective against BA.1.1 compared to BA.1, the neutralising activity of cilgavimab was reduced by almost 1,700-fold.

Despite the decrease in activity of the cilgavimab component, the Evusheld combination still showed inhibitory activity against BA.1.1 with a 176-fold reduction compared to D614G. Small (no change to 5-fold) reductions in neutralisation activity were observed with cilgavimab and Evusheld against BA.2. The authors also observed lower binding affinity of tixagevimab or cilgavimab Fab fragments to Omicron lineage RBDs, with the exception of cilgavimab and BA.2, which is

consistent with neutralisation trends for each mAb. Overall, these data demonstrate that the Evusheld combination shows reduced yet residual activity against strains from all three tested Omicron lineages.

Recognising that Evusheld might act *in-vivo* through a combination of mechanisms that are not fully reflected by in vitro neutralisation potency assays, the authors evaluated the effects of the mutations observed in BA.1, BA.1.1 and BA.2 on efficacy in animals. To assess the efficacy of Evusheld in vivo, they administered a single 200 µg (~10 mg/kg total) dose to K18-hACE2 transgenic mice by intraperitoneal injection one day prior to intranasal inoculation with BA.1, BA.1.1, or BA.2 strains. Although Omicron lineage viruses are less pathogenic in mice, they still replicate to high levels in the lungs of K18-hACE2 mice. Nonetheless, as preliminary studies suggested slightly different kinetics of replication and spread in mice, they harvested samples at 7 dpi for BA.1 and BA.1.1 and 6 dpi for BA.213. Evusheld treatment differentially reduced viral burden in the lungs of mice against D614G (>400,000-fold reduction in viral RNA), BA.1 (92-fold reduction in viral RNA), BA.1.1 (4-fold reduction in viral RNA), and BA.2 (>100,000-fold reduction in viral RNA).

As independent metrics of protection, the authors went on to measure cytokine and chemokine levels in lung homogenates and analysed lung sections for pathology from Evusheld treated animals infected with Omicron variant strains. All infected K18-hACE2 mice receiving isotype control mAbs had increased expression levels of several pro-inflammatory cytokines and chemokines such as G-CSF, GM-CSF, IFN-γ, IL-1β, IL-6, CXCL-10, CCL-2, and CCL-4 when compared to uninfected mice. In contrast, mice treated with Evusheld and infected with BA.1 or BA.2 but not BA.1.1. showed reduced levels of pro-inflammatory cytokines and chemokines, which is consistent with effects on viral burden.

Histopathological analysis of lungs from isotype-treated, but not Evusheld treated, D614G-infected K18-hACE2 mice at 7 dpi showed evidence of pneumonia with immune cell infiltration, alveolar space consolidation, and oedema. Although infection of rodents with BA.1, BA.1.1, or BA.2 strains results in less pathogenesis than D614G strains13–16, focal pneumonia still was observed in isotype control mAb-treated, Omicron strain-infected K18-hACE2 mice. In comparison, Evusheld treatment prevented immune cell infiltration and airspace consolidation.

Overall, these experiments suggest that despite losses in neutralising potency in cell culture, Evusheld treatment can limit inflammation and pathogenesis in the lung caused by Omicron variants.

Francis Crick Institute (17) (new published data)

> *Wu, M.Y., Carr, E.J., Harvey, R., Mears, H.V., Kjaer, S., Townsley, H., Hobbs, A., Ragno, M., Herman, L.S., Adams, L. and Gamblin, S., 2022. WHO's Therapeutics and COVID-19 Living Guideline on mAbs needs to be reassessed. The Lancet.*

Summary: As referred to in Question A6, this study potentially provides an explanation why *in-vivo* effectiveness of protection is observed despite reported losses in viral neutralisation assays with ACE2-overexpressing cells.

In contrast with studies that use viral neutralisation assays with ACE2-overexpressing cells, these authors utilised an assay calibrated with the WHO International Standard for anti-SARS-CoV-2 immunoglobulin and reported neutralisation titres in International Units – an assay useful for standardised comparisons of different monoclonal antibodies against various variants. Using this assay, the authors calculated IC50 values by fitting a four-parameter dose–response curve to 288 independent data points, generated from three independent repeats of 12 independent titrations, each consisting of two technical replicates of a four-point dilution series against live SARS-CoV-2 variants.

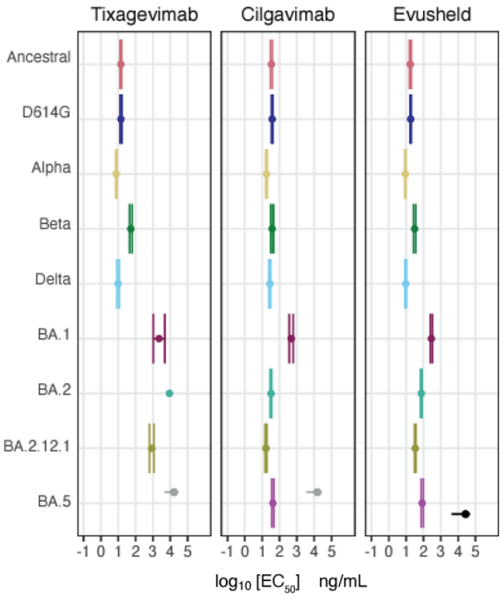
In addition to the more rigorous and internationally recognised methodology utilised, the authors also reported confidence intervals, rather than just point estimates. As referred to in A6, the reporting of confidence intervals is essential to evaluate the significance of any possible changes in neutralisation; particularly when considering IC90 values, which lie close to the plateau of the dose–response curve and are inherently noisy, both in cell-based assays and in fitting of a dose–response curve.

The authors reported strong neutralisation for Evusheld against all omicron variants tested (all dominant VOC circulating in UK), with IC50s reported for BA.1, BA.2, BA.2.12.1, BA4/5 displayed in Table 4. As referred to in A6, the conclusions made by the authors here are also supported by real-world evidence in France, Israel, and the

USA in which Evusheld has been shown to be efficacious; reducing both symptomatic COVID-19, and severe COVID-19 and/or death during variants in which Focosi et al supposedly reports a loss of neutralisation activity.

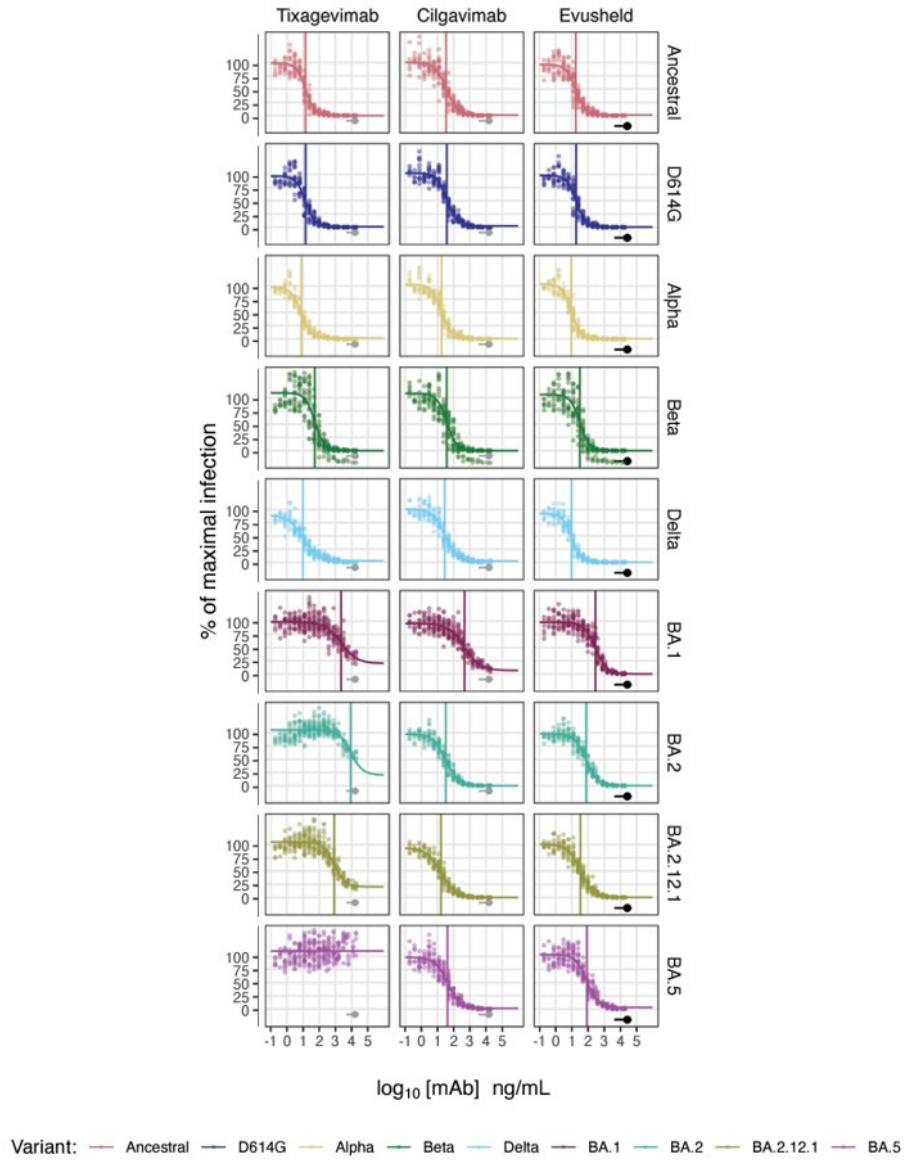
The EC50 value and its 95% confidence interval (error bars) are shown for each combination of monoclonal antibody and SARS-CoV-2 variant as shown in Figure 1. For each mAb, the mean serum concentration at maximum (grey point) and twice its standard deviation (grey error line), and at 28 days post-administration (black points) and twice its standard deviation (black error line) was obtained from its Summary of Product Characteristics (Figure 7).

Figure 7: IC50 values and confidence intervals for neutralisation of SARS-CoV-2 variants by monoclonal antibodies (mAbs)



For each combination of mAb and SARS-CoV-2 variant, 288 independent data points are shown (Figure 8), which were generated from 3 independent repeats of 12 independent titrations, each consisting of 2 technical replicates of a 4-point dilution series against live SARS-CoV-2 virus. EC50 values (solid vertical lines) by were calculated fitting a 4-parameter dose-response curve (solid curves) to this data.

Figure 8: Neutralisation of SARS-CoV-2 variants by monoclonal antibodies (mAbs)



Systematic review methods.

A8. CS Section B2.1.1, B2.1.1.1 and Appendix D1.1. Please confirm if the systematic review was prospectively planned, including targeted updates. Please clarify why the included studies in the systematic review reported in the CS (Section B2.1.1.1) do not directly correspond to the included studies in the systematic review reported in Appendix D, Table 5. In addition, please explain how the non-Evusheld studies in Appendix D, Table 5 meet the intervention inclusion criteria in Table 4 (i.e. LAABs, including Evusheld® (combination of tixagevimab [AZD8895] and cilgavimab [AZD1061])?

Response:

The SLR and its rolling updates were prospectively planned, and the methods were pre-specified in the protocol. The explanation as to why the non-Evusheld studies in Appendix D, Table 5 met the intervention inclusion criteria are as follows:

The SLR included RCTs that evaluated the efficacy of Evusheld, or any of the monoclonal antibodies/oral antiviral treatment listed as the comparator (bamlanivimab, etesevimab, casirivimab, imdevimab, casirivimab + imdevimab, ADG20, and molnupiravir), compared with each other and/or a vaccine booster, standard of care/best practice, or placebo. This is consistent with the research question. Please find below the interventions and comparators listed together.

Table 6: Intervention and comparator eligibility criteria

Criteria	Inclusion	Exclusion
Interventions	• Evusheld® (combination of tixagevimab [AZD8895] and cilgavimab [AZD1061]) • Bamlanivimab (also known as LY-CoV555 and LY3819253) • Etesevimab (also known as LY-CoV016 and LY3832479) • Casirivimab (also known as REGN10933) • Imdevimab (also known as REGN10987) • Casirivimab + imdevimab (the brand name for the combination of both is REGEN-COV®) • ADG20 • Molnupiravir (Lagevrio® [also known as MK-4482 and EIDD-2801])	Any other treatments
Comparators	• Any of the above interventions • Vaccine booster (i.e., third dose of any vaccine) • Standard of care / best practice • Placebo	Any other treatments

The targeted updates to identify RWE were also prospectively planned, refer to Question A5 for further information.

A9. CS Section B2.1.2, p32-33. Please detail the methods on how the targeted updates to the systematic review were conducted (e.g. searches, selection, data extraction, quality assessment, data synthesis). In addition, please explain how the real-world evidence and other observational studies identified by the targeted updates meet the inclusion criteria for the systematic literature review (e.g. Table 4, Appendix D.1.1, p8-11 excludes all non-trial evidence including real-world evidence and observational evidence).

Response:

Two updates to the SLR are being conducted. 1) Rolling updates to the clinical SLR, and 2) systematic reviews to identify the most up to date literature reporting on the

neutralising effect of Evusheld and on clinical effectiveness (as detailed in Question A5).

Rolling updates to clinical SLR

The rolling updates used similar methods to the original SLR. Systematic searches were conducted bi-weekly in the pre-specified databases. Records from the searches were screened against the same PICOS criteria were from the original SLR. Data from included studies were extracted by one reviewer, and each data point was validated by a second, independent reviewer. Any disagreements were discussed with a third, senior reviewer. The quality assessment was exported from COVID-NMA, which uses Cochrane RoB 2 to appraise the risk of bias. Data were summarised in two ways: in detail in the DET, and as top-level information in a slide deck.

Targeted updates to identify e.g., RWE

Refer to Question A5.

A10. CS Section B2.1.2, p32-33 and CS Appendix D1.1, Table 4. Please explain why some types of observational evidence such as comparative (Chen et al. 2022 [preprint at https://www.medrxiv.org/content/10.1101/2022.09.16.22280034v1]) and non-comparative evidence from immunocompromised patients (Nguyen et al., [available at: https://pubmed.ncbi.nlm.nih.gov/35926762/; Ordaya et al [available at: https://pubmed.ncbi.nlm.nih.gov/35859990/; Benotmane et al., [available at: https://pubmed.ncbi.nlm.nih.gov/35713984/) were not identified and or included as supporting evidence in the CS.

Response:

The studies referred to were identified in the regular systematic reviews described in Question A5, however, they were subsequently excluded for inclusion. Please refer to Table 7 for an overview of the reasons for not including them in the submission as supportive evidence.

Table 7: Reason for non-inclusion as supporting evidence

Reference	Eligibility criteria*	Reason for non-inclusion
Chen et al. 2022	III	Study did not use authentic Evusheld
Nguyen et al. 2022	I	Not reporting relevant outcomes**
Ordaya et al. 2022	I	Not reporting relevant outcomes**
Benotmane et al. 2022	I	Not reporting relevant outcomes**

* Refer to question A5 for the regular systematic review eligibility criteria. ** Relevant outcomes: measurement of clinical effectiveness against control arm.

A11. CS Appendix D1.1, Table 4. Please explain why health-related quality of life was not an outcome of interest for the systematic literature review of clinical-effectiveness.

Response:

Health-related quality of life (HRQoL) was addressed by the HRQoL SLR (see CS Appendix H). This SLR summarised the evidence for utility values, utility decrements, utility index, as well as selected quality of life scores (SF-12, SF-36, EQ-5D).

A12. CS Section B2.1.1., and Appendix D.1.4. Please provide further details of all the studies (published and unpublished) that were identified at full text and excluded (with reason) in the systematic review and related update. Please confirm whether any potentially relevant non-English studies were excluded (published and unpublished) from the CS (Appendix D.1. p7)? If so, what impact would these have had on the results, if any?

Response:

Please find below the list of the studies excluded at full text level with the corresponding reasons (Table 8).

The SLR searches were limited to articles published in the English language because most of the evidence relevant to this appraisal was expected to have been published in English. Whilst it is acknowledged that this approach has the potential to introduce a language bias, the risk of excluding high quality RCTs is minimal, and

there is no impact on the final conclusions as shown in recent research on this topic.(25) None of the studies reviewed at full-text stage were excluded from the clinical SLR due to not being published in English.

Table 8: List of excluded studies at full-text level with reasons

Author	Title	Issue	Journal	Pages	Volume	Year	Reason for exclusion
O'Brien, et al	Subcutaneous REGEN-COV Antibody Combination for Covid-19 Prevention	-	MedRxiv : the Preprint Server for Health Sciences	17	17	2021	Duplicate
NR	Study of MK-4482 for Prevention of Coronavirus Disease 2019 (COVID-19) in Adults (MK-4482-013)	-	clinicaltrials.gov	-	-	2021	Publication type or Study design not of interest
Khoo et al	Optimal dose and safety of molnupiravir in patients with early SARS-CoV-2: a Phase I, open-label, dose-escalating, randomised controlled study	-	The Journal of antimicrobial chemotherapy	-	-	2021	Population not of interest
Holman et al	Accelerated first-in-human clinical trial of EIDD-2801/MK-4482 (molnupiravir), a ribonucleoside analog with potent antiviral activity against SARS-CoV-2	1	Trials	561	22	2021	Publication type or Study design not of interest
Copin et al.	The monoclonal antibody combination REGEN-COV protects against SARS-CoV-2 mutational escape in preclinical and human studies	15	Cell	3949-3961.e11	184	2021	Publication type or Study design not of interest

Abbreviations: COVID-19 – Coronavirus disease 2019; NR – Not reported; SARS-CoV-2 – Severe acute respiratory syndrome coronavirus 2

A13. CS Section B2.1.1 and Appendix D1.1. Please confirm if study selection, data extraction and quality assessment was undertaken independently by a minimum of two reviewers for each systematic review (original and updated) in the clinical and cost sections. If not, please justify**.**

Response:

In the clinical efficacy SLR, the study selection during the stages of title and abstract and full text review was conducted by two independent reviewers, with any potential conflicts consulted with/resolved by a third reviewer. Data extraction was conducted by one investigator, and each data point extracted was validated by a second, senior investigator. Any disagreements were resolved through discussion with a third reviewer. The quality appraisal method was pre-specified in the SLR protocol: where available, the risk of bias assessment carried out by COVID-NMA was used. In any instances where this risk of bias assessment was not done by COVID-NMA, the quality assessment was to be conducted by one investigator, and validated by a second, senior investigator. The RCT clinical rolling updates replicated the methods of the original SLR.

A14. CS Section B.2.2.1, and Appendix F. Please confirm whether a systematic review of adverse effects was undertaken for Evusheld (current licensed and higher dose)? If not, please justify and provide details of the validity, robustness and reliability of the review approach taken (e.g. how relevant studies were selected, data extracted [including consistency of definitions], quality assessed and data synthesised). In addition, what was the rationale for only reporting up to 10 adverse events (AEs) from selected categories in Table 4, Appendix D.1.1?

Response:

A systematic review was not undertaken for Evusheld for current licensed and higher doses. The search strategy for the clinical SLR (Table 4 of Appendix D) includes safety outcomes in the eligibility criteria of the SLR, including AEs and SAEs.

Further searches through EMBASE and clinicaltrials.gov were conducted to supplement the clinical SLR. All studies and publications reporting outcomes on Evusheld (for licensed and higher doses and outside the target population) were included in Appendix F.

Given the many emerging treatments for COVID-19, it was expected that studies would report a large volume of AEs, and that many of those would be observed in a very small proportion of individuals. Further, at the time of the original SLR (October 2021), there was not a well-defined consensus on the AEs that were specifically of interest in this population. For these reasons, it was decided to focus on the 10 most common AEs in the studies identified. This ensured a sufficient breadth of information while reducing the burden of less valuable data.

The MedDRA system organ classification is well established and widely used, and this approach allowed to capture the most commonly reported adverse events in a structured manner, i.e., blood/lymphatic system, metabolism/nutrition system, nervous system, gastrointestinal system, skin and subcutaneous, musculoskeletal and connective tissue, general disorders and administration site conditions.

A15. CS Appendix D1.3. The CS Appendix D1.3. suggests that critical appraisal in the systematic review was performed using the Cochrane Risk of Bias 2 tool for RCTs. However, it appears that the RCTs included in the systematic review were assessed using the minimum criteria specified in PMG24. Please clarify if this is correct? If so, please also complete the conflicts of interest domain, undertake additional domain assessments of the bias in selection of the reported results and provide an overall assessment of the quality of trials included in the assessment. In addition, please clarify why the quality assessment results of some studies were directly exported from the COVID-NMA database (CS Appendix D1.3, p17) and which studies this applied to. Was this approach prospectively planned? If so, why and what impact would these different methods have had on the quality assessment results, if any.

Response:

The quality appraisal method was pre-specified in the SLR protocol. We planned to use, where available, the risk of bias assessment carried out by COVID-NMA. In any instances where this was not available, then the quality assessment was to be conducted by one investigator, and validated by a second, senior investigator. Quality appraisal was not conducted if the study was reported only in a conference abstracts, due to the limited information available by default in conference abstracts.

The risk of bias assessment was exported from the COVID-NMA database for the NCT04452318 study (O'Brien, 20215, O'Brien, 20216). This approach had no impact on the quality assessment results, because COVID-NMA used Cochrane's Risk of Bias 2 (RoB 2) tool to appraise quality, which is a method widely accepted by HTA bodies. The quality appraisal methods used by COVID-NMA are described in the COVID-NMA protocol.2

Please find below (Table 9) the detailed quality assessment of RCTs by Cochrane's Risk of Bias 2 (RoB 2).

Table 9: Quality assessment of included RCT studies

	Randomisation	Deviations from intervention	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall Judgement
BLAZE-2(26)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Painter, 2021(27)	Some concerns	Low risk	Low risk	Low risk	Low risk	Some concerns
O'Brien, 2021(28) O'Brien, 2021(29)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
PROVENT(30)	Conference abstract					

The authors of the study publications (26–30) did not declare any conflicts of interest.

A16. CS Appendix D1.3. Please complete the ArRoWS critical appraisal tool for real world evidence (https://pubmed.ncbi.nlm.nih.gov/33011384/) for all relevant sources discussed in the CS.

Response:

Both Young-Xu et al. 2022 and Kertes et al. 2022 performed well in the ArRoWS critical appraisal tool for real world evidence suggesting the studies are high-quality studies. Both publications received 'good' in all questions, apart from the item relating to whether the exposure measures were clearly defined and appropriate, and in the case of Kertes, some weaknesses relating to the fact that no matching occurred. This information was not presented in either publication. For a full-break down of the ArRoWS results, please refer to Table 10.

Table 10: ArRoWS critical appraisal tool for real world evidence

Item	Young-Xu et al. 2022	Kertes et al. 2022
1. Is the research question or objective(s) clear?	Good	Good
2. Is the study sample representative of its target population?	Good	Good
3. Has a sample size, power calculation or measure of uncertainty (e.g., confidence intervals, standard errors) been provided?	Yes	Yes
4. Are the exposure measures clearly defined and appropriate?	Unclear	Unclear
5. Is/are the outcome(s) clearly defined and appropriate?	Good	Good
6. Are confounders clearly defined and appropriate?	Good	Poor
7. Are the statistical analyses clearly defined and appropriate?	Good	Good
8. Are the limitations of the study defined and appropriate?	Good	Good
9. Have the authors drawn appropriate conclusions from their results?	Good	Good
Cohort studies		
A1. Are the methods of follow up defined and appropriate?	N/A	N/A
A2. Is the length of follow up sufficient to ascertain outcomes?	N/A	N/A
A3. If the authors are measuring treatment effects, is the analysis appropriate (e.g. matching, propensity scoring, instrumental variables)?	N/A	N/A
Case-control and comparative effectiveness studies		
A4. Have the authors explained their choice of cases and controls?	Good	Good

A5. If a matched case-control study, have the authors described their matching criteria?	Good	N/A
A6. If a matched case-control study, was matching taken into account in the analysis?	Good	N/A
Electronic database studies		
A7. Have the authors listed/referenced (from previous literature) a code set for relevant tests, procedures, treatments and clinical events (e.g. ICD codes, Read codes)?	Good	Good

Abbreviations: ICD – International classification of diseases; N/A – Not applicable.

A17. CS Section B2.1.1. and Appendix D.1.4. It is usual for company submissions to include a section describing details of all completed and ongoing studies that should provide additional evidence in the next 12 months for the indication being appraised. Please provide this information. In particular we note that there is a randomised, open-label, dose-ranging study in adults and paediatric individuals (≥ 12 years of age) to assess the safety, immunogenicity, pharmacokinetics, and pharmacodynamics of AZD7442, for pre-exposure prophylaxis of COVID-19 (ENDURE) which is not described in the submission [https://clinicaltrials.gov/ct2/show/NCT05375760]. Please describe the dosing regimens being explored in this study and how these relate to the company's proposition within the submission of a 600mg dose repeated at 6 months.

Response:

Details of all completed and ongoing studies in the Evusheld clinical development program that should provide additional evidence in the next 12 months for the indication being appraised are presented in Table 11 below.

Table 11: Study Status of Clinical Studies in Evusheld Drug Development Program Supporting the Prophylaxis Indication

Study D-code	Study name	Current status[a]	Participants randomised	First subject in	Forecasted final CSR
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
D8850C00002	PROVENT	Ongoing	5197	21 November 2020	30 December 2022
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
D8850C00003	STORM CHASER	Ongoing	1121	12 February 2020	30 December 2022
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a]Per AstraZeneca standards a study is considered ongoing until the CSR is final. Abbreviations: CSR – clinical study report; FTIH – first time in human; NA – not applicable; PK – pharmacokinetic; TBC – to be confirmed.

AstraZeneca is conducting Study (ENDURE) D8850C00010 to meet the requirement outlined in the CDER Memorandum. ENDURE is a Phase II randomized, open-label, multicentre, dose-ranging study to assess the safety, immunogenicity, PK, and PD profiles of EVUSHELD repeat dose regimens. The study will enrol adults and paediatric individuals (≥ 12 years of age weighing at least 40 kg) who are moderately to severely immunocompromised due to an underlying disease or who are taking immunosuppressive medications and therefore unable to mount an adequate immune response to COVID-19 vaccine.

Approximately 200 adults and paediatric individuals, who meet the eligibility criteria, will be randomised in a 1:1 ratio to one of 2 EVUSHELD treatment arms:

- Arm A (100 participants): EVUSHELD 600 mg administered IM on Day 1 followed by 300 mg IM Q3M for 12 months (a total of 5 doses)
- Arm B (100 participants): EVUSHELD 1200 mg administered IV on Day 1 followed by 600 mg IM Q6M for 12 months (a total of 3 doses)

An EoT visit will be conducted at 15 months in both arms (3 months after the final dose of EVUSHELD). After the EoT Visit, the participant will enter the follow-up period. Participants will be followed for safety for an additional 9 months after the EoT Visit, ie, through 12 months after the participant's final dose of EVUSHELD.

The study started in May 2022 and is expected to be completed in July 2024. The CSR is expected in

. Specific dates are contingent on recruitment in ENDURE and could change based on the date first subject in is achieved.

[redacted]

In addition, AstraZeneca has comprehensive global real-world evidence programme to assess the effectiveness of EVUSHELD PrEP. The primary objectives of this study are to estimate the effectiveness of AZD7442 for the prevention of symptomatic as well as severe SARS-CoV-2 infection when used in prophylactic setting. One study also aims to evaluate the emergence of viral variants in individuals administered EVUSHELD PrEP.

List of committed studies are below:

- **D8850R00016, EVEREST VALOR C19 DoD;** US Secondary Utilisation/Effectiveness Prophylaxis within the Department of Defense health system. This study is a regulatory commitment to the UK MHRA and US FDA
- **D8850R00023 EVEREST -Emergence of viral variants/ Evusheld utilisation.** This study is a regulatory commitment to MHRA
- **D8850R00017 EVEREST VALOR C19 UPMC;** US Secondary Utilisation/Effectiveness Prophylaxis (UPMC). This study is a company commitment to generate effectiveness evidence in immunocompromised individuals with documented suboptimal response to COVID-19 vaccines
- **D8850R00014 EVEREST VALOR C19 Veterans Affairs (VA);** US Secondary Utilisation/Effectiveness Prophylaxis (VA) in elderly immunocompromised individuals

- **D8850R00002 VALOR C19 Israel- Secondary Utilisation/Effectiveness Prophylaxis**; Utilisation and effectiveness of AZD7442 in vaccinated populations that respond poorly to vaccination.
- **D8850R00018 EVEREST French** Secondary Utilisation/Effectiveness Prophylaxis (SNDS), Secondary EU Utilisation and effectiveness of AZD7442 eligible population, including immunocompromised
- Pre-Exposure Prophylaxis of COVID-19 in Immunocompromised Patients using the Monoclonal Antibody EVUSHELD (AZD7442)

A18. CS Section B2.10.1.2., p88 and B3.1.3 p90 suggest that the incidence of serious adverse events (SAEs) was similar between the Evusheld and placebo groups in the PROVENT and TACKLE trials. However, the SmPC suggests that a higher proportion of individuals who received Evusheld compared to placebo reported myocardial infarction and cardiac failure serious adverse events in the TACKLE and PROVENT trials. Please confirm which statement is correct.

Response:

AstraZeneca consider both statements to be accurate.

It is acknowledged that a slightly higher proportion of individuals receiving Evusheld experienced cardiac SAEs in PROVENT and TACKLE, however detailed analysis concludes the absence of a causal relationship.(31)

In PROVENT, all serious cardiac AEs occurred in people with cardiac risk factors or a history of CVD. Furthermore, numbers of MACE events were low overall (0.69% and 0.58% for Evusheld and placebo respectively) in the context of a high-risk populations in whom MACE event rates in the range 4.5% to 5.4% per year might be expected.(32)

In TACKLE, numbers of cardiac events were lower still (0.4%% and 0.2% for Evusheld and placebo respectively; and one sudden cardiac death reported on Evusheld).

In general, the safety data presented in the CS supports that Evusheld is well tolerated, and that the incidence of SAEs is similar between Evusheld and placebo at both 300mg and 600mg. AstraZeneca has observed no consistent patterns in the occurrence of Cardiac Disorder SAEs across Phase III studies which would suggest an association of Evusheld and Cardiac Disorder events.

Clinical outcomes

A19. CS Table 20. Please clarify why the 20 cases of COVID-19 for the placebo arm in Table 24 do not match the 22 cases in the second row, second column of Table 23? The EAG would expect these to match given that both are based on cases of SARS-CoV-2 RT-PCR-positive symptomatic illness, both are described as not being censored (at time of unblinding and/or COVID-19 vaccination) and both are described as using the primary analysis data cut-off.

Response:

Table 24 – a summary of qualifying symptoms for primary endpoint – has fewer participants because there are two events that occurred in the placebo arm for which no symptom information was available. These two subjects had a severe or critical case of COVID-19 leading to hospitalisation. These events were recorded based on the COVID-19 related Adverse Event leading to hospitalisation rather than the symptom assessment and positive test.

A20. PRIORITY Please provide baseline characteristics and key outcome measures (symptomatic infection, severe or critical illness, emergency department visits, hospitalisations) in the PROVENT subpopulation of immunocompromised (including approaches to handling missing data, if any) who are within the scope of this STA, separated by arm.

Response:

The requested tables are included in the response based on 29 Aug 2021 data cut-off, and are presented in Appendix C. Since the tables are summaries only, no missing data handling methods were applied.

A21. Please clarify if the COVID-19 related hospitalisation outcome from the PROVENT study was a pre-specified outcome defined in the protocol or an outcome specified post-hoc.

Response:

The COVID-19 related hospitalisation outcome was a post hoc analysis of PROVENT. A post hoc analysis of the number of participants hospitalised due to COVID-19, regardless of prior vaccination or unblinding, was performed for the primary and median 6-month follow-up analyses.(33)

A22. PRIORITY In regard to the PROVENT trial and the outcomes in Figure 10 of the CS showing time to first COVID-19 RT-PCR-positive symptomatic illness

a) Please present a plot of the unsmoothed empirical hazard function for both treatment arms

b) Please provide an assessment of the proportional hazards assumption

c) Please comment on the plausibility of the constant hazard ratio used to represent the relative efficacy between Evusheld and placebo

Response:

a) The requested figure is included in the response (Figure 9). Life-table methodology was used with weekly and monthly interval censoring to obtain non-parametric estimates of the hazard function by days since first dose in each arm. Participants are contacted by telephone weekly throughout the study to assess COVID-19 symptoms, therefore a week interval is expected to reflect the appropriate level of left and right censoring in the hazard. The hazards obtained during a monthly interval are also presented to show the broader picture.

Figure 9: Weekly and Monthly Hazards by Study Day (Full Pre-exposure Analysis Set, DCO Date: 05MAY2021)

Hazards derived using lifetable methodology with weekly and monthly (30 day) interval censoring.
Data presented is from the primary analysis which included only efficacy data

b) A log (-log) plot to assess proportionality of hazard is provided in Figure 10.

Figure 10: Log of Negative Log of Survival Functions (Full Pre-exposure Analysis Set, DCO Date: 05MAY2021)

Time presented on log2 scale. If hazards are proportional then lines expected to be parallel.
Data presented is from the primary analysis which included only efficacy data.

c) Visual assessment of the log (-log) plot to assess proportionality of hazard (PH) indicates that the curves remain parallel, which supports the PH assumption, meaning that the HR is representative over the presented time period.

A23. PRIORITY In regard to the PROVENT trial and the outcomes in Figure 2 of the key study publication by Levin et al. (2022) showing time to first SARS-CoV-2 RT-PCR-Positive symptomatic illness:

a) Please describe how Figure 10 in the CS differs from Figure 2 provided in the Levin et al. (2022) paper (and confirm whether this is the same data presented in Figure 1 of the FDA fact sheet referred to in A3).

b) Please present a plot of the unsmoothed empirical hazard function for both treatment arms for the data shown in Figure 2 of Levin et al. (2022)

c) Please provide an assessment of the proportional hazards assumption using data from the longer follow-up for the data shown in Figure 2 of Levin et al. (2022)

Response:

a) Figure 10 in the PROVENT CSR is based on the primary analysis lock (data cut-off 05 May 2021). The figures presented in the Levin paper and FDA EUA Fact Sheet are based on a subsequent database lock (data cut-off 29 Aug 2021).

b) Please see Figure 11 below which illustrates the unsmoothed empirical hazard function for both treatment arms for the data shown in Figure 2 of the Levin et al, (2022) publication.

Figure 11: Weekly and Monthly Hazards by Study Day (Full Pre-exposure Analysis Set, DCO Date: 29AUG2021)

Hazards derived using lifetable methodology with weekly and monthly (30 day) interval censoring.
Data presented is from the five month interim analysis which included safety and efficacy data.

c) A log (-log) plot to assess proportionality of hazard is provided (based on data cut off 29 Aug 2021) is presented in Figure 12 below. Visual assessment of the log (-log) plot to assess proportionality of hazard (PH) indicates that the curves remain parallel, which supports the PH assumption, meaning that the HR is representative over the presented time period.

Figure 12: Log of Negative Log of Survival Functions (Full Pre-exposure Analysis Set, DCO Date: 29AUG2021)

Time presented on log2 scale. If hazards are proportional then lines expected to be parallel.
Data presented is from the five month interim analysis which included safety and efficacy data.

A24. PRIORITY With regards to the real-world evidence study reported by Young-Xu et al. (2022).

a) Please confirm which prognostic factors and treatment-effect modifiers have been included in the propensity score matching reported by Young-Xu et al. (2022) and comment on whether any relevant which prognostic factors or treatment-effect modifiers are missing?

b) Please confirm which process was utilised by Young-Xu et al. (2022) to identify and select the factors included in the propensity score matching?

c) Does the company believe that there may still be residual confounding present in the analysis reported by Young-Xu et al. (2022), despite performing a propensity score matching as well as a difference-in-difference analysis?

d) Please comment on the generalisability of the results published by Young-Xu et al. (2022) to the population of interest in this appraisal.

e) How appropriate does the Company think the hazard ratio (HR) estimates obtained from the propensity scoring analyses are, for example, in regard to the proportional hazards assumption which underpins HR estimates?

f) Please comment on the appropriateness of applying a constant HR (estimated the propensity scoring analysis) in the economic model

Response:

a) A full list of propensity score covariates are listed in Table 12 and Table 13. (4)

Prognostic factors

Included prognostic factors are in line with current knowledge of COVID-19 risk factors. (34) The matching included the following:

- Gender
- Age
- Race/ethnicity
- BMI
- Comorbidities (Table 13)
- Care Assessment Need (CAN) score[1]

Treatment-effect modifiers

- Number of vaccinations

The included prognostic factors and treatment effect modifiers are relevant and capture the key factors expected to influence the risk of severe COVID-19 outcomes, and Evusheld effectiveness. Prior COVID-19 infection was not included and could have potentially been a relevant treatment-effect modifier to explore. However, patients who were diagnosed with COVID-19 via positive RT-PCR test within 3 months of the date (or pseudo-date for controls) of Evusheld administration were excluded from the analysis. (4)

[1] CAN is a statistical model used by Veterans Health (VA) administration to identify high risk patients in terms of probability of hospital admission or death.

Table 12: Patient characteristics before and after propensity score matching, and standardised mean differences(4)

	Before Matching			After Matching		
	Controls (N=251,756)	Cases (N= 1,848)	SMD	Controls (N=6,354)	Cases (N= 1,733)	SMD
Sex						
Female	29,114 (12%)	160 (9%)	-9.7	558 (9%)	154 (9%)	0.4
Male	222,642 (88%)	1,688 (91%)	9.7	5,796 (91%)	1,579 (91%)	-0.4
Age at 31 Dec 2021 Mean St Dev	64.6 (14.7)	67.5 (10.9)	22.6	68.1 (11.5)	67.4 (11.0)	-5.7
Age Category						
18-49	41,873 (17%)	131 (7%)	-29.8	493 (8%)	126 (7%)	-1.9
50-64	63,835 (25%)	448 (24%)	-2.6	1,378 (22%)	420 (24%)	6.1
65-69	31,171 (12%)	291 (16%)	9.7	952 (15%)	268 (15%)	1.3
70-74	52,227 (21%)	531 (29%)	18.6	1,861 (29%)	491 (28%)	-2.1
75-79	34,498 (14%)	300 (16%)	7.1	1,125 (18%)	284 (16%)	-3.5
>79	28,152 (11%)	147 (8%)	-11	545 (9%)	144 (8%)	-1
Race / Ethnicity						
Black: non-Hispanic Black	49,021 (19%)	285 (15%)	-10.7	804 (13%)	277 (16%)	9.5
Hispanic any race	15,899 (6%)	79 (4%)	-9.1	237 (4%)	76 (4%)	3.3
Other	18,802 (7%)	139 (8%)	0.2	452 (7%)	130 (8%)	1.5
White: non-Hispanic White	168,034 (67%)	1,345 (73%)	13.2	4,861 (77%)	1,250 (72%)	-10
Rurality						
Highly rural	3,021 (1%)	18 (1%)	-2.2	69 (1%)	18 (1%)	-0.5
Rural	80,926 (32%)	507 (27%)	-10.3	1,778 (28%)	477 (28%)	-1
Urban	167,809 (67%)	1,323 (72%)	10.7	4,507 (71%)	1,238 (71%)	1.1
Number of vaccinations						

0 dose vaccine	67,753 (27%)	98 (5%)	-61.5	286 (5%)	88 (5%)	2.7
2 dose vaccine (includes 1 dose of Janssen)	184,003 (73%)	1,750 (95%)	61.5	6,068 (95%)	1,645 (95%)	-2.7
3rd dose of vaccine	75,869 (30%)	1,364 (74%)	97.2	4,691 (74%)	1,260 (73%)	-2.5
		Others				
Urinary Tract Infection	10,161 (4%)	112 (6%)	9.3	319 (5%)	106 (6%)	4.8
Nursing Home use	3,113 (1%)	31 (2%)	3.7	99 (2%)	28 (2%)	0.5
BMI Category						
BMI Mean St Dev	32.5 (357.8)	29.3 (11.8)	-1.3	30.4 (36.0)	29.3 (12.1)	-4.1
Missing	11,478 (5%)	55 (3%)	-8.3	239 (4%)	52 (3%)	-4.2
Normal: BMI less than 26	56,600 (22%)	530 (29%)	14.2	1,703 (27%)	493 (28%)	3.7
Overweight / obese: BMI greater than or equal to 26	183,678 (73%)	1,263 (68%)	-10.1	4,412 (69%)	1,188 (69%)	-1.9

Abbreviations: BMI – Body Mass Index; SMD – Standardised mean difference; St Dev – Standard deviation. Source: Young-Xu et al. 2022, Appendix III (4)

Table 13: Covariates in propensity score (4)

	Priority					
Missing	**S (S)**	**S (S)**	**S**	**S (S)**	**S (S)**	**S**
1	50,829 (20%)	393 (21%)	2.7	1,169 (18%)	371 (21%)	7.5
2	19,355 (8%)	130 (7%)	-2.5	434 (7%)	124 (7%)	1.3
3	35,754 (14%)	266 (14%)	0.5	959 (15%)	250 (14%)	-1.9
4	865 (0%)	S (S)	S	20 (0%)	S (S)	S
5	52,304 (21%)	330 (18%)	-7.4	1,170 (18%)	308 (18%)	-1.7
6	24,324 (10%)	205 (11%)	4.7	720 (11%)	185 (11%)	-2.1
7	16,473 (7%)	129 (7%)	1.7	569 (9%)	121 (7%)	-7.3
8	51,805 (21%)	385 (21%)	0.6	1,311 (21%)	364 (21%)	0.9
CHARLSON COMORBIDITY INDEX						

Mean St Dev	1.6 (2.1)	2.7 (2.3)	52.1	2.4 (2.3)	2.6 (2.3)	9.7
0	104,906 (42%)	360 (19%)	-49.6	1,581 (25%)	355 (20%)	-10.5
1	49,818 (20%)	227 (12%)	-20.6	1,044 (16%)	223 (13%)	-10.1
2	38,077 (15%)	422 (23%)	19.8	1,270 (20%)	394 (23%)	6.7
3	21,247 (8%)	260 (14%)	17.9	839 (13%)	245 (14%)	2.7
4	13,497 (5%)	205 (11%)	21	548 (9%)	186 (11%)	7.1
5 to 6	14,699 (6%)	236 (13%)	24	664 (10%)	213 (12%)	5.8
7 to 8	6,769 (3%)	105 (6%)	15	268 (4%)	91 (5%)	4.9
9+	2,743 (1%)	32 (2%)	5.4	140 (2%)	26 (2%)	-5.2
COMORBIDITIES						
Asthma	41,011 (16%)	313 (17%)	1.7	958 (15%)	289 (17%)	4.4
Cancer	30,842 (12%)	670 (36%)	58.3	1,844 (29%)	597 (34%)	11.7
Coronary Artery Disease	35,504 (14%)	312 (17%)	7.7	1,041 (16%)	286 (17%)	0.3
Cancer Metastatic	7,327 (3%)	49 (3%)	-1.6	325 (5%)	49 (3%)	-11.7
Congestive Heart Failure	17,451 (7%)	190 (10%)	12	485 (8%)	173 (10%)	8.3
Chronic Kidney Disease	26,551 (11%)	442 (24%)	36	1,125 (18%)	391 (23%)	12.1
Chronic Obstructive Pulmonary Disease	44,214 (18%)	347 (19%)	3.2	1,056 (17%)	321 (19%)	5
Cardiovascular disease	11,256 (4%)	86 (5%)	0.9	318 (5%)	74 (4%)	-3.5
Dementia	4,057 (2%)	S (S)	S	89 (1%)	S (S)	S
Diabetes Mellitus w/ complications	26,865 (11%)	293 (16%)	15.3	815 (13%)	268 (15%)	7.6
Diabetes Mellitus w/o complications	41,315 (16%)	291 (16%)	-1.8	1,021 (16%)	275 (16%)	-0.5
Dyslipidemia	77,066 (31%)	656 (35%)	10.4	2,186 (34%)	612 (35%)	1.9
HIV	983 (0%)	30 (2%)	12.4	54 (1%)	22 (1%)	4.1

Hypertension	130,311 (52%)	1,111 (60%)	16.9	3,694 (58%)	1,029 (59%)	2.5
Liver disease, mild	12,834 (5%)	167 (9%)	15.4	455 (7%)	160 (9%)	7.6
Liver disease, severe	1,367 (1%)	32 (2%)	11.2	60 (1%)	27 (2%)	5.5
Myocardial infarction (history)	5,516 (2%)	68 (4%)	8.8	161 (3%)	63 (4%)	6.4
Para / hemiplegia	1,475 (1%)	26 (1%)	8.3	34 (1%)	25 (1%)	9.2
Peptic ulcer disease	1,440 (1%)	18 (1%)	4.6	49 (1%)	17 (1%)	2.3
Peripheral vascular disease	15,586 (6%)	148 (8%)	7.1	457 (7%)	140 (8%)	3.3
Rheumatoid arthritis	18,168 (7%)	200 (11%)	12.6	798 (13%)	195 (11%)	-4
Renal disease	28,839 (11%)	488 (26%)	38.9	1,312 (21%)	429 (25%)	9.8
Immunocompromised	81,540 (32%)	1,336 (72%)	87.2	4,225 (66%)	1,226 (71%)	9.2
CARE ASSESSMENT NEEDS SCORE						
CAN Mortality 1 year Mean St Dev	0.06 (0.09)	0.09 (0.11)	34.8	0.07 (0.11)	0.09 (0.10)	13
CAN Mortality 1 year						
CAN 00 to 30	67,134 (27%)	148 (8%)	-50.9	915 (14%)	146 (8%)	-18.9
CAN 31 to 55	55,120 (22%)	262 (14%)	-20.2	1,350 (21%)	248 (14%)	-18.2
CAN 56 to 75	51,362 (20%)	459 (25%)	10.6	1,502 (24%)	439 (25%)	3.9
CAN 76 to 90	51,091 (20%)	608 (33%)	28.8	1,657 (26%)	568 (33%)	14.7
CAN 96 up	22,606 (9%)	304 (16%)	22.6	792 (12%)	269 (16%)	8.8
ENCOUNTERS						
0-9	78,582 (31%)	177 (10%)	-55.7	1,298 (20%)	164 (9%)	-31.1
10-29	109,576 (44%)	676 (37%)	-14.2	2,896 (46%)	634 (37%)	-18.4
30-59	47,472 (19%)	627 (34%)	34.7	1,578 (25%)	597 (34%)	21.2

Abbreviations: CAN – Care assessment need; HIV – Human Immunodeficiency Virus; St Dev – Standard deviation; VA – Veterans Health. Source: Young-Xu et al. 2022, Appendix III (4)

b) Details on the selection and identification of variables are not provided in the publication(4). However, UK clinical experts consulted have validated their appropriateness for use in the propensity score analysis. Furthermore, propensity score models were used to account for observable baseline differences, and extensive consideration was given to testing the robustness of the matching. Refer to Table 12 for standardised mean differences (SMD) between the Evusheld and matched-control groups; a successful match was defined as when at least 90% of the covariates included in the model had an SMD of ≤10.

c) Based on the robustness of the matching in terms of included covariates, alignment with factors impacting clinical practice and robustness testing, we do not have reason to suspect any significant residual confounding that would impact the observed results.

d) The population included in this study aligns well with the population of interest for this appraisal, which was a main reason for including it in our modelled base-case:

    I. 84% and 92% were immunocompromised in the Evusheld and control group, respectively, which is aligned to the target population for Evusheld of people with the highest risk of poor COVID-19 outcomes.

    II. 95% of patients had received COVID-19 vaccination, which is aligned with the proportion expected to be vaccinated in the highest-risk, immunocompromised population; according to the ONS, 88% of people surveyed in the England had at least 3 doses in May 2022 (12).

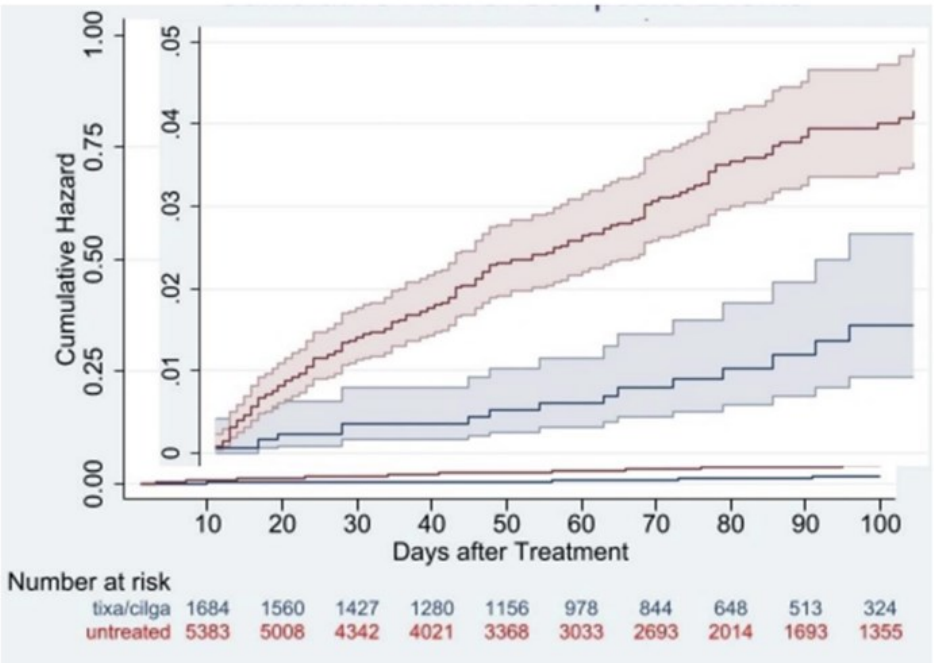
    III. The study population was exposed to Omicron surges (BA.1, BA.2 and BA.2.12.1), which aligns closely with the current predominant circulating variants of concern in the UK (Omicron [B.1.1.529], sub-lineages BA.1, BA.2, BA.4 and BA.5).(35)

    IV. 83% of patients received the 600mg Evusheld dose, which is the dose expected to be given in clinical practice.

Whilst patients were predominately male and older than expected in UK clinical practice, subgroup analyses from PROVENT have shown no significant differences in treatment effect for gender or age.

e) Inferences with regards to the appropriateness of the proportional hazards assumption relating to the hazard ratio from Young-Xu et al. (2022) are difficult to make given that the paper does not provide the data over time for the test-confirmed SARS-CoV-2 infection rates. (4) However, the paper does present the cumulative risk of a composite endpoint over time (see Figure 3 in the paper) – where the composite endpoint is comprised of SARS-CoV-2 infection rates, COVID-19 hospitalisations, or all-cause mortality. The cumulative hazard rates were digitised from this graph and highlight that the curves continue to separate over time. Therefore, based on what is provided in the literature, there is no reason to expect that the assumption of proportional hazards does not hold.

Figure 13: Cumulative risk of composite COVID-19 outcomes for Evusheld recipients compared to untreated controls(4)



Composite COVID-19 outcomes were SARS-CoV-2 infection, COVID-19 hospitalisation, or all-cause mortality.

f) As described in e) based on the available evidence, there is no reason to expect that the proportional hazards assumption does not hold, and therefore is an appropriate assumption for the economic model.

Literature searching

A25. CS, Appendix Tables 2 (p7), 11-15 (p29-31), and 30 (p118). In all the traditional database searches, limited terms for the population COVID-19 were applied, including field-restricted searching to titles only. Please explain the rationale for this search approach and its implications on the sensitivity of the search? The EAG also notes that there is a living COVID search filter by NICE: Levay P, Finnegan A. (2021) The NICE COVID-19 search strategy for Ovid MEDLINE and Embase: developing and maintaining a strategy to support rapid guidelines. https://www.medrxiv.org/content/10.1101/2021.06.11.21258749v1

Response:

The population search terms were limited to titles only in order to balance the sensitivity and precision of the searches. The risk of missing relevant studies was mitigated by using additional efforts such as citation chasing. Please note that the search strategy used the most relevant keywords as recommended by NICE ("COVID-19", SARS-COV-2", "coronavirus").

A26. CS, Appendix D.1.4.(p17) targeted literature searches have been conducted bi-monthly since October 2021. Please explain why the original SLR searches were not updated by the company and replaced by targeted searches and please provide the search terms used in the database searches listed in Table 6 (page 18)?

Response:

The methods used in the clinical rolling updates followed those from the original SLR methods in terms of study selection (two independent reviewers, with any potential conflicts consulted with/resolved by a third reviewer), quality assessment (use, where available, the risk of bias assessment carried out by COVID-NMA; if

unavailable, the quality assessment was to be conducted by one investigator, and validated by a second, senior investigator), and data extraction (extraction conducted by one investigator, and each data point extracted validated by a second, senior investigator; any disagreements resolved through discussion with a third reviewer).

The key difference between the original SLR and the rolling updates was narrowing the data sources to those in Table 14 below, since the L-OVE COVID already includes PubMed and EMBASE in their searches.

Table 14: Targeted updates database searches

Search strategy	Inclusion
L-OVE COVID database	• Cochrane Database of Systematic Reviews • Pubmed • EMBASE • The Cumulative Index to Nursing and Allied Health Literature • PsycINFO • Literatura Latinoamericana y del Caribe en Ciencias de la Salud • Database of Abstracts of Reviews of Effects • The Campbell Collaboration online library • JBI Database of Systematic Reviews and Implementation • EPPI-Centre Evidence Library
Grey literature searches	• ICTRP Search Portal (WHO's clinical trial platform) • ClinicalTrials.gov • EU Clinical Trials Register: Clinical trials for COVID-19 • MedRxiv pre-prints • BioRxiv pre-prints • NICE Rapid Guideline and Summaries on COVID-19 • EMA Coronavirus disease (COVID-19) database • FDA Coronavirus Disease 2019 (COVID-19) database

Abbreviations: CDSR – Cochrane database of systematic reviews; COVID-19 – Coronavirus disease 2019; EMA – European Medicines Agency; FDA – US Food and Drug Administration; ICTPR – International clinical trials registry platform; NICE – National Institute for Health and Care Excellence; SARS-CoV-2 – Severe acute respiratory syndrome coronavirus 2; WHO –World Health Organisation

Table 15 to Table 22 below present the search terms used in the database searches listed in CS Table 6.

Table 15: COVID L-OVE

Search Number	Search Terms
1	long-acting antibodies

2	AZD7442
3	AZD8895
4	AZD1061
5	AZD-7442
6	AZD-8895
7	AZD-1061
8	Tixagevimab
9	Cilgavimab
10	Evusheld
11	monoclonal antibodies
12	Bamlanivimab
13	LY-CoV555
14	LYCoV555
15	LY3819253
16	LY-3819253
17	Etesevimab
18	LY-CoV016
19	LYCoV016
20	LY3832479
21	LY-3832479
22	JS016
23	NP005
24	NP-005
25	Casirivimab
26	REGN10933
27	REGN-10933
28	Imdevimab
29	REGN10987
30	REGN-10987
31	regen-cov
32	regencov
33	Ronapreve
34	adg20
35	adg-20
36	adintrevimab
37	molnupiravir
38	MK-4482

39	MK4482
40	EIDD-2801
41	EIDD2801
42	Lagevrio
43	Nirmatrelvir-ritonavir
44	Ritonavir-nirmatrelvir
45	Paxlovid
46	Remdesivir
47	veklury

Table 16: ICTRP Search Portal

Search Number	Search Terms
1	Prevent* OR prophyla* (title search) AND (long-acting antibodies OR AZD7442 OR AZD8895 OR AZD1061 OR AZD-7442 OR AZD-8895 OR AZD-1061 OR Tixagevimab OR Cilgavimab OR Evusheld OR monoclonal antibodies OR Bamlanivimab OR LY-CoV555 OR LYCoV555 OR LY3819253 OR LY-3819253 OR Etesevimab OR LY-CoV016 OR LYCoV016 OR LY3832479 OR LY-3832479 OR JS016 OR NP005 OR NP-005 OR Casirivimab OR REGN10933 OR REGN-10933 OR Imdevimab OR REGN10987 OR REGN-10987 OR regen-cov OR regencov OR Ronapreve OR adg20 OR adg-20 OR adintrevimab OR molnupiravir OR MK-4482 OR MK4482 OR EIDD-2801 OR EIDD2801 OR lagevrio OR Nirmatrelvir-ritonavir OR Ritonavir-nirmatrelvir OR Paxlovid OR Remdesivir OR veklury)

Table 17: ClinicalTrials.gov

Search Number	Search Terms
1	prevent* or prophylaxis | Completed Studies | Studies With Results | COVID-19 | long-acting antibodies OR AZD7442 OR AZD8895 OR AZD1061 OR AZD-7442 OR AZD-8895 OR AZD-1061 OR Tixagevimab OR Cilgavimab OR Evusheld
2	prevent* or prophylaxis | Completed Studies | Studies With Results | COVID-19 | monoclonal antibodies OR Bamlanivimab OR LY-CoV555 OR LYCoV555 OR LY3819253 OR LY-3819253 OR Etesevimab OR LY-CoV016 OR LYCoV016 OR LY3832479 OR LY-3832479 OR JS016 OR NP005 OR NP-005
3	prevent* or prophylaxis | Completed Studies | Studies With Results | COVID-19 | Etesevimab OR LY-CoV016 OR LYCoV016 OR LY3832479 OR LY-3832479 OR JS016 OR NP005 OR NP-005 OR Casirivimab OR REGN10933 OR REGN-10933 OR Imdevimab OR REGN10987 OR REGN-10987 OR regen-cov OR regencov OR Ronapreve
4	prevent* or prophylaxis | Completed Studies | Studies With Results | COVID-19 | adg20 OR adg-20 OR adintrevimab OR molnupiravir OR MK-4482 OR MK4482 OR EIDD-2801 OR EIDD2801 OR lagevrio OR Nirmatrelvir-ritonavir OR Ritonavir-nirmatrelvir OR Paxlovid OR Remdesivir OR veklury

Table 18: EUCTR

Search Number	Search Terms
1	COVID-19 AND (prevent* OR prophylaxis*); with results

Table 19: MedRxiv/BioRxiv – combined search

Search Number	Search Terms
1	"COVID-19 AND (prevent* OR prophylaxis*) AND ("long-acting antibodies" OR AZD7442 OR AZD8895 OR AZD1061 OR AZD-7442 OR AZD-8895)"
2	""COVID-19 AND (prevent* OR prophylaxis*) AND (AZD-1061 OR tixagevimab OR cilgavimab OR Evusheld)"
3	""COVID-19 AND (prevent* OR prophylaxis*) AND (Bamlanivimab OR LY-CoV555 OR LYCoV555 OR LY3819253 OR LY-3819253 OR Etesevimab)" "
4	"""COVID-19 AND (prevent* OR prophylaxis*) AND (LY-CoV016 OR LYCoV016 OR LY3832479 OR LY-3832479 OR JS016 OR NP005 OR NP-005)" "
5	"""COVID-19 AND (prevent* OR prophylaxis*) AND (Casirivimab OR REGN10933 OR REGN-10933)" "
6	"""COVID-19 AND (prevent* OR prophylaxis*) AND (Imdevimab OR REGN10987 OR REGN-10987 OR regen-cov OR regencov OR Ronapreve)"
7	"""COVID-19 AND (prevent* OR prophylaxis*) AND (adg20 OR adg-20 OR adintrevimab)" "
8	"""COVID-19 AND (prevent* OR prophylaxis*) AND (molnupiravir OR MK-4482 OR MK4482 OR EIDD-2801 OR EIDD2801 OR lagevrio)" "
9	""COVID-19 AND (prevent* OR prophylaxis*) AND (Nirmatrelvir OR ritonavir OR Paxlovid OR Remdesivir OR veklury)""

Table 20: NICE Rapid Guideline and Summaries on COVID-19

Search Number	Search Terms
1	NICE Rapid Guidelines
2	NICE Evidence summaries on COVID-19

Table 21: EMA COVID-19 Database

Search Number	Search Terms
1	Screened for (prevent* or prophylaxis) AND (long-acting antibodies OR AZD7442 OR AZD8895 OR AZD1061 OR AZD-7442 OR AZD-8895 OR AZD-1061 OR Tixagevimab OR Cilgavimab OR Evusheld OR monoclonal antibodies OR Bamlanivimab OR LY-CoV555 OR LYCoV555 OR LY3819253 OR LY-3819253 OR Etesevimab OR LY-CoV016 OR LYCoV016 OR LY3832479 OR LY-3832479 OR JS016 OR NP005 OR NP-005 OR Casirivimab OR REGN10933 OR REGN-10933 OR Imdevimab OR REGN10987 OR REGN-10987 OR regen-cov OR regencov OR Ronapreve OR adg20 OR adg-20 OR adintrevimab OR molnupiravir OR MK-4482 OR MK4482 OR EIDD-2801 OR EIDD2801 OR lagevrio OR Nirmatrelvir-ritonavir OR Ritonavir-nirmatrelvir OR Paxlovid OR Remdesivir OR veklury)

Table 22: FDA COVID-19 Database

Search Number	Search Terms
1	Screened for (prevent* or prophylaxis) AND (long-acting antibodies OR AZD7442 OR AZD8895 OR AZD1061 OR AZD-7442 OR AZD-8895 OR AZD-1061 OR Tixagevimab OR Cilgavimab OR Evusheld OR monoclonal antibodies OR Bamlanivimab OR LY-CoV555 OR LYCoV555 OR LY3819253 OR LY-3819253 OR Etesevimab OR LY-CoV016 OR LYCoV016 OR LY3832479 OR LY-3832479 OR JS016 OR NP005 OR NP-005 OR Casirivimab OR REGN10933 OR REGN-10933 OR Imdevimab OR REGN10987 OR REGN-10987 OR regen-cov OR regencov OR Ronapreve OR adg20 OR adg-20 OR adintrevimab OR molnupiravir OR MK-4482 OR MK4482 OR EIDD-2801 OR EIDD2801 OR lagevrio OR Nirmatrelvir-ritonavir OR Ritonavir-nirmatrelvir OR Paxlovid OR Remdesivir OR veklury)

A27. CS, Appendix D.1.4. (p18) As of May 2022, seven new publications have been identified and listed in Table 7 Rolling update results (p19) since October 2021 searches. Can you please confirm whether new studies have been identified since May 2022, given the high publication output rates in this field and emerging evidence in the other Omicron variants?

Response:

The RCT rolling updates identified one new publication (on post-exposure prophylaxis) between May 2022 and end of July 2022:

> *Herman, G.A., O'Brien, M.P., Forleo-Neto, E., Sarkar, N., Isa, F., Hou, P., Chan, K.C., Bar, K.J., Barnabas, R.V., Barouch, D.H. and Cohen, M.S., 2022. Efficacy and safety of a single dose of casirivimab and imdevimab for the prevention of COVID-19 over an 8-month period: a randomised, double-blind, placebo-controlled trial. The Lancet Infectious Diseases.*

This was a secondary publication to the already identified study NCT04452318 (O'Brien, 2021(28) O'Brien, 2021(29)).

A28. CS Appendix D.1 Table 1 (p5), please explain why clinical trial registries such as WHO International Clinical Trials Registry Platform (ICTRP) and ClinicalTrials.gov were not included and searched in the original SLR, only in the targeted update database searches (Table 6, p18)?

Response:

WHO's ICTRP and ClinicalTrials.gov were included in the original SLR, via the COVID-NMA website. The original SLR searched COVID-NMA, among other living databases. The COVID-NMA living database includes regular searches on WHO ICTRP and ClinicalTrials.gov. The methods are detailed in the COVID-NMA protocol (see Appendix 3 in the COVID-NMA protocol for the list of electronic databases used by COVID-NMA).(36)

A29. CS Appendix D.1 Table 2 (p7), please explain how non-RCT and observational evidence (prophylactic) were retrieved and identified, given that the searches in Table 2 (p6) were restricted by applying an RCT filter (statements 18-19) to find RCT evidence only?

Response:

Non-RCT and observational evidence are continuously identified in the regular systematic reviews conducted by AstraZeneca to identify up to date literature on the neutralising effect of Evusheld and clinical effectiveness, as detailed in Question A5.

A30. CS Appendix D.1. Table 3 (p8), please explain why keywords for the intervention (Evusheld, tixagevimab or cilgavimab) were not searched or selected from the drop-down list of interventions in the COVID L-OVE database?

Response:

The brand name and substance name-specific keywords were not available in the COVID L-OVE database search engine at the date of the searches in October 2021.

Evusheld was covered by searching the keywords “AZD7442” and “long-acting antibody”.

A31. CS Section B2.10 and Appendix F. Please clarify if other sources of evidence were searched for adverse events (AEs) e.g. the MHRA Yellow Card Scheme, EduraVigilance database?

Response:

Other sources of evidence were not searched for adverse events related to Evusheld. AstraZeneca does not have additional access to the MHRA Yellow Card Scheme or EduraVigilance database beyond that of a standard member of the public. Both sources have since been searched, however, and no additional data on adverse events were available.

Section B: Clarification on cost-effectiveness data

For any scenarios requested in Section B, please ensure these are implemented as user-selectable options in the economic model so that these can be combined.

Furthermore, if the company chooses to update its base case results, please ensure that cost-effectiveness results, sensitivity and scenario analyses incorporating the revised base case assumptions are provided with the response along with a log of changes made to the company base case.

Response:

Following clarification questions from the EAG, we have revised the base case as follows:

1. GP nurse time has been reduced from 1.5 hours to 0.5 hours (see B2)
2. Adverse event rates for Evusheld and standard of care are based on the TACKLE study (see B4)
3. Hospitalisation risk for standard of care has been updated to 18.02% based on the peer reviewed publication, now available following initial submission (see B7)
4. A minor typographical error has been identified, whereby the proportion of patients not hospitalised with long COVID-19 has been updated from 34.5% to 34.8% (see B14)
5. Long COVID-19 cost has been updated to £2,500 to account for organ damage and additional consequences not associated with chronic fatigue – aligned with the ongoing NICE MTA of therapeutics for people with COVID-19 [TA10936]

The revised base case results, sensitivity and scenario analyses are presented in Appendix B. Please note that ICERs presented are based on the PAS discount for the price of Evusheld. Additional analyses using the list price were requested by

NICE on the 14th November and are included in an addendum titled “Additional CE and BI analyses using the list price of Evusheld”.

The revised base case has reduced from the originally submitted base case of £12,290 per quality adjusted life year (QALY) to £8,111 per QALY. Incremental cost-effectiveness ratios (ICERs) for all sensitivity analyses and scenarios provided in Appendix B, and as part of this response, are below £20,000 per QALY. As such, Evusheld remains a cost-effective use of NHS resources.

Table 23: Step change from original base-case to revised base-case

		Total costs	QALYs	Incremental Results: Evusheld vs Comparator			
				Costs	QALYs	ICER	INMB (£30,000 per QALYs)
Original base case	**No prophylaxis**	[redacted]	[redacted]	[redacted]	[redacted]	£ 12,290	[redacted]
	Evusheld	[redacted]	[redacted]				
Base case with 38.48% updated	**No prophylaxis**	[redacted]	[redacted]	[redacted]	[redacted]	£ 12,247	[redacted]
	Evusheld	[redacted]	[redacted]				
Addressed 0.5 hours of nurse admin (B2)	**No prophylaxis**	[redacted]	[redacted]	[redacted]	[redacted]	£ 11,791	[redacted]
	Evusheld	[redacted]	[redacted]				
TACKLE adverse events (B4)	**No prophylaxis**	[redacted]	[redacted]	[redacted]	[redacted]	£ 11,400	[redacted]
	Evusheld	[redacted]	[redacted]				
Updated Shields et al. (2022) (B7)	**No prophylaxis**	[redacted]	[redacted]	[redacted]	[redacted]	£ 11,084	[redacted]
	Evusheld	[redacted]	[redacted]				
Long COVID-19 cost updated	**No prophylaxis**	[redacted]	[redacted]	[redacted]	[redacted]	£ 8,111	[redacted]
	Evusheld	[redacted]	[redacted]				

Abbreviations: ICER – incremental cost-effectiveness ratio; INMB – incremental net monetary benefit; QALY –quality adjusted life year

Target population and prioritisation

B1. PRIORITY The study by Bertrand et al. (2022) compared COVID-19 infection rates between kidney transplant patients who were classified as “protected” based on their response to previous COVID-19 vaccination and patients who were considered “unprotected” based on their response to previous vaccination (who then either received or did not receive Evusheld). Unprotected patients were defined as those with a complete vaccine scheme and no or weak humoral response (<264 binding antibody units [BAU]/ml) 1 month after the last vaccination injection. Please explain whether a similar definition could be applied in the target population for Evusheld to prioritise patients for Evusheld. Please comment specifically on whether the required tests would be available within the NHS and whether there is any evidence on the effectiveness of Evusheld within a subgroup of the target population defined in this manner.

Response:

The target population for this submission is aligned to those who are deemed to be at the greatest risk of COVID-19 outcomes, as identified in the independent advisory report commissioned by the Department for Health and Social Care, and which has subsequently been used as the basis of the emergency commissioning and deployment of COVID-19 therapeutics(37).

This population is – overall – at a significantly increased risk of adverse COVID-19 outcomes despite the availability of COVID-19 vaccines and the high degree of vaccine uptake in this population. Specifically, in relation to serology testing, the report states, “no given threshold of antibody levels could correlate sufficiently with levels of protection for general clinical use. Given that the recommendations concerned those in the community in whom ready access to anti-SARS-CoV-2 serology was not available, the group elected to defer further consideration of the matter until more data was available and potentially clinical capacity to offer community serology monitoring”(37).

Given the lack of consensus, no diagnostic test should be required as Evusheld is expected to offer significant clinical benefit to the entire target population. This position is supported by a number of RWE studies, such as those from the US,

France, and Israel, in whom patients were predominantly immunocompromised and well vaccinated, yet Evusheld still conferred a statistically significant, clinically meaningful, and durable protection against symptomatic COVID-19, and hospitalisation and/or death.(4,5,19,38)

Bertrand is the only source of evidence that confirms effectiveness of Evusheld in "unprotected" patients as defined by weak humoral response. The threshold they utilised is somewhat arbitrary. Bertrand was conducted during a period when the French authorities recommended serology testing as a screening tool, with an antibody level <264 BAU/ml as the defined threshold for eligibility. However, in March 2022 the authorities removed this requirement in light of the lack of a global consensus.(39)

Administration and dosing schedule

B2. PRIORITY Please explain the rationale for assuming that the costs of administration would be equivalent to 1.5 hours of GP nurse time. This implies that a primary care nurse will spend all of their time during this period administering the drug to and monitoring a single patient and assumes that the space required to monitor the patient is available within the GP practice for this duration. These assumptions do not allow for any efficiencies to be gained from multiple patients being monitored simultaneously. The SmPC also states that "administration should be under conditions where management of severe hypersensitivity reactions, such as anaphylaxis, is possible". This implies the availability of other members of the GP team to deal with the immediate management and transfer to secondary care of any patient experiencing anaphylaxis. Given that the period of monitoring required is significantly greater than that required for other routine vaccinations given in primary care, please provide alternative costings for outpatient administration.

Response:

The SmPC for Evusheld details that the length of observation following injection administration is at least 1 hour.(40) Given this, the model assumes Evusheld will require 1.5 hours of nurse time, assuming 0.5 hours required for administration, and 1 hour of subsequent monitoring.

AstraZeneca acknowledge that this does not allow for any efficiencies to be gained from multiple patients being monitored simultaneously and is likely an over-estimate of the administration cost in clinical practice.

In response to the EAG's question, the base case has been revised assuming 0.5 hours of nurse time, encompassing the administration element but removing the monitoring time thereafter.

This assumes monitoring can be conducted whilst nurses tend to other duties, therefore not incurring additional costs. This more closely matches practices in vaccination centres, where many individuals are treated and monitored at the same time.

The removal of 1 hour of monitoring post receiving treatment, reduced the original base case ICER from £12,290) to £11,833 (Table 25).

Table 24: Original base-case results

Technologies	Total costs	QALYs	Costs	QALYs	ICER	INMB (£30,000 per QALYs)
No prophylaxis	[redacted]	[redacted]	[redacted]	[redacted]	£ 12,290	[redacted]
Evusheld	[redacted]	[redacted]				

Abbreviations: ICER – incremental cost-effectiveness ratio; INMB – incremental net monetary benefit; QALY – quality adjusted life year

Table 25: Scenario with reduced nurse time

Technologies	Total costs	QALYs	Costs	QALYs	ICER	INMB (£30,000 per QALYs)
No prophylaxis	[redacted]	[redacted]	[redacted]	[redacted]	£ 11,833	[redacted]
Evusheld	[redacted]	[redacted]				

Abbreviations: ICER – incremental cost-effectiveness ratio; INMB – incremental net monetary benefit; QALY – quality adjusted life year

B3. PRIORITY- CS, p108 provides the rationale for modelling a second dose of Evusheld given at 6 months saying, “Redosing was chosen at 6-months to align with the medial follow-up duration from the PROVENT study, where clinical efficacy and safety has been demonstrated”. Given that no evidence is provided in the submission on the effectiveness of the second dose, the EAG believes that it would be helpful for the committee to see a scenario analysis in which Evusheld is given once only and the outcomes in the acute phase are based on a 6-month time-frame. Please provide this scenario analysis.

Response:

In the base case, a re-dosing at 6 months was conservatively assumed as clinical experts estimated a treatment effect of 6 to 12 months based on only one dose at 6-months, when considering the clinical evidence package for Evusheld.

In particular, results from the PROVENT sub-study shows comparable serum concentrations at Day 29 between patients receiving their first 6-monthly dose and patients receiving their second 6-monthyl dose of Evusheld (see Response to A1). Furthermore, modelled PK data shows that 6-monthly dosing using the 600mg dose maintains the minimum protective concentration against tested VoCs (see Response to A2).(2)

However, in response to the EAG’s question, a scenario with one Evusheld treatment over a 6-month infection period was modelled by:

- Reducing the SoC infection rate from a 12 month to 6-month rate (22.58% to 11.29%).
- Treatment-related adverse events were halved to account for only one dose being given.
- All three efficacy sources used in the model are based on one dose with a median follow up less than or equal to 6 months and therefore efficacy data were not adjusted when considering a 6-month infection rate.
- Utility gain associated with Evusheld was halved to account for only 6-months of protection being provided.

- Administration and treatment costs associated with Evusheld re-treatment at 6-months were removed.

Results assuming one dose of Evusheld over a 6-month infection period show that the revised ICER decreases to £8,071, £10,479 and £5,932 using Young-Xu et al. 2022 (Table 27) (4), Kertes et al. 2022 (Table 28)(19), and PROVENT (Table 29)(33), respectively. These results are also likely conservative as Evusheld utility gains are assumed to be 0 after 6 months, although protection will likely last longer than 6 months.

Table 26: Revised base-case results

Technologies	Total costs	QALYs	Costs	QALYs	ICER	INMB (£30,000 per QALYs)
No prophylaxis	[redacted]	[redacted]	[redacted]	[redacted]	£ 8,111	[redacted]
Evusheld	[redacted]	[redacted]				

Abbreviations: ICER – incremental cost-effectiveness ratio; INMB – incremental net monetary benefit; QALY – quality adjusted life year

Table 27: No retreatment at 6 months scenario results – Young Xu 2022 (4)

Technologies	Total costs	QALYs	Costs	QALYs	ICER	INMB (£30,000 per QALYs)
No prophylaxis	[redacted]	[redacted]	[redacted]	[redacted]	£ 8,071	[redacted]
Evusheld	[redacted]	[redacted]				

Abbreviations: ICER – incremental cost-effectiveness ratio; INMB – incremental net monetary benefit; QALY – quality adjusted life year

Table 28: No retreatment at 6 months scenario results – Kertes et al. 2022 (33)

Technologies	Total costs	QALYs	Costs	QALYs	ICER	INMB (£30,000 per QALYs)
No prophylaxis	[redacted]	[redacted]	[redacted]	[redacted]	£ 10,479	[redacted]
Evusheld	[redacted]	[redacted]				

Abbreviations: ICER – incremental cost-effectiveness ratio; INMB – incremental net monetary benefit; QALY – quality adjusted life year

Table 29: No retreatment at 6 months scenario results – PROVENT 2022 (33)

Technologies	Total costs	QALYs	Costs	QALYs	ICER	INMB (£30,000 per QALYs)
No prophylaxis	[redacted]	[redacted]	[redacted]	[redacted]	£ 5,932	[redacted]
Evusheld	[redacted]	[redacted]				

Abbreviations: ICER – incremental cost-effectiveness ratio; INMB – incremental net monetary benefit; QALY – quality adjusted life year

B4. Please clarify why adverse events in the model have been based on the PROVENT study in which a 300mg dose was used instead of the TACKLE study in which the 600mg dose was used, given that the company anticipates usage at a 600mg dose in clinical practice. Please provide a scenario analysis incorporating the incidence of serious adverse events from the TACKLE study.

Response:

Adverse events in the model were based on the PROVENT study, since this considered randomised controlled evidence in a pre-exposure prophylaxis population, and as such may be considered a more generalisable population to the decision problem than the TACKLE study, which considers treatment in out-patients who have tested positive with COVID-19.(7,33)

AstraZeneca acknowledge that the TACKLE study may provide a more robust estimation of the safety profile for the 600mg dose, which is the anticipated dose to be used in clinical practice and which was presented in the original submission for the purpose of demonstrating the safety profile of the 600mg dose.

In response to the EAG's question the base case has been revised, incorporating the incidence of serious adverse events from the TACKLE study (Table 30).(7)

Table 30: Prophylaxis related AE Incidence (Over 12 months)

	PROVENT (Levin et al. 2022)(33)		TACKLE (7)	
Adverse event	**No prophylaxis**	**Evusheld**	**No prophylaxis**	**Evusheld**
Infections and Infestations	0.58%	0.46%	8.20%	5.53%
Injury, Poisoning or Procedural Complications	0.92%	0.23%	0.44%	0.00%
Nervous System Disorders	0.00%	0.52%	0.67%	0.22%
Cardiac Disorders	0.12%	0.35%	0.22%	0.44%
Gastrointestinal Disorders	0.12%	0.35%	0.44%	0.00%
Renal and Urinary Disorders	0.12%	0.35%	0.22%	0.44%

Abbreviations: AE – Adverse event

The incorporation of serious adverse events from the TACKLE study (7), reduced the original base case ICER from £12,290 (Table 31) to £11,899 (Table 32).

Table 31: Original base-case results

Prophylaxis	Total costs	QALYs	Costs	QALYs	ICER	INMB (£30,000 per QALYs)
No prophylaxis	[redacted]	[redacted]	[redacted]	[redacted]	£ 12,290	[redacted]
Evusheld	[redacted]	[redacted]				

Abbreviations: ICER – incremental cost-effectiveness ratio; INMB – incremental net monetary benefit; QALY – quality adjusted life year

Table 32: Adverse event source (TACKLE) scenario results (7)

Prophylaxis	Total costs	QALYs	Costs	QALYs	ICER	INMB (£30,000 per QALYs)
No prophylaxis	[redacted]	[redacted]	[redacted]	[redacted]	£ 11,899	[redacted]
Evusheld	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

Abbreviations: ICER – incremental cost-effectiveness ratio; INMB – incremental net monetary benefit; QALY – quality adjusted life year

Risk of infection, hospitalisation, and ICU admission

B5. PRIORITY- The infection risk assumed in the model is based on historical data for the infection rate in the general population and is not specific to the target population for Evusheld. Whilst we acknowledge that predicting future infection risks is difficult, we believe it would be helpful for the committee to be able to consider a range of scenarios given the uncertainty associated with estimating future infection risks. Please provide a range of scenarios exploring plausible alternative infection risks in the target population for the 12-month period that follows the anticipated date of implementation for NICE's guidance on this technology.

Response:

The submitted cost-effectiveness model used the most relevant, up to date data from the gov.uk website to inform the baseline infection risk (22.58% at 12-months) and post 12-months infection risk (12.01% every 6-months).

These data are based on general population statistics and are therefore considered conservative estimates for people at the highest-risk of poor COVID-19 outcomes or unsuitable to vaccination, who based on expert clinical feedback, are at a higher risk of infection and severe outcomes compared to the general population.

AZ acknowledge there is uncertainty in future infection rates. However, the target population is classified as high-risk and will likely remain susceptible to serious infection despite increasing vaccination rates. Therefore, any future changes in the general population rates are unlikely to be fully reflected in the high-risk subgroup.

Nevertheless, to assist NICE in assessing the robustness of the cost effectiveness results, four scenarios have been conducted:

- Scenario 1: -20% for the baseline infection risk (18.07%) and post 12-months infection risk (12.01%) - Table 34
- Scenario 2: +20% for the baseline infection risk (27.10%) and post 12-months infection risk (12.01%) - Table 35

- Scenario 3: Baseline infection risk (22.58%) and -20% and post 12-months infection risk (8.72%) - Table 36
- Scenario 4: Baseline infection risk (22.58%) and +20% and post 12-months infection risk (13.07%) - Table 37

Table 34 to Table 37 show the results of the scenario analyses. A 20% reduction in the baseline infection risk (Scenario 1) increases the revised ICER from £8,111 to £10,955. A 20% increase in the baseline infection risk (Scenario 2) decreases the revised ICER from £8,111 to £5,924. A 20% reduction in the future infection risks (Scenario 3) reduces the revised ICER from £8,111 to £8,100. A 20% increase in the baseline infection risk (Scenario 4) increases the revised ICER from £8,111 to £8,122.

Whilst there are minor differences in the ICER when considering alternative baseline infection risks (Scenarios 1 and 2), it should be noted that this parameter value used the most up to date data upon submission and can be considered generalisable to infection risks in the near future.

AstraZeneca acknowledge that there is uncertainty relating to the future infection risks post 12-months. However, Scenarios 3 and 4 demonstrate that exploring this uncertainty has a negligible impact on the cost-effectiveness results.

Table 33: Revised base-case results

Technologies	Total costs	QALYs	Costs	QALYs	ICER	INMB (£30,000 per QALYs)
No prophylaxis	[redacted]	[redacted]	[redacted]	[redacted]	£ 8,111	[redacted]
Evusheld	[redacted]	[redacted]				

Abbreviations: ICER – incremental cost-effectiveness ratio; INMB – incremental net monetary benefit; QALY – quality adjusted life year

Table 34: Annual infection risk scenario results - -20% baseline infection risk

Technologies	Total costs	QALYs	Costs	QALYs	ICER	INMB (£30,000 per QALYs)
No prophylaxis	[redacted]	[redacted]	[redacted]	[redacted]	£ 10,955	[redacted]
Evusheld	[redacted]	[redacted]				

Abbreviations: ICER – incremental cost-effectiveness ratio; INMB – incremental net monetary benefit; QALY – quality adjusted life year

Table 35: Annual infection risk scenario results - +20% baseline infection risk

Technologies	Total costs	QALYs	Costs	QALYs	ICER	INMB (£30,000 per QALYs)
No prophylaxis	[redacted]	[redacted]	[redacted]	[redacted]	£ 5,924	[redacted]
Evusheld	[redacted]	[redacted]				

Abbreviations: ICER – incremental cost-effectiveness ratio; INMB – incremental net monetary benefit; QALY – quality adjusted life year

Table 36: Annual infection risk scenario results - -20% future infection risks

Technologies	Total costs	QALYs	Costs	QALYs	ICER	INMB (£30,000 per QALYs)
No prophylaxis	[redacted]	[redacted]	[redacted]	[redacted]	£ 8,100	[redacted]
Evusheld	[redacted]	[redacted]				

Abbreviations: ICER – incremental cost-effectiveness ratio; INMB – incremental net monetary benefit; QALY – quality adjusted life year

Table 37: Annual infection risk scenario results - +20% future infection risks

Technologies	Total costs	QALYs	Costs	QALYs	ICER	INMB (£30,000 per QALYs)
No prophylaxis	[redacted]	[redacted]	[redacted]	[redacted]	£ 8,122	[redacted]
Evusheld	[redacted]	[redacted]				

Abbreviations: ICER – incremental cost-effectiveness ratio; INMB – incremental net monetary benefit; QALY – quality adjusted life year

B6. The uncertainty around the risk of infection incorporated within the probabilistic sensitivity analysis (PSA) appears to be very narrow (22.58%, 95% CI 22.57% to 22.59%). Please clarify how this confidence interval has been calculated and whether this accurately captures the uncertainty around the future risk of COVID-19 within a 12-month period, rather than the uncertainty in the historical estimate of infection risk. Please update the model to incorporate a confidence interval within the PSA which reflects the true uncertainty around this parameter. We acknowledge that such an estimate may need to be based on expert elicitation. If this approach is taken, please document the methods of the elicitation exercise.

Response:

The confidence interval was calculated using a national dataset comprising the entire UK population, which explains why the interval is very narrow. We consider that this is reflective of the uncertainty surrounding this input currently at 12-months, though we recognise, as described in Question B5, that infection risk may be uncertain past 12-months.

To demonstrate the influence of infection risks at and beyond 12 months, four scenarios have been conducted which varies these parameters by +/-20% - see response to Question B5.

Furthermore, a scenario has been ran incorporating an artificially large confidence interval of +/- 20% in the PSA. The results of the scenario show that the PSA ICER is stable; [redacted] with the revised base case (Table 38) versus [redacted] with the scenario analysis (Table 39).

Table 38: Revised base-case PSA

Technologies	Total costs	QALYs	Costs	QALYs	ICER	INMB (£30,000 per QALYs)
No prophylaxis	[redacted]	[redacted]	[redacted]	[redacted]	£ 7,906	[redacted]
Evusheld	[redacted]	[redacted]				

Abbreviations: ICER – incremental cost-effectiveness ratio; INMB – incremental net monetary benefit; QALY – quality adjusted life year

Table 39: Scenario analysis using +/-20% in the PSA

Technologies	Total costs	QALYs	Costs	QALYs	ICER	INMB (£30,000 per QALYs)
No prophylaxis	[redacted]	[redacted]	[redacted]	[redacted]	£ 7,887	[redacted]
Evusheld	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

Abbreviations: ICER – incremental cost-effectiveness ratio; INMB – incremental net monetary benefit; QALY – quality adjusted life year

B7. PRIORITY Shields et al. (2022) (CS, ref 46) which has been used to calculate the hospitalisation rate is described in the reference list as “Data on file” and “in press” and the paper does not appear to have been included in the reference pack. Please supply a copy of this paper, or a study report, so the methods can be properly scrutinised. The data within the model sheet ‘calculations’ appear to suggest that a hospitalisation rate is available for the subgroup who were double vaccinated at the time of infection. Please describe how the hospitalisation rate differed in this group and please provide a scenario analysis exploring this alternative parameter input.

Response:

The Shields et al. 2022 proofs cited in the submission has now been fully published with an update of the latest PIN case series data included.(41) The base case has therefore been revised based on the updated data provided in the publication. All previous data referencing Shields et al. 2022 should be disregarded.

Shields et al. 2022 assessed the impact of vaccination on hospitalisation and mortality from COVID-19 in patients with primary and secondary immunodeficiency in the UK, which aligns closely with the target population for the submission. (41)

In the primary immunodeficiency cohort (N=117), 92.3% had two prior vaccines and 81.2% had three prior vaccines. In the secondary immunodeficiency cohort (N=38), 97.4% had two prior vaccines and 91.8% (N=35/38) had three prior vaccines. (41)

Subgroup analysis on hospitalisation rates in those who were double vaccinated at the time of infection has not been published (41) however whole population results from the study showed that 17.9% (N=21/117) of patients with primary immunodeficiency and 18.4% (N=7/38) of patients with secondary immunodeficiency required hospitalisation. A weighted average of 18.06% is used in the revised base case analysis.(41)

The 'calculations' sheet within the model cites the data from the Shields publication. The cohort labelled "untreated, no prior COVID- 19, 2x vaccinated" includes patients who were infected for the first time after receipt of two vaccine doses but received no inpatient or outpatient treatment for COVID-19 (i.e., antivirals, monoclonal antibodies, steroids, or biologic therapies). This subgroup only includes patients that are not treated as inpatients or outpatients and is a subgroup of the primary and secondary immunocompromised populations. Due to the small sample size in this subgroup and the lack of data, subgroup analysis could not be performed. However, it should be noted that the revised base case analysis includes individuals who have been both double and triple vaccinated.(41) The incorporation of the published Shields et al 2022, reduced the original base case ICER from £12,290 (Table 40) to £11,955 (Table 41).

Table 40: Original base-case results

Technologies	Total costs	QALYs	Costs	QALYs	ICER	INMB (£30,000 per QALYs)
No prophylaxis	[redacted]	[redacted]	[redacted]	[redacted]	£ 12,290	[redacted]
Evusheld	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

Abbreviations: ICER – incremental cost-effectiveness ratio; INMB – incremental net monetary benefit; QALY – quality adjusted life year

Table 41: Shields et al. 2022 scenario analysis (41)

Technologies	Total costs	QALYs	Costs	QALYs	ICER	INMB (£30,000 per QALYs)
No prophylaxis	[redacted]	[redacted]	[redacted]	[redacted]	£ 11,955	[redacted]
Evusheld	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

Abbreviations: ICER – incremental cost-effectiveness ratio; INMB – incremental net monetary benefit; QALY – quality adjusted life year

B8. PRIORITY The latest figures from the Coronavirus UK dashboard show that as of 28th of September 2022, 160 of the 7,024 patients in hospital with COVID-19 in England (2.3%) were in ventilation beds. (https://coronavirus.data.gov.uk/details/healthcare?areaType=nation&areaName=England). This figure is significantly lower than the one currently used in the model (15.4%). Please clarify why the most recent figure was not used and calibrate the model using the latest data. We suggest that in doing so, you assume that the excess patients on invasive ventilation from Cusinato et al. (2022) are re-distributed according to the proportions reported by Cusinato et al. (2022) for the COVID-19 second wave.

Response:

Though data specific to the target population Evusheld were unavailable at the time of response to the EAG's questions, there are data available which clearly demonstrate a higher probability of mechanical ventilation in patients with COVID-19 who are high-risk due to other co-morbidities.

- Simonnet et al. (2020) reported on a single centre in France and found that of the 124 patients with obesity and hospitalised with coronavirus, 85 of them require mechanical ventilation (68.55%). (42)
- Liang et al. (2020) reported on a nationwide study in China and found that patients with cancer had a higher risk of severe events, defined as the percentage of patients being admitted to the intensive care unit requiring invasive ventilation, or death, compared to patients without cancer (39% vs. 8%, respectively).(43)
- Chavez-MacGregor et al. (2022) reported on a US claims analysis and found that the rates of mechanical ventilation were 2.2% for patients without cancer and 6.8% for patients with cancer. (44)

Therefore, using mechanical ventilation rates from the general population are likely to underestimate the cost-effectiveness of Evusheld.

Nevertheless, in response to the EAG's question, two scenario analyses have been conducted (Table 44-Table 45):

- Scenario 1: Using the second wave from Cusinato et al. (45)
- Scenario 2: Using the gov.uk data(46) for ventilation beds and the second wave data from Cusinato et al. (45) to estimate the remaining distribution of hospital cases
    - The proportion of ventilation beds across all hospital cases was averaged from 6th October 2021 to 5th October 2022 is 4.92%. Note: this estimate is based on the general population and not those patients at high-risk i.e., aligning with the proposed population for Evusheld.

Table 42: Hospitalisation distribution scenario analysis

	Original (Total, Cusinato et al) (45)	**Sensitivity 1: Second Wave (Cusinato et al)** (45)	**Sensitivity 2: gov.uk accessed Oct 2022 for ventilation** (46) **and second wave (Cusinato et al)** (45)
No Oxygen Therapy	26.10%	26.90%	29.40%
Low-flow Oxygen Therapy	40.70%	37.90%	41.42%
Non-invasive Ventilation or High-flow Oxygen	17.80%	22.20%	24.26%
Invasive Mechanical Ventilation or ECMO	15.40%	13.00%	4.92%

Abbreviations: ICER – incremental cost-effectiveness ratio

Table 44 and Table 45 show the results of the scenario analyses. Scenario 1 using the second wave from Cusinato et al. (45) increases the revised ICER from £8,111 (Table 43) to £8,294 (Table 44). Scenario 2 using the gov.uk data for ventilation beds and the second wave data from Cusinato et al. (45) increases the ICER from £8,111 to £9,312.

Table 43: Revised base-case results

Technologies	Total costs	QALYs	Costs	QALYs	ICER	INMB (£30,000 per QALYs)
No prophylaxis	[redacted]	[redacted]	[redacted]	[redacted]	£ 8,111	[redacted]
Evusheld	[redacted]	[redacted]				

Abbreviations: ICER – incremental cost-effectiveness ratio; INMB – incremental net monetary benefit; QALY – quality adjusted life year

Table 44: Hospitalisation distribution scenario analysis – Second Wave (Cusinato et al) (45)

Technologies	Total costs	QALYs	Costs	QALYs	ICER	INMB (£30,000 per QALYs)
No prophylaxis	[redacted]	[redacted]	[redacted]	[redacted]	£ 8,294	[redacted]
Evusheld	[redacted]	[redacted]				

Abbreviations: ICER – incremental cost-effectiveness ratio; INMB – incremental net monetary benefit; QALY – quality adjusted life year

Table 45: Hospitalisation distribution scenario analysis – gov.uk (46) accessed Oct 2022 for ventilation and second wave (Cusinato et al) (45)

Technologies	Total costs	QALYs	Costs	QALYs	ICER	INMB (£30,000 per QALYs)
No prophylaxis	[redacted]	[redacted]	[redacted]	[redacted]	£ 9,312	[redacted]
Evusheld	[redacted]	[redacted]				

Abbreviations: ICER – incremental cost-effectiveness ratio; INMB – incremental net monetary benefit; QALY – quality adjusted life year

B9. PRIORITY Given the uncertainty regarding the effectiveness of Evusheld against current and future variants (see FDA warning referred to in question A3 and differences in neutralisation across variants within in vivo data discussed in question A4), please conduct a threshold analysis exploring the minimum relative risk reduction (RRR) required for cost-effectiveness when applying the company's other preferred assumptions and inputs. Please present the thresholds when applying a willingness to pay of both £20,000 per QALY and £30,000 per QALY.

Response:

As described in responses to Questions A2-A5, there is a substantial body of evidence that Evusheld neutralises current VOCs in the UK and clinical effectiveness has been shown across alpha, beta, delta and omicron variants – evidenced by both randomised controlled evidence and real world evidence. Nevertheless, we acknowledge that Evusheld may not by effective against all potential VOCs circulating in the UK in the future.

As requested by the EAG, threshold analyses were conducted using the Solver Add-In within the cost-effectiveness model.

The relative risk reduction (RRR) of symptomatic infection is 66.00% in the base case. This can be reduced to 6.64% and still maintain an ICER<£20,000. Furthermore, with no reduction in symptomatic infection i.e., 0.00 the ICER was £22,194; owing to the RRR for hospitalisation if symptomatic and quality of life benefits induced through treatment with Evusheld.

The RRR reduction in hospitalisation, if symptomatic is 61.76% in the base case. With no reduction in severity if symptomatic the ICER is £9,553; owing to the RRR of symptomatic infection and quality of life benefits induced through treatment with Evusheld.

To explore this further, a two-way sensitivity analysis was conducted varying the efficacy related to Evusheld i.e., the reduction in infection risk and the reduction in hospitalisation by +/-10% and +/-20%. The results of this analysis are presented in Table 46 and show that all scenarios are well below the £20,000 /QALY threshold.

Table 46: Two-way sensitivity analysis considering the efficacy of Evusheld (using revised base-case results)

		Reduction in infection with Evusheld				
		52.80%	59.40%	66.00%*	72.60%	79.20%
Reduction in hospitalisation with Evusheld	49.41%	£10,421	£9,353	£8,379	£7,485	£6,664
	55.59%	£10,189	£9,174	£8,244	£7,387	£6,596
	61.76%*	£9,963	£8,999	£8,111*	£7,290	£6,529
	67.94%	£9,744	£8,828	£7,981	£7,194	£6,463
	74.12%	£9,529	£8,660	£7,853	£7,100	£6,397

*base case

B10. PRIORITY Please clarify why the infection rate in subsequent years is the same for the Evusheld and the no prophylaxis arm despite differing infection rates in the year after receiving either Evusheld or no prophylaxis. Is it assumed that prior infection provides no future immunity and does not in any way reduce the susceptibility to infection or the risk of severe infection in future years?

Response:

As discussed in Section B3.2.3, following advice from the EAG during the decision problem meeting on the 17th of August 2022 a post-hoc adjustment was made to the model to estimate the impact of reinfection on the cost-effectiveness results.

Here, the possibility for COVID-19 infection risk after 12 months was considered by adjusting the total cost and QALY results derived from the structure described above and is described in full in section B3.3.5. In the absence of data, a simplifying assumption was made that the infection rates observed over the period August 2021 to August 2022 would be experienced in future years.

Based on the model structure and implementation of infection risk after 12-months, it is assumed that infection provides no future immunity, and does not in any way reduce the susceptibility to infection or the risk of severe infection in future years. Evidence suggests that this assumption is not unreasonable.(47)

Nevertheless, as can be seen in response to Question B5, the impact to the ICER on alternative infection rates in subsequent years is negligible.

Risk of long COVID and duration of long COVID

B11. PRIORITY The mean duration of long COVID based on the lognormal distribution fitted to the ONS data by Metry et al. (2022) was given as 108.6 weeks. This was based on ONS data showing that within the cohort self-reporting long COVID, 72% of patients had long COVID for more than 12 weeks, 42% for more than 1 year and 22% for more than 2 years. The latest ONS data (see link below) show that of people with self-reported long COVID, 83% reported they first had (or suspected they had) COVID-19 at least 12 weeks previously, 45% at least one year previously, and 22% at least two years previously. For comparison, please provide the mean duration of long COVID from the company's adjusted lognormal distribution and provide the time point at which the proportion experiencing long COVID reached 22%. Please also provide a scenario using the latest ONS data to estimate duration of long COVID.
[lhttps://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/bulletins/prevalenceofongoingsymptomsfollowingcoronaviruscovid19infectionintheuk/1september2022]

Response:

Using the log-normal adjusted curve presented in the base case, the proportion of patients in the long COVID health state reduces to 22% at approximately 4.5 years. The mean duration of long COVID is 5.0 years.(13)

The predictions from the adjusted log-normal curve are appropriate when compared with the ONS estimates referred to by the EAG, as the ONS data is community self-report data, which is likely to underestimate the duration of long COVID for patients who are hospitalised. Furthermore, the high-risk immunocompromised patient population are less likely to rebound from long COVID as quickly as the general population, on which the ONS data is based, given the underlying comorbidities.

For a more appropriate comparison, the % of non-hospitalised patients reaches 22% at approximately 3 years (between cycles 6 and 7) which is broadly in line with the ONS data, and accounts for the fact that this represents a high-risk population.

In response to the EAG's question and the clarification call (date: 13th October 2022), a log-normal curve has been fitted to the updated ONS data referred to by the EAG and is shown in Figure 14.

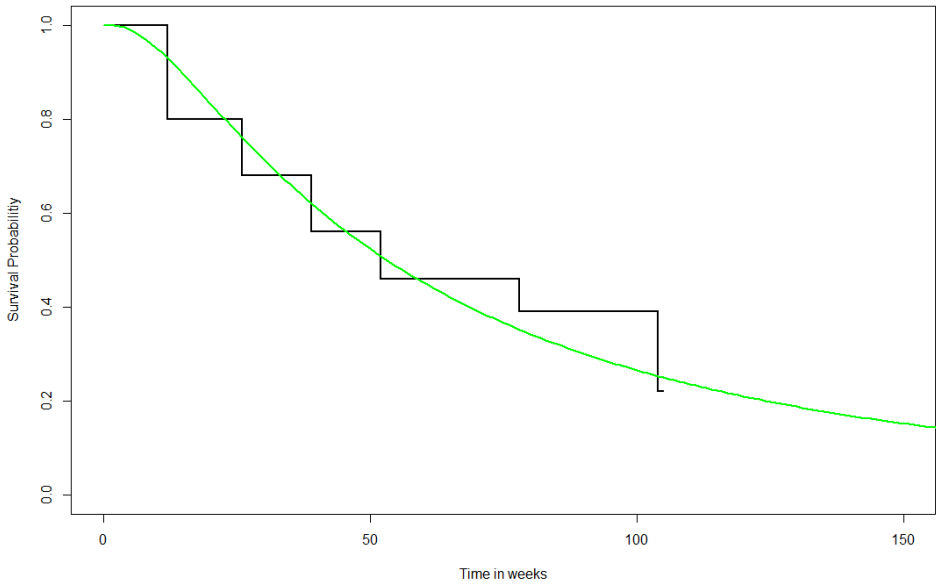
Three scenarios have also been conducted using:

- Scenario 1: The original log-normal curve without calibration from Evans et al. (2022)(48) - Table 48
- The updated data and a log-normal curve with calibration from Evans et al. (2022) (48) - Table 49
- The updated data and a log-normal curve without calibration from Evans et al. (2022) (48) - Table 50

The predicted probability of long-COVID over time for each of these scenarios compared to the base case is shown in Figure 15.

The use of the latest data (October 2022) and including the calibration increases the ICER from £8,111 (Table 47) to £13,050 (Table 49). Without the calibration, a similar increase is observed between the original submission data and the latest data (October 2022); from £15,831 (Table 48) to £16,473 (Table 50).

Figure 14: Probability of long COVID – ONS 6th October 2022 data set compared with the log-normal parametric curve



Abbreviations: ONS – Office for National Statistics

Figure 15: Long COVID scenario analyses

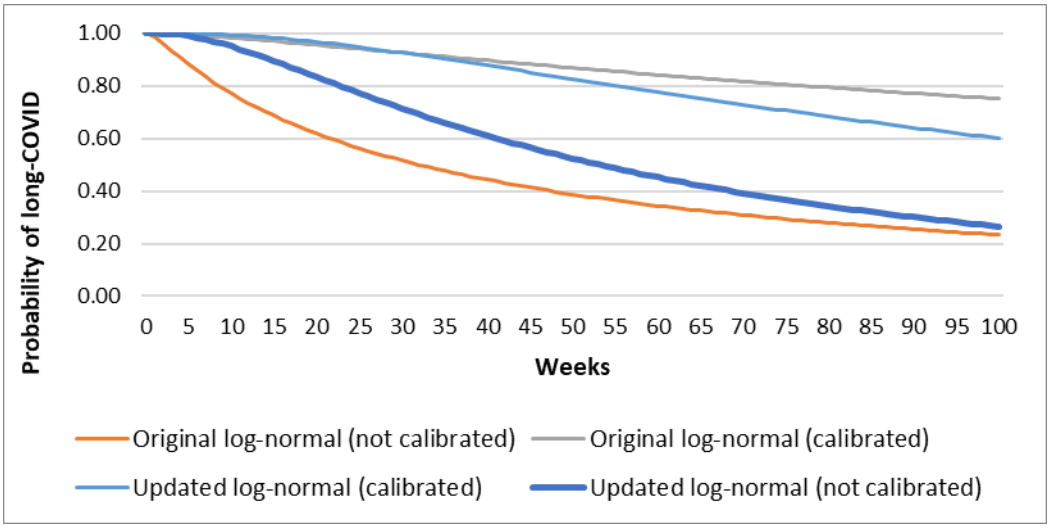


Table 47: Base-case results – original log-normal, calibrated

Technologies	Total costs	QALYs	Costs	QALYs	ICER	INMB (£30,000 per QALYs)
No prophylaxis	[redacted]	[redacted]	[redacted]	[redacted]	£ 8,111	[redacted]
Evusheld	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

Abbreviations: ICER – incremental cost-effectiveness ratio; INMB – incremental net monetary benefit; QALY – quality adjusted life year

Table 48: Long-COVID scenario analysis – Sensitivity 1: Original (not calibrated)

Technologies	Total costs	QALYs	Costs	QALYs	ICER	INMB (£30,000 per QALYs)
No prophylaxis	[redacted]	[redacted]	[redacted]	[redacted]	£ 15,831	[redacted]
Evusheld	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

Abbreviations: ICER – incremental cost-effectiveness ratio; INMB – incremental net monetary benefit; QALY – quality adjusted life year

Table 49: Long-COVID scenario analysis – Sensitivity 2: Oct data (calibrated)

Technologies	Total costs	QALYs	Costs	QALYs	ICER	INMB (£30,000 per QALYs)
No prophylaxis	[redacted]	[redacted]	[redacted]	[redacted]	£ 13,050	[redacted]
Evusheld	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

Abbreviations: ICER – incremental cost-effectiveness ratio; INMB – incremental net monetary benefit; QALY – quality adjusted life year

Table 50: Long-COVID scenario analysis – Sensitivity 3: Oct data (not calibrated)

Technologies	Total costs	QALYs	Costs	QALYs	ICER	INMB (£30,000 per QALYs)
No prophylaxis	[redacted]	[redacted]	[redacted]	[redacted]	£ 16,473	[redacted]
Evusheld	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

Abbreviations: ICER – incremental cost-effectiveness ratio; INMB – incremental net monetary benefit; QALY – quality adjusted life year

B12. PRIORITY The long COVID costs and disutilities are being applied for the full duration of the time horizon (46 years). Please explain why it is reasonable to assume a fixed cost per person and a fixed level of disutility for every year, going forwards 46 years, for a health condition which has only been documented since 2020. The current assumption suggests that there will be no reduction in resource use or symptoms within the long COVID diagnosed population due either to improved management or reduced disease burden over time. Please provide scenarios exploring alternative plausible assumptions such as resolution of long COVID symptoms at 2, 3, 5 or 10 years.

Response:

Table 51 shows the predicted proportion of patients with long COVID across a 20-year time horizon within the cost-effectiveness model. Table 52 shows these data as a proportion of the infected population.

As shown, the proportion of patients predicted to have long COVID reduces throughout the model time horizon, such that by 10-years less than 3% of the total model population and less than 13% of those infected are experiencing long COVID, this further reduces to less than 2% and 9% at 15-years, respectively.

As costs and disutilities are applied to this declining proportion of patients throughout the model time horizon, the impact of constant costs or disutilities reduces over time. This assumption aligns with the assumptions used in the EAG model for TA10936 I.e., costs and utility decrements were applied for the duration of long COVID in the base case.

Table 51: Predicted proportion of patients with long COVID over time (all patients)

	0.5 years	2 years	5 years	10 years	15 years	20 years
No prophylaxis	9.12%	6.76%	4.62%	2.89%	1.95%	1.32%
Evusheld	2.79%	2.14%	1.46%	0.92%	0.62%	0.42%

Table 52: Predicted proportion of patients with long COVID over time (infected patients)

	0.5 years	2 years	5 years	10 years	15 years	20 years
No prophylaxis	40.40%	29.92%	20.44%	12.81%	8.63%	5.84%
Evusheld	36.27%	27.85%	19.03%	11.93%	8.04%	5.44%

The current assumption does assume that there will be no reduction in resource use or symptoms within the long COVID diagnosed population due either to improved management or reduced disease burden over time. This assumption is in line with NICE technology appraisals which do not account for future improvements or cures in disease areas.

As agreed with the EAG during the clarification call on 13th October 2022, scenarios exploring alternative long COVID assumptions, including the EAG's assumptions regarding a mean duration of 2 years (as per the ongoing NICE MTA of therapeutics for people with COVID-19 [TA10936]), have been presented in response to Question B11.

B13. PRIORITY The current model setting applies post-acute disutilities, stratified by severity experienced during hospital stay, for the whole duration of long COVID. Please comment on the clinical validity of such an assumption. Additionally, please present a scenario where these disutilities persist for a shortened period of time (e.g. patients discharged from ICU experience the disutility for the mean duration of post-intensive care syndrome), and then a smaller disutility applies in the long-term.

Response:

Evidence from the literature suggests that disutilities associated with long COVID persist over the long-term and are clinically valid.

Base case utility inputs for long COVID are sourced from Evans 2021(49) and Evans 2022(48) reporting on the national PHOSP-COVID study in thousands of patients hospitalised with COVID in the UK pre –covid and after up to 12-months follow up.

Results from Evans 2022 showed a sustained average utility decrement over the first year following discharge for patients not recovered from long COVID (disutility of 0.19 and 0.22 at 5- and 12-months compared to pre-COVID utility; see Figure 16 and Table 53). (48)

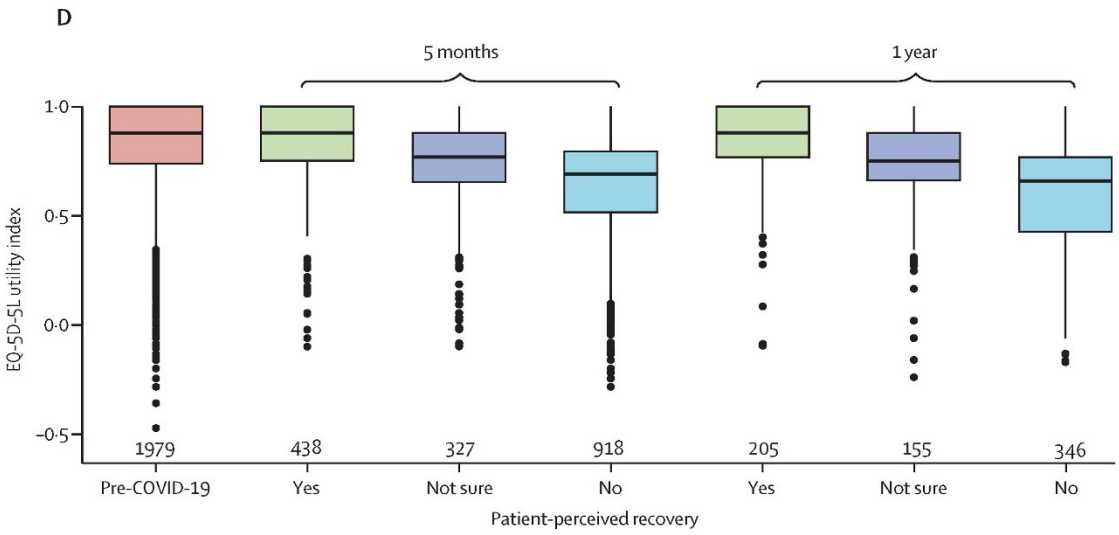
Data from Evans 2022 was also stratified by recovery status (fully recovered, not sure and not recovered).(48) Results showed that utility for recovered patients had returned to pre-COVID levels (see Figure 16) at 12-months which strongly indicates that the disutility decrement demonstrated for 'not recovered' patients is associated with the symptoms of long COVID and not related the effects of conditions such as post-intensive care syndrome. (48)

Furthermore, Evans 2022 included over 50% of patients with WHO severity class 3-5 (associated the less severe health states; Not hospitalised assistance needed-3, Hospitalised requiring no oxygen therapy-4 and Hospitalised requiring oxygen-5) and less than 30% in the most severe health state. Given this, the effects of hospital-related syndromes in the reported long COVID utility decrement are limited.(48)

Table 53: Digitised long COVID EQ-5D values - Evans 2022 (48)

	Original (calibrated log-normal)
Pre- COVID	0.89
5 months – not recovered	0.70
12 months – not recovered	0.67

Figure 16: EQ-5D-5L utility for non-recovered hospitalised patients – Evans 2022 (48)



AstraZeneca are not aware of any data beyond 12-months to support a waning in the disutility. However, an exploratory analysis is presented below whereby the utility associated with long COVID is reduced linearly to 50% of the original value (for each health state) after 5-years (Table 56). This analysis increased the revised ICER from £8,111 (Table 55) to £9,146 (Table 56).

Table 54: Disutility applied to patients with long COVID in scenario analysis

	Annual Disutility (Mean)					
From	0 years	1 years	2 years	3 years	4 years	5 years
To	1 years	2 years	3 years	4 years	5 years	100 years
Not hosp - no assistance needed	0.15	0.14	0.12	0.11	0.09	0.08
Not Hosp - assistance needed	0.15	0.14	0.12	0.11	0.09	0.08
No Oxygen Therapy	0.15	0.14	0.12	0.11	0.09	0.08
Low-flow Oxygen Therapy	0.15	0.14	0.12	0.11	0.09	0.08
Non-invasive Ventilation or High-flow Oxygen	0.19	0.17	0.15	0.13	0.11	0.09
Invasive Mechanical Ventilation or ECMO	0.36	0.32	0.29	0.25	0.22	0.18

Abbreviations: ECMO – Extracorporeal membrane oxygenation

Table 55: Revised base-case results

Technologies	Total costs	QALYs	Costs	QALYs	ICER	INMB (£30,000 per QALYs)
No prophylaxis	[redacted]	[redacted]	[redacted]	[redacted]	£ 8,111	[redacted]
Evusheld	[redacted]	[redacted]				

Abbreviations: ICER – incremental cost-effectiveness ratio; INMB – incremental net monetary benefit; QALY – quality adjusted life year

Table 56: Long COVID utility linearly reducing to 50% of year 1 value post year 5 – scenario results

Technologies	Total costs	QALYs	Costs	QALYs	ICER	INMB (£30,000 per QALYs)
No prophylaxis	[redacted]	[redacted]	[redacted]	[redacted]	£ 9,146	[redacted]
Evusheld	[redacted]	[redacted]				

Abbreviations: ICER – incremental cost-effectiveness ratio; INMB – incremental net monetary benefit; QALY – quality adjusted life year

B14. PRIORITY Please clarify whether the cited proportion of 34.5% of patients with long COVID at 7 months following infection not leading to hospitalisation, from Augustin et al. (2021), is the proportion of the original cohort of 958 COVID-19 infected patients or the proportion of the patients with outcome data at 7 months. If the latter, then please provide a scenario which uses the proportion of the original cohort still reporting long COVID symptoms at 7 months.

Response:

AstraZeneca would like to highlight that the proportion of patients with long COVID at 7 months appears to be an error and the updated proportion is 34.84% (123/353) for those in the not hospitalised- no assistance and assistance needed health states.(50) This has been incorporated into the revised base case.

The base case analysis considers long COVID at 7 months as a proportion of patients with outcomes data at 7 months.

As with Kaplan Meier estimates, it is appropriate to determine the probability of an event based on the numbers at risk. Conducting a scenario whereby the number of people with long-COVID at a follow-up period is divided by the number at risk at baseline, would assume that all patients lost to follow-up did not have long COVID; this is hypothesis generating and unvalidated.

Augustin et al. (2021) reports that of the patients presenting at 7-months (n=353), 123 have long COVID (34.84%).(50) The choice of using 7-months follow-up data is because it aligns with the cycle length within the cost-effectiveness model (6-months).

Augustin et al. (2021) also reports the proportion of presenting patients with long COVID at 4-months follow-up: 123/442 (27.83%).(50) A scenario analysis has been conducted with these alternative data, which increases the revised ICER from £8,111 (Table 57) to £9,220 (Table 58).

Table 57: Revised base-case results

Technologies	Total costs	QALYs	Costs	QALYs	ICER	INMB (£30,000 per QALYs)
No prophylaxis	[redacted]	[redacted]	[redacted]	[redacted]	£ 8,111	[redacted]
Evusheld	[redacted]	[redacted]				

Abbreviations: ICER – incremental cost-effectiveness ratio; INMB – incremental net monetary benefit; QALY – quality adjusted life year

Table 58: Long COVID, non-hospitalised scenario analysis – 4-month data from Augustin et al. (2021) (50)

Technologies	Total costs	QALYs	Costs	QALYs	ICER	INMB (£30,000 per QALYs)
No prophylaxis	[redacted]	[redacted]	[redacted]	[redacted]	£ 9,220	[redacted]
Evusheld	[redacted]	[redacted]				

Abbreviations: ICER – incremental cost-effectiveness ratio; INMB – incremental net monetary benefit; QALY – quality adjusted life year

B15. PRIORITY Please describe how the study by Augustin et al. (2021) was identified and selected from the literature. In addition, as this study reports a German cohort, please confirm whether you identified any data sources from the UK which provide an estimate of the incidence of long COVID in patients infected with COVID-19 who were not hospitalised, such as the 10 UK longitudinal studies and the analysis of UK Electronic Health Records described by Thompson et al. (2022). Please explain why a German cohort was selected in preference to one of the UK data sources identified by Thompson et al. (2022). [Thompson 2022: https://www.nature.com/articles/s41467-022-30836-0#Tab2]

Response:

The study by Augustin et al. (2021) was identified through targeted literature searches. The study is well conducted, with a high number of patients included (n=958) and it reports the proportion of patients having at least one COVID-19 symptom at seven months, aligning with the requirements in the cost-effectiveness model.(50) Importantly, COVID-19 symptoms were evaluated consistently through self-reporting and evaluation by a trained physician, in line with the NICE definition of long-COVID.(51)

Thompson et al. (2022) identify three UK studies reporting on long-COVID in a patient population who have not been hospitalised: ALSPAC-G1 (n=668)(52), ALSPAC-G0 (n=446)(53) and BiB (n=110)(54).

The Avon Longitudinal Study of Children and Parents (ALSPAC) was established to understand how genetic and environmental characteristics influence health and development in parents and children. All pregnant women resident in a defined area in the Southwest of England, with an expected date of delivery between 1st April 1991 and 31st December 1992, were eligible. These women have been followed over the last 19–22 years.(52) The G0 cohort includes women and their partners and the G1 cohort also includes their children.(53)

The Born in Bradford (BiB) cohort study was established in 2007 to examine how genetic, nutritional, environmental, behavioural, and social factors impact on health and development during childhood, and subsequently adult life in a deprived multi-ethnic population. (54)

Neither ALSPAC or BiB populations are generalisable to the UK general population or the target population. Furthermore, both cohorts report smaller sample sizes than those reported in Augustin et al. (2021).(50)

Thompson et al. (2022) also report on UK national primary care records (EHR), covering >95% of the population, but these data are limited to those seeking care, obtaining a diagnosis of long COVID, and gaining a subsequent diagnostic code. The paper acknowledges the limitations associated with the proportion of long-COVID cases from this data source.(55)

B16. PRIORITY A recent commentary by Brightling and Evans (Lancet 2022; 400: 411-413) describes results from a longitudinal study in the Netherlands (Ballering et al. Lancet. 2022; 400: 452-461) which found that a proportion of controls not reporting COVID-19 infection also had at least one core long COVID symptom, albeit at a rate lower than reported in patients with COVID-19 (8.7% versus 21.4%). This suggests that not all long COVID symptoms may be directly attributable to COVID-19 infections. Please explain whether the analysis by Augustin et al. (2021) accounted for this phenomenon of long COVID symptoms being reported in individuals without COVID-19 infection. Please conduct a scenario analysis either using a source which accounted for this phenomenon or conduct a scenario which adjust the rates from Augustin et al. (2021) accordingly.

Response:

Augustin et al. (2021) reported on a prospective, longitudinal study of patients with coronavirus, no control group was considered. Therefore, no comparative results are available for with people without coronavirus.

Based on a general population studied in the Netherlands by Ballering et al. (2022), 40.65% of the reported COVID symptoms were attributable to non-COVID co-morbidities (8.7%/21.4%). Whereas 59.35% of the reported COVID symptoms were attributable to COVID ((21.4%-8.7%)/21.4%). (56)

As described in response to B11, the high-risk immunocompromised patient population are less likely to rebound from long COVID as quickly as the general population, and as such estimates from Ballering et al. are unlikely to be representative of those in the target population.(56)

Even if the costs and health-related quality of life are not directly attributable to COVID, these should be considered within the model base case for two reasons:

- The impact on the patient and the healthcare system is still prevalent regardless of the root cause of the symptoms, and
- Pre-existing symptoms may be compounded by the presence of COVID.

Nevertheless, in response to the EAG's question, a scenario analysis has been conducted varying the proportion of 34.8% with long COVID at 7-months for patients not hospitalised to 20.65% (34.8% x 59.35%) to account for this reported phenomenon. This scenario increases the revised ICER from £8,111 (Table 59) to £10,459 (Table 60)

Table 59: Revised base- case results

Technologies	Total costs	QALYs	Costs	QALYs	ICER	INMB (£30,000 per QALYs)
No prophylaxis	[redacted]	[redacted]	[redacted]	[redacted]	£ 8,111	[redacted]
Evusheld	[redacted]	[redacted]				

Abbreviations: ICER – incremental cost-effectiveness ratio; INMB – incremental net monetary benefit; QALY – quality adjusted life year

Table 60: Long COVID distribution scenario analysis

Technologies	Total costs	QALYs	Costs	QALYs	ICER	INMB (£30,000 per QALYs)
No prophylaxis	[redacted]	[redacted]	[redacted]	[redacted]	£ 10,459	[redacted]
Evusheld	[redacted]	[redacted]				

Abbreviations: ICER – incremental cost-effectiveness ratio; INMB – incremental net monetary benefit; QALY – quality adjusted life year

B17. In addition, the commentary by Brightling and Evan (2022) makes references to studies showing that vaccination status (Antonelli Lancet Infect Dis 2022; 22: 43–55.) and the variant of COVID-19 (Antonelli Lancet 2022;399: 2263–64.) both have an impact on the risk of long COVID following infection. Please comment on whether the data from Augustin et al. (2021) reflect the risk of long COVID going forward given the current level of vaccination in the target population and the current dominant strain of COVID.

Response:

In the base-case, the proportion of non-hospitalised patients assumed to suffer with long COVID was 34.8% sourced from Augustin et al. (2021). At the time of the study, patients were unvaccinated. However, given that patients in the immunocompromised population have both comorbidities and an inadequate response to vaccination, AstraZeneca believe the rate reported by Augustin et al. (2021) to be an approximation of the long COVID rate in the target population.

The study referenced by the EAG (Antonelli et al. 2022) is a community-based case control study in the general population (only ~20% with ≥ 1 comorbidity) and while it showed vaccination was associated with a reduced odds of long COVID (0.51, 0.32-0.82) these results are not generalisable to the target Evusheld population.(57)

The population considered for treatment with Evusheld PrEP are those who have had an inadequate response (and thus have inadequate protection) to vaccination or are not able to be vaccinated at all. The study did not report long COVID odds ratios (OR) for patients with baseline comorbidities, however results did show that for older adults who had received their first vaccine dose, but not their second (partial protection), kidney disease (OR 1·95, 95% CI 1·14–3·31; p=0·014), heart disease (1·30, 1·03–1·65; p=0·031), and lung disease (1·27, 1·02–1·59; p=0·030) were associated with postvaccination infection. This supports that these patients may experience a higher rate of long COVID compared with the general population given that baseline comorbidities were associated with infection despite vaccination.

The alpha variant was the dominant variant at the time of the Augustin et al. 2021 study.(50) Antonelli et al. 2022, the study referenced by the EAG, is a case-control observational study investigating the risk of long COVID associated with delta and

omicron variants.(58) Results of the study showed 4.5% of patients with the omicron variant experienced long COVID (≤4 weeks) compared with 10.8% in those with the delta variant however no comparison to the alpha variant is provided. The long COVID rates reported in Antonelli et al. 2022 are not comparable to Augustin et al. 2021 as the percentage of patients with long COVID is calculated from both symptomatic and asymptomatic infections based on an unknown proportion. This is not appropriate for the model structure which requires the percent of non-hospitalised patients with symptomatic infection who have long COVID; 95.5% of those included in Augustin et al. 2021 had symptomatic infection.(50)

Though AZ question the generalisability of the findings from the studies referenced by the EAG to the patient population in question, AZ agree there is a degree of uncertainty around the future long COVID rates in the target population. In part, this is due to the fact COVID is a new disease which is evolving at a rapid pace and thus any data analysis carries an inherent level of uncertainty. Given this, scenario analysis to quantify the uncertainty around the proportion of patients with long COVID, the duration of long COVID and the cost/ HRQoL impact has been presented in response to questions B11, B12, B13 and B16 and shows little impact on the ICER.

Mortality

B18. Please explain why the HR for mortality for patients recovered from COVID following ICU admission (HR=2.26) is applied for 11 cycles of 6 months when it is described as being applied for 5 years. In addition, this HR appears to have been calculated as the product of the HR for immunocompromised patients (HR=1.7) and the HR for patients discharged from ICU (HR=1.33). As both are described as being relative to the general population, please justify whether the product of these or the maximum of these should be applied. Using the product implies that ICU increases mortality over and above the presence of any condition that would predispose the patient to requiring ICU care. Please clarify that this is in line with the analysis conducted to estimate the HR reported by Sheinson et al. (2021).

Response:

The HR for mortality for recovered patients following ICU admission is applied up to and including the 11th cycle (time at start of cycle 5 years). The HR is applied as the product of the HR for the immunocompromised population and the HR following discharge from ICU as described by the EAG. While both estimates are relative to the general population, AstraZeneca believe it is likely that there are compounding effects of being both severely immunocompromised and recovering from invasive ventilation in ICU. AstraZeneca believe it is reasonable to assume that a person who is severely immunocompromised and recovering from invasive ventilation would have a higher risk of morbidity compared to an otherwise healthy person recovering from invasive ventilation. As described in response to B19, the HR reported in Sheinson et al (2021)(59) is taken from Lone et al. (2016).(60) Here, the relative risk of death for an ICU cohort compared to hospital control subjects was reported to be 1.33 following adjustment for confounders including comorbidity, inferring that the analysis is in line with using the product method.

B19. Please explain the rationale for applying the HR described by Sheinsen et al. (2021) as "the hazard ratio for post-discharge mortality for ventilated patients vs general population" to patients who received high-flow oxygen or non-invasive mechanical ventilation? Is the increased risk of post-discharge mortality (which is associated with ICU admission requiring organ support, such as invasive mechanical ventilation) likely to be applicable to patients requiring only non-invasive ventilation or high-flow oxygen? If possible, please explore this with reference to the methods used in the original source study, which Sheinsen et al. (2021) cite as being Lone et al. (2016). Please provide a scenario analysis in which the HR for mortality following ICU admission is applied only to those having invasive mechanical ventilation or ECMO.

Response:

The hazard ratio reported in Lone et al. (2016) is the relative risk of death for an ICU cohort compared to hospital control subjects; this is reported to be 1.33 following adjustment for confounders.(60) The ICU cohort included patients receiving mechanical ventilation (60.5%). However, a significant portion of the cohort did not receive mechanical ventilation (39.5%). Therefore, we consider that the reported hazard ratio is appropriate to apply to all patients hospitalised within the economic model.

In response to the EAG's question, an extreme scenario analysis has been conducted applying this hazard ratio only to patients having invasive mechanical ventilation or ECMO. The scenario increases the revised ICER from £8,111 (Table 61) to £8,133 (Table 62). However, as already discussed, this scenario ignores the increased risk of mortality among other hospitalised patients.

Table 61: Revised base-case results

Technologies	Total costs	QALYs	Costs	QALYs	ICER	INMB (£30,000 per QALYs)
No prophylaxis	[redacted]	[redacted]	[redacted]	[redacted]	£ 8,111	[redacted]
Evusheld	[redacted]	[redacted]				

Abbreviations: ICER – incremental cost-effectiveness ratio; INMB – incremental net monetary benefit; QALY – quality adjusted life year

Table 62: Hazard ratio for mortality post-discharge scenario analysis

Technologies	Total costs	QALYs	Costs	QALYs	ICER	INMB (£30,000 per QALYs)
No prophylaxis	[redacted]	[redacted]	[redacted]	[redacted]	£ 8,133	[redacted]
Evusheld	[redacted]	[redacted]				

Abbreviations: ICER – incremental cost-effectiveness ratio; INMB – incremental net monetary benefit; QALY – quality adjusted life year

Quality of life sources

B20. PRIORITY The same utility decrement is applied for long COVID for patients who are hospitalised but not needing supplemental oxygen and those not requiring hospitalisation. These estimates have been obtained from a hospitalised cohort reported by Evans et al. (2021). Given that Evans et al. (2021) found that the greatest change in quality of life occurred in those with the highest WHO severity scores requiring the greatest level of support within hospital, please explain why it is reasonable to apply the figures estimated from hospitalised patients to non-hospitalised patients who will have less severe disease. Please explore the sensitivity of the model to this parameter by providing a scenario analysis exploring plausible alternative estimates of the utility decrement in non-hospitalised patients reporting long COVID symptoms.

Response:

AstraZeneca are not aware of any literature describing utility inputs for patients with long COVID who are not hospitalised. As such, the base case analysis relies on an assumption of equal utility for those not requiring hospitalisation and those in the least severe hospitalised health states I.e., hospitalised but not needing supplemental oxygen.

In response to the EAG's question, a scenario analysis is provided whereby:

- the difference in utility between 'non-invasive ventilation' and 'low-flow oxygen' health states in the base case is calculated: 0.1884-0.1542 = 0.0343
- The calculated utility decrement between the two most severe health states is applied to the 'Hospitalised: No oxygen required' health state to estimate the non-hospitalised utility. 0.1542-0.343=0.1199

The scenario increases the revised ICER from £8,111 (Table 63) to £8,520 (Table 64).

Table 63: Revised base-case results

Technologies	Total costs	QALYs	Costs	QALYs	ICER	INMB (£30,000 per QALYs)
No prophylaxis	[redacted]	[redacted]	[redacted]	[redacted]	£ 8,111	[redacted]
Evusheld	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

Abbreviations: ICER – incremental cost-effectiveness ratio; INMB – incremental net monetary benefit; QALY – quality adjusted life year

Table 64: Post-discharge disutility non-hospitalised patients scenario analysis

Technologies	Total costs	QALYs	Costs	QALYs	ICER	INMB (£30,000 per QALYs)
No prophylaxis	[redacted]	[redacted]	[redacted]	[redacted]	£ 8,520	[redacted]
Evusheld	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

Abbreviations: ICER – incremental cost-effectiveness ratio; INMB – incremental net monetary benefit; QALY – quality adjusted life year

B21. PRIORITY Please clarify why the estimates of utility loss in Table 53, which were based on 5 month data from Evans et al. (2021) have been 'uplifted' by a factor of 1.71 when there was no significant change in EQ-5D-5L utility between 5 months and 1 year in patients who had scores recorded at both points according to Table 2 of Evans et al. (2022).

Response:

Evans et al. 2021 reported utility values for patients following hospital discharge from COVID-19 at 5 months follow up (EQ-5D-5L) stratified by severity (Table 65) reproduced below for reference. However, these utility values are not for patients with long COVID only; they included 28.85% recovered patients and 19.5% not sure of recovery status. Given this, the utility values reported in Evans 2021 are not representative of those patients only with long COVID.

More recent data from Evans 2022 reported utility at 5- and 12-months post discharge and did report utility stratified by recovery status. Results showed a 0.19

and 0.22 decrement in utility at 5- and 12 –months, respectively, for patients who had reported as not recovered only (estimates from digitised data (Figure 16) are presented in (Table 54).

While Evans 2022 reported data for patients with long COVID only, there were no utility data stratified by disease severity as was given in Evans 2021.

The severity of illness in the patient populations of Evans 2021 and Evans 2022 were comparable and so it was assumed that:

1. The data from Evans 2022 was the most appropriate mean estimate for patients with long COVID (not recovered)

2. The distribution of disutility associated with severity given in Evans 2021 (included recovered and non-recovered) was representative of the distribution between severity classes for non-recovered patients.

Therefore, the utility values reported in Evans 2021 (Table 65) were uplifted by a factor of 1.71 (0.22/0.13) to ensure the estimates were reflective of patients with long COVID only. Indeed, the fact that utility differences were not significant in Evans 2022 between months 5 and 12, does not impact the requirement to update Evans 2021 data accordingly using the most appropriate data at month 12.

Table 65: EQ-5D-5L disutility values post discharge (5 months) – Evans et al. 2021

	WHO class 3-4	WHO class 5	WHO class 6	WHO class 7-9	Total
Pre-COVID-19	0.82	0.84	0.82	0.87	0.84
Post – COVID-19	0.72	0.76	0.69	0.67	0.71
Change	-0.09	-0.09	-0.11	-0.21	-0.13

Abbreviations: COVID-19 – Coronavirus disease 2019; EQ-5D – Euroqol 5 dimensions 5 level; WHO – World Health Organisation

B22. PRIORITY Please clarify how the utility decrement quoted as being 0.22 from Evans et al. (2022) has been calculated and how it relates to the estimate of 0.13 from Evans et al. (2021) (as these two figures have been used to estimate the uplift 1.71=0.22/0.13). Are both estimated versus pre-COVID utility regardless of the patient's status as recovered or not, or are both comparing recovered versus not recovered patients? If equivalent data are provided in both papers, please explain why the later figures are not used directly? If the data are not calculated in an equivalent manner, please explain how they be compared to calculate an uplift?

Response:

Please see the response to Question B21.

B23. Are the estimates of utility change stratified by WHO classification, reported in Table 53, estimated for all patients within that WHO classification regardless of whether they recovered? If so, then could the larger utility decrements for higher WHO classification scores be driven by a higher proportion not recovering rather than demonstrating a greater utility decrement in those not recovered?

Response:

As described in response to question B21, the utility estimates provided in Table 53 of the company submission represent both 'recovered' and 'non-recovered' patients. The proportion of patients who have recovered in each WHO classification is shown in Table 66 below. While there is a greater proportion of 'not-recovered' patients in the most severe state (WHO class 7-9), the proportion of 'not recovered' patients in WHO classes 3-6 is relatively constant indicating that the utility decrements associated with those in the 'not-recovered' state is not driven solely by a higher proportion of 'not-recovered' patients in each health state. AstraZeneca acknowledge the uncertainty here with the inclusion of an 'unsure' state; for this reason, results from this study were not used in isolation. As described in response to B22, data from Evans et al. (2022) provided a mean estimate for patients who had 'not-recovered' only, which was used in conjunction with data from Evans et al. (2021) (see response to B21 for further detail).

Table 66: Recovery status by WHO class – Evans 2022 Appendix A (SR6a)

	WHO class 3-4	WHO class 5	WHO class 6	WHO class 7-9	Total
Recovered	30.9%	36.3%	28.5%	18.8%	28.8%
Not recovered	45.5%	44.8%	45.1%	67.9%	51.7%
Unsure	23.6%	18.9%	26.4%	13.3%	19.5%

Abbreviations: COVID-19 – Coronavirus disease 2019; EQ-5D – Euroqol 5 dimensions 5 level; WHO – World Health Organisation

B24. Section B3.4.32. The CS describes two studies reporting quality of life following ICU admission for COVID-19 from Table 34 of Appendix H and two further studies reporting EQ-5D utility scores for relevant states (Nakshbandi et al. and Han et al.) However, further studies are described in Table 33 of Appendix H which appear to report EQ-5D utility scores for relevant health states (Garrigues 2020, Taboada 2021, Ojeda 2021, Tran 2021, de la Plaza 2022, Halpin 2021, Said 2021, Meys 2020, and Lerum 2021.) Please explain why none of the studies identified in Table 33 of Appendix H that reported EQ-5D utility data were deemed relevant for the health economic analysis.

Response:

The HRQoL SLR identified plausible and robustly sourced utility values for COVID-19 for pre-exposure and asymptomatic post-exposure sub-populations. The studies identified were assessed for their relevance to the health economic analysis. The TLR was conducted alongside to identify utility estimates that had been used in previously published health economic evaluations of treatments for COVID-19. Reported utilities which correspond with the defined health states and are representative of the modelled population were key criteria for selecting appropriate values for the base case.

The acute phase utilities sourced from Rafia et al. 2022, and long-COVID utilities sourced from Evans et al. 2021 and adjusted using Evans et al. 2022 were selected as base-case inputs to ensure consistency with the ScHARR model.(48,49,61) The ScHARR model was specifically developed to assess UK individuals at high-risk of

requiring hospital care due to COVID-19. This alignment with our target population, as well as the strict quality-control and legitimacy associated with ScHARR assessments ultimately led to the choice of Rafia et al. 2022 and Evans et al. 2022, despite other sources identified in the SLR being plausible alternatives, particularly for long-COVID (Halpin 2021 and Garrigues 2020).(48,61–63)

Furthermore, when compared against Rafia et al. 2022 and Evans et al. 2022, many of the alternative studies in Table 33 of Appendix H were deemed less relevant to inform the health economic analysis for a number of reasons including smaller sample sizes (de la Plaza 2022, Lerum 2021), or populations that were not representative of the model population in terms of mean age and comorbidities, or limited to small geographical areas which may not be generalisable (Meys 2020, Tran 2021, Ojeda 2021, Said 2021, Taboada 2021). (48,61,64–70)

In addition, the alternative utility sources were reported in a way which did not fit our modelled health states as appropriately as Rafia et al. 2022 and Evans et al. 2022, which provided utility decrements for each hospitalised state in the acute period or stratified by WHO classification in the longer term. The use of utilities from the referenced studies would have required mapping to the defined health states and additional assumptions, ultimately producing greater uncertainty.

As identified in the deterministic sensitivity analysis (DSA), health state utilities have little impact on the ICER and are not key drivers of the model. To quantify the uncertainty around utility estimates, plausible lower and upper bounds were tested in the DSA which covered sufficient variation in disutility comparable to the alternative values sourced in the SLR, as can be seen in Table 62 of the company submission. Health state utilities were found to have very little impact on the ICER in the DSA as depicted in Figure 17.

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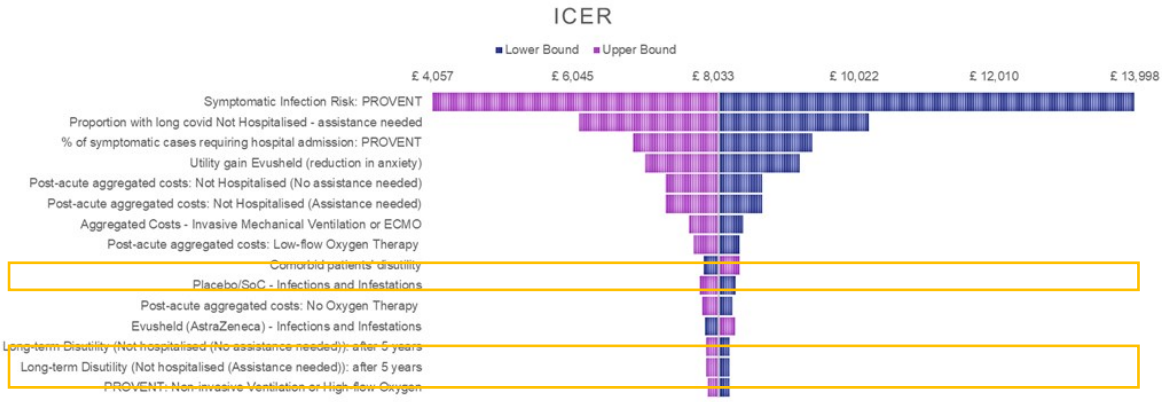
Figure 17: Tornado diagram – utility analyses highlighted



Abbreviations: ECMO – Extracorporeal membrane oxygenation; ICER – Incremental cost-benefit ratio; SoC – Standard of care

B25. Please describe how the utility decrement of 0.19 for acute COVID-19 infection not requiring hospitalisation has been estimated. Please identify the original source study/studies used to derive the decrement and report whether the source(s) of this estimate complies with the NICE reference case.

Response:

There were no utility estimates specific to symptomatic COVID-19 infection identified through the SLR. Previously published health economic evaluations of treatments for COVID-19 (Kelton et al. 2021(71) Whittington et al. 2022(72) and Jovanoski et al. 2022 (73) used a value of 0.19 which was originally sourced from an influenza modelling study which complies with the NICE reference case (Smith et al. 2002(74)).

Smith et al. (2002) reported a utility of 0.84 for the 'well' population aged 55-64 derived from Gold et al. 1998.(75) Gold et al. estimated utility weights using the Health and Limitations Index (HALeX) developed by the National Center the Health Statistics using a sample from the general US population.(75) Smith et al. (2002) also reported an untreated influenza illness utility weight of 0.65, taken from Sacket et al. 1978.(76) Sacket et al. reported a mean daily health state disutility for home confinement for an unnamed contagious disease using a time-trade off method in the general Canadian population. (76)

The difference between the utilities reported by Gold et al. 1998 (0.84) and Sacket et al. (1978) is calculated as 0.19 and has been used to estimate the utility decrement

associated with COVID-19.(75,76) Based on the findings of the SLR, AstraZeneca are not aware of a more appropriate estimate.

B26. CS Section B3.4.5.6. p150 The CS states that 'UK clinicians advised that the availability of Evusheld would cause an instant improvement in high-risk immunocompromised patients…' Please provide supportive evidence for this statement. Was this informed by expert elicitation, if so, how many clinicians were involved and how many supported this statement. When discussing this issue, were the clinicians informed about the FDA guidance (referred to in question A3) in which clinicians are advised to inform patients about the increased risk of COVID-19 due to variants not neutralised by Evusheld.

Response:

The statement was informed by expert elicitation. As discussed in Question A3, interviews with three UK clinical experts directly treating high-risk, immunocompromised patients were conducted on the 22nd and 26th of July 2022. These expert opinions came from leading UK clinical academics (professors of immunology, clinical immunology, and haematology).

The FDA added the advice to inform patients about the increased risk of COVID-19 due to certain variants on 3rd October 2022. Following this update, in subsequent discussions between AstraZeneca and these experts they continued to express support for the benefit of Evusheld.

In addition, as discussed in Question A3, the statement is further supported by 125 clinicians across 17 specialities who have expressed considerable support and requirement from patient groups to receive Evusheld in a consensus statement(8), and in an open letter from 18 charities representing patient groups across relevant populations(9).

In the recent NICE ACM for the multiple technology appraisal (MTA) of Therapeutics for people with COVID-19 conducted on 18th October 2022, patient groups and representatives unanimously expressed that treatment options to prevent severe

COVID-19 symptoms provide immediate relief and improvement to high-risk immunocompromised patients:

"Any therapeutic which prevents a hospital stay has a value that extends beyond just the patient, but impacts on their family as a whole."

- Down's Syndrome Association representative

"Having quick and safe access to treatments in the community has been a relief and gives people a bit more confidence to return to their previous routines and activities."

- MS Society representative

Abbreviations: MS – Multiple sclerosis

These citations refer to post-exposure protection, consequently the assumption can be drawn that being protected from contracting COVID-19 in the first place, as well as being more protected in case of infection, would incur similar if not higher benefit. This is reflected in a quote from a patient representative at the MTA meeting who said "*patents feel they are being stalked by COVID-19. They would much rather be protected from COVID-19 than have to wait for treatments after contracting the virus.*".

Adverse events

B27. Please indicate what definition of SAEs has been used to derive the data in Table 49 and please provide an exact reference to where this data has come from either in the cited peer-reviewed article or within the CSR. Do these figures come from doubling the incidence reported in Table 30 but restricting only to those SAEs with more than 5 per arm for either arm? If so, please clarify what grade of AE constitutes a SAE?

Response:

The serious adverse event (SAE) incidence rates from Table 30 and 49 of the company submission is based on PROVENT trial data reporting participants with at least one SAE. This data was sourced from the supplementary appendix (Table S5) to Levin et al. 2022.(33)

A SAE is defined as an AE occurring during any study phase that meets one or more of the following criteria: (33)

- Results in death
- Is immediately life threatening
- Requires inpatient hospitalisation or prolonged existing hospital stay
- Results in persistent or significant disability or incapacity
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardise the participant or require to treatment to prevent one of the outcomes above

The severity rating scale by grades is not used to define SAEs. The definition sourced from the PROVENT clinical study protocol highlights the distinction between serious and severe AEs. Severity is a measure of intensity, whereas seriousness is defined by the criteria above. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE unless it meets the criteria.(2)

AZ can confirm that the AE incidence figures in Table 49 are derived from Table 30 by doubling the incident rate as to account for retreatment at 6 months in the model.

Due to the low incident rate, only SAEs with ≥5 incidences, equivalent to ≥0.1 in the sample of 5197 (PROVENT 2022), were used in the model.

Probabilistic sensitivity analysis

B28. The daily costs, number of days and aggregate costs for hospitalisation all have a flag for being included in the PSA. Please clarify why this is necessary if the aggregate costs are simply the daily cost multiplied by the number of days.

Response:

The cost-effectiveness model provides two options to costing hospitalisations: (1) using “bundled” or “aggregated” costs which reflect the total costs for each of the hospitalisation health states or (2) using “daily” costs which are then multiplied by the number of days. The parameters feeding into these options include rows 27:32 (“bundled” or “aggregated”), rows 40:45 (“daily”) and rows 51:56 (number of days) on the “Resource Use” sheet. These parameters are fed through the “Parameters” sheet and varied in the PSA. The overall costs are then calculated using the inputs from the “Parameters” sheet in rows 15:20 on the “Resource Use” sheet; these calculated inputs do not then go through the “Parameter” sheet again. Therefore, there is no double counting within the PSA.

Note: whilst the overall costs are calculated by the daily cost multiplied by the number of days (under the “daily” option), the aggregated costs are separate inputs used under the “bundled” option.

B29. Please confirm whether the long COVID costs are varied within the PSA, as the values in the array named “mLTAggCost” do not appear to link forward to any model calculations. Instead the values in the array named “mLTCost” appear to be used within the Markov calculation but that array links back to cell “Calculations!F238” which does not appear to vary within the PSA. Please clarify.

Response:

This has been corrected in the version uploaded to NICE docs on 26th October (*titled ID6136 tixagevimab-cilgavimab CEM with revised base case and EAG scenarios v2.0 26.10 CiC*); the array “mLTCost” which is used in the model calculations now uses values from “iLTAggCost” which go through the “Parameter” sheet. The PSA results with the revised base case and long-COVID costs included are presented in Table 67. Note: the inclusion of the uncertainty related to long-COVID costs has a negligible impact on the probabilistic results; the updated probabilistic ICER (£7,906) aligns with the original probabilistic ICER presented in the model sent on the 21st October (£7,932) i.e., without this correction

Table 67: Revised base case - probabilistic analysis results including uncertainty relating to long-COVID costs

Technologies	Total costs	QALYs	Costs	QALYs	ICER	INMB (£30,000 per QALYs)
No prophylaxis	[redacted]	[redacted]	[redacted]	[redacted]	£ 7,906	[redacted]
Evusheld	[redacted]	[redacted]				

Abbreviations: ICER – incremental cost-effectiveness ratio; INMB – incremental net monetary benefit; QALY – quality adjusted life year

B30. The distribution of cases across the hospitalised and non-hospitalised states does not appear to have been included within the PSA according to the flags within the parameter sheet (all cells to the right of the array named “mCDNoPropT” are zero). Please explain how uncertainty regarding this distribution has been captured.

Response:

The distribution of cases across the hospitalised and non-hospitalised states is calculated based on three parameters:

- “mRiskHospPbo” i.e., the proportion of symptomatic cases requiring hospital admission from PROVENT
- “mPropAssistance” i.e., the proportion of non-hospitalised patients requiring no assistance
- “mHospDist” i.e., the distribution of hospitalisation sourced from Cusinato et al. 2022 (varied sources in response to Clarification Question B8)

These parameters are varied within the PSA and are sourced from inputs going through the “Parameters” sheet. Therefore, including the calculated resulting distribution would double count any uncertainty associated with these inputs.

Disaggregated results by health state

B31. The disaggregated results summarising QALY gain by health state in Appendix J, Table 43, do not summarise all QALY gains and losses within the model. The total QALYs and incremental QALYs in the final row of this table should match those reported in Table 64 of CS Document B. The results appear to be summarised according to the outcomes experienced in the decision-tree phase of the model. If that is the intended format, then please add a row for the patients who are not infected in the acute phase. The QALYs shown should cover all gains during both the acute and long-term phases of the model. If there are QALY gains that apply equally to all patients regardless of health state, then please either include these within each health state or provide as an additional row. Please provide an updated Table 43 (Appendix J) summarising all QALY gains by health state and ensure that the source of these figures can be located in the submitted model for validation.

Response:

The disaggregated QALYs for the revised base case are presented in Table 68 – these are also included on the "CE Results" sheet in the cost-effectiveness model. These QALYs align with the revised base case.

Table 68: Disaggregated health state QALYs (revised base case)

	QALY intervention (Evusheld)	QALY comparator (Placebo)	Increment	Absolute increment	% Absolute increment
Acute Phase					
Recovered	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Long Covid	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Not Infected/Asymptomatic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Death	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Long-term Markov					
Infected - Not hosp - no assistance needed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Infected - Not Hosp - assistance needed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Infected - No Oxygen Therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Infected - Low-flow Oxygen Therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	QALY intervention (Evusheld)	QALY comparator (Placebo)	Increment	Absolute increment	% Absolute increment
Infected - Non-invasive Ventilation or High-flow Oxygen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Infected - Invasive Mechanical Ventilation or ECMO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Not Infected	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Re-infection	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]		

Abbreviations: ECMO – Extracorporeal membrane oxygenation; QALY – quality-adjusted life year

B32. The disaggregated costs by health state shown in Appendix J, Table 44 do not include all costs within the model. The final line of this table should match the incremental costs in Table 64 of Document B. If summarising outcomes according to the patient's health status within the acute phase model, then please add a row for the health state for non-infected patients. Please amend Appendix Table 44 to include all costs falling on patients within each health state or add additional rows to include costs falling outside of the health states. Please provide an updated Table 44 (Appendix J) summarising all costs by health state and ensure that the source of these figures can be located in the submitted model for validation.

Response:

The disaggregated costs presented in for the revised base case are presented in Table 69 – these are also included on the "CE Results" sheet in the cost-effectiveness model. These costs align with the revised base case.

Table 69: Disaggregated health state costs (revised base case)

	Cost intervention (Evusheld)	Cost comparator (Placebo)	Increment	Absolute increment	% Absolute increment
Acute Phase					
Recovered	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Long Covid	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Not Infected/Asymptomatic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Death	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Long-term Markov					

	Cost intervention (Evusheld)	Cost comparator (Placebo)	Increment	Absolute increment	% Absolute increment
Infected - Not hosp - no assistance needed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Infected - Not Hosp - assistance needed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Infected - No Oxygen Therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Infected - Low-flow Oxygen Therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Infected - Non-invasive Ventilation or High-flow Oxygen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Infected - Invasive Mechanical Ventilation or ECMO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Not Infected	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Re-infection	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]		

Abbreviations: ECMO – Extracorporeal membrane oxygenation

Section C: Textual clarification and additional points

C1. The CS section B2.8.1.5.b states on page 80 “For the key secondary endpoint, the efficacy of Evusheld compared with placebo was consistent across pre-defined subgroups (see Appendix E for further details).” However, Appendix E states that the subgroup results for PROVENT are presented in the main submission and refers the reader back to section B.2.9.15 which does not exist. Please provide the evidence supporting this statement which is missing from Appendix E.

Response:

The efficacy of Evusheld versus placebo was consistent across-predefined subgroups for both primary and secondary endpoints. Results for primary and secondary endpoints are presented below in Table 70 and Table 71, respectively, and in Figures 11 and 12 of the CS.

Post hoc analyses were also conducted to assess efficacy of Evusheld for the IC sub-population, who accounted for 18.3% of the PROVENT population. Details are provided in question A20 above, and in Section B.2.8.1.5.a of the CS.

Table 70: Efficacy for Incidence of First SARS-CoV-2 RT-PCR-positive Symptomatic Illness by Subgroup Primary Analysis (Full Pre-Exposure Analysis Set)- Primary endpoint

Subgroup	Interaction P-value	Evusheld (N=3441)		Placebo (N=1731)		RRR (95% CI)
		n	Observed Events (%)	n	Observed Events (%)	
Age at informed consent	[redacted]					
< 60 years		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>= 60 years		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age at informed consent	[redacted]					
< 65 years		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>= 65 years		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age at informed consent	[redacted]					
< 75 years		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>= 75 years		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sex	[redacted]					
Male		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Female		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Race	[redacted]					
American Indian or Alaska Native		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Asian		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Black or African American		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Subgroup	Interaction P-value	Evusheld (N=3441)		Placebo (N=1731)		RRR (95% CI)
		n	Observed Events (%)	n	Observed Events (%)	
Native Hawaiian or Other Pacific Islanders		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
White		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ethnicity	[redacted]					
Hispanic or Latino		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Not Hispanic or Latino		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Resident in long-term care facility	[redacted]					
Yes		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Increased risk of exposure to infection with SARS-CoV-2	[redacted]					
Yes		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Increased risk for inadequate response to active immunization	[redacted]					
Yes		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Region	[redacted]					
North America		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
United Kingdom		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Subgroup	Interaction P-value	Evusheld (N=3441)		Placebo (N=1731)		RRR (95% CI)
		n	Observed Events (%)	n	Observed Events (%)	
European Union		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Country	[redacted]					
United States		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
United Kingdom		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Belgium		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
France		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spain		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
COVID-19 co-morbidities	[redacted]					
None		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
At least one		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
High risk for severe COVID-19 at baseline	[redacted]					
Yes		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
History of Obesity (>30 kg/m^2)	[redacted]					
Yes		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Obesity (>= 30 kg/m^2)	[redacted]					
Yes		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Subgroup	Interaction P-value	Evusheld (N=3441)		Placebo (N=1731)		RRR (95% CI)
		n	Observed Events (%)	n	Observed Events (%)	
No		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Morbid Obesity (>= 40 kg/m^2)	[redacted]					
Yes		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chronic kidney disease	[redacted]					
Yes		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diabetes	[redacted]					
Yes		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Immunosuppressive disease	[redacted]					
Yes		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Immunosuppressive treatment	[redacted]					
Yes		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CV disease	[redacted]					
Yes		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Subgroup	Interaction P-value	Evusheld (N=3441)		Placebo (N=1731)		RRR (95% CI)
		n	Observed Events (%)	n	Observed Events (%)	
No		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
COPD	[redacted]					
Yes		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chronic liver disease	[redacted]					
Yes		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]					
Yes		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Asthma	[redacted]					
Yes		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cancer	[redacted]					
Yes		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Smoking	[redacted]					
Yes		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Subgroup	Interaction P-value	Evusheld (N=3441)		Placebo (N=1731)		RRR (95% CI)
		n	Observed Events (%)	n	Observed Events (%)	
No		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sickle cell disease	[redacted]					
Yes		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI– confidence interval; COPD– chronic obstructive pulmonary disease; CV– cardiovascular disease; NE– Not estimable; RRR– Relative risk reduction

Table 71: Efficacy for Incidence of Post-Treatment Response for SARS-CoV-2 Nucleocapsid Antibodies by Subgroup (Full pre-exposure analysis set)- Secondary endpoint

Subgroup	Interaction P-value	Evusheld (N=3441)		Placebo (N=1731)		RRR (95% CI)
		n	Observed Events (%)	n	Observed Events (%)	
Number of Participants with negative baseline		[redacted]		[redacted]		
Age at informed consent	[redacted]					
< 60 years		[redacted]		[redacted]	[redacted]	[redacted]
>= 60 years		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age at informed consent	[redacted]					
< 65 years		[redacted]		[redacted]	[redacted]	[redacted]
>= 65 years		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age at informed consent	[redacted]					

Subgroup	Interaction P-value	Evusheld (N=3441)		Placebo (N=1731)		RRR (95% CI)
		n	Observed Events (%)	n	Observed Events (%)	
< 75 years						
>= 75 years						
Sex						
Male						
Female						
Race						
American Indian or Alaska Native						
Asian						
Black or African American						
Native Hawaiian or Other Pacific Islanders						
White						
Ethnicity						
Hispanic or Latino						
Not Hispanic or Latino						
Resident in long-term care facility						
Yes						
No						
Increased risk of exposure to infection with						
Yes						
No						

Subgroup	Interaction P-value	Evusheld (N=3441)		Placebo (N=1731)		RRR (95% CI)
		n	Observed Events (%)	n	Observed Events (%)	
Increased risk for inadequate response to active immunization						
Yes						
No						
Region						
North America						
United Kingdom						
European Union						
Country						
United States						
United Kingdom						
Belgium						
France						
Spain						
COVID-19 co-morbidities						
None						
At least one						
High risk for severe COVID-19 at baseline						
Yes						
No						

Subgroup	Interaction P-value	Evusheld (N=3441)		Placebo (N=1731)		RRR (95% CI)
		n	Observed Events (%)	n	Observed Events (%)	
History of Obesity (>30 kg/m^2)						
Yes						
No						
Obesity (>= 30 kg/m^2)						
Yes						
No						
Morbid Obesity (>= 40 kg/m^2)						
Yes						
No						
Chronic kidney disease						
Yes						
No						
Diabetes						
Yes						
No						
Immunosuppressive disease						
Yes						
No						
Immunosuppressive treatment						
Yes						

Subgroup	Interaction P-value	Evusheld (N=3441)		Placebo (N=1731)		RRR (95% CI)
		n	Observed Events (%)	n	Observed Events (%)	
No						
CV disease						
Yes						
No						
COPD						
Yes						
No						
Chronic liver disease						
Yes						
No						
Hypertension						
Yes						
No						
Asthma						
Yes						
No						
Cancer						
Yes						
No						

Subgroup	Interaction P-value	Evusheld (N=3441)		Placebo (N=1731)		RRR (95% CI)
		n	Observed Events (%)	n	Observed Events (%)	
Smoking						
Yes						
No						
Sickle cell disease						
Yes						
No						

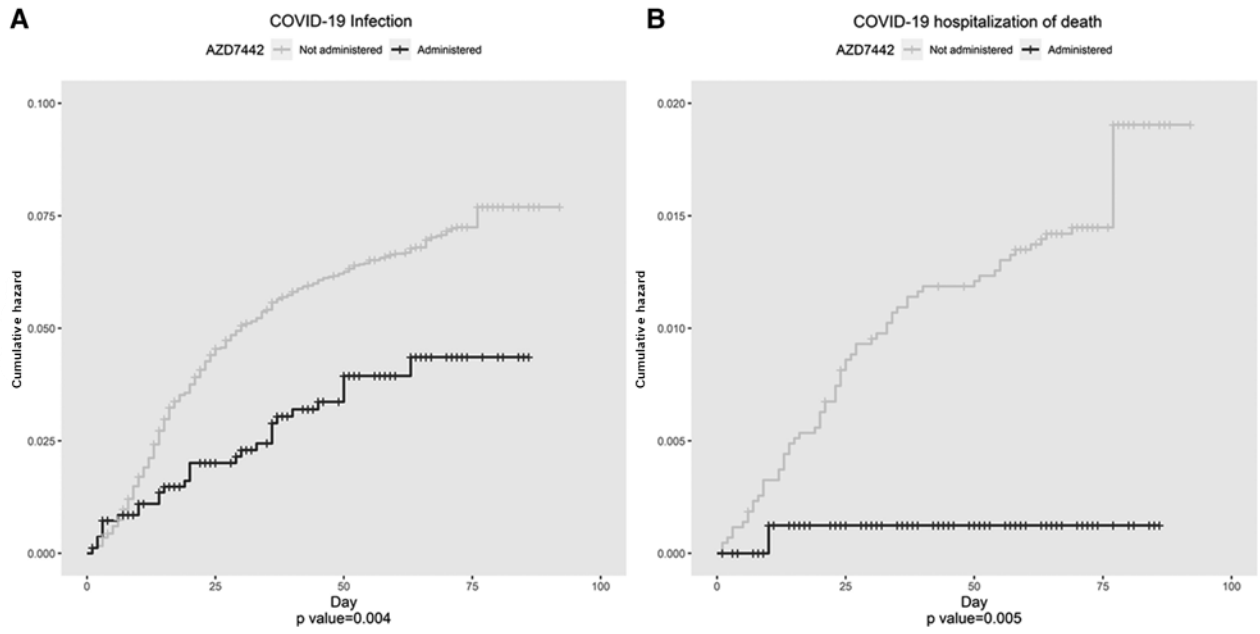
Abbreviations: CI– confidence interval; COPD– chronic obstructive pulmonary disease; CV– cardiovascular disease; NE– Not estimable; RRR– Relative risk reduction

C2. Please clarify if CS, Figure 14 is labelled incorrectly. The vertical axis is labelled as the hazard ratio, implying a comparison between groups that provides a single figure, but plot lines are provided for both groups suggesting that it is actually showing the cumulative hazards by study group**.**

Response:

Figure 14 was aligned with the published manuscript; however, AstraZeneca acknowledge that the figure shows the Kaplan-Meier cumulative hazard. Please see below for an update to figure 14 and 15 of the CS.

Figure 72: (A) Infection and (B) severe disease rates over time by Evusheld administration status, Kaplan-Meier cumulative hazard:(19)



C3. The numbers in Table 40 do not appear to match those in the model (e.g. Table 40 suggests that 7.66% are infected but model the model suggests this is 7.68%). Please clarify if this is a typo in Table 40 and the correct figures are those in the model. If so, please provide a corrected Table 40.

Response:

AZ acknowledge that there was a typographical error in Table 40 of the company submission. Table 73 below presents the correct values based on the model

submitted on the 22nd of September titled ID6136 tixagevimab–cilgavimab Cost-effectiveness analysis v1.0 ACIC.

Table 73. Overall distribution of hospitalised and non-hospitalised patients (Evusheld) – corrected version of Table 40 from the company submission

	Young-Xu et al. 2022 (base case) (4)	PROVENT (scenario) (2)	Kertes et al. 2022 (scenario) (19)
Not infected	92.32%	96.12%	88.48%
Not hospitalised – no assistance needed	3.59%	1.88%	5.39%
Not hospitalised – assistance needed	3.59%	1.88%	5.39%
No oxygen therapy	0.13%	0.03%	0.19%
Low-flow oxygen therapy	0.20%	0.05%	0.30%
NIV or high-flow oxygen	0.09%	0.02%	0.13%
IMV or ECMO	0.08%	0.02%	0.11%

Abbreviations: AN – Assistance needed; ECMO – Extracorporeal membrane oxygenation; IMV – Invasive mechanical ventilation; NAN – No assistance needed; NIV – Non-invasive ventilation.

C4. Please provide clinical study reports for the PROVENT RCT. These are cited in the submission (references 81 and 82), but as far as we can see, these are not included in the reference pack. If these are included, then please indicate the file name so we can identify the file.

Response:

AstraZeneca would like to highlight that references 81 and 82 are duplicates. The CSR has been included in the updated reference pack (file name: d8850c00002-clinical-study-report_APPROVED).

C5. The title of Table 30 says “Deaths and AEs with an outcome of death”. Please clarify if these events actually refer to any ‘AEs with an outcome of death’ as implied by the header for Table 30 or only to serious adverse events as implied by the first row of the table?

Response:

AstraZeneca would like to highlight that there is an error in the table. The table header is correct, and the table refers to deaths and any other AEs that cause an outcome of death. The correct version should be as follows (Table 74):

Table 74: Deaths and Adverse Events with an Outcome of Death by System Organ Class and Preferred Term, Safety Analysis Set, June 2021 DCO – corrected version of Table 30 in company submission

	Number (%) of Participants	
System Organ Class Preferred Term	**AZD7442 300 mg IM (N = 3461)**	**Placebo (N = 1736)**
Total number of deaths	[redacted]	[redacted]
Deaths related to COVID-19[a]	[redacted]	[redacted]
Participants with at least one AE with an outcome of death	[redacted]	[redacted]
Cardiac disorders	[redacted]	[redacted]
Arrhythmia	[redacted]	[redacted]
Myocardial infarction	[redacted]	[redacted]
Infections and infestations	[redacted]	[redacted]
COVID-19	[redacted]	[redacted]
Septic shock	[redacted]	[redacted]
Injury, poisoning and procedural complications	[redacted]	[redacted]
Overdose	[redacted]	[redacted]
Toxicity to various agents	[redacted]	[redacted]
Nervous system disorders	[redacted]	[redacted]
Dementia Alzheimer's type	[redacted]	[redacted]
Renal and urinary disorders	[redacted]	[redacted]
End stage renal disease	[redacted]	[redacted]
Renal failure	[redacted]	[redacted]
Respiratory, thoracic and mediastinal disorders	[redacted]	[redacted]
Acute respiratory distress syndrome	[redacted]	[redacted]

[a] Based on the adjudicated cause of death.
AEs are defined as any adverse event that started or worsened in severity on or after the first dose of IMP. AEs are coded using the MedDRA dictionary, version 24.0.
AEs are sorted alphabetically by SOC, and within each SOC, PTs are sorted by decreasing order of total frequency. Participants with multiple events in the same preferred term are counted only once in that preferred term. Participants with events in more than one preferred term are counted once in each of those preferred terms. Participants with events in more than one preferred term within the same SOC will be counted only once in that SOC. Percentages are based on the number of participants in the analysis set by arm.
Abbreviations: AE– adverse event; COVID-19– coronavirus disease 19; IM– intramuscular; IMP– investigational medicinal product; MedDRA– Medical Dictionary for Regulatory Activities; N– number of participants in the safety analysis set; PT– preferred term; SOC– system organ class
Source: (2)(DCO: 29 June 2021).

C6. The total QALYs in Table 65 for the PSA base-case results do not seem to match (to 2s.f.) the results showing in the submitted model, however, the incremental QALYs and ICERs do match and the scatter plot similarity suggests that the results come from the same model run. Please confirm if this is a typo and the incremental QALYs should be [redacted] for no prophylaxis and Evusheld respectively.

Response:

AZ would like to confirm that this is indeed a typographical error. A corrected version of Table 65 from the company submission, document B, is provided below in Table 75 (based on the model submitted on the 22nd of September titled ID6136 tixagevimab–cilgavimab Cost-effectiveness analysis v1.0 ACIC).

Table 75: PSA results: corrected version of Table 65 from company submission.

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)
No prophylaxis	[redacted]	[redacted]	[redacted]				
Evusheld	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	11,916

Abbreviations: ICER – Incremental cost-effectiveness ratio; LYG – Life years gained; QALYs – Quality-adjusted life years

C7. PRIORITY Violato et al. (2022) (CS, Doc B, reference 55) does not appear to have been included in the reference pack and is described as “in press”. This documented is cited as the source of the HRQoL associated with shielding which is a key model input. Please provide a copy of this document so the methods can be properly scrutinised.

Response:

The requested reference has been added to the reference pack.

C8. CS, Doc B, Reference 32 is described as 'Data on File', however the citation on page 21 appears to relate to an estimate of the proportion of the UK population who are not able to be fully vaccinated. The EAG does not believe that this is likely to have come from data only available within the company's primary research. Please provide the original source for this statistic of 0.00067% of the population not being able to be fully vaccinated.

Response:

The 0.00067% was calculated based the estimated number of people who would be contraindicated to vaccination in the US (2,217 people, sourced from *Centers for Disease Control and Prevention* (77)) expressed as a percentage of the US population (332,763,177 at date of calculation), as follows:

$$\left(\frac{2{,}217}{332{,}763{,}177}\right) * 100$$

Refer to Table 76 for a breakdown of vaccine adverse events reported in the 2,217 people estimated contraindicated to vaccination.

Table 76: VAERS Adverse Cases Reported – Anaphylaxis Myocarditis, Pericarditis, and Pericardial Effusion

Age Group (years)	Total	Anaphylaxis	Myocarditis/Pericarditis/ Pericardial Effusion
18-64	1,615	210	1,405
65+	1,885	60	210
Unknown	1,916	31	NA
Total	2,217	301	1,615

Abbreviations: NA – Not available, VAERS – Vaccine Adverse Events Reporting System. Limitations and assumptions: Cases where Myocarditis was present along with Pericarditis/Pericardial Effusion have been counted in Myocarditis only to avoid double counting. Cases where Pericarditis was present along with Pericardial Effusion, have been counted in Pericarditis only

C9. CS, Doc B, Reference 45: Please provide either an exact web link to the cited document or a copy of the cited document.

Response:

The exact web link to the cited document is: https://www.icnarc.org/DataServices/Attachments/Download/c28fc446-6046-ed11-9149-00505601089b

A copy of the cited document is included in the updated reference pack (file name: ICNARC_COVID report).

C10. CS, Doc B, Reference 47: This reference is described as an 'Analysis of hospital admissions in England' with the authors being AstraZeneca and the only reference given as ‘Data on File’. Please provide a summary of this analysis so that the data and methods supporting the statements can be properly scrutinised.

Response:

The analysis was commissioned by AstraZeneca working with a 3rd party (Harvey Walsh, part of the OpenHealth group) to analyse COVID-19 related hospital admissions in England. A summary of the analysis, including in-depth information on the methods used is provided in Appendix D. As described in the Protocol Synopsis, one of the primary objectives of the analysis was to determine the total number of COVID-19 hospitalisations (primary diagnosis) and COVID-19 hospitalisation among immunocompromised adults (as defined by Table 8.1 in Appendix D) in England; overall and stratified by COVID-19 wave (variant-based) and COVID-19 vaccination status.

Due to the time required to perform the analysis and the urgent need for the data the analysis was broken down into 2 separate stages of delivery:

- **Stage 1:** The total number of COVID-19 hospitalisations (primary diagnosis) amongst immunocompromised adults during the 12 months to 30th May 2022 (irrespective of vaccination status)

- **Stage 2:** The total number of COVID-19 hospitalisations (primary diagnosis) amongst immunocompromised adults from January 2020 to 30th May 2022 stratified by COVID-19 wave and COVID-19 vaccination status

Attached as Appendix E (Stage 1) and F (Stage 2) are the data from the 2 separate stages of analysis.

In relation to the statements made in our submission, below is a description of how these were quantified along with where the relevant data is contained within the appendices. For ease, the relevant data is **written in red text** in the appendices.

Statement 1

> *These results are consistent with a recent analysis of Hospital Episode Statistics data looking at hospital admissions in England for a 12-month period ending May 30, 2022, which demonstrated that immunocompromised people that had received three or more COVID-19 vaccinations were disproportionally affected by COVID-19 compared to non-immunocompromised people that had also received three or more COVID-19 vaccinations*

Supporting data: As of 30th May 2022, [redacted] patients who had received 3+ COVID-19 vaccines had been hospitalised for COVID-19 (Appendix F / T1. Baseline characteristics / AB7), of which [redacted] (Appendix F / T1. Baseline characteristics / AC7) were immunocompromised. This accounts for [redacted] of all COVID-19 admissions in the cohort of patients who have received 3+ vaccines, even though this population accounts for only a small proportion of the population in England (https://www.gov.uk/guidance/access-community-based-treatments-for-coronavirus-covid-19).

Statement 2

> *This analysis also demonstrated that in-hospital mortality was approximately 50% higher in the highest risk population compared to the general population.*

Supporting data: For the 12-month period ending May 30th, 2022, in-patient mortality for immunocompromised patients admitted to hospital for COVID-19

(primary diagnosis) was [redacted] (Appendix E / Table 2. HCRU and costs / E37) compared to [redacted] in the non-immunocompromised population (Appendix E / Table 2. HCRU and costs / F37)

Statement 3

> *Patients who survived and were discharged had a longer mean length of stay, especially those who received respiratory support*

Supporting data: For the 12-month period ending May 30th, 2022, mean length of stay for immunocompromised adults was [redacted] (Appendix E / Table 2. HCRU and costs / E28) compared to [redacted] for non-immunocompromised individuals (Appendix E / T2. HCRU and costs / F28). In the cohort of patients receiving respiratory support the mean length of stay was [redacted] (Appendix E / Table 2. HCRU and costs / E56) and [redacted] (Appendix E / Table 2. HCRU and costs / F56) respectively.

C11. CS, Doc B, Reference 50: This reference is described as 'Data on File'. Please provide the research supporting the statement on page 25 to which this citation is attributed.

Response:

The 'Data on File" reference in turn refers to the following sources to support the statement:

> *Manca R, De Marco M, Venneri A. The Impact of COVID-19 Infection and Enforced Prolonged Social Isolation on Neuropsychiatric Symptoms in Older Adults With and Without Dementia: A Review. Front Psychiatry. 2020;11:585540.*(78)
>
> *Usher K, Bhullar N, Jackson D. Life in the pandemic: Social isolation and mental health. J Clin Nurs. 2020;29(15-16):2756-2757.*(79)

C12. CS, Doc B, Reference 68: This is described as UK expert interviews with the source being 'Data on File'. Please provide a summary of the methods used in the UK expert interviews including the number approached, the number of respondents, and, if possible, minutes of these meetings or summary reports.

Response:

Please refer to Questions A3 and B26 for details on the UK expert interviews.

C13. CS, Doc B, Reference 137: Please provide a copy of the cited reference that provides the time to symptom resolution data cited in Table 51. The document in the reference pack named "Institute for Clinical and Economic Review - 2021 - Special Assessment COVID-19–Modeling Analysis Pla.pdf" appears to be a copy and paste of a web page with multiple linked documents and does itself not contain the cited data.

Response:

The exact web link to the cited document is: https://osf.io/q854h

A copy of the cited document is included in the updated reference pack (file name: ICER_COVID_19_Modeling_Analysis_Plan).

C14. Please clarify if the correct references are cited on page 22 of the Appendices (63, 64, 79, 82). Reference 79 appears to be a quality-of-life study and reference 82 appears to be a news article about remdesivir. References 63 and 64 appear to relate to studies by Xu et al. and Kertes et al. from the context in the text but the references in the bibliography do not appear to correspond accordingly. If these are the correct references, then please clarify how they support the statement they are

cited against. If they are not the correct references, please supply the correct references and clarify how they support the statements made.

(NB: If there is systematic problem with the bibliography provided within the appendices then please submit an updated document with a corrected bibliography.)

Response:

AstraZeneca acknowledge that there is an error in the reference list. A new version of the appendices has been submitted with updated references and bibliography.

In response to the question, the correct references are:

- Tuekprakhon A, Nutalai R, Dijokaite-Guraliuc A, et al. Antibody escape of SARS-CoV-2 Omicron BA.4 and BA.5 from vaccine and BA.1 serum. Cell 2022;185(14):2422-2433 e13. DOI: 10.1016/j.cell.2022.06.005.
- Young-Xu Y, Epstein L, Marconi VC, et al. Tixagevimab/Cilgavimab for Prevention of COVID-19 during the Omicron Surge: Retrospective Analysis of National VA Electronic Data. medRxiv. (https://www.medrxiv.org/content/medrxiv/early/2022/05/29/2022.05.28.22275716.full.pdf).
- Dejnirattisai W, Huo J, Zhou D, et al. SARS-CoV-2 Omicron-B.1.1.529 leads to widespread escape from neutralising antibody responses. Cell 2022;185(3):467–484.e15. DOI: 10.1016/j.cell.2021.12.046.
- Kertes J, David SSB, Engel-Zohar N, et al. Association between AZD7442 (tixagevimab-cilgavimab) administration and SARS-CoV-2 infection, hospitalization and mortality. Clinical Infectious Diseases 2022. DOI: 10.1093/cid/ciac625

C15. Appendix D Figure 7. Please provide references for all of the papers for which suffixes are given in Figure 7.

Response:

Please find an updated version of Figure 7 from the appendices. The references for each of the suffixes are found below Figure 18.

Figure 18: Evusheld maintains activity against variants of concern, including most omicron sub-lineages

1. National Center for Advancing Translational Sciences. Evusheld: tixagevimab (tixagevimab) and cilgavimab (cilgavimab) mAbs for SARS-CoV-2 antiviral resistance information (version 5). National Center for Advancing Translational Sciences website. https://opendata.ncats.nih.gov/variant/datasets?id=107. Accessed August 25, 2022.

2. Dejnirattisai W, Zhou D, Supasa P, et al. Antibody evasion by the P.1 strain of SARS-CoV-2. Cell. 2021;184:2939-2954.e9.

3. Chen RE, Zhang X, Case JB, et al. Resistance of SARS-CoV-2 variants to neutralisation by monoclonal and serum-derived polyclonal antibodies. Nat Med. 2021;27:717-726.

4. Liu C, Ginn HM, Dejnirattisai W, et al. Reduced neutralisation of SARS- CoV-2 B.1.617 by vaccine and convalescent serum. Cell. 2021;184:4220-4236.e13.

5. Bruel T, Hadjadj J, Maes P, et al. Serum neutralisation of SARS-CoV-2 Omicron sublineages BA.1 and BA.2 in patients receiving monoclonal antibodies. Nat Med. 2022; 28:1297-1302.

6. Dejnirattisai W, Huo J, Zhou D, et al. SARS-CoV-2 Omicron-B.1.1.529 leads to widespread escape from neutralising antibody responses. Cell. 2022;185:467-484.e15.

7. VanBlargan LA, Errico JM, Halfmann PJ, et al. An infectious SARS-CoV-2 B.1.1.529 Omicron virus escapes neutralisation by therapeutic monoclonal antibodies. Nat Med. 2022;28:490-495.

8. Case JB, Mackin S, Errico J, et al. Resilience of S309 and AZD7442 monoclonal antibody treatments against infection by SARS-CoV-2 Omicron lineage strains [preprint published online March 18, 2022]. bioRxiv. 2022. https://doi.org/10.1101/2022.03.17.484787. Accessed August 25, 2022.

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10. Tuekprakhon A, Huo J, Nutalai R, et al. Further antibody escape by Omicron BA.4 and BA.5 from vaccine and BA.1 serum [preprint article and supplementary appendix published online May 23, 2022]. bioRxiv. 2022. https://www.biorxiv.org/content/10.1101/2022.05.21.492554v1. Accessed August 25, 2022.

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14. Takashita E, Yamayoshi S, Simon V, et al. Efficacy of antibodies and antiviral drugs against Omicron BA.2.12.1, BA.4, and BA.5 subvariants. N Engl J Med. 2022;387:468-470.

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C16. Please clarify how the data in Appendix D Figure 6 correspond to outcomes reported in the individual studies cited as “77–83,85–87”.

Response:

Similarly, to C14, AstraZeneca acknowledge that there is an error in the reference list. A new version of the appendices has been submitted with updated references and bibliography.

In response to the question, the corresponding references to figure 6 can be found below. Please note that the correct references have been updated in the submitted appendix.

1. VanBlargan LA et al. An Infectious SARS-CoV-2 B.1.1.529 Omicron Virus Escapes Neutralisation by Therapeutic Monoclonal Antibodies. Nature Medicine 2022. 2022;28:490-495. doi:10.1038/s41591-021-01678-y

2. Dejnirattisai W et al. SARS-CoV-2 Omicron-B.1.1.529 Leads to Widespread Escape from Neutralising Antibody Responses. Cell. 2022;185(3):467-484.e15. doi:10.1016/J.CELL.2021.12.046

3. US Food and Drug Administration FACT SHEET FOR HEALTHCARE PROVIDERS: EMERGENCY USE AUTHORISATION FOR EVUSHELDTM (Tixagevimab Co-Packaged with Cilgavimab). Published online 2021. https://www.fda.gov/media/154701/download [Last accessed: July 2022]

4. Tuekprakhon A et al. Antibody Escape of SARS-CoV-2 Omicron BA.4 and BA.5 from Vaccine and BA.1 Serum. Cell. Published online 2022. doi:10.1016/J.CELL.2022.06.005

5. Chen M et al. Construction and Applications of SARS-CoV-2 Pseudoviruses: A Mini Review. International Journal of Biological Sciences. 2021;17(6):1574. doi:10.7150/IJBS.59184

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C17. Please explain why the footnote in Table 15 in the company submission makes reference to Young-Xu et al. (2022) when table header refers to the PROVENT study.

Response:

AstraZeneca would like to highlight that there is an error in the text. The reference (82) is correct; however, the text should refer to the “AstraZeneca PROVENT CSR (82)”.

References

1. AstraZeneca. A Phase III Randomized, Double-blind, Placebo-controlled, Multi-center Study in Adults to Determine the Safety and Efficacy of AZD7442, a Combination Product of Two Monoclonal Antibodies (AZD8895 and AZD1061), for Pre-exposure Prophylaxis of COVID-19. [Internet]. clinicaltrials.gov; 2022 Jan [cited 2022 Jul 12]. Report No.: NCT04625725. Available from: https://clinicaltrials.gov/ct2/show/NCT04625725

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Appendices

Appendix A

Evusheld RWE search string:

(((((((((Spike protein, SARS-CoV-2[Supplementary Concept])) AND (((monoclonal antibod[Title/Abstract]) OR (mAb[Title/Abstract]) OR ("antibody combination"[Title/Abstract]) OR ("neutralising antibody"[Title/Abstract]) OR ("neutralising antibody"[Title/Abstract])))))) OR (((((monoclonal antibod*[Title/Abstract]) OR (mAb[Title/Abstract]) OR ("antibody combination"[Title/Abstract]) OR ("neutralising antibody"[Title/Abstract]) OR ("neutralising antibody"[Title/Abstract])))) AND (((AstraZeneca[Title/Abstract]) OR (Regeneron[Title/Abstract]) OR ("Eli Lilly"[Title/Abstract]) OR (AbCellera[Title/Abstract]) OR ("NIH Vaccines Research Center"[Title/Abstract]) OR (Takeda[Title/Abstract]) OR (Tychan[Title/Abstract]) OR ("SingHealth Investigational Medicine Unit"[Title/Abstract]) OR (Celltrion[Title/Abstract]) OR ("Vir Biotechnology"[Title/Abstract]) OR (GlaxoSmithKline[Title/Abstract]) OR (Samsung[Title/Abstract]) OR ("WuXi Biologics"[Title/Abstract]) OR (Biogen[Title/Abstract])))))) OR (((AZD7442[Title/Abstract]) OR (((tixagevimab[Title/Abstract]) OR (((cilgavimab[Title/Abstract]) OR (((sotrovimab[Title/Abstract]) OR (((molnupiravir[Title/Abstract]) OR (((paxlovid[Title/Abstract]) OR (((ADG20[Title/Abstract]) OR (Adintrevimab[Title/Abstract]) OR (REGN-COV2[Title/Abstract]) OR (LY-CoV555[Title/Abstract]) OR ("antibody from recovered patients"[Title/Abstract]) OR (TY027[Title/Abstract]) OR (CT-P59[Title/Abstract]) OR (VIR-7831[Title/Abstract]) OR (VIR-7832[Title/Abstract]) OR ("VIR 7831"[Title/Abstract]) OR (VIR7831[Title/Abstract]) OR ("VIR 7832"[Title/Abstract]) OR (VIR7832[Title/Abstract]) OR (casirivimab[Title/Abstract]) OR (imdevimab[Title/Abstract]) OR (bebtelovimab[Title/Abstract]) OR (LY-CoV1404[Title/Abstract]) OR (regdanvimab[Title/Abstract]) OR (ensovibep[Title/Abstract]) OR (bamlanivimab[Title/Abstract]) OR (STI-9167[Title/Abstract]) OR (COVISHIELD[Title/Abstract]) OR (Sorrento Therapeutics[Title/Abstract]) OR (58G6[Title/Abstract]) OR (etesevimab[Title/Abstract]))))) AND (((((COVID-19[MeSH Terms]) OR (SARS-CoV-2[MeSH Terms])))) OR (("covid-19"[Title/Abstract] OR "covid 19"[Title/Abstract] OR "corona"[Title/Abstract] OR "coronae"[Title/Abstract] OR "child"[Title/Abstract] OR "children"[Title/Abstract] OR "adolescents"[Title/Abstract] OR "coronas"[Title/Abstract] OR "corona virus"[Title/Abstract] OR "Novel Corona Virus"[Title/Abstract] OR "corona virus disease"[Title/Abstract] OR "SARS-CoV-2"OR "Coronavirus disease"[Title/Abstract] OR "Coronavirus disease 2019"OR "nCOV"OR "n-COV"[Title/Abstract])))))) NOT (((Review Literature[MeSH Major Topic]) OR (Review[Publication Type])))))*

Appendix B

B3.1 Base case results

B3.1.1 Base case incremental cost-effectiveness analysis results

Evusheld generates [redacted] incremental QALYs and £[redacted] incremental costs over a lifetime horizon compared with no prophylaxis, resulting in an ICER of £ 8,111 per QALY gained. Disaggregated base case results are presented in Appendix J.

Appendix J to follow with questions B31 and B32.

Table 77: Base case results

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)
No prophylaxis	[redacted]	[redacted]	[redacted]	[redacted]	£ 8,111
Evusheld	[redacted]	[redacted]			

Abbreviations: ICER – Incremental cost-effectiveness ratio; LYG – Life years gained; QALYs – Quality-adjusted life years

B3.2 Exploring uncertainty

Updated sensitivity analyses have been conducted to explore structural and parameter uncertainty.

B3.2.1 Probabilistic sensitivity analysis

Updated PSA was conducted to explore the impact of model parameters uncertainty on the results.

The mean values for total costs, LYs, QALYs, and incremental cost per QALY gained for Evusheld versus no prophylaxis through 1,000 simulations of the PSA are presented in Table 78. In the PSA, Evusheld generates [redacted] incremental QALYs and [redacted] incremental costs over a lifetime horizon compared with no prophylaxis, resulting in an ICER of £7,906 per QALY gained (similar to the base case).

The corresponding ICEP and CEAC are presented in Figure 16 and Figure 20, respectively.

Table 78: PSA results

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)
No prophylaxis	[redacted]	[redacted]	[redacted]	[redacted]	£ 7,906
Evusheld	[redacted]	[redacted]			

Abbreviations: ICER – Incremental cost-effectiveness ratio; LYG – Life years gained; QALYs – Quality-adjusted life years

Figure 19: Incremental cost- effectiveness plane

Abbreviations: PSA – Probabilistic sensitivity analysis

Figure 20: Cost-effectiveness acceptability curve

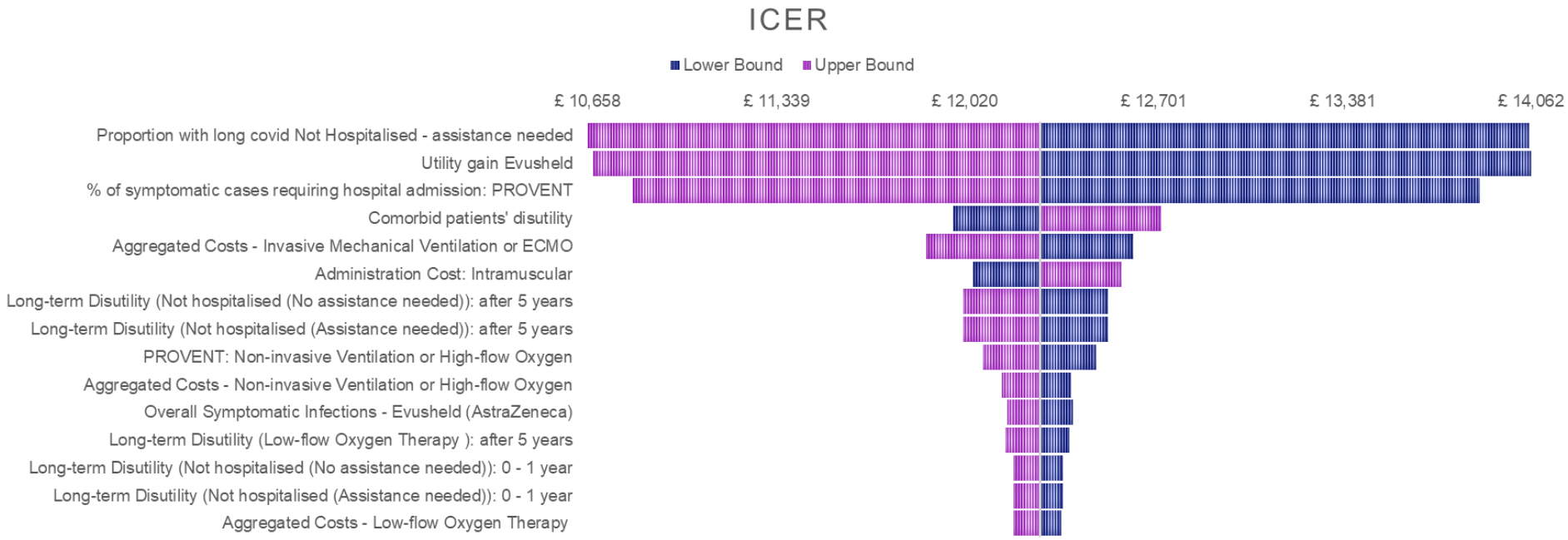
Abbreviations: NMB – Net medical benefit

B3.2.2 Deterministic sensitivity analysis

Updated deterministic one-way sensitivity analysis (OWSA) was conducted to explore the level of uncertainty in the model results.

The OWSA tornado diagram presenting the 15 most sensitive parameters for the sub-population of interest is presented in Figure 21. Table 79 presents the OWSA results for these 15 parameters. The model was most to the proportion of patients with long COVID in the non-hospitalised- assistance needed health state. All scenarios resulted in ICERs significantly below £20,000 per QALY.

Figure 21: Tornado diagram



Abbreviations: ECMO – Extracorporeal membrane oxygenation; ICER – Incremental cost-effectiveness ratio

Table 79: DSA results

ICER		
Parameter	**Lower bound**	**Higher Bound**
Proportion with long covid Not Hospitalised - assistance needed	£ 14,055	£ 10,658
Utility gain Evusheld	£ 14,062	£ 10,678
% of symptomatic cases requiring hospital admission: PROVENT	£ 13,877	£ 10,823
Comorbid patients' disutility	£ 11,978	£ 12,729
Aggregated Costs - Invasive Mechanical Ventilation or ECMO	£ 12,627	£ 11,881
Administration Cost: Intramuscular	£ 12,048	£ 12,584
Long-term Disutility (Not hospitalised (No assistance needed)): after 5 years	£ 12,536	£ 12,014
Long-term Disutility (Not hospitalised (Assistance needed)): after 5 years	£ 12,536	£ 12,014
PROVENT: Non-invasive Ventilation or High-flow Oxygen	£ 12,493	£ 12,085
Aggregated Costs - Non-invasive Ventilation or High-flow Oxygen	£ 12,403	£ 12,153
Overall Symptomatic Infections - Evusheld (AstraZeneca)	£ 12,409	£ 12,173
Long-term Disutility (Low-flow Oxygen Therapy): after 5 years	£ 12,397	£ 12,167
Long-term Disutility (Not hospitalised (No assistance needed)): 0 - 1 year	£ 12,373	£ 12,194
Long-term Disutility (Not hospitalised (Assistance needed)): 0 - 1 year	£ 12,373	£ 12,194
Aggregated Costs - Low-flow Oxygen Therapy	£ 12,367	£ 12,196

Abbreviations: DSA – Deterministic sensitivity analysis; ICER – Incremental cost-effectiveness ratio

Scenario analysis

Table 80 details updated scenario analyses results for Evusheld versus no prophylaxis. Results were most sensitive to the efficacy source (Kertes et. Al 2022). Results were least sensitive to hospitalisation disutility (ScHARR report). All scenarios resulted in ICERs below £ 16,473 per QALY.

Table 80: Scenario analysis results

Description	Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)
Base case	**No prophylaxis**	[redacted]	[redacted]	[redacted]	[redacted]	£ 8,111
	Evusheld	[redacted]	[redacted]			
Discount rate: 0%	**No prophylaxis**	[redacted]	[redacted]	[redacted]	[redacted]	£ 9,812
	Evusheld	[redacted]	[redacted]			
Discount rate: 6%	**No prophylaxis**	[redacted]	[redacted]	[redacted]	[redacted]	£ 8,791
	Evusheld	[redacted]	[redacted]			
Reinfection: Not applied	**No prophylaxis**	[redacted]	[redacted]	[redacted]	[redacted]	£ 8,057
	Evusheld	[redacted]	[redacted]			
Efficacy source: PROVENT	**No prophylaxis**	[redacted]	[redacted]	[redacted]	[redacted]	£ 5,961
	Evusheld	[redacted]	[redacted]			
Efficacy source: Kertes et al. 2022	**No prophylaxis**	[redacted]	[redacted]	[redacted]	[redacted]	£ 10,533
	Evusheld	[redacted]	[redacted]			

% with long COVID at discharge: Evans et al. 2021	**No prophylaxis**	[redacted]	[redacted]	[redacted]	[redacted]	£ 9,095
	Evusheld	[redacted]	[redacted]			
Apply utility benefit associated with Evusheld treatment: 82%	**No prophylaxis**	[redacted]	[redacted]	[redacted]	[redacted]	£ 8,651
	Evusheld	[redacted]	[redacted]			
Hospitalisation disutility: ScHARR report	**No prophylaxis**	[redacted]	[redacted]	[redacted]	[redacted]	£ 8,100
	Evusheld	[redacted]	[redacted]			
Post-acute HRQoL: Evans 2021	**No prophylaxis**	[redacted]	[redacted]	[redacted]	[redacted]	£ 10,206
	Evusheld	[redacted]	[redacted]			

Abbreviations: COVID – Coronavirus disease; HRQoL – Health-related quality of life; ICER – Incremental cost-effectiveness ratio; LYG – Life years gained; QALYs – Quality-adjusted life years; ScHARR – School of health and related research

Appendix C

Table 81 Number (%) of Participants with COVID-19 Related Hospitalisations Before Day 183 (Full Pre-exposure Analysis Set, for Participants in the Immunocompromised Groups)

Number of participants with COVID-19 related hospitalisations before Day 183, n (%)	[redacted]	[redacted]	[redacted]
Hospitalisation due to COVID-19 whole on treatment	[redacted]	[redacted]	[redacted]
Hospitalisation due to COVID-19 – treatment policy	[redacted]	[redacted]	[redacted]

Table 82: Efficacy for Incidence of First COVID-19-related Emergency Department Visit by Day 183, While on-treatment Estimand (Full Pre-exposure Analysis Set, for Participants in the Immunocompromised Groups)

	Statistic	**Evusheld**	**Placebo**
First COVID-19-related emergency department visit by Day 183	N	[redacted]	[redacted]
	n (%)	[redacted]	[redacted]
	RRR	[redacted]	
	RRR (95% CI)	[redacted]	
	P value	[redacted]	

Table 83: Efficacy for Incidence of First Severe or Critical SARS-CoV-2 RT-PCR-positive Symptomatic Illness by Day 183, While On-treatment Estimand (Full Pre-exposure Analysis set, for Participants in the Immunocompromised Groups)

	Statistic	Evusheld	Placebo
First severe or critical SARS-CoV-2 RT-PCR-positive symptomatic illness by Day 183	N	[redacted]	[redacted]
	n (%)	[redacted]	[redacted]
	RRR	[redacted]	
	RRR (95% CI)	[redacted]	
	P value	[redacted]	

Table 84: COVID-19 Risk Assessment (Full Analysis Set, for Participants in the Immunocompromised Groups)

	[redacted]	[redacted]	[redacted]
Increase risk for inadequate response to active immunisation	[redacted]	[redacted]	[redacted]
Elderly	[redacted]	[redacted]	[redacted]
Obese (BMI ≥30 kg/m^2)	[redacted]	[redacted]	[redacted]
Congestive heart failure	[redacted]	[redacted]	[redacted]
COPD	[redacted]	[redacted]	[redacted]
Chronic kidney disease	[redacted]	[redacted]	[redacted]
Chronic liver disease	[redacted]	[redacted]	[redacted]
Immunocompromised state	[redacted]	[redacted]	[redacted]

Intolerant of vaccine	[redacted]	[redacted]	[redacted]
Increased risk of exposure to infection	[redacted]	[redacted]	[redacted]
Health care work	[redacted]	[redacted]	[redacted]
Industrial setting with high risk	[redacted]	[redacted]	[redacted]
Military personnel	[redacted]	[redacted]	[redacted]
Student in dormitory	[redacted]	[redacted]	[redacted]
Other living with high density proximity	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]

Table 85: Demographic and Other Baseline Characteristics (Full Pre-Exposure Analysis Set, for Participants in the Immunocompromised Groups)

Characteristic		[redacted]	[redacted]	[redacted]
Country, n (%)	US	[redacted]	[redacted]	[redacted]
	UK	[redacted]	[redacted]	[redacted]
	Belgium	[redacted]	[redacted]	[redacted]
	France	[redacted]	[redacted]	[redacted]
	Spain	[redacted]	[redacted]	[redacted]
Region, n (%)	North America	[redacted]	[redacted]	[redacted]
	UK	[redacted]	[redacted]	[redacted]
	European Union	[redacted]	[redacted]	[redacted]

Age (years)	N	[redacted]	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]	[redacted]
	Median	[redacted]	[redacted]	[redacted]
Age group, n (%)	≥18 and <60	[redacted]	[redacted]	[redacted]
	≥60 and <70)	[redacted]	[redacted]	[redacted]
	≥70 and <80	[redacted]	[redacted]	[redacted]
	≥80	[redacted]	[redacted]	[redacted]
	≥60	[redacted]	[redacted]	[redacted]
	≥65	[redacted]	[redacted]	[redacted]
	≥75	[redacted]	[redacted]	[redacted]
Sex, n (%)	Male	[redacted]	[redacted]	[redacted]
Ethnicity, n (%)	Hispanic or Latino	[redacted]	[redacted]	[redacted]
	No Hispanic or Latino	[redacted]	[redacted]	[redacted]
	Not reported	[redacted]	[redacted]	[redacted]
	Unknown	[redacted]	[redacted]	[redacted]
Race, n (%)	White	[redacted]	[redacted]	[redacted]
	Black or African American	[redacted]	[redacted]	[redacted]
	Asian	[redacted]	[redacted]	[redacted]
	American Indian or	[redacted]	[redacted]	[redacted]

	Alaska Native			
	Native Hawaiian or other Pacific Islander	[redacted]	[redacted]	[redacted]
	Not reported	[redacted]	[redacted]	[redacted]
	Unknown	[redacted]	[redacted]	[redacted]
	Other	[redacted]	[redacted]	[redacted]
	Missing	[redacted]	[redacted]	[redacted]
Baseline weight (kg)	Mean (SD)	[redacted]	[redacted]	[redacted]
	Median	[redacted]	[redacted]	[redacted]
Height (cm)	Mean (SD)	[redacted]	[redacted]	[redacted]
	Median	[redacted]	[redacted]	[redacted]
Baseline BMI (kg/m^2)	Mean (SD)	[redacted]	[redacted]	[redacted]
	Median	[redacted]	[redacted]	[redacted]
Baseline BMI category, n (%)	<18.5 kg/m^2	[redacted]	[redacted]	[redacted]
	≥18.5 and <25 kg/m^2	[redacted]	[redacted]	[redacted]
	≥25 and < 30 kg/m^2	[redacted]	[redacted]	[redacted]
	≥30 and <40 kg/m^2	[redacted]	[redacted]	[redacted]
	≥40 kg/m^2	[redacted]	[redacted]	[redacted]

	Missing	[redacted]	[redacted]	[redacted]
Under home or other confinement, n (%)	Yes	[redacted]	[redacted]	[redacted]
Resident in long-term care facility	Yes	[redacted]	[redacted]	[redacted]
Smoking status, n (%)	Never	[redacted]	[redacted]	[redacted]
	Former	[redacted]	[redacted]	[redacted]
	Current	[redacted]	[redacted]	[redacted]
ECOG status	0	[redacted]	[redacted]	[redacted]
	1	[redacted]	[redacted]	[redacted]
	>1	[redacted]	[redacted]	[redacted]
	Missing	[redacted]	[redacted]	[redacted]
SARS-CoV-2 status at baseline, n (%)	Negative	[redacted]	[redacted]	[redacted]
	Missing	[redacted]	[redacted]	[redacted]
Any COVID-19 comorbidities at baseline, n (%)		[redacted]	[redacted]	[redacted]
Any high risk for severe COVID-19 at baseline, n (%)		[redacted]	[redacted]	[redacted]
History of obesity (>30 kg/m^2)		[redacted]	[redacted]	[redacted]
Obesity (≥30 kg/m^2)		[redacted]	[redacted]	[redacted]
Morbid obesity (≥40 kg/m^2)		[redacted]	[redacted]	[redacted]
Chronic kidney disease		[redacted]	[redacted]	[redacted]
Diabetes		[redacted]	[redacted]	[redacted]
Immunosuppressive disease		[redacted]	[redacted]	[redacted]

Immunosuppressive treatment		[redacted]	[redacted]	[redacted]
CV disease		[redacted]	[redacted]	[redacted]
COPD		[redacted]	[redacted]	[redacted]
Chronic liver disease		[redacted]	[redacted]	[redacted]
Hypertension		[redacted]	[redacted]	[redacted]
Asthma		[redacted]	[redacted]	[redacted]
Cancer		[redacted]	[redacted]	[redacted]
Smoking		[redacted]	[redacted]	[redacted]
Sickle cell disease		[redacted]	[redacted]	[redacted]

Appendix D

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
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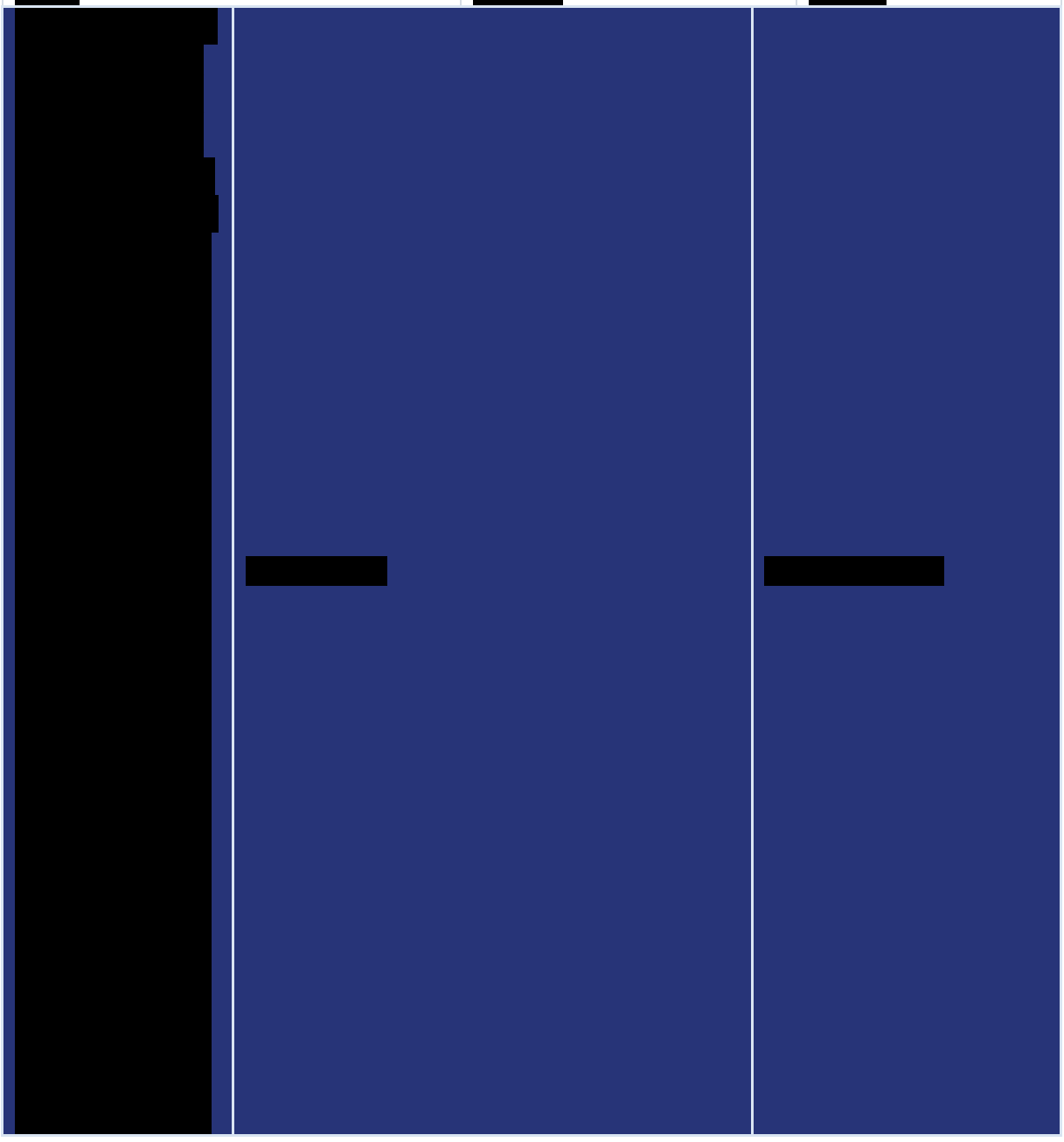

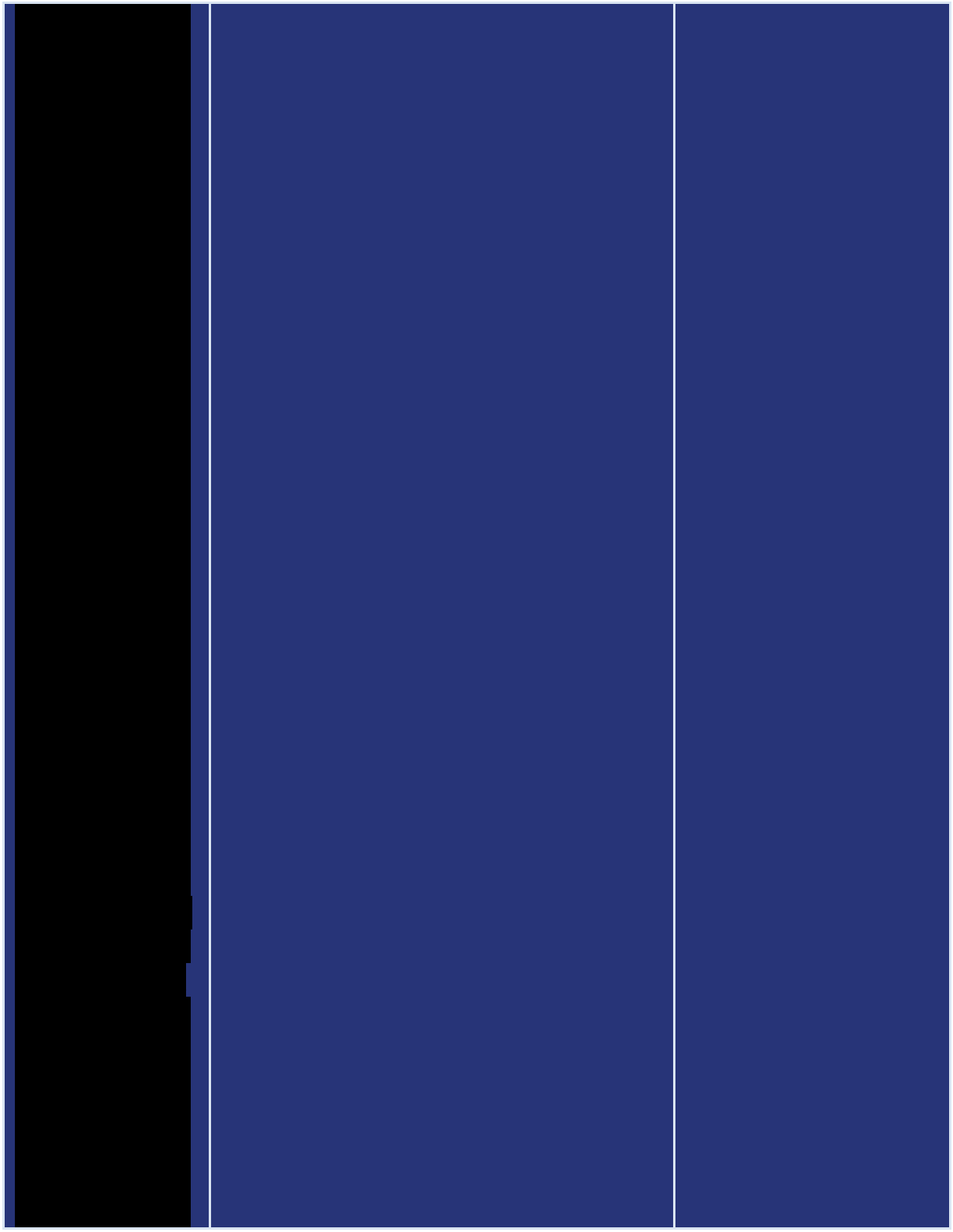

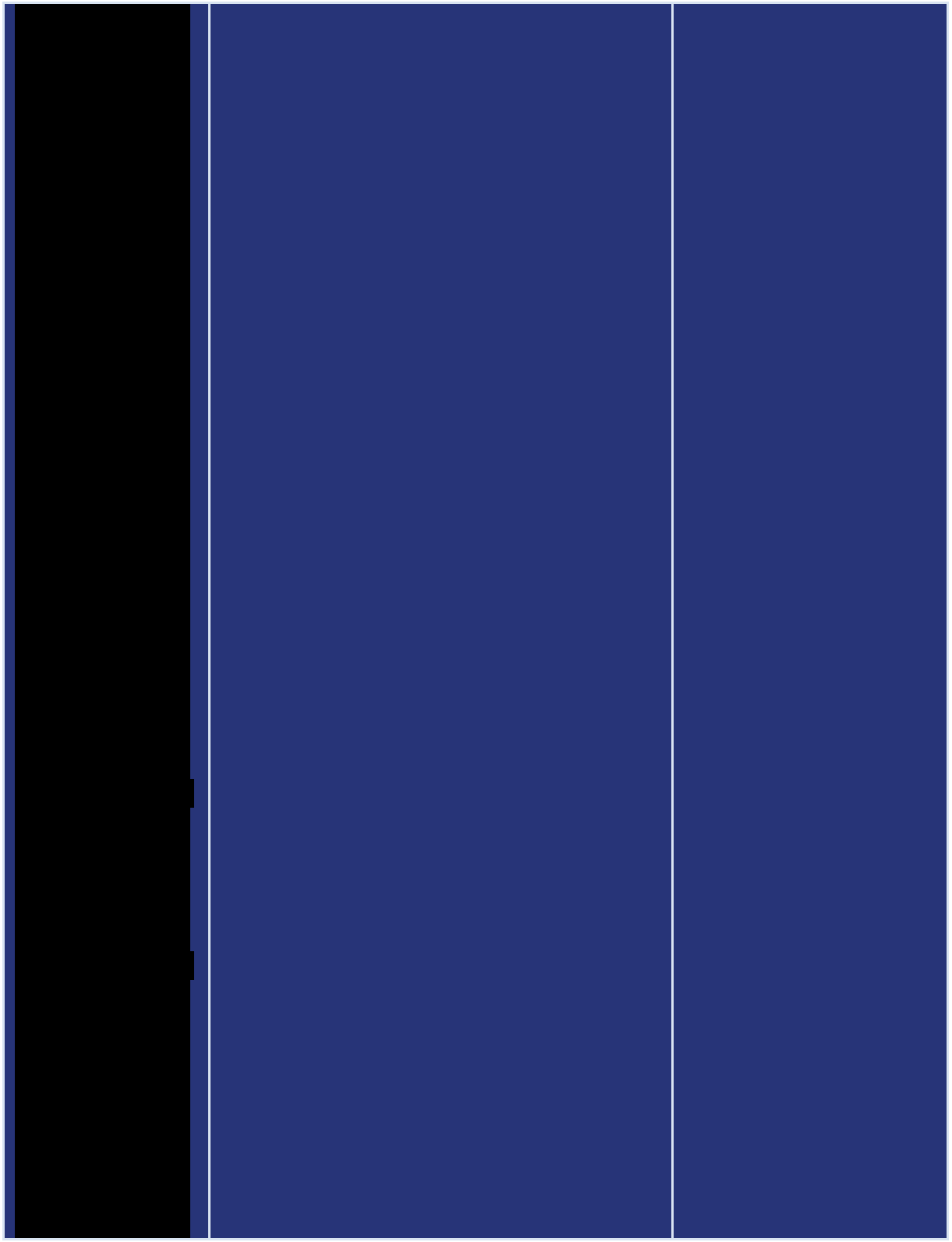

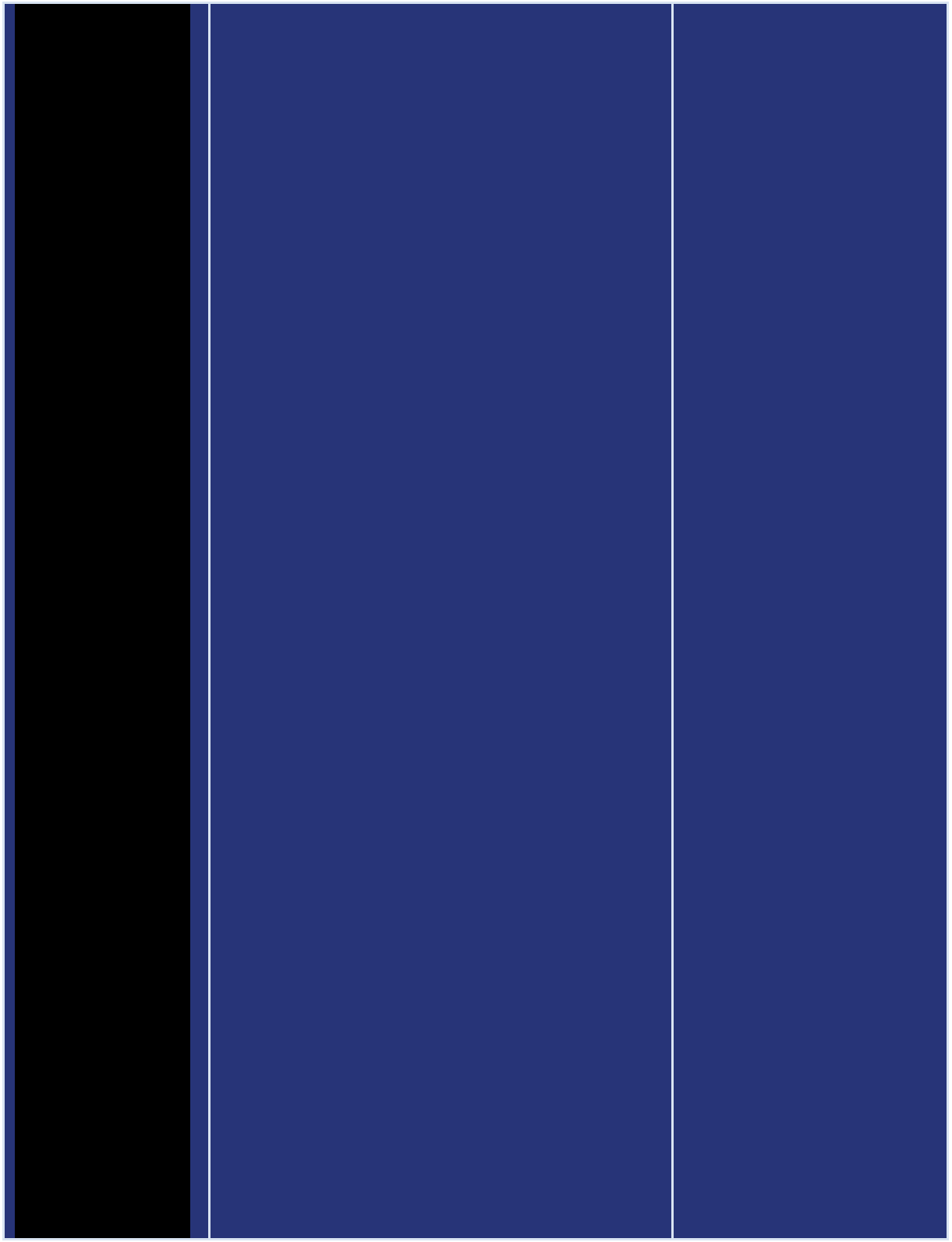

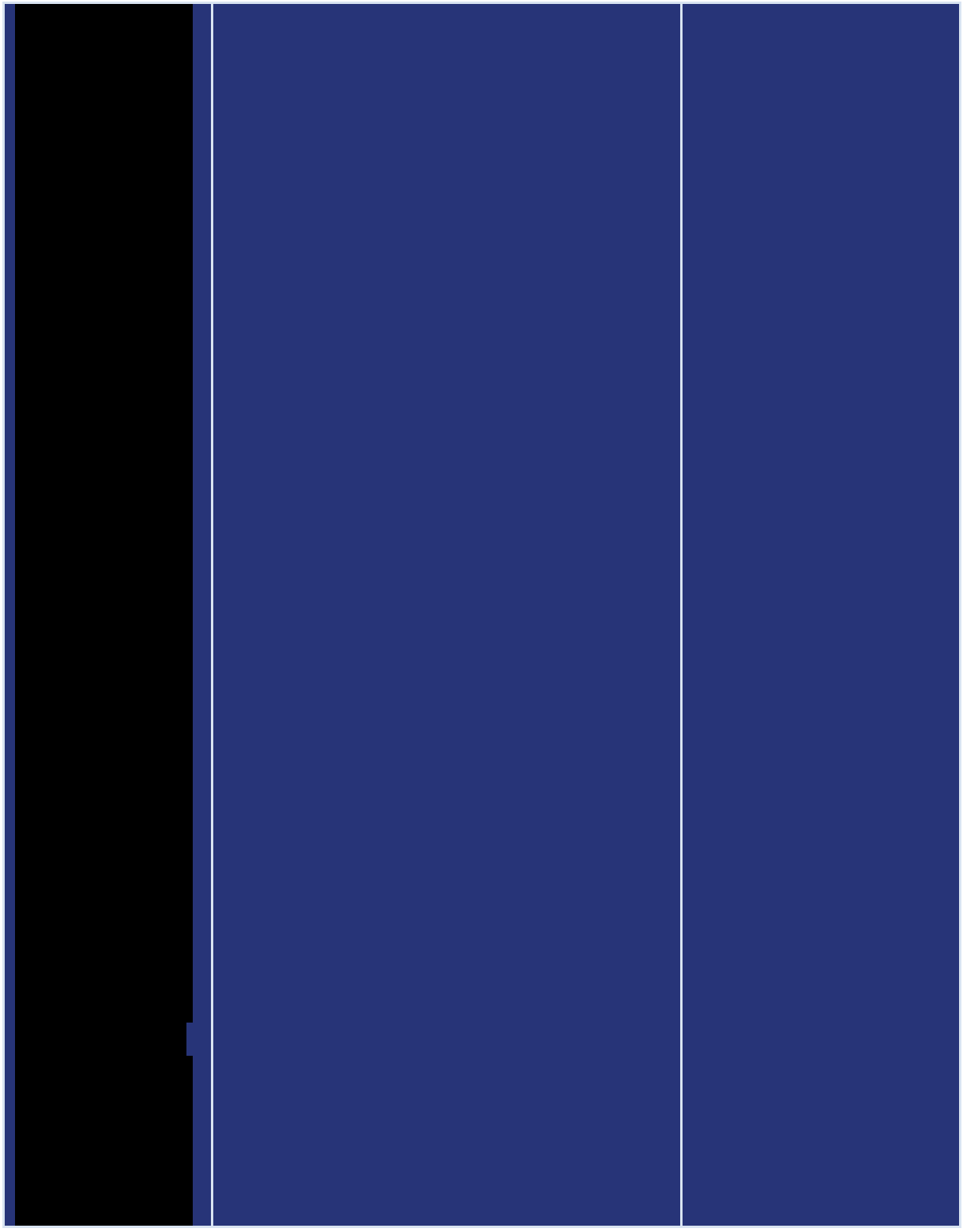

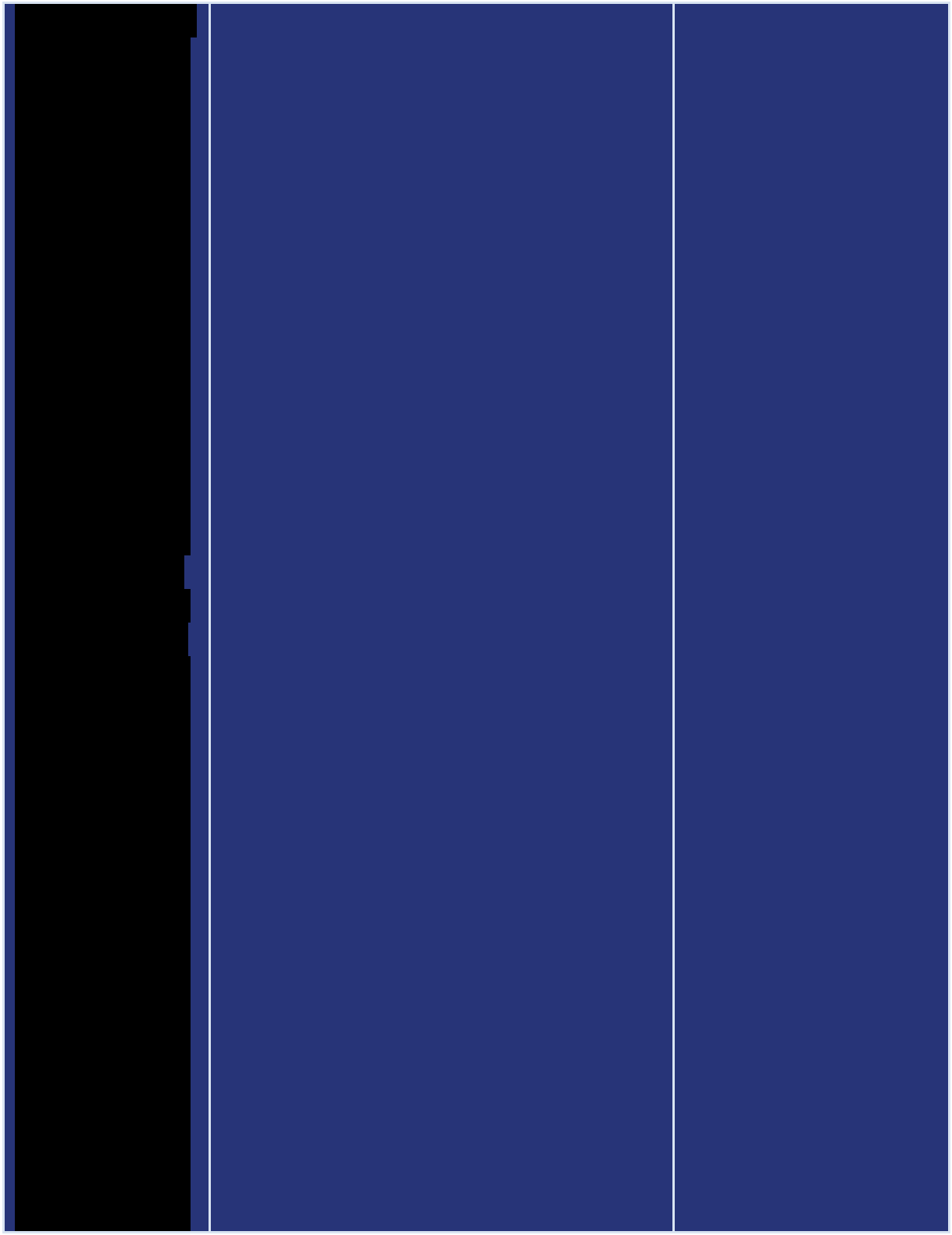

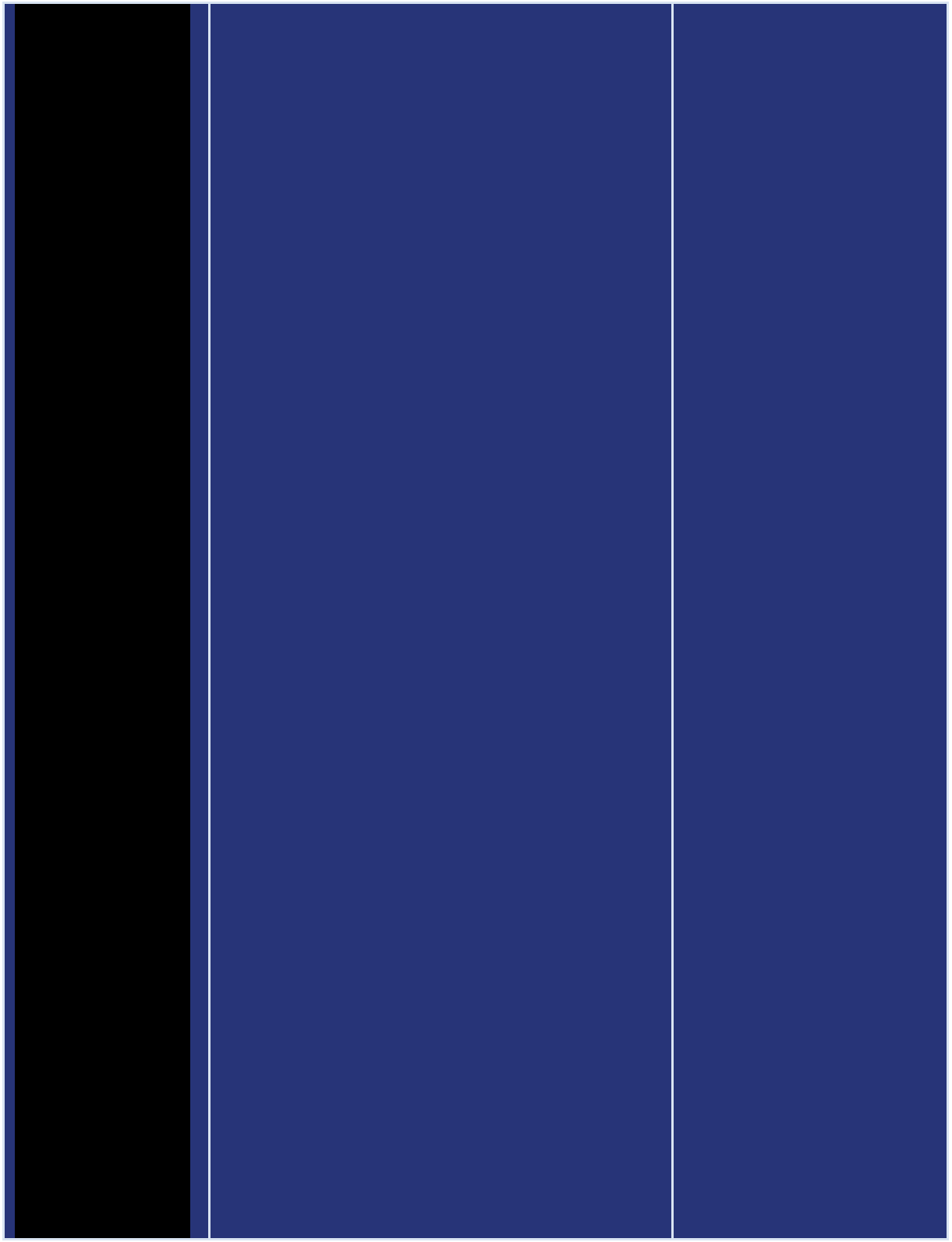

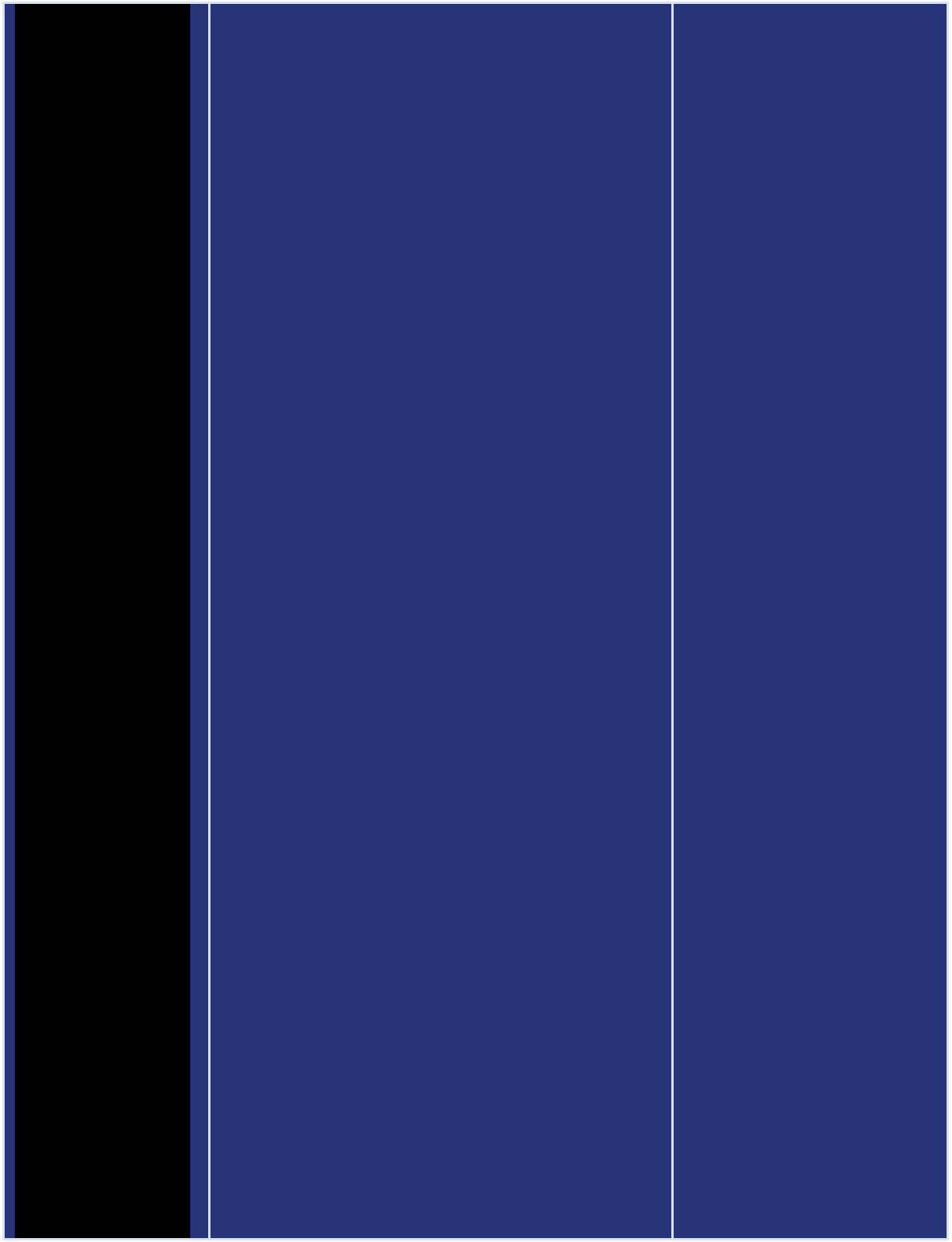

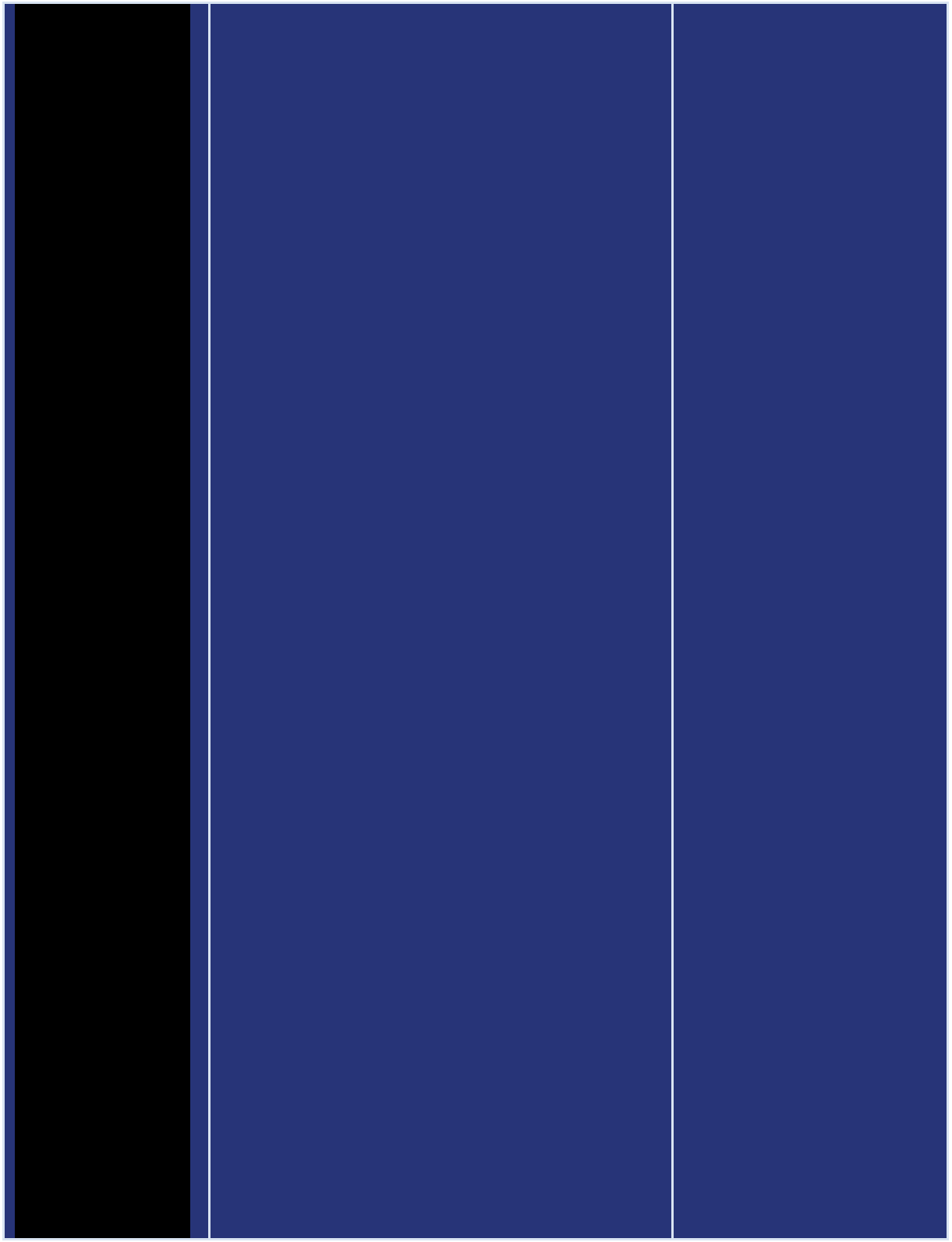

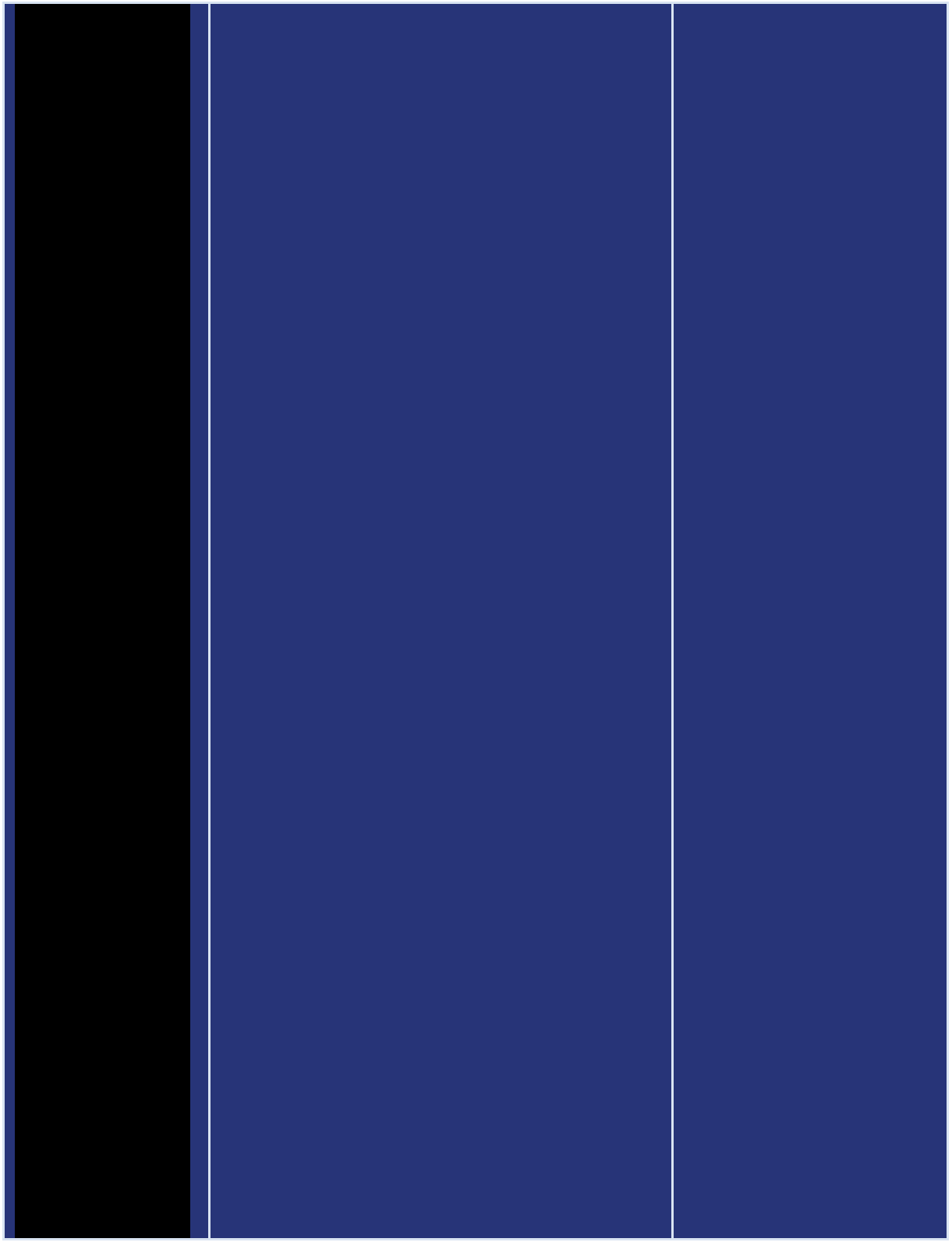

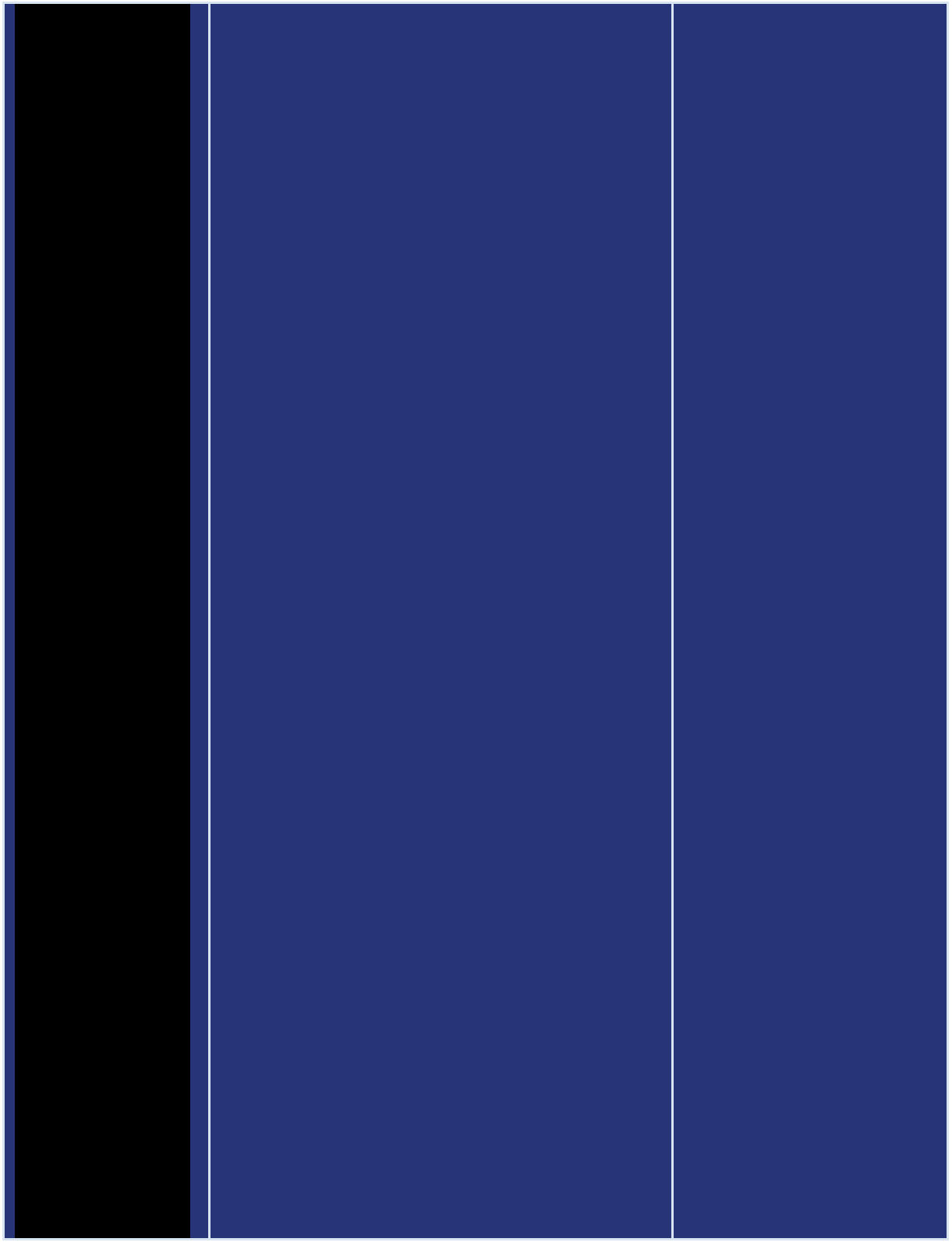

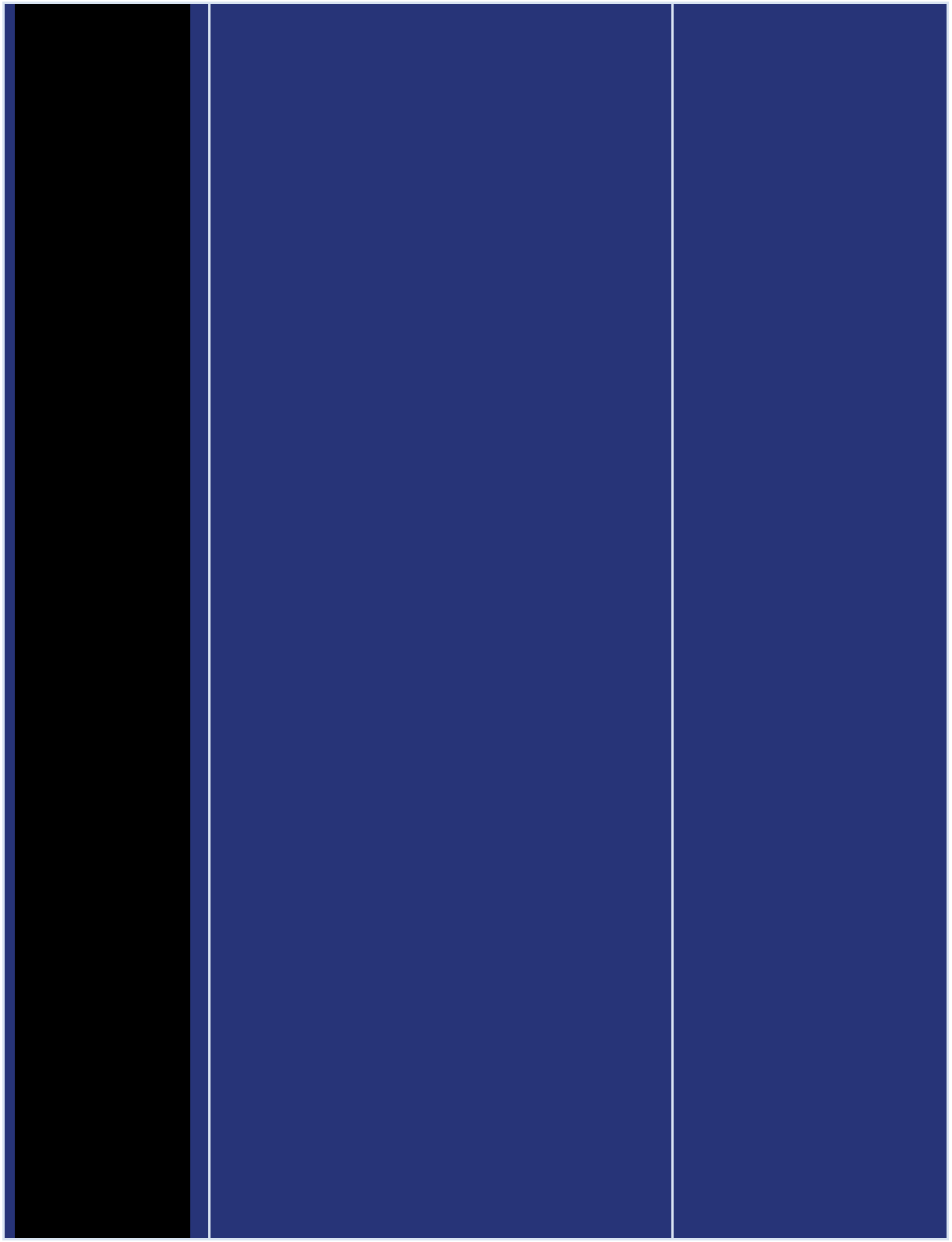

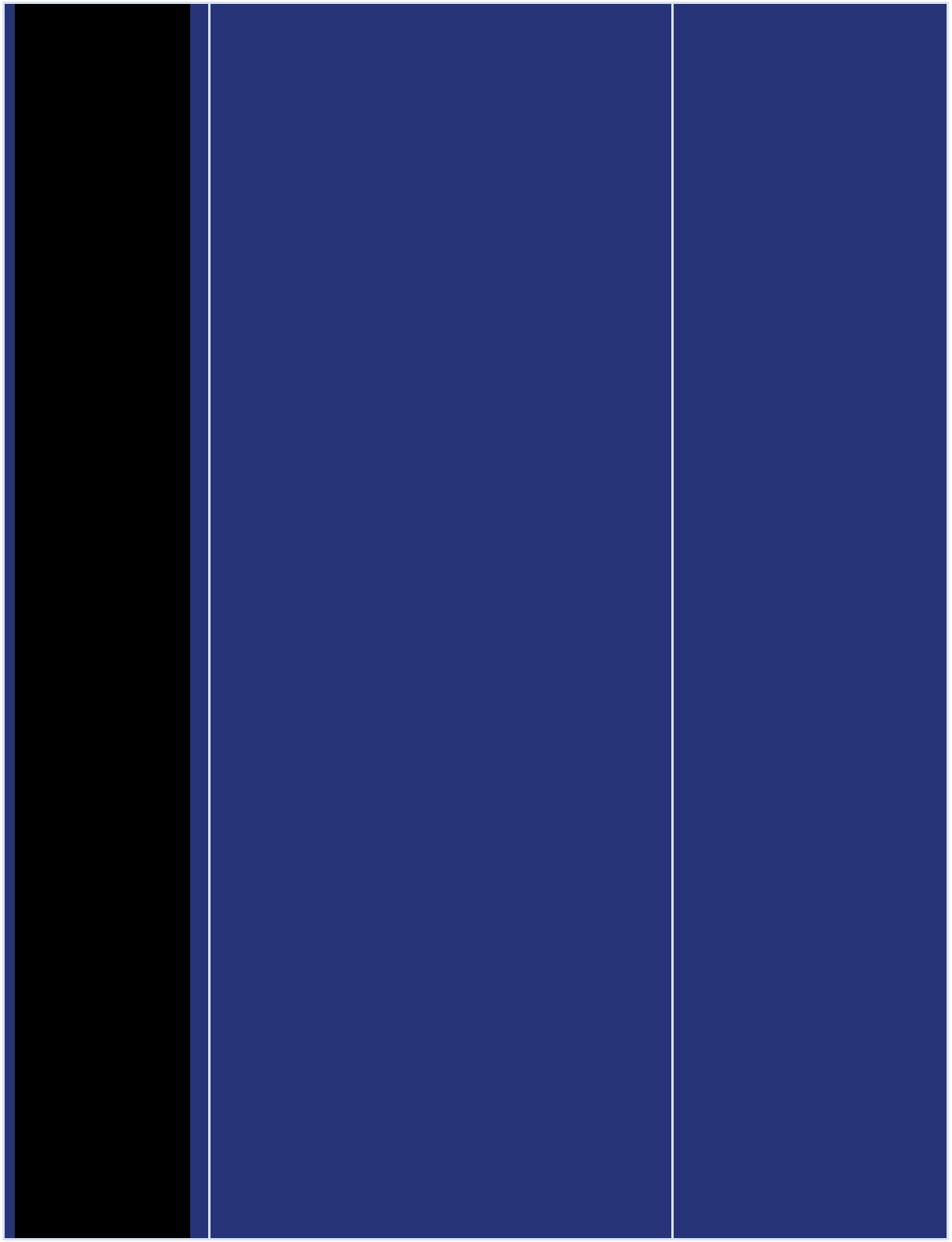

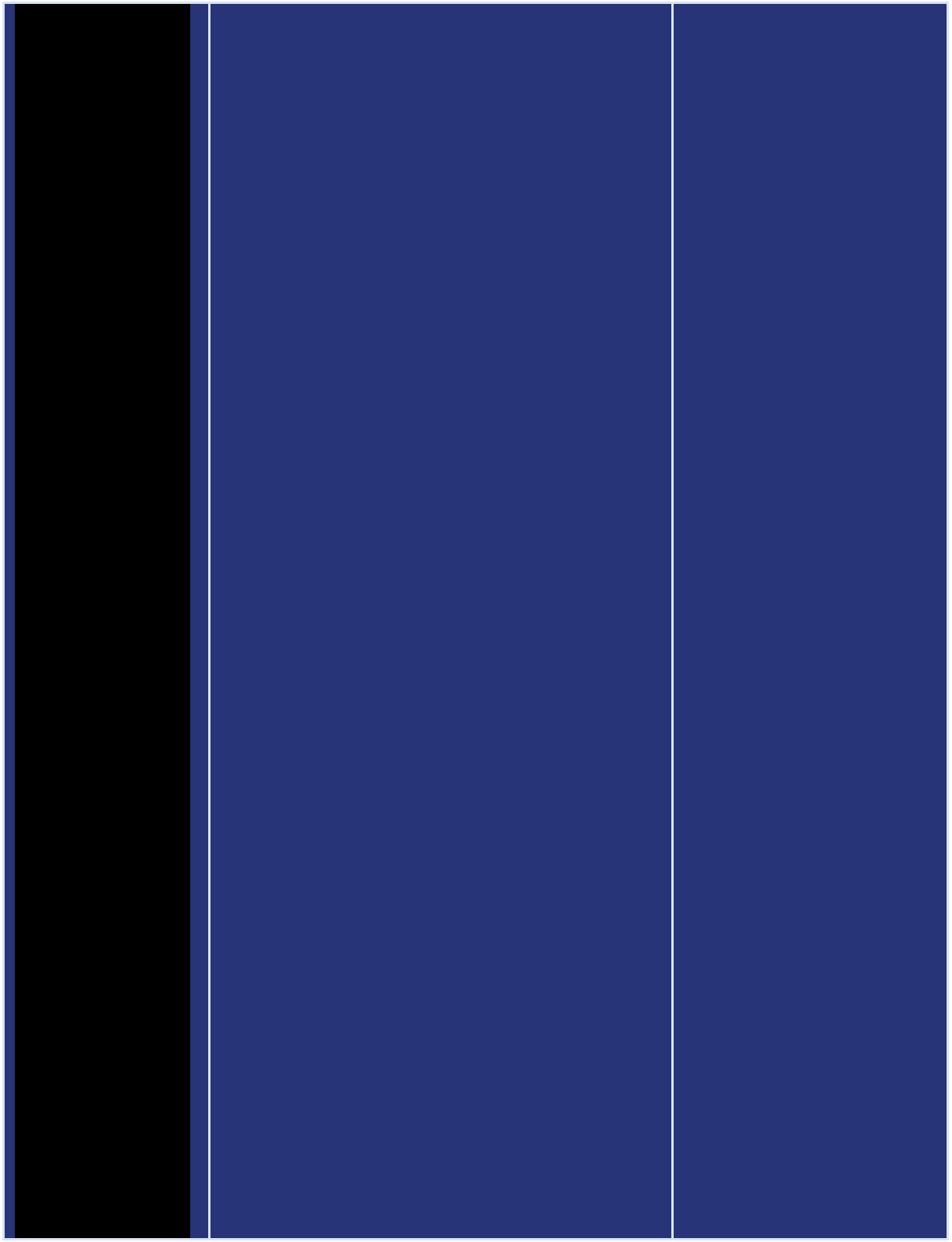

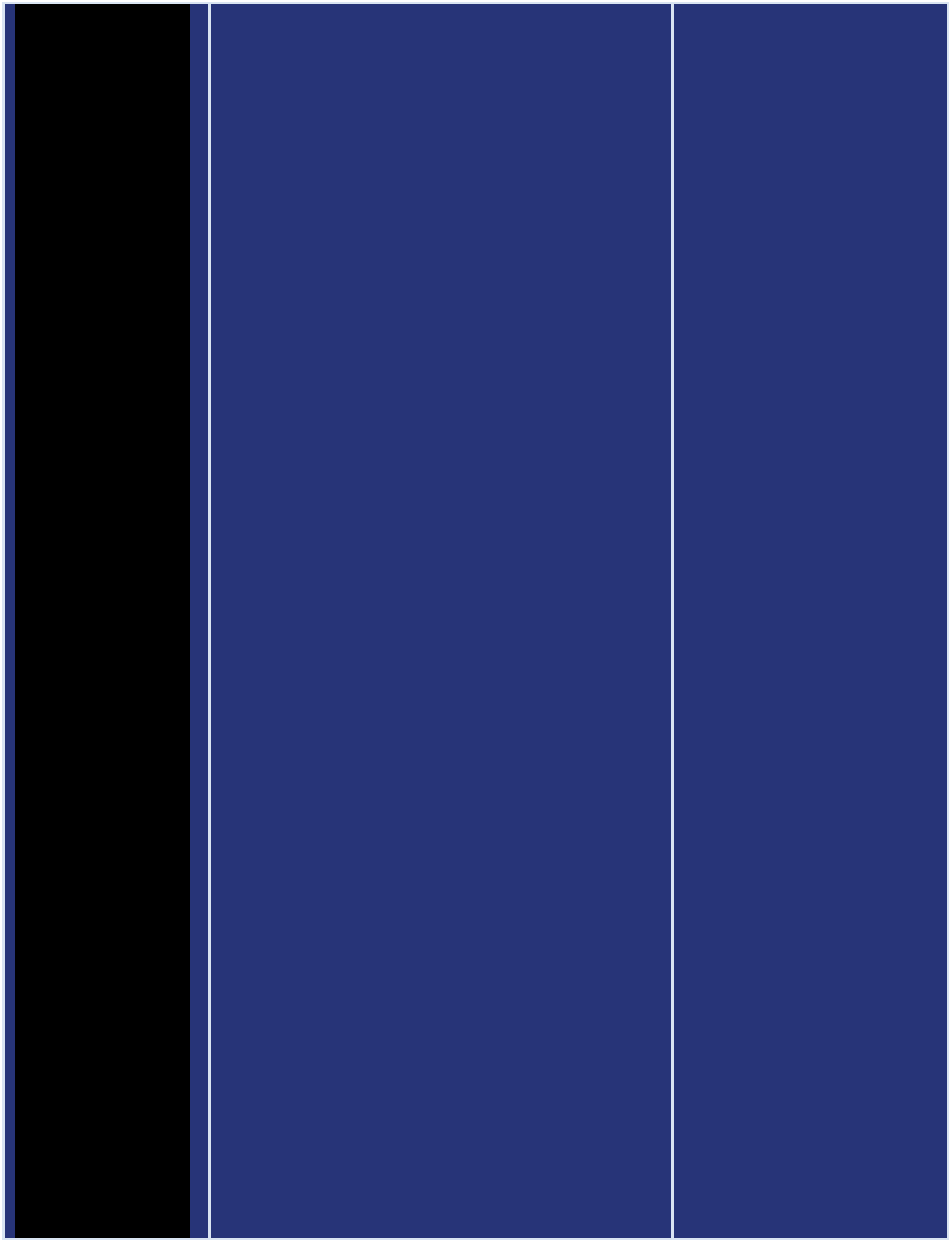

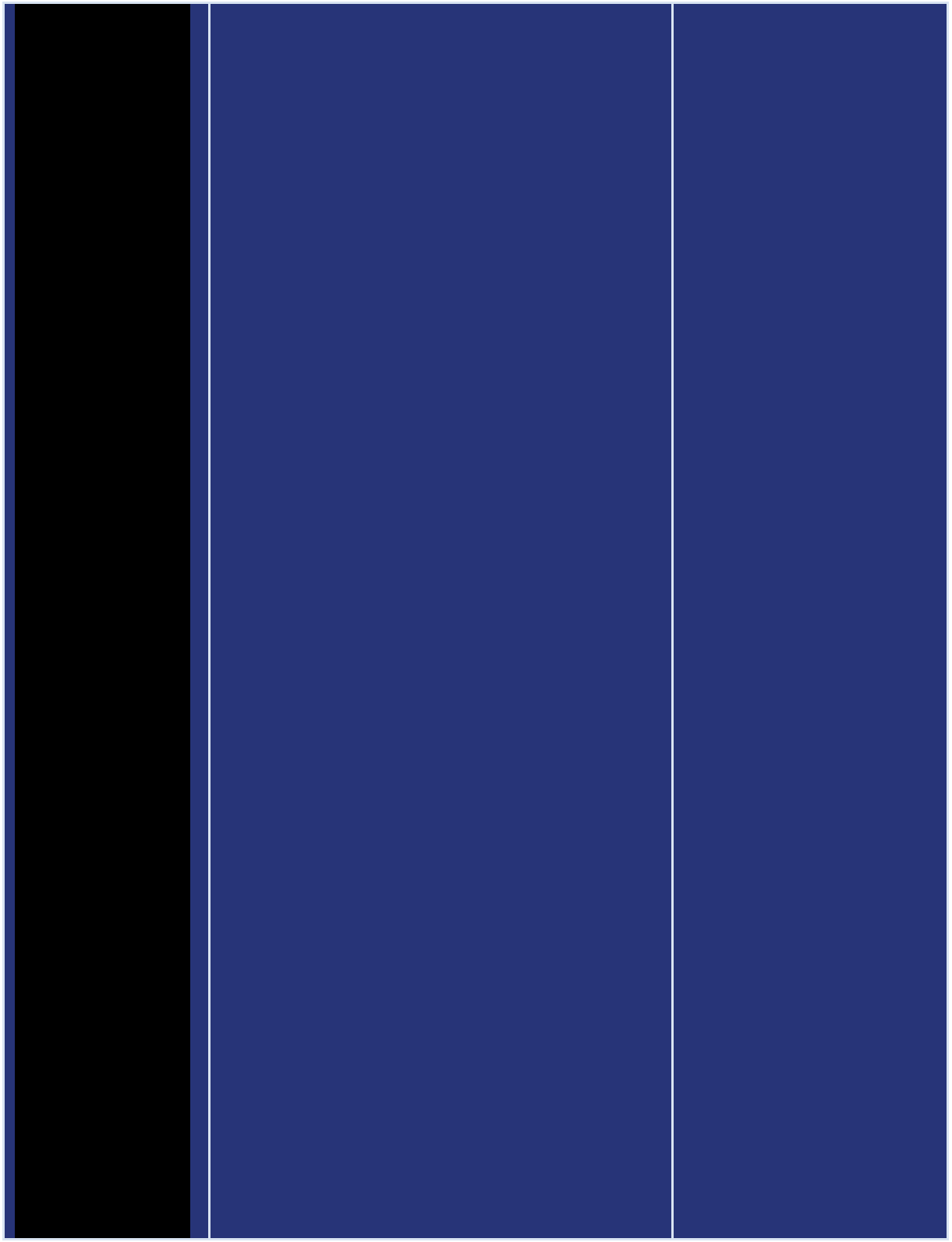

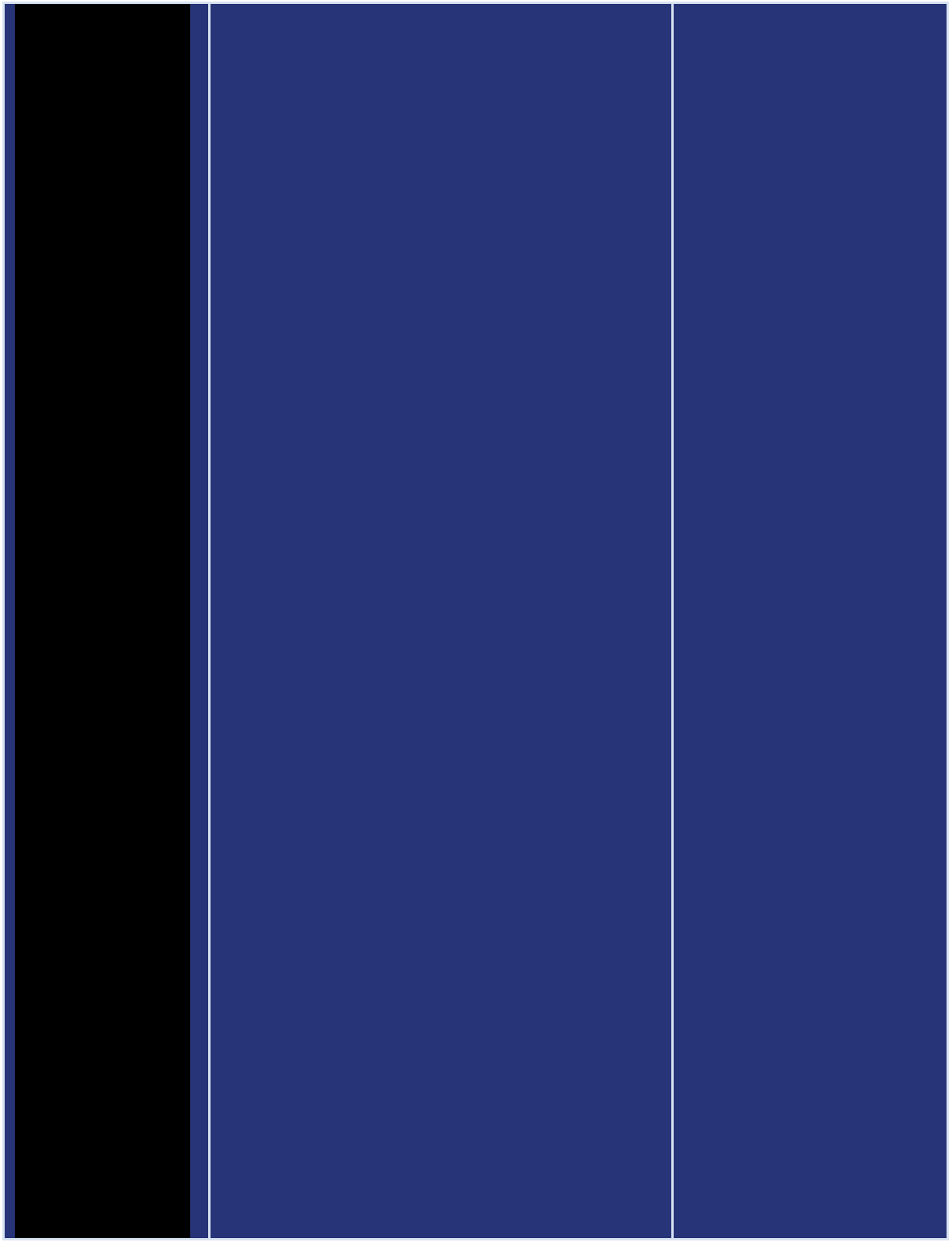

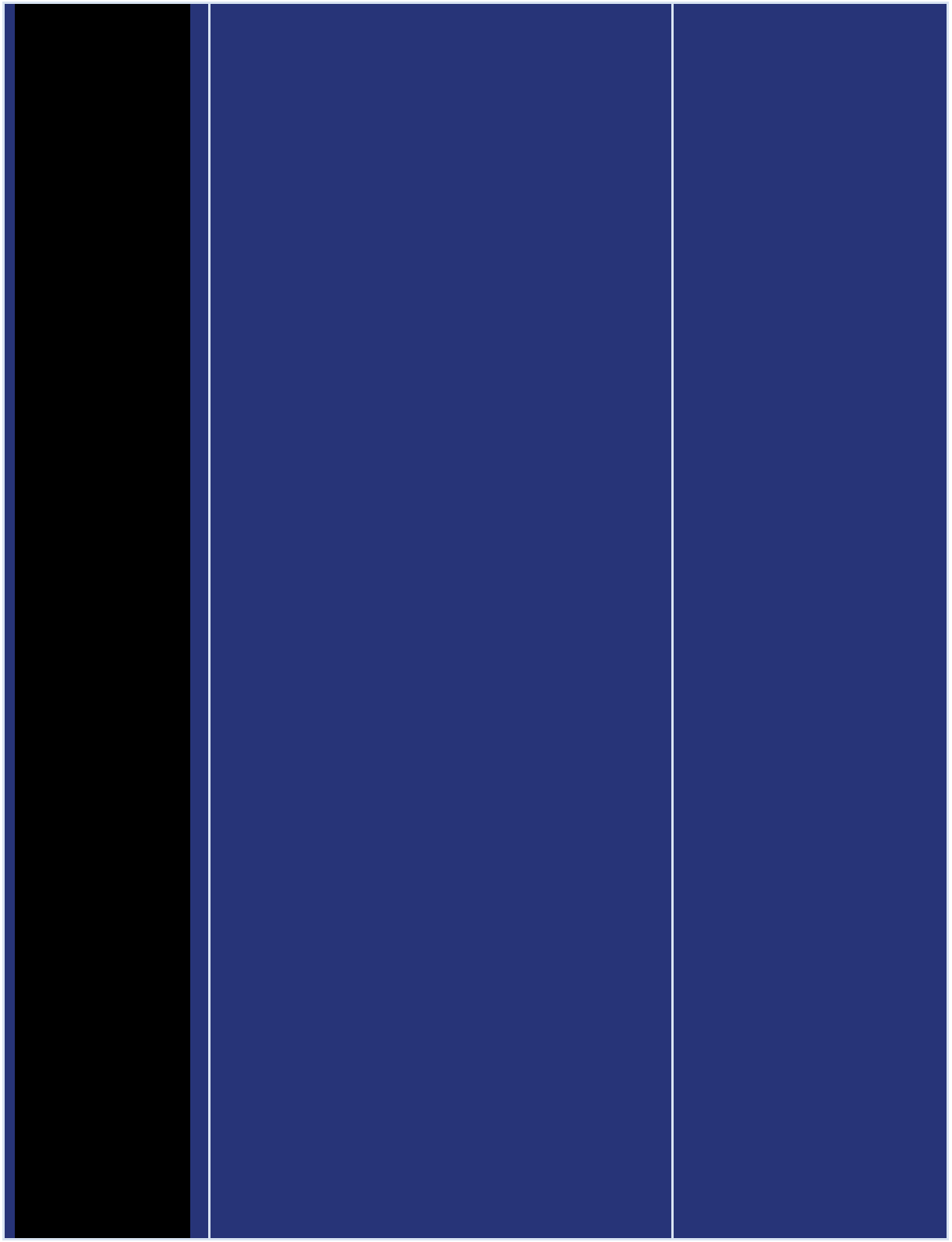

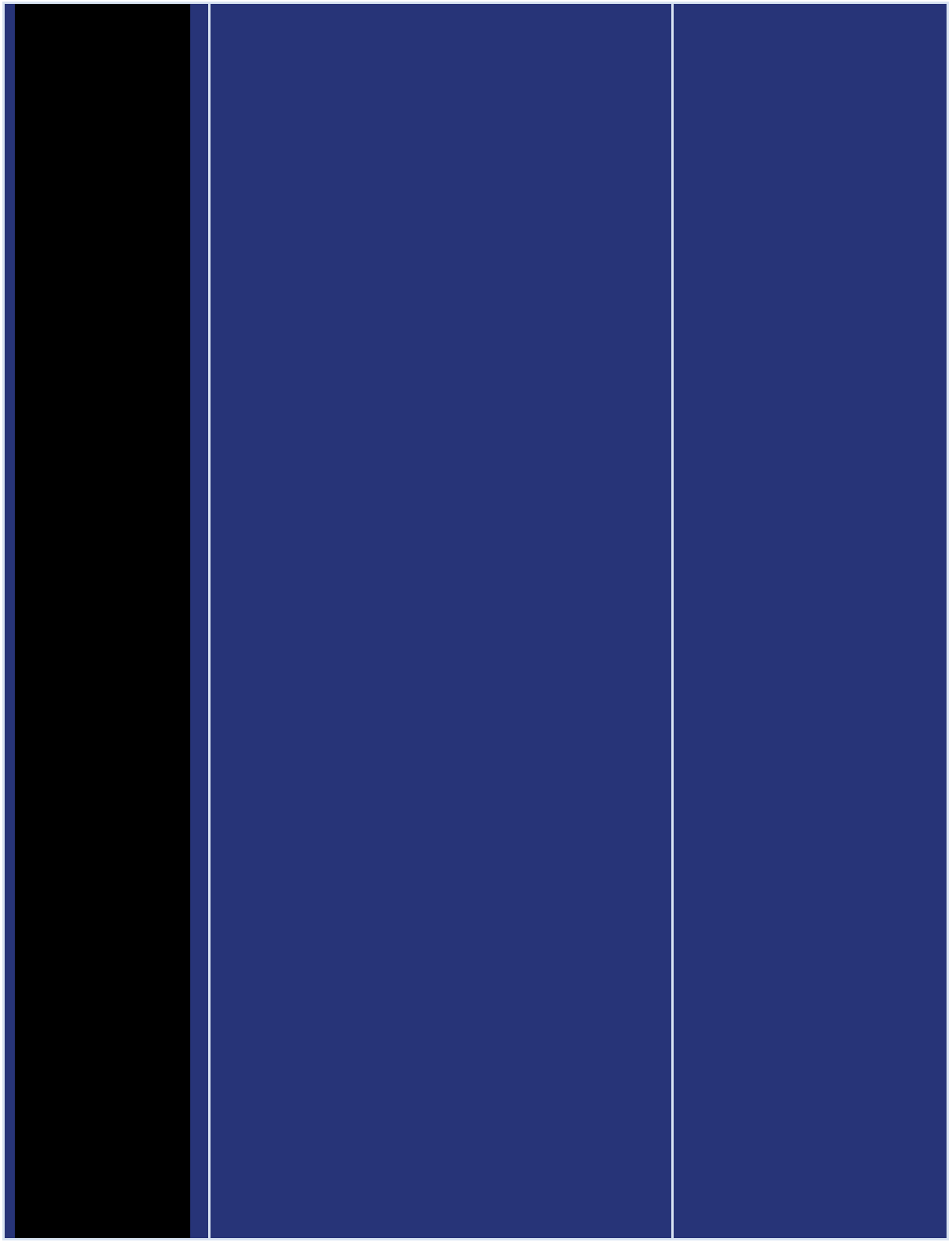

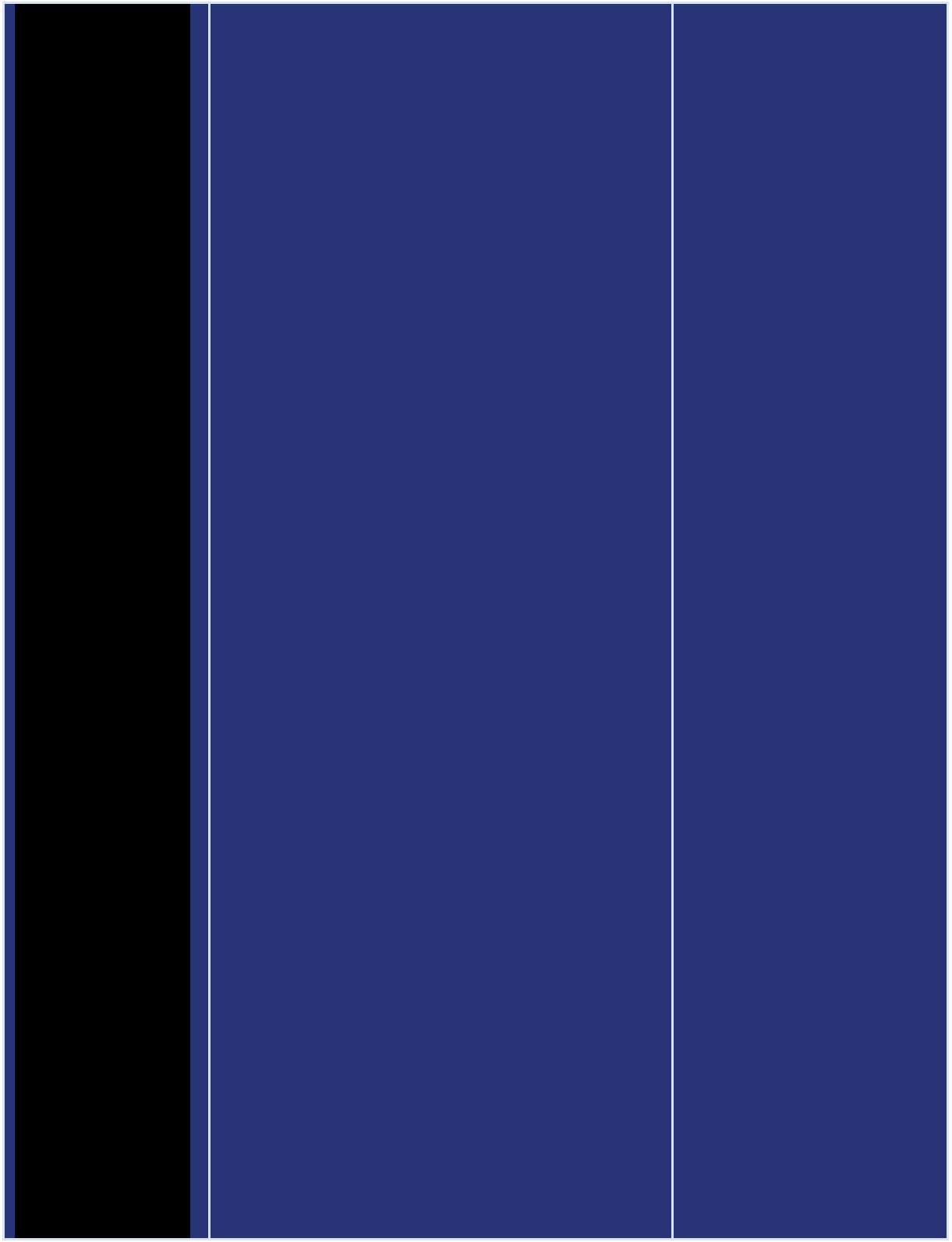

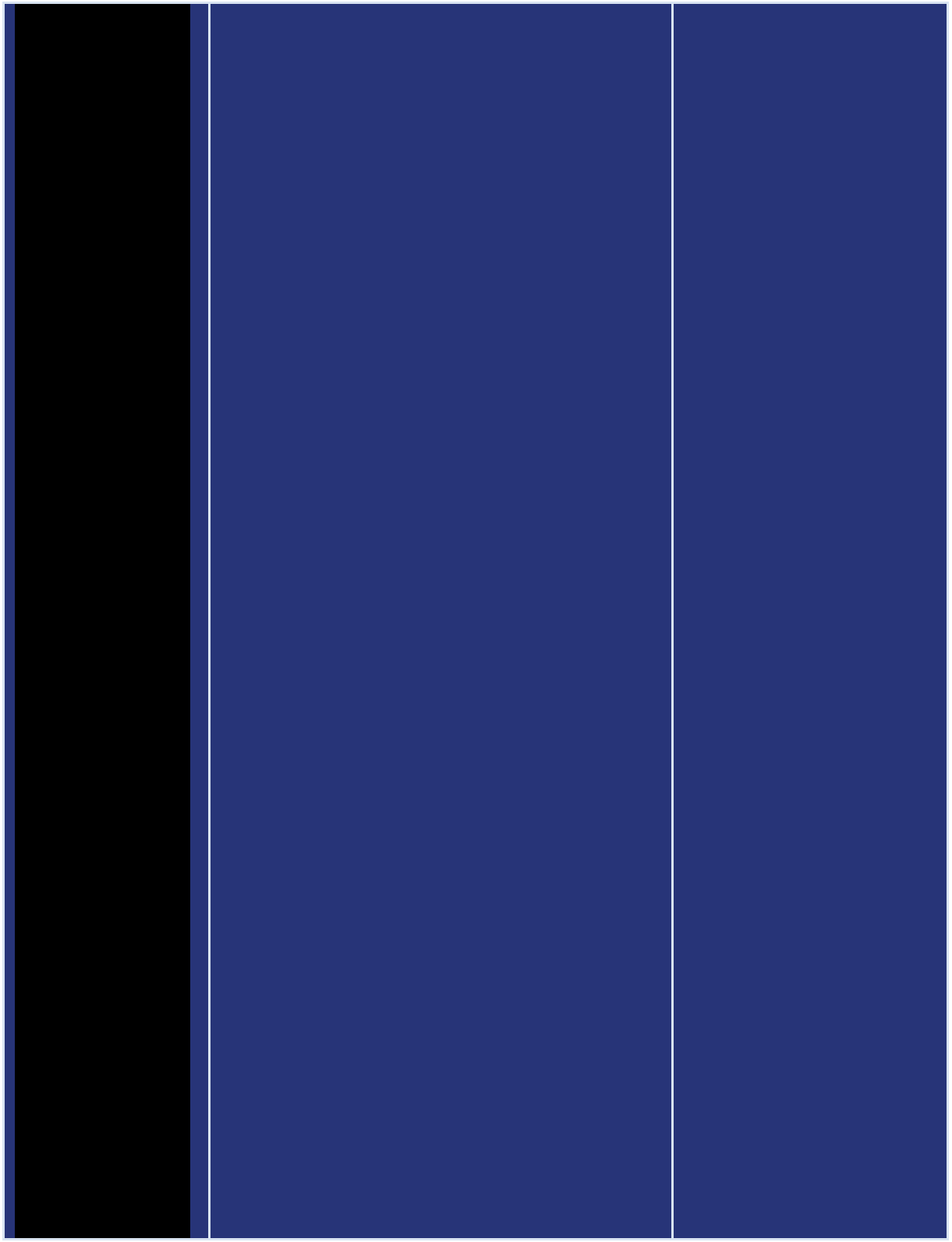

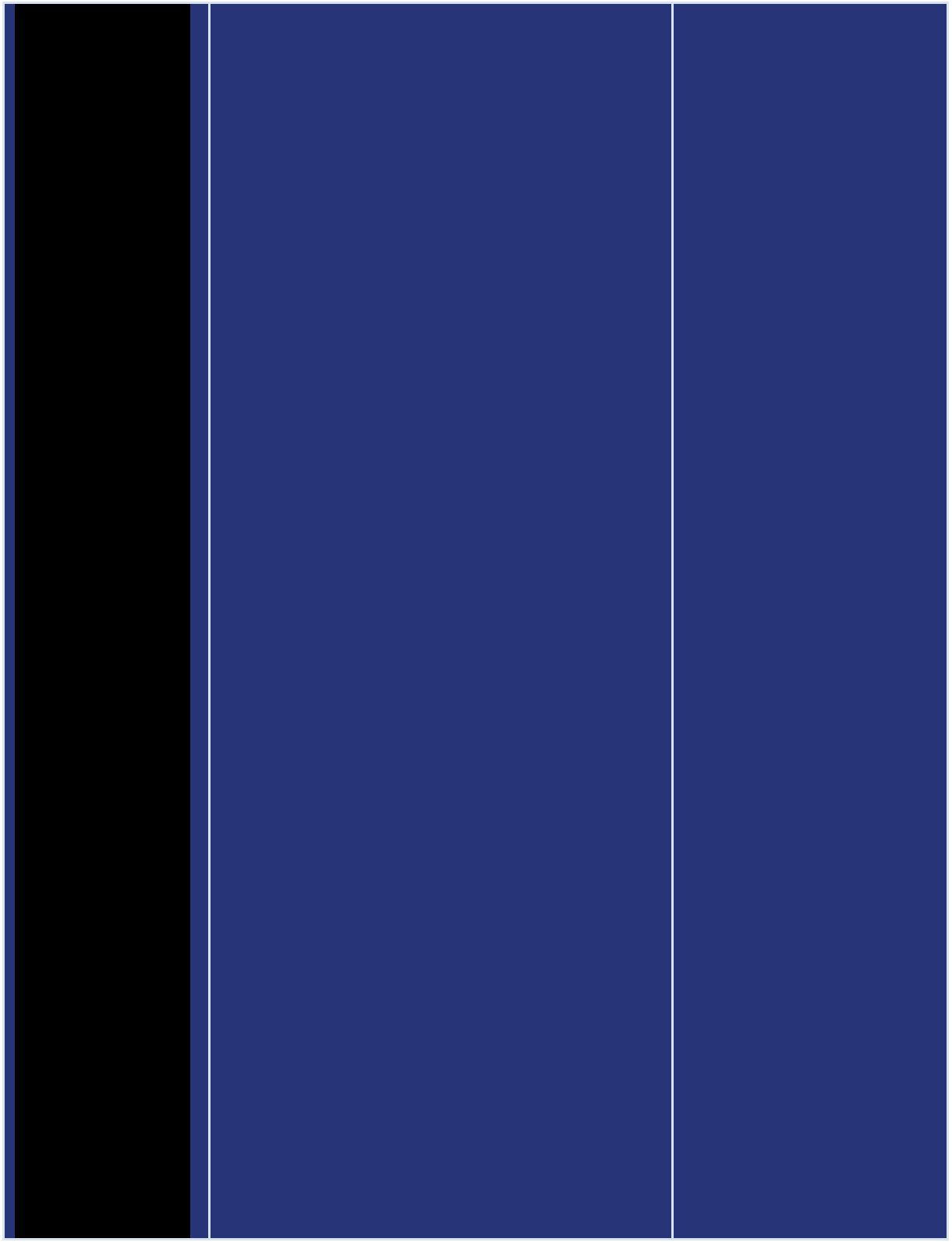

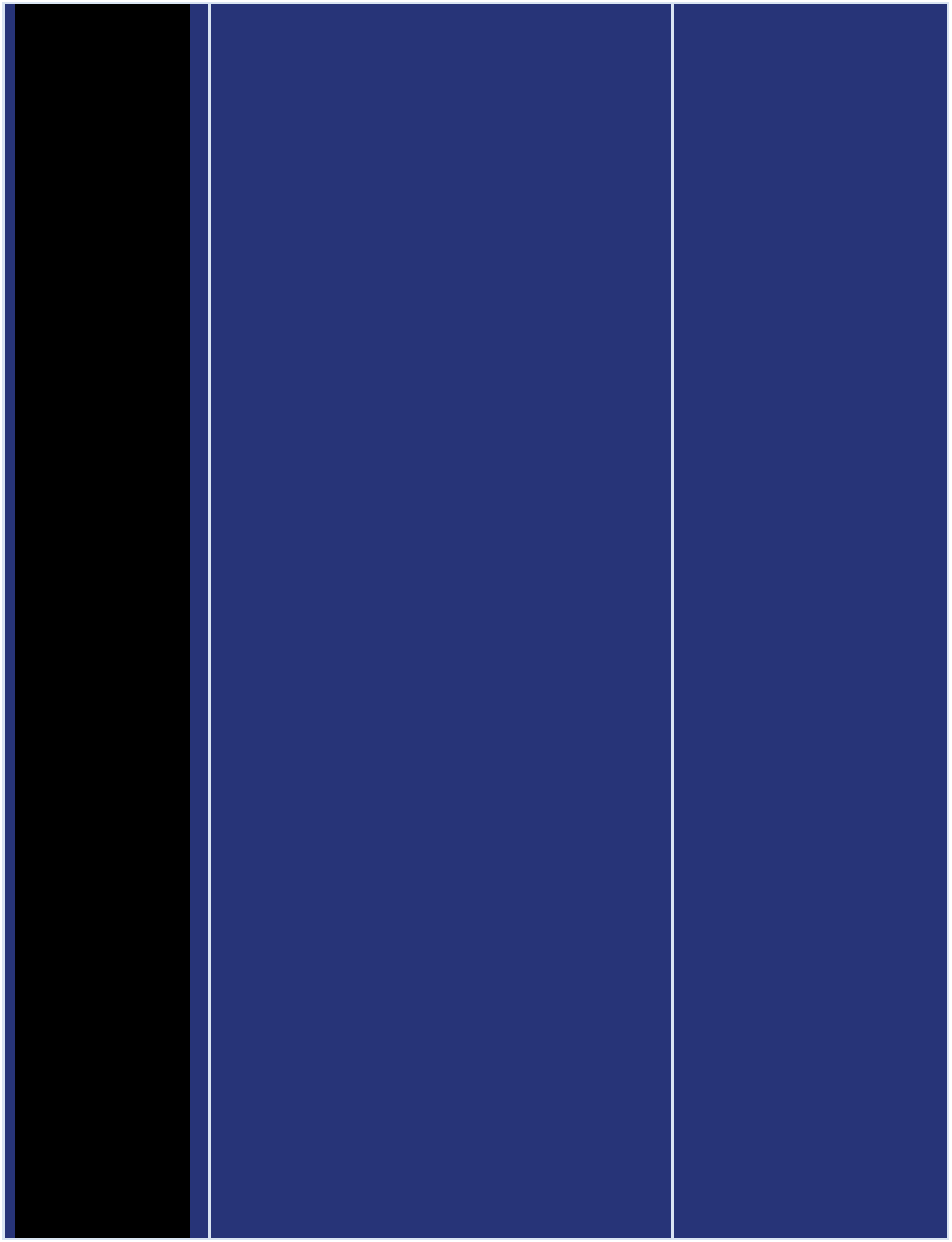

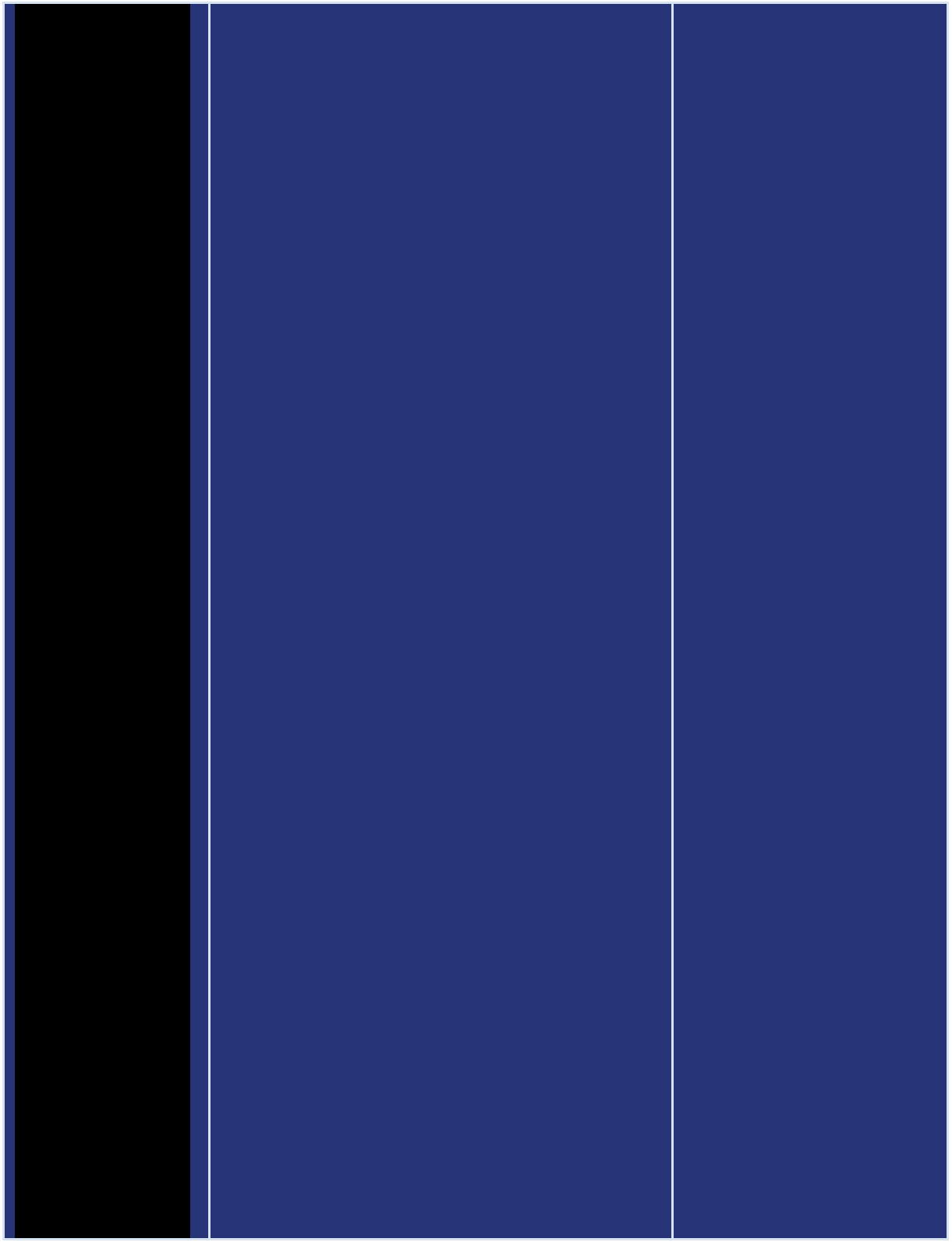

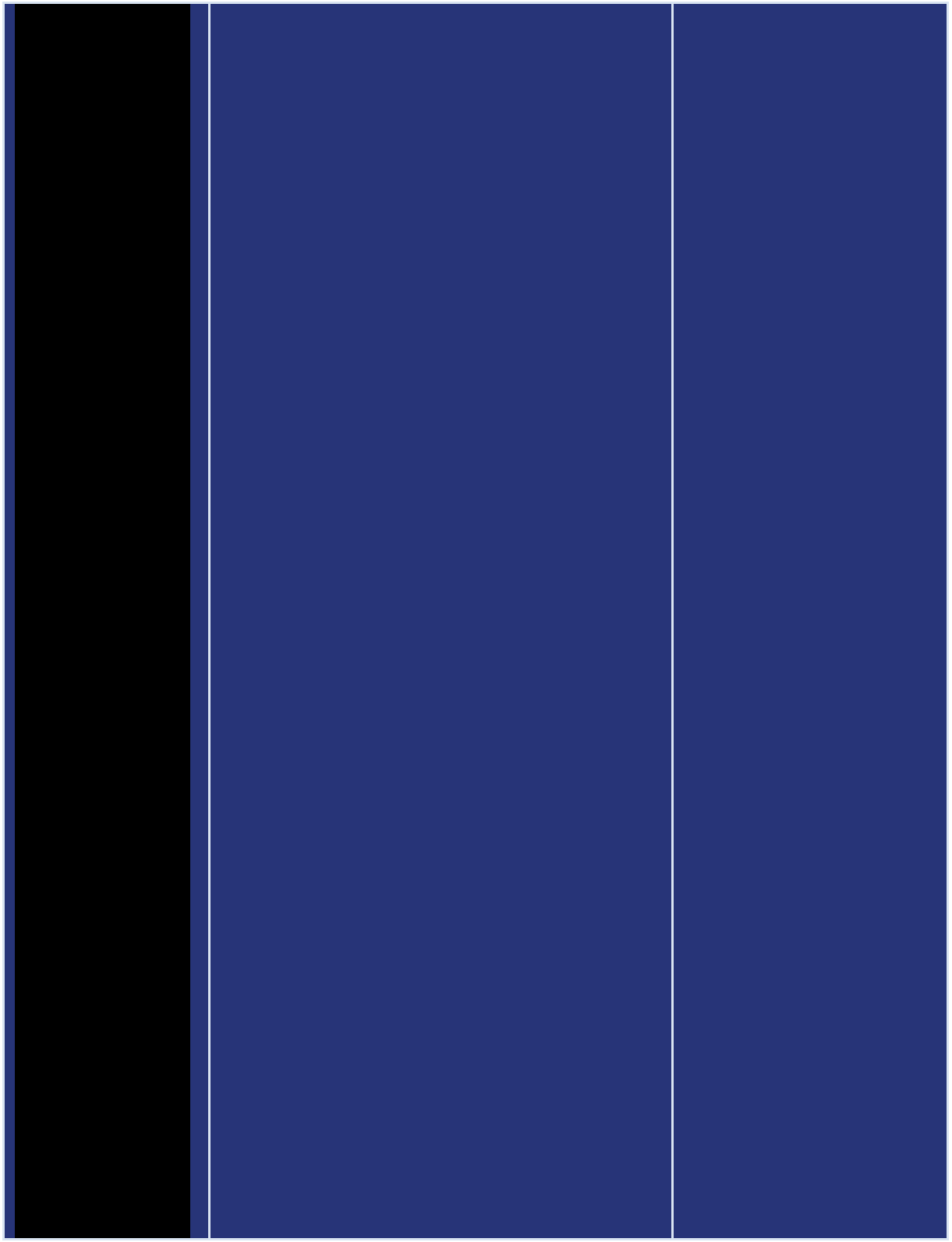

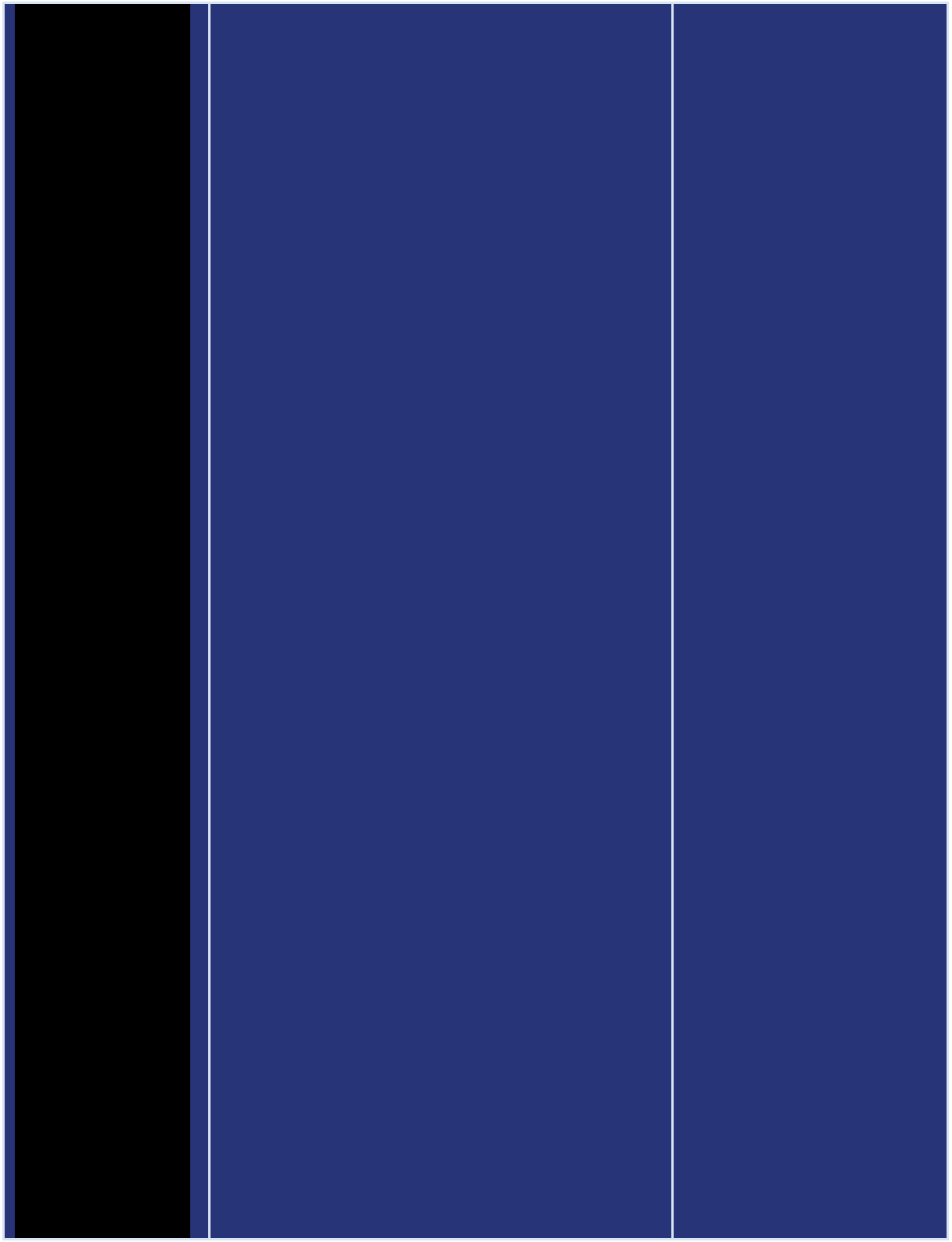

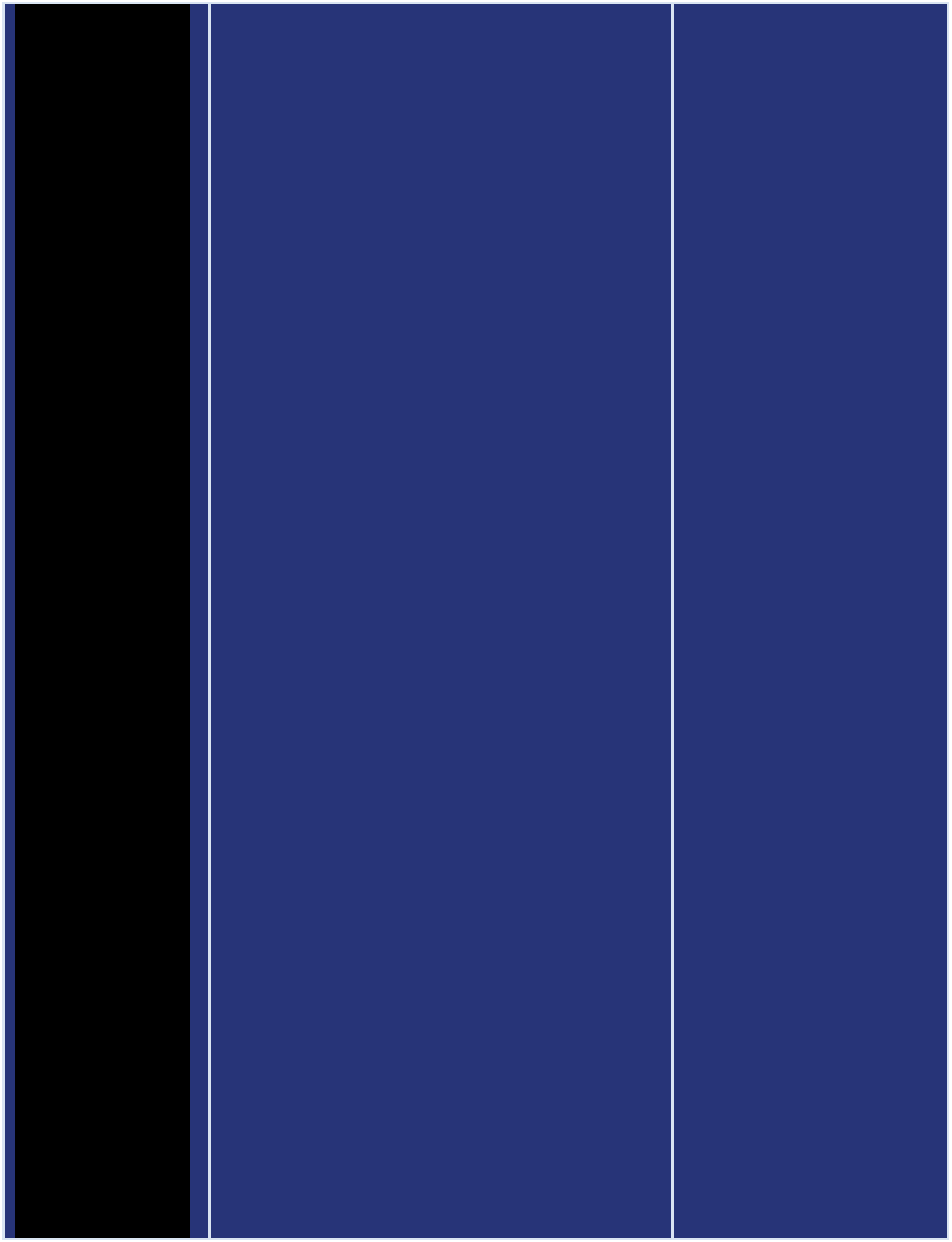

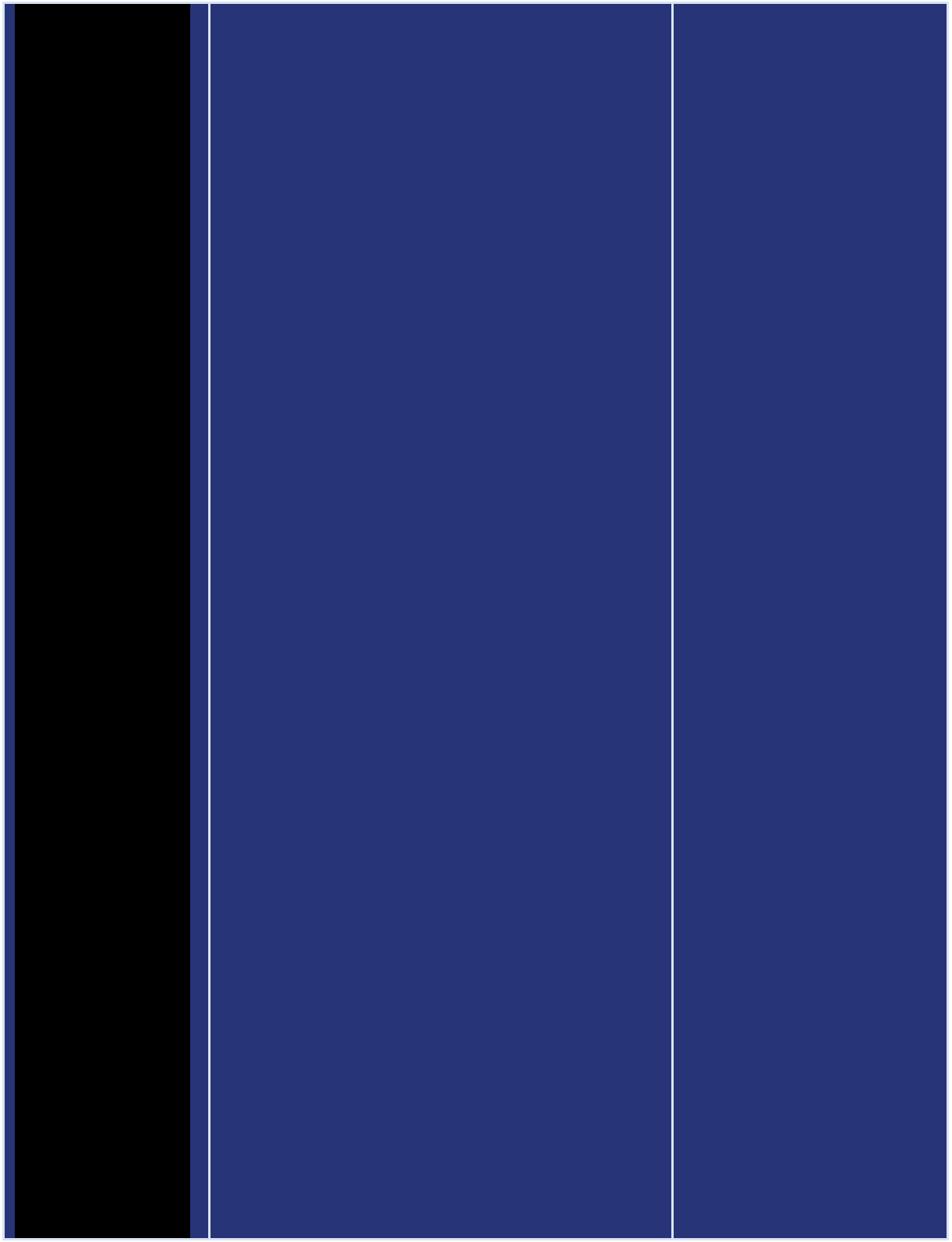

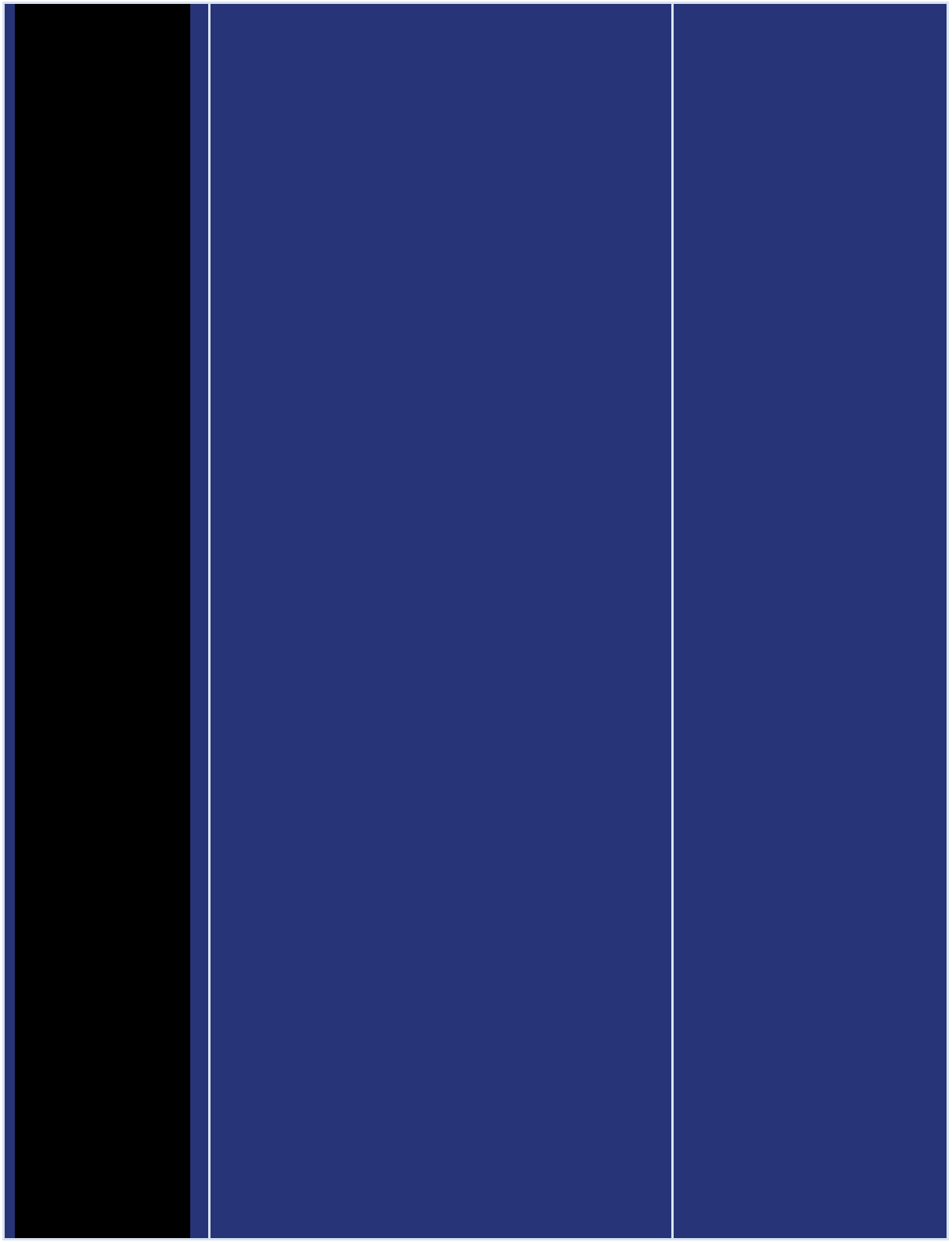

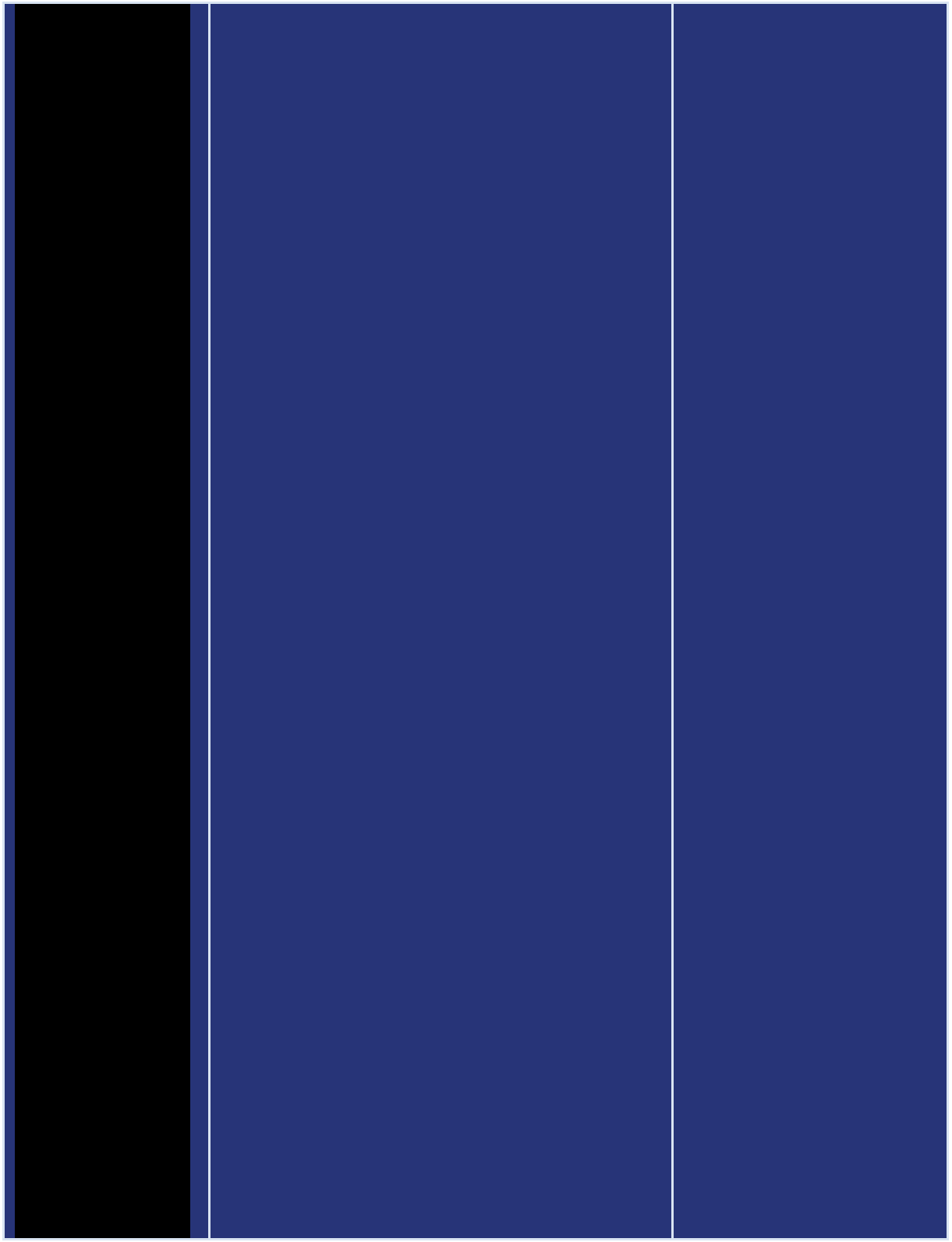

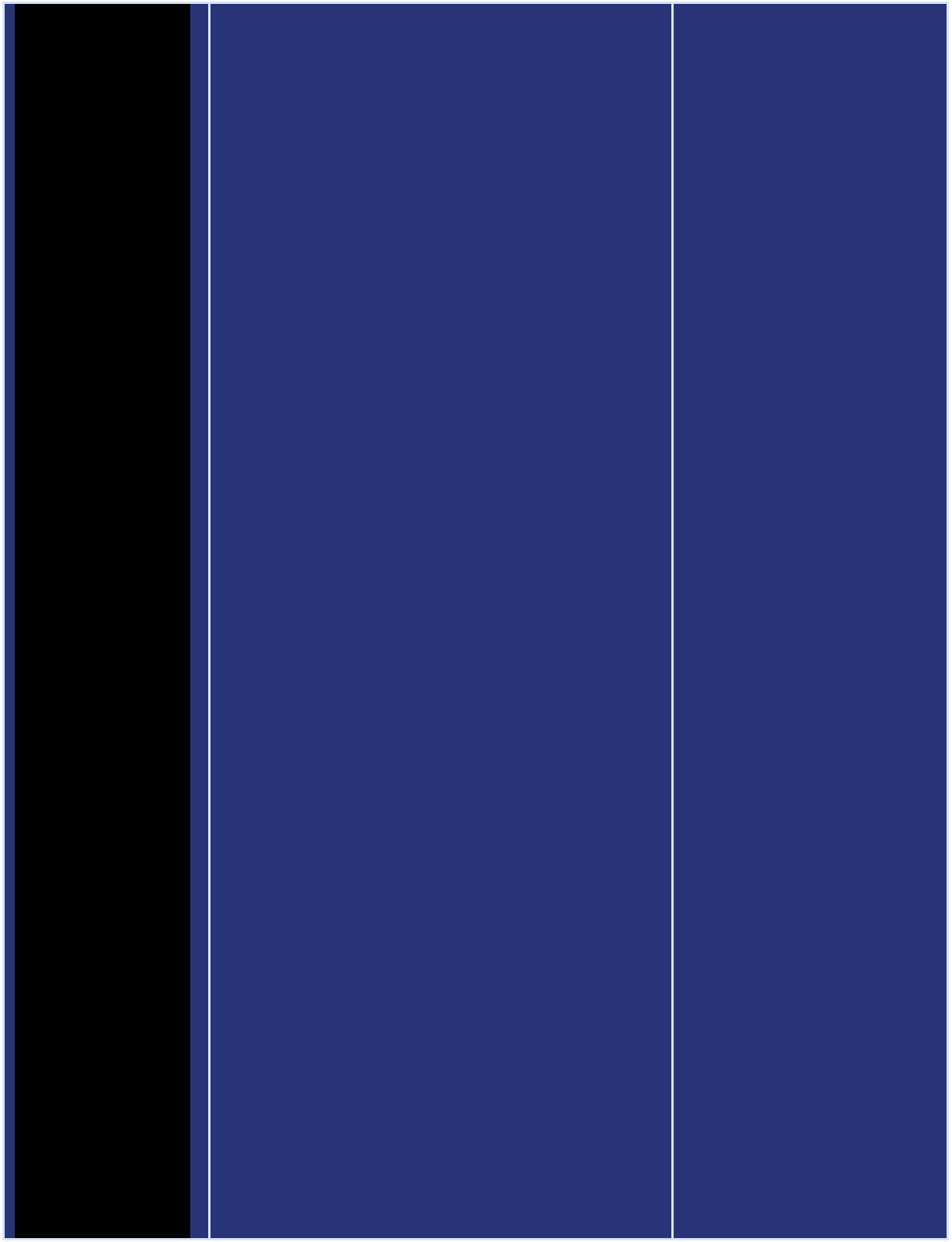

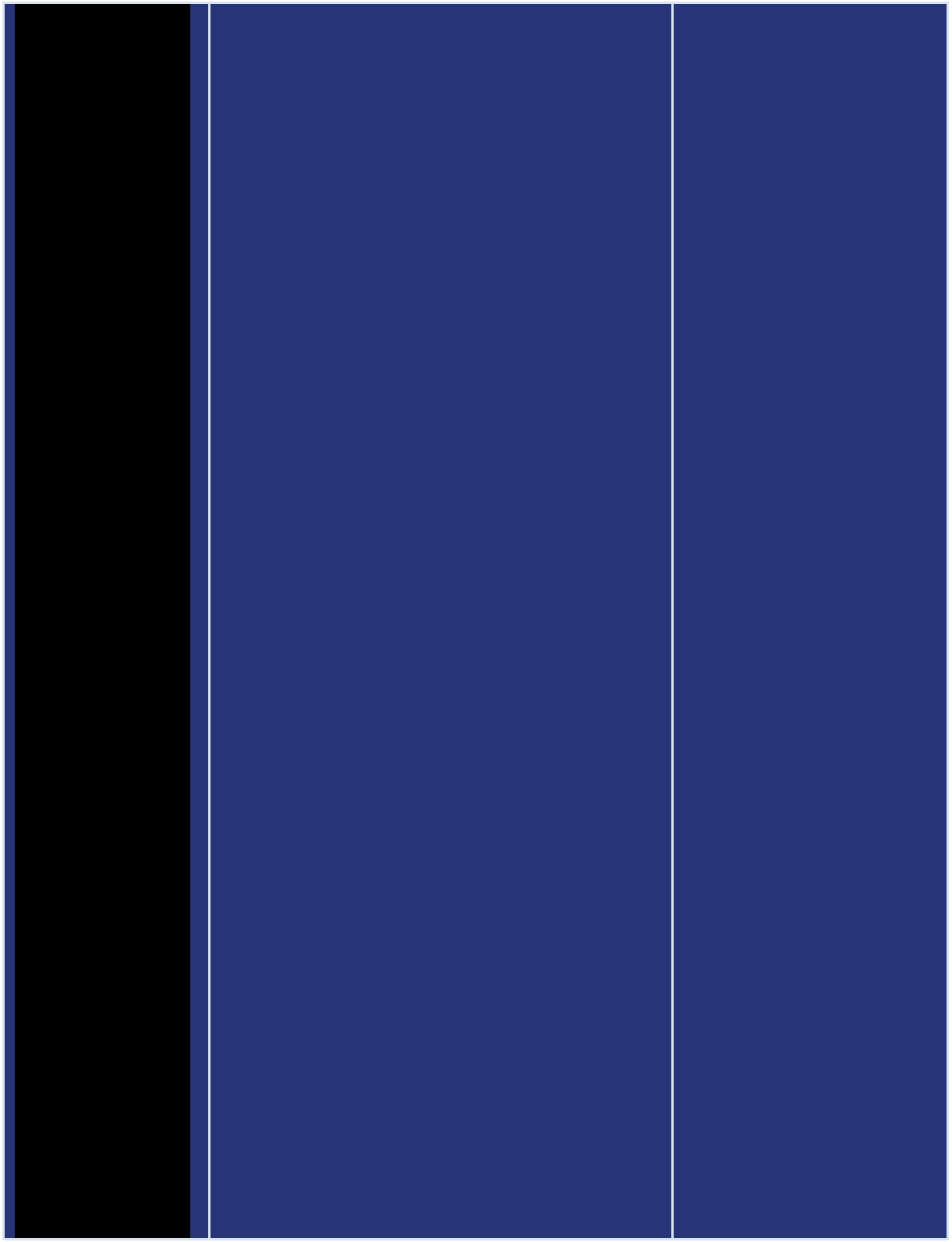

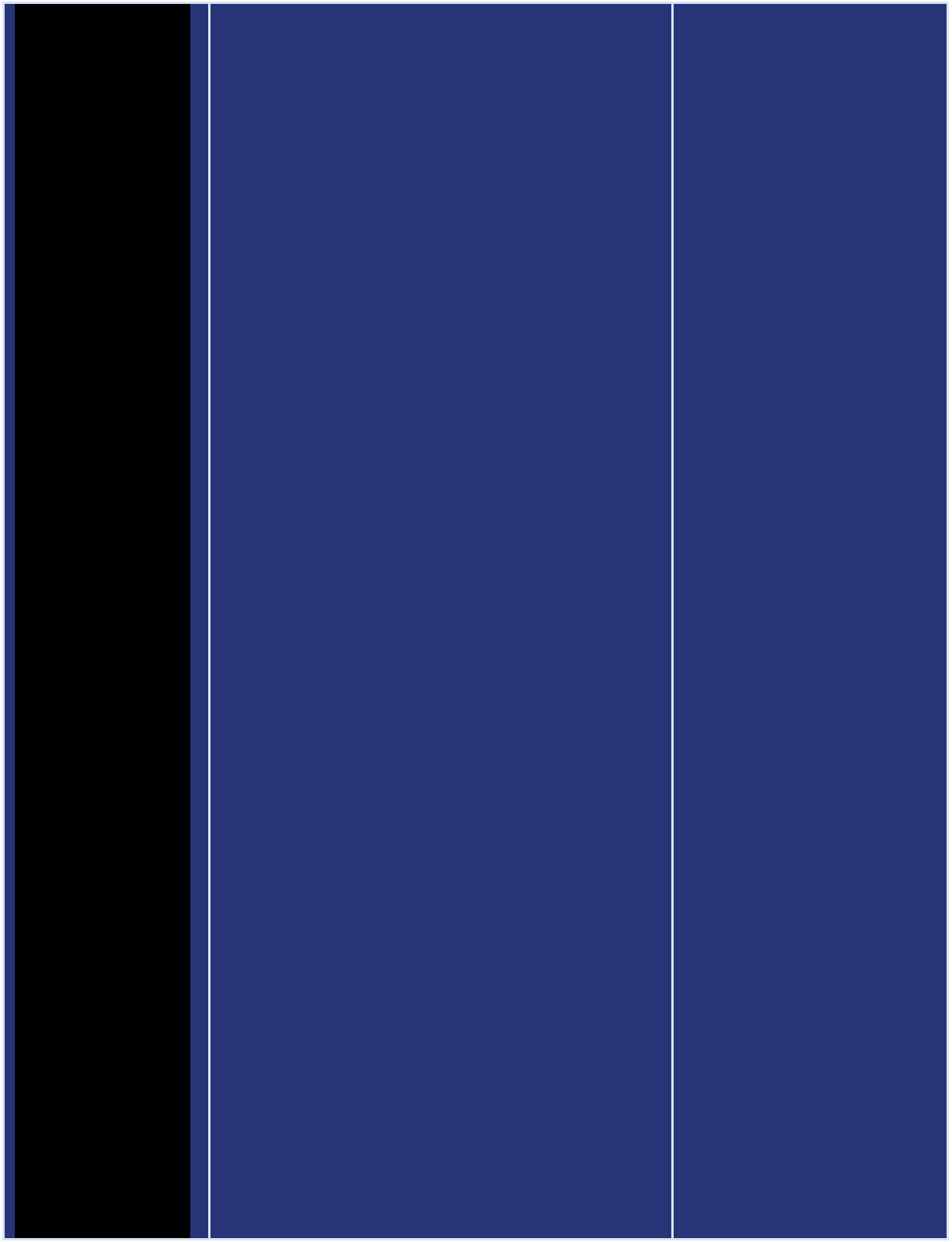

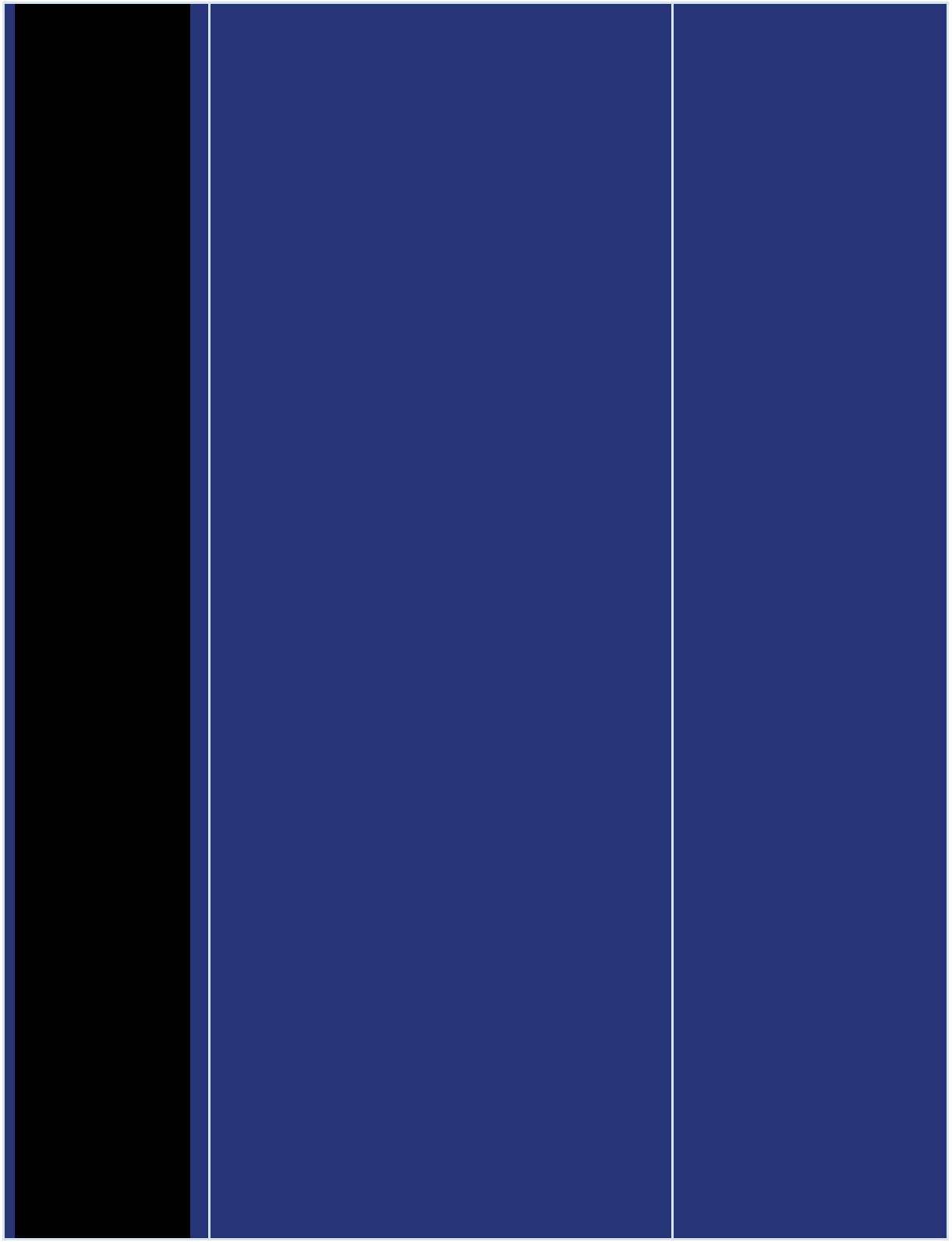

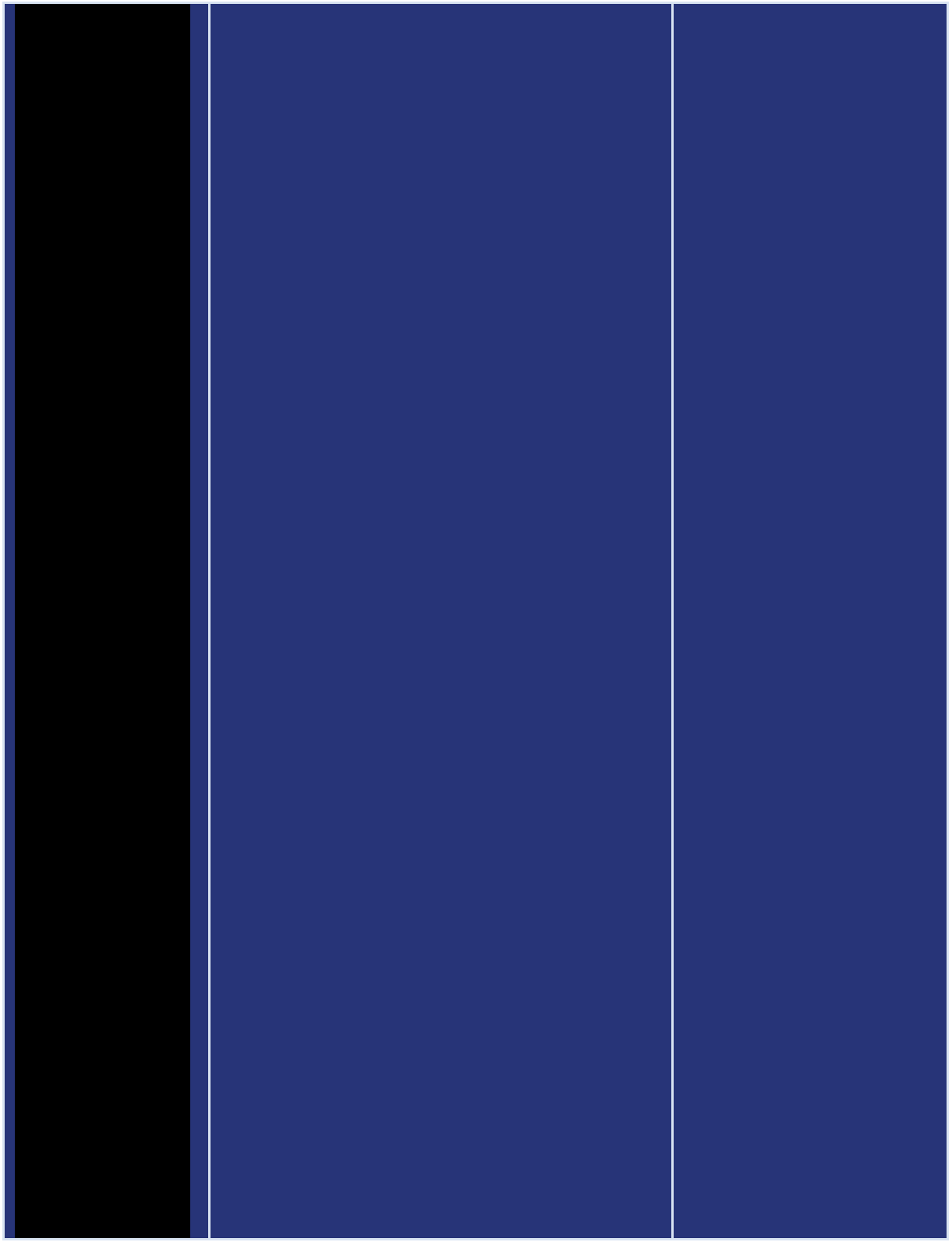

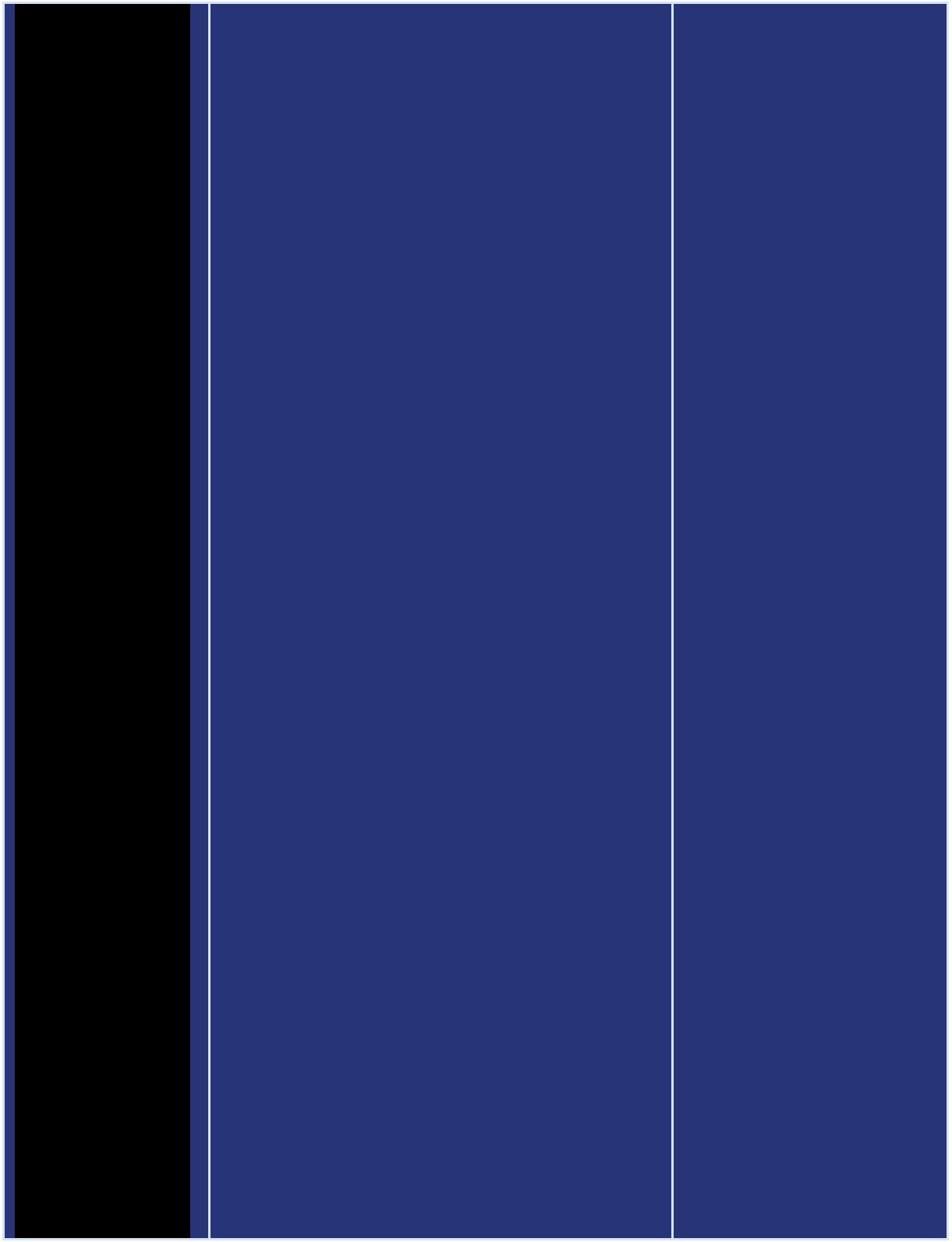

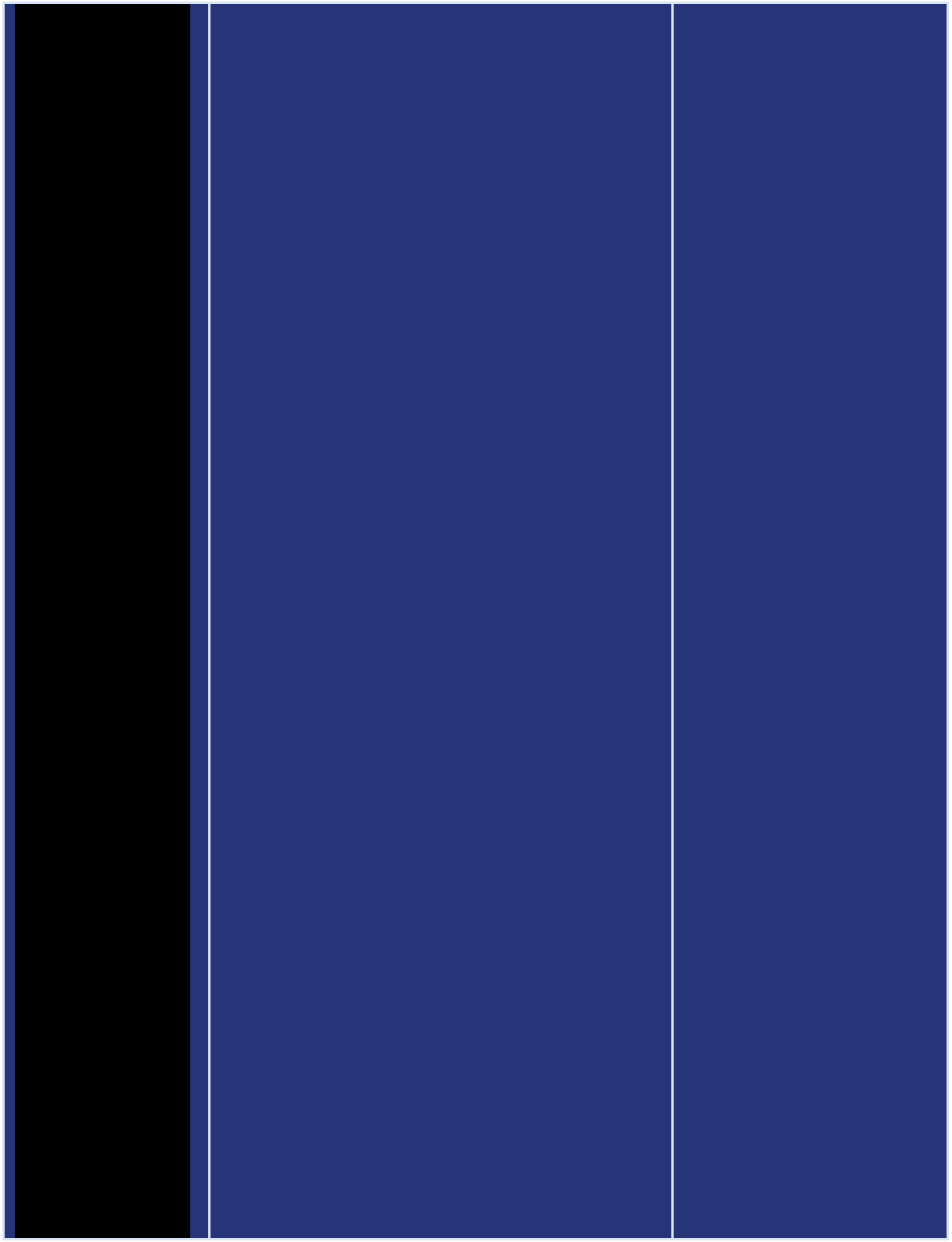

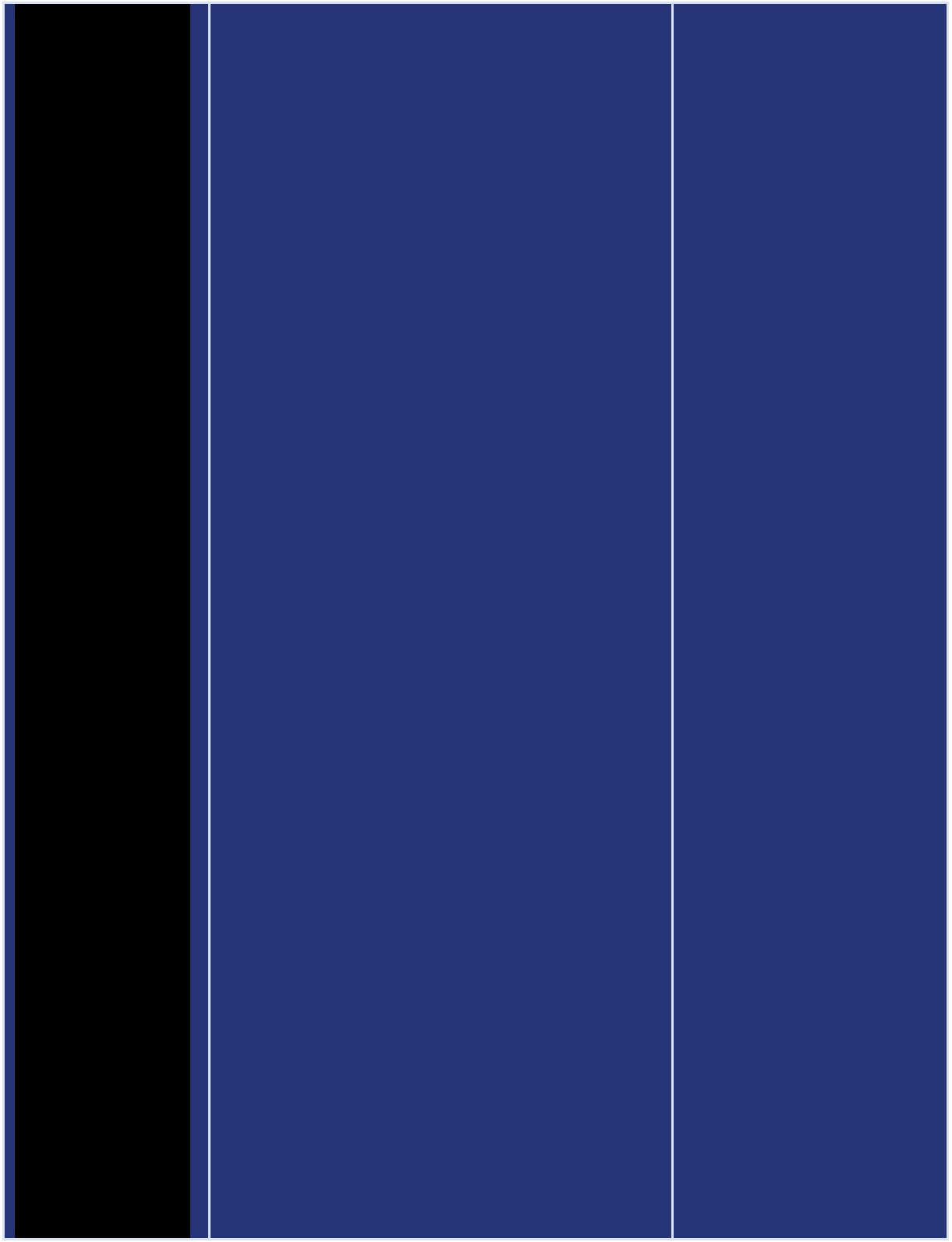

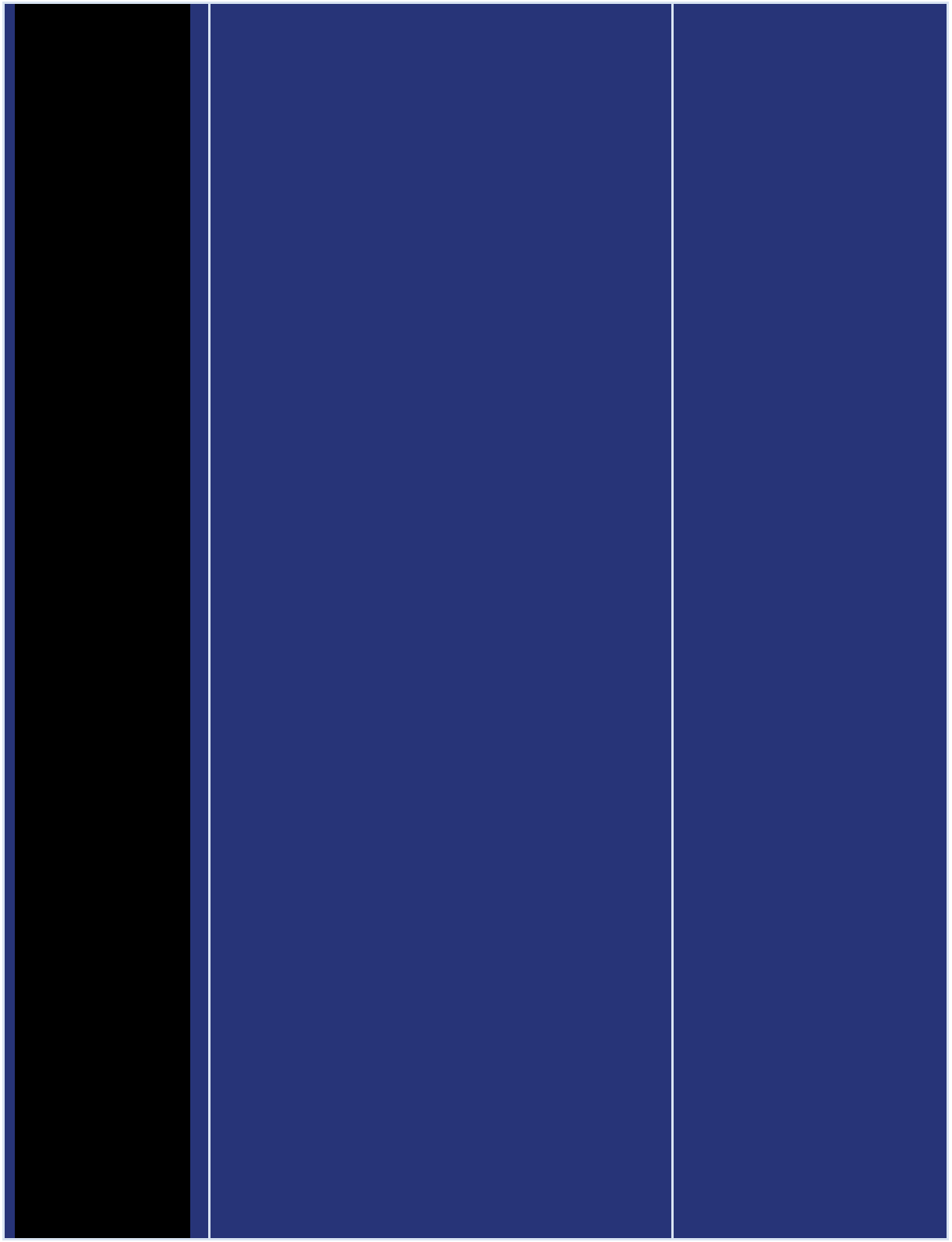

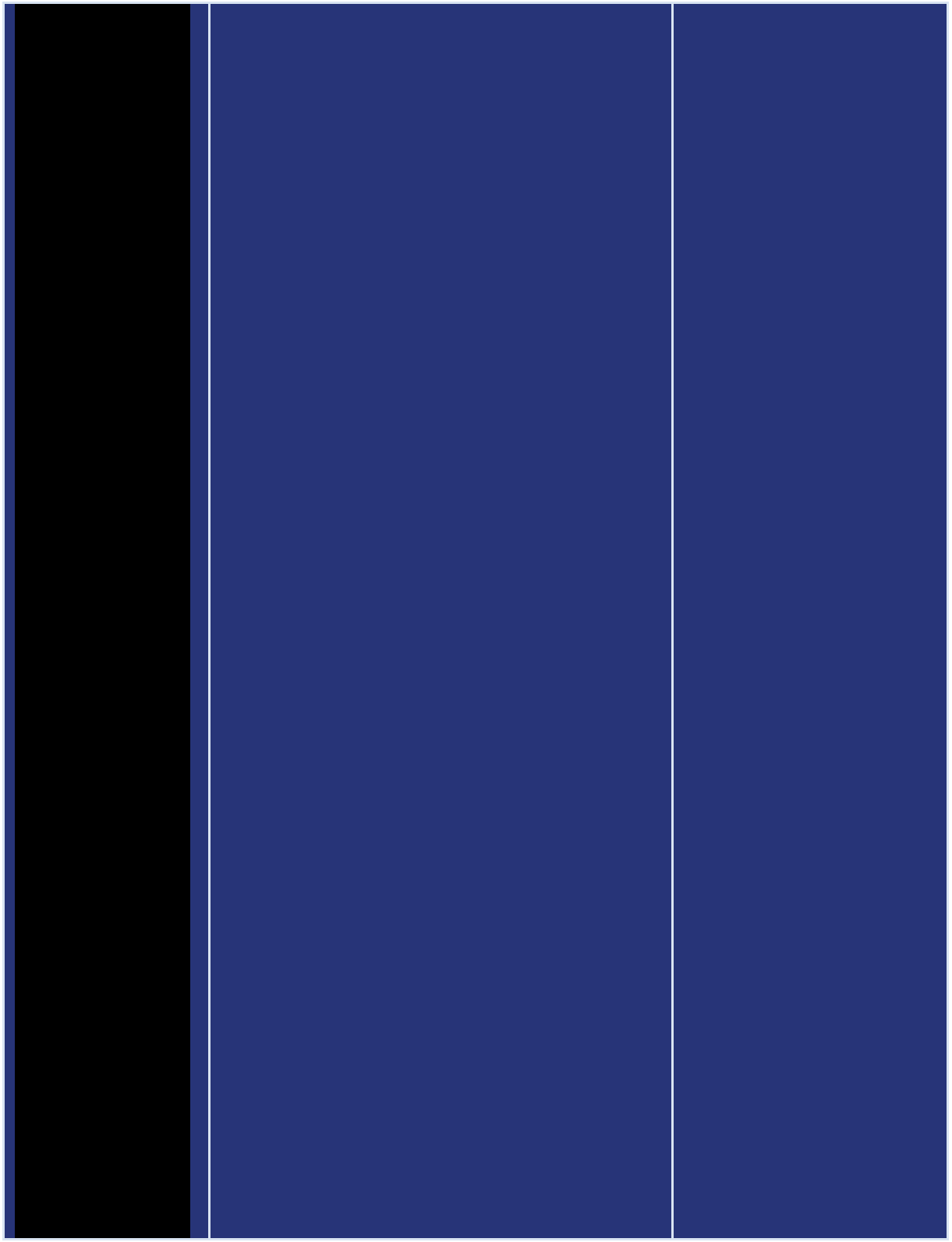

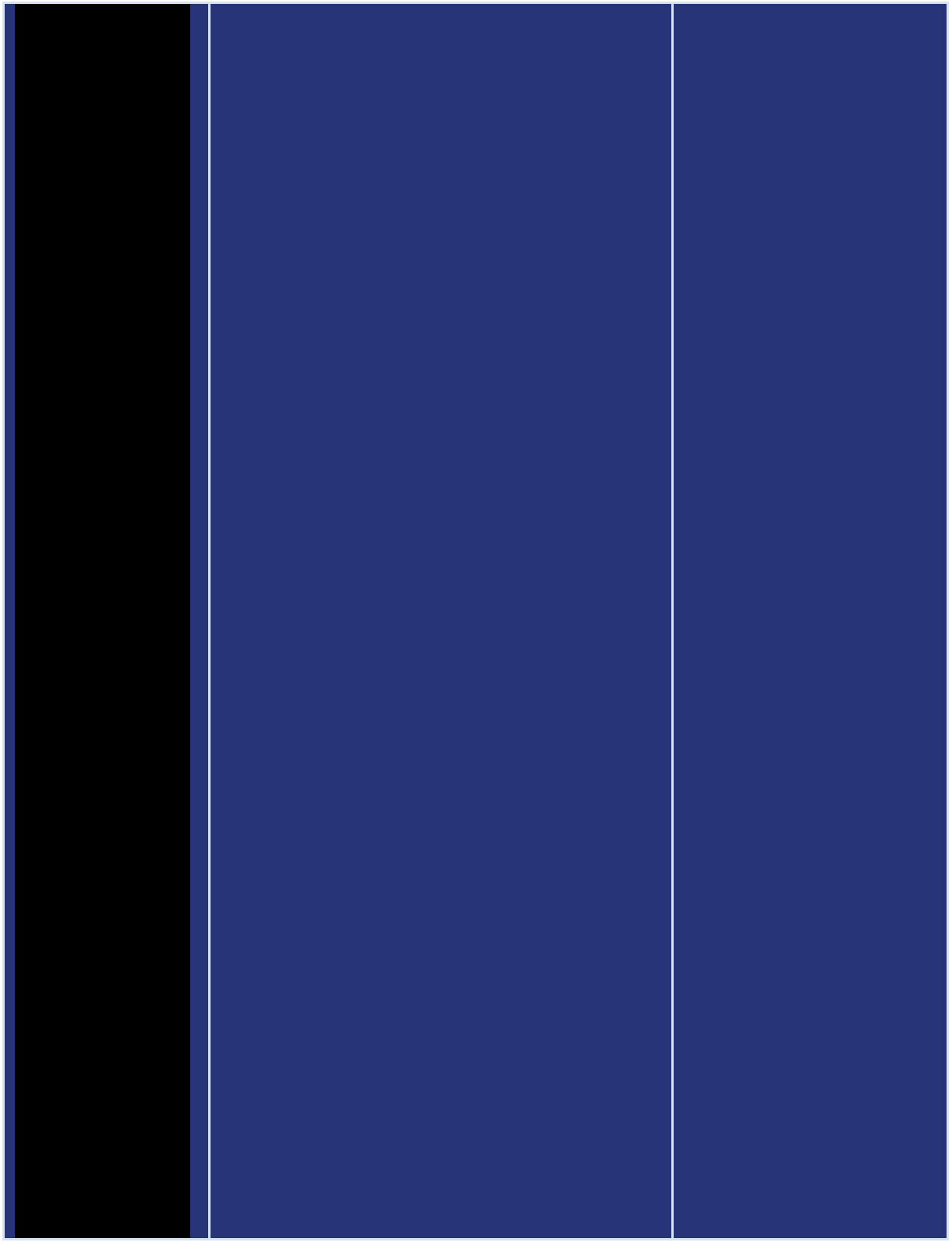

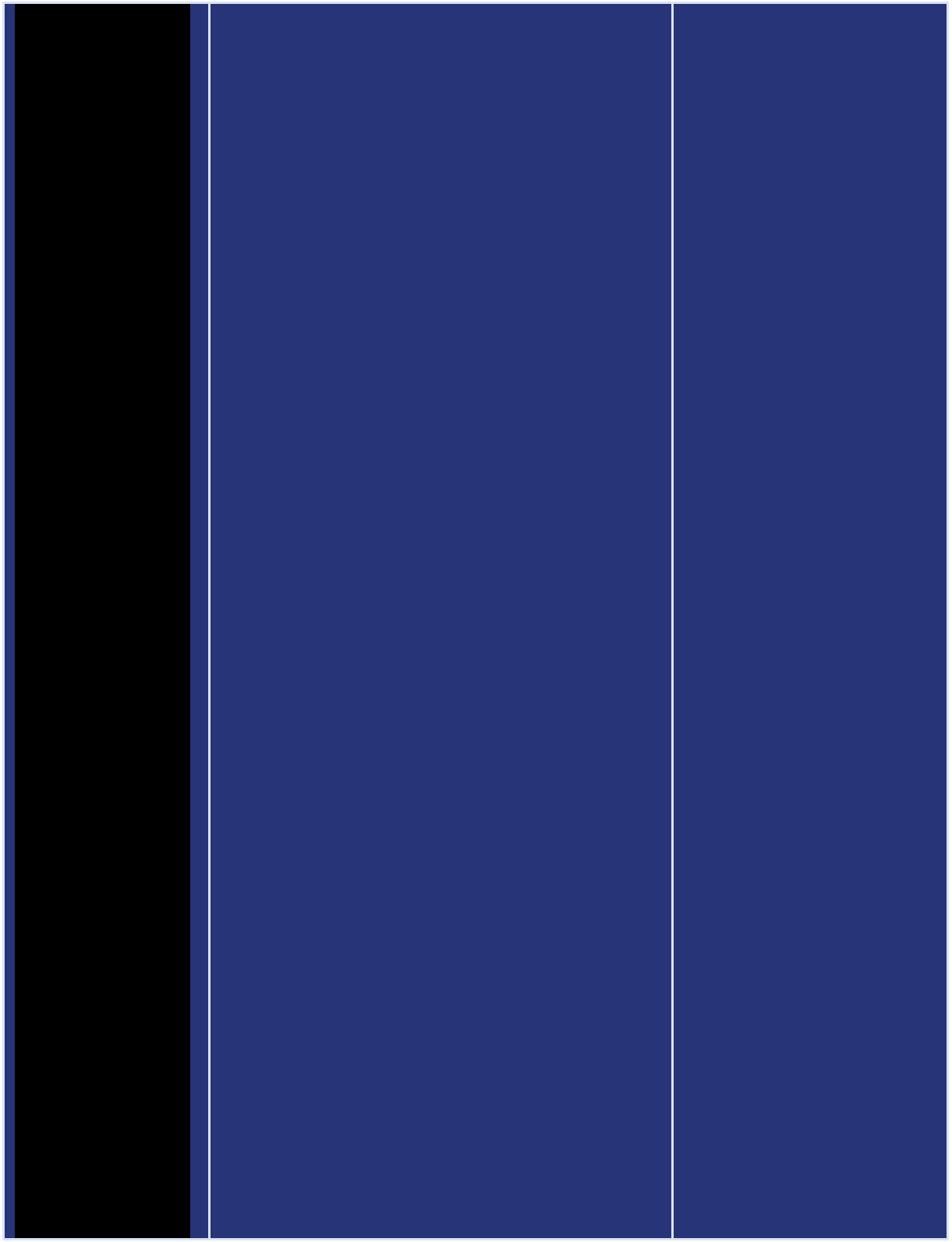

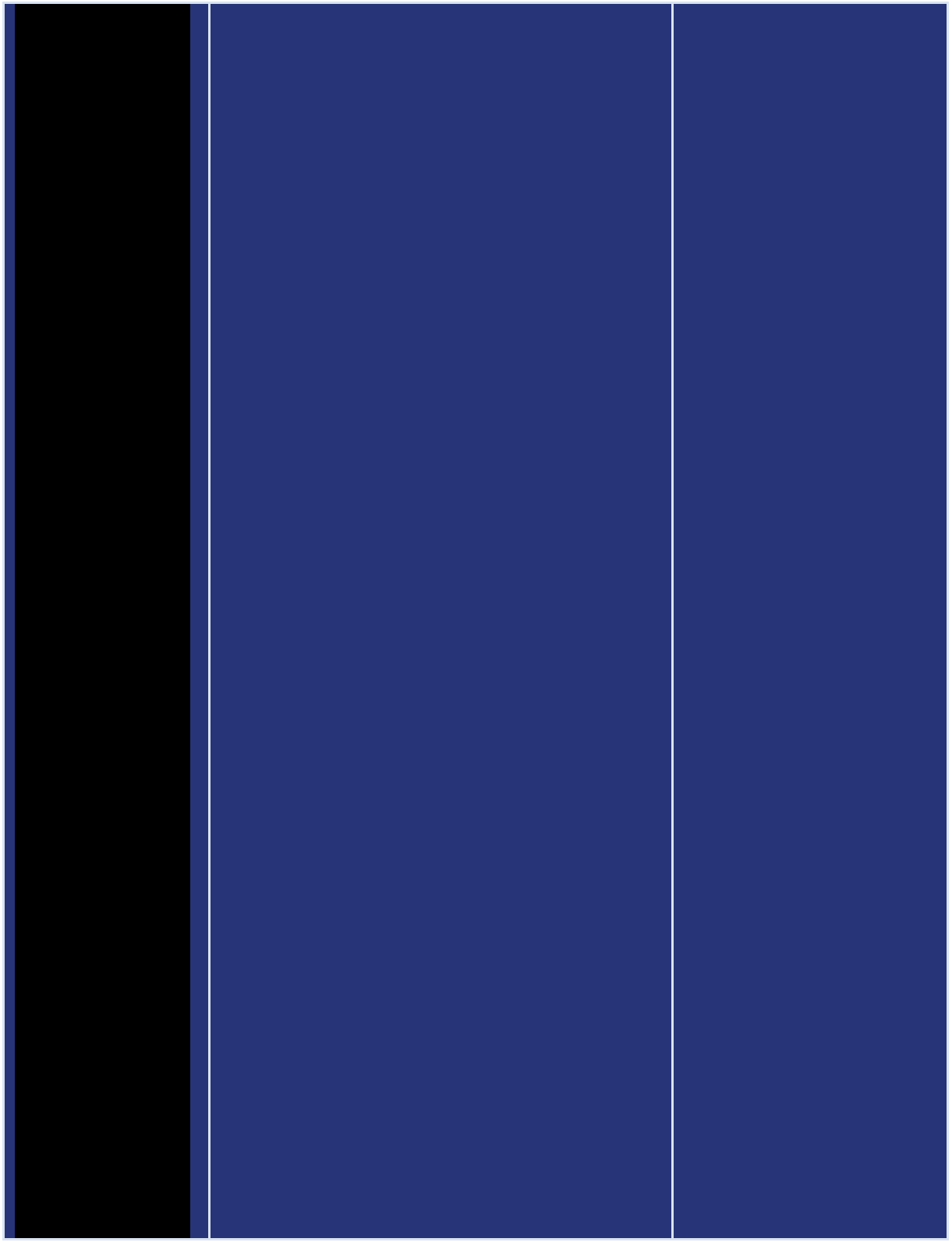

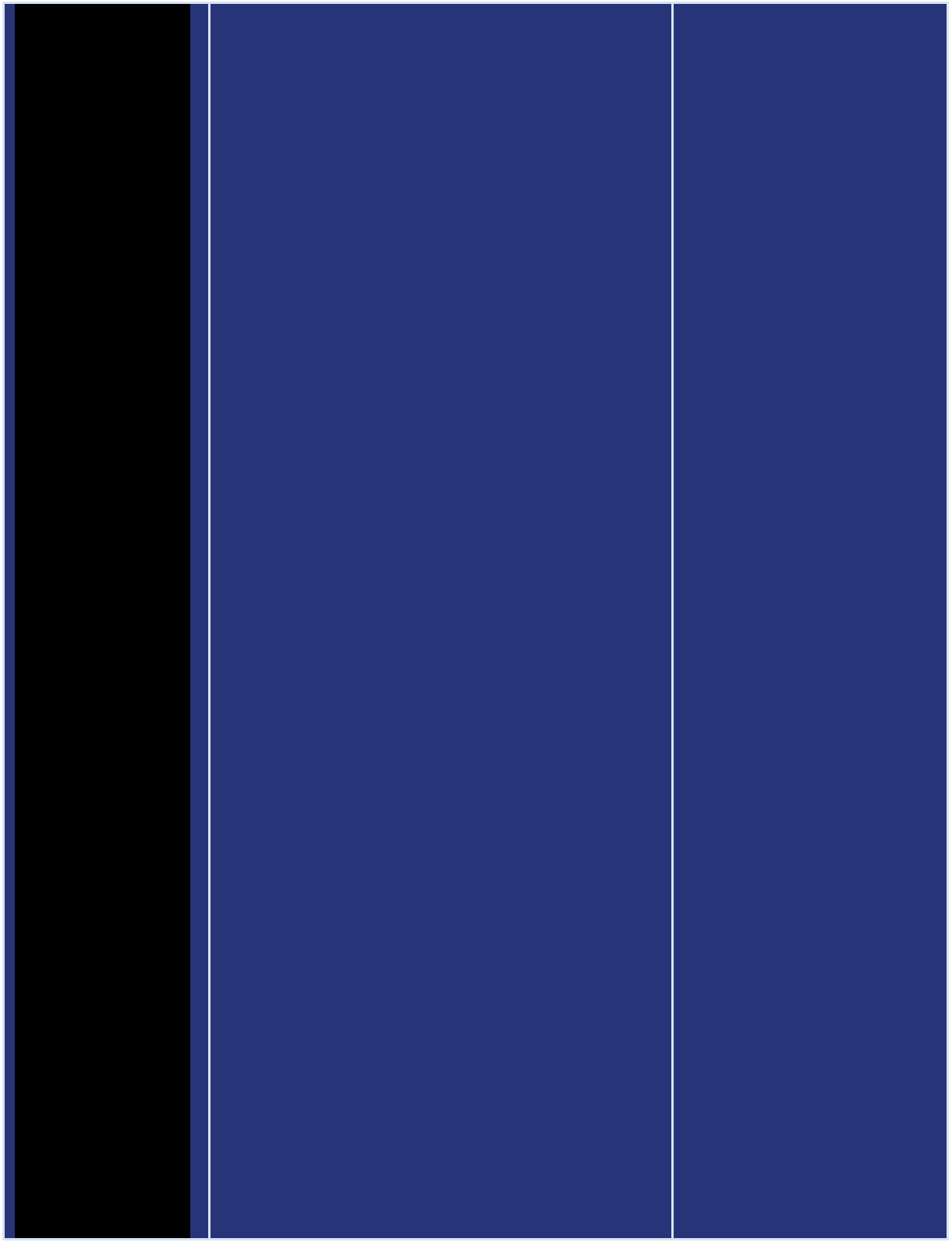

[redacted]	[redacted]	[redacted]
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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Tixagevimab–cilgavimab for preventing COVID-19 [ID6136]

Additional CE and BI analyses using the list price of Evusheld

December 2022

File name	Version	Contains confidential information	Date
[ID6136]_tixagevimab–cilgavimab_CE_BI_results_at_list_price_amended_redaction	2.0	Yes	22/12/2022

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1 Introduction

1.1 Cost-effectiveness analysis

This document contains model outcomes not applying a patient access scheme (PAS). The analyses are based on the base-case as per the EAG responses submitted to the EAG October 28th, 2022 (Table 1). The list price of Evusheld is £1,600 per 600 mg dose.

Table 1: Revised base-case results, PAS applied (as submitted to the EAG October 28th, 2022)

Technologies	Total costs	QALYs	Costs	QALYs	ICER	INMB (£30,000 per QALYs)
No prophylaxis	[redacted]	[redacted]	[redacted]	[redacted]	£ 8,111	[redacted]
Evusheld	[redacted]	[redacted]				

Abbreviations: ICER – Incremental cost-effectiveness ratio; LYG – Life years gained; QALYs – Quality-adjusted life years

The model results in section 2 and section **Error! Reference source not found.** were produced using version 'ID6136 tixagevimab-cilgavimab CEM with revised base case and EAG scenarios v2.0 26.10 CiC of the model', uploaded to NICE docs on November 14th, 2022.

1.2 Budget impact analysis

The budget impact results in this document are in line with the results submitted to NICE September 21st, 2022 (Table 2). The only amendment is that the PAS is not applied. The list price of Evusheld is £1,600 per 600 mg dose.

Table 2: Expected budget impact, PAS applied (as submitted to NICE September 21st, 2022)

	Year 1	Year 2	Year 3	Year 4	Year 5
Eligible population for treatment with Evusheld	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Population expected to receive Evusheld	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost of treatment pathway without Evusheld (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost of treatment pathway with Evusheld (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net budget impact (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

2 Cost-effectiveness analysis (no PAS)

2.1 Base case incremental cost-effectiveness analysis results

Evusheld generates [redacted] incremental QALYs and £[redacted] incremental costs over a lifetime horizon compared with no prophylaxis, resulting in an ICER of [redacted] per QALY gained.

Table 3: Base case results (no PAS)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
No prophylaxis	[redacted]	[redacted]	[redacted]					
Evusheld	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER – Incremental cost-effectiveness ratio; LYG – Life years gained; QALYs – Quality-adjusted life years

2.2 Probabilistic sensitivity analysis

The mean values for total costs, LYs, QALYs, and incremental cost per QALY gained for Evusheld versus no prophylaxis through 1,000 simulations of the PSA are presented in Table 4. In the PSA, Evusheld generates [redacted] incremental QALYs and [redacted] incremental costs over a lifetime horizon compared with no prophylaxis, resulting in an ICER of [redacted] per QALY gained (similar to the base case).

The corresponding ICEP and CEAC are presented in Figure 1 and Figure 2, respectively.

Table 4: PSA results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
No prophylaxis	[redacted]	[redacted]	[redacted]					
Evusheld	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER – Incremental cost-effectiveness ratio; LYG – Life years gained; QALYs – Quality-adjusted life years

Figure 1: Incremental cost- effectiveness plane

Abbreviations: PSA – Probabilistic sensitivity analysis

Figure 2: Cost-effectiveness acceptability curve

Abbreviations: NMB – Net medical benefit

2.3 Deterministic sensitivity analysis

The OWSA tornado diagram presenting the 15 most sensitive parameters for the sub-population of interest is presented in Figure 3. Table 5 presents the OWSA results for these 15 parameters. The model was most to the proportion of patients with long COVID in the non-hospitalised- assistance needed health state. [redacted]

Table 5: DSA results

Parameter	ICER (£)	
	Upper bound	Lower bound
Symptomatic Infection Risk: PROVENT	[redacted]	[redacted]
Proportion with long covid Not Hospitalised - assistance needed	[redacted]	[redacted]
% of symptomatic cases requiring hospital admission: PROVENT	[redacted]	[redacted]
Utility gain Evusheld (reduction in anxiety)	[redacted]	[redacted]
Post-acute aggregated costs: Not Hospitalised (No assistance needed)	[redacted]	[redacted]
Post-acute aggregated costs: Not Hospitalised (Assistance needed)	[redacted]	[redacted]
Aggregated Costs - Invasive Mechanical Ventilation or ECMO	[redacted]	[redacted]
Post-acute aggregated costs: Low-flow Oxygen Therapy	[redacted]	[redacted]
Comorbid patients' disutility	[redacted]	[redacted]
Placebo/SoC - Infections and Infestations	[redacted]	[redacted]
Long-term Disutility (Not hospitalised (No assistance needed)): after 5 years	[redacted]	[redacted]
Long-term Disutility (Not hospitalised (Assistance needed)): after 5 years	[redacted]	[redacted]
PROVENT: Non-invasive Ventilation or High-flow Oxygen	[redacted]	[redacted]

Abbreviations: DSA – Deterministic sensitivity analysis; ICER – Incremental cost-effectiveness ratio

Figure 3: Tornado diagram

Abbreviations: ECMO – Extracorporeal membrane oxygenation; ICER – Incremental cost-effectiveness ratio

2.4 Scenario analysis (submission)

Table 6 details scenario analyses results for Evusheld versus no prophylaxis. Results were most sensitive to discount rates for costs and outcomes, efficacy sources, and post-acute HRQoL. Results were least sensitive to removing post year one infection. [redacted]

Table 6: Scenario analysis results

Description	Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	ICER versus baseline (£/QALY)
Base case	**No prophylaxis**	[redacted]	[redacted]	[redacted]				
	Evusheld	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Discount rate: 0%	**No prophylaxis**	[redacted]	[redacted]	[redacted]				
	Evusheld	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Discount rate: 6%	**No prophylaxis**	[redacted]	[redacted]	[redacted]				
	Evusheld	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Reinfection: Not applied	**No prophylaxis**	[redacted]	[redacted]	[redacted]				
	Evusheld	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Efficacy source: PROVENT	**No prophylaxis**	[redacted]	[redacted]	[redacted]				
	Evusheld	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Efficacy source: Kertes et al. 2022	**No prophylaxis**	[redacted]	[redacted]	[redacted]				
	Evusheld	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
% with long COVID at discharge: Evans et al. 2021	**No prophylaxis**	[redacted]	[redacted]	[redacted]				
	Evusheld	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Apply utility benefit associated with Evusheld treatment: 82%	**No prophylaxis**	[redacted]	[redacted]	[redacted]				
	Evusheld	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hospitalisation disutility: ScHARR report	**No prophylaxis**	[redacted]	[redacted]	[redacted]				
	Evusheld	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Post-acute HRQoL: Evans 2021	**No prophylaxis**	[redacted]	[redacted]	[redacted]				
	Evusheld	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: COVID – Coronavirus disease; HRQoL – Health-related quality of life; ICER – Incremental cost-effectiveness ratio; LYG – Life years gained; QALYs – Quality-adjusted life years; ScHARR – School of health and related research

2.5 Scenario analysis (EAG responses)

Table 7: Scenario analyses from EAG responses

EAG question number and description	Technologies	Total costs (£)	QALYs	Costs (£)	QALYs	ICER	INMB (£30,000 per QALY) (£)
B2. Scenario with reduced nurse time	**No prophylaxis**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Evusheld	[redacted]	[redacted]				
B3. No retreatment at 6 months scenario results – Young Xu	**No prophylaxis**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Evusheld	[redacted]	[redacted]				
B3. No retreatment at 6 months scenario results – Kertes	**No prophylaxis**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Evusheld	[redacted]	[redacted]				
B3. No retreatment at 6 months scenario results – PROVENT	**No prophylaxis**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Evusheld	[redacted]	[redacted]				
B4. Adverse event source (TACKLE) scenario results	**No prophylaxis**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Evusheld	[redacted]	[redacted]				
B5. Annual infection risk scenario results - +20% baseline infection risk	**No prophylaxis**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Evusheld	[redacted]	[redacted]				
	No prophylaxis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

B5. Annual infection risk scenario results - -20% future infection risks	**Evusheld**	[redacted]	[redacted]				
B5. Annual infection risk scenario results - +20% future infection risks	**No prophylaxis**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Evusheld	[redacted]	[redacted]				
B6. Scenario analysis using +/-20% in the PSA	**No prophylaxis**						
	Evusheld						
B7. Shields et al. 2022 scenario analysis	**No prophylaxis**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Evusheld	[redacted]	[redacted]				
B8. Hospitalisation distribution scenario analysis – Second Wave (Cusinato et al)	**No prophylaxis**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Evusheld	[redacted]	[redacted]				
B8. Hospitalisation distribution scenario analysis – gov.uk (46) accessed Oct 2022 for ventilation and second wave (Cusinato et al)	**No prophylaxis**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Evusheld	[redacted]	[redacted]				
B11. Long-COVID scenario analysis – Sensitivity 1: Original (not calibrated)	**No prophylaxis**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Evusheld	[redacted]	[redacted]				
	No prophylaxis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

B11. Long-COVID scenario analysis – Sensitivity 2: Oct data (calibrated)	**Evusheld**	[redacted]	[redacted]				
B11. Long-COVID scenario analysis – Sensitivity 3: Oct data (not calibrated)	**No prophylaxis**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Evusheld	[redacted]	[redacted]				
B13. Long COVID utility linearly reducing to 50% of year 1 value post year 5 – scenario results	**No prophylaxis**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Evusheld	[redacted]	[redacted]				
B14. Long COVID, non-hospitalised scenario analysis – 4-month data from Augustin et al. (2021)	**No prophylaxis**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Evusheld	[redacted]	[redacted]				
B.16 Long COVID distribution scenario analysis	**No prophylaxis**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Evusheld	[redacted]	[redacted]				
B19. Hazard ratio for mortality post-discharge scenario analysis	**No prophylaxis**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Evusheld	[redacted]	[redacted]				
B20. Post-discharge disutility non-hospitalised patients scenario analysis	**No prophylaxis**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Evusheld	[redacted]	[redacted]				

Abbreviations: COVID ─ Coronavirus disease; HRQoL ─ Health-related quality of life; ICER ─ Incremental cost-effectiveness ratio; LYG ─ Life years gained; QALYs ─ Quality-adjusted life years

3 Budget impact results

3.1 Estimated annual budget impact (no PAS)

Table 8: Expected budget impact, no PAS

	Year 1	Year 2	Year 3	Year 4	Year 5
Eligible population for treatment with Evusheld	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Population expected to receive Evusheld	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost of treatment pathway without Evusheld (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost of treatment pathway with Evusheld (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net budget impact (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

NICE National Institute for Health and Care Excellence

Single Technology Appraisal
Tixagevimab–cilgavimab for preventing COVID-19 [ID6136]
Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you

1.Your name	[redacted]
2. Name of organisation	Action for Pulmonary Fibrosis
3. Job title or position	[redacted] I am immune-suppressed (IS) having received a lung transplant for pulmonary fibrosis in 2016. In these comments, we will use the term **Evusheld** rather than Tixagevimab–cilgavimab
4a. Brief description of the organisation (including who funds it). How many members does it have?	APF is a patient driven charity involving a growing community of patients, families, researchers and healthcare professionals striving to find a cure for pulmonary fibrosis so that everyone affected by the disease has a better future. APF supports patients and families and raises awareness of pulmonary fibrosis through campaigning, fundraising and educates GPs and other HCPs about the disease. We advocate for improved treatment and care for those living with pulmonary fibrosis and also shape and fund research to improve quality of life for people living with pulmonary fibrosis and to find a cure. Most of APF's funds are donated by patients and their families, through fundraising events and donations. We also receive limited funding from pharmaceutical companies, for specific projects, and charitable foundations. We do not have members, but we inform, empower and support thousands of patients and their families living with pulmonary fibrosis across the UK to improve quality of life and life expectancy. We do this in the main through a network of over 60 patient and carer-led support groups, peer-led

	telephone support and expert information, co-produced by patients and healthcare professionals, which is available on and off-line. Two groups of pulmonary fibrosis patients are immune-suppressed. People who (1) have had a lung transplant (approx. 200 people) and (2) those with pulmonary fibrosis linked to connective tissue disease (e.g., Rheumatoid Arthritis-ILD) and other auto-immune diseases – over 5,000 people.
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] **If so, please state the name of the company, amount, and purpose of funding.**	No
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	APF is in constant touch with patients are carers living with pulmonary fibrosis, including those who are immune suppressed. For the purposes of this evaluation, we held individual and group interviews and discussions with over 20 people living with pulmonary fibrosis who are immune suppressed.

Living with the Condition

Living with the condition **6. How has shielding from COVID-19 affected vulnerable people?**	Most pulmonary fibrosis patients have been shielding since the start of the pandemic in March 2022. In 2020 and 2021 we mostly stayed at home, only venturing outside for essential visits to our GP or hospital. We rarely saw our families and friends. This was incredibly hard to do and led to many people having mental health problems and being prescribed anti-depressants and other treatments. Since the NHS introduced post-infection COVID treatments for IS patients in December 2021 (e.g Paxlovid, Sotrovimab) some IS patients have started going out more but generally avoid public transport and rarely enter buildings such as theatres or restaurants, because of the risk of contagion. Immune-suppressed patients are disappointed when we hear government ministers say that covid is over. This may be true for most of the population, but it is not for the 500,000 immune suppressed people in the UK see things! **We still cannot lead a normal life.** ***Lung transplant patient*** *My wife and I have now been shielding for 2 years and 7 months. During that time we have not been inside a building other than our house, the GP Surgery and outpatients at the hospital. We used to be gregarious, seeing friends and going to theatres and restaurants. But no more. It's hard even to remember the life we used to have. This year (2022) has been better because of the post-infection covid treatments reduce the danger of getting severe Covid and the good weather has meant we have been able to see our family and grandchildren outside, and even meet friends outdoors. Bur winter is coming and we will be locked down again until the Spring.* *We were angry when Boris Johnson declared 'Freedom Day' in July 2021 with a big fanfare because freedom for the majority (no face masks etc) meant increased risk and continued shielding for the hundreds of thousands of people who are immune suppressed.* *And now, just as with Freedom Day, government ministers tell us covid is a thing of the past. Maybe for the majority but not for those of us who are immune suppressed.* ***We are still limited by Covid in everything we do!***

Unmet need

7. Is there an unmet need for patients with this condition?	Yes. There is an urgent need for a prophylactic therapy to reduce the risk of immune suppressed people becoming infected with COVID-19. With such a drug, immune suppressed people would feel better able to get outside the house and lead more normal lives. ***Patient living with RA-ILD (rheumatoid arthritis-ILD)*** *I take immune-suppressants for pulmonary fibrosis linked to my rheumatoid arthritis. I have had all six covid vaccinations but there has been no antibody response. My doctors advise me to be very careful, so I am essentially shielding at home. I do sometimes go out for a walk in the park and occasionally meet friends for a coffee at an outdoor café, but not in winter. If we had Evusheld I would feel much more confident in going out and re-establishing my life.* ***I am grateful for the government's post-infection treatments but wouldn't it be better stop us getting Covid in the first place?***

Advantages of the technology

8. What do patients or carers think are the advantages of the technology? • How would having a prophylactic treatment available impact the day-to-day lives of vulnerable people? (for example, how would it change the activities people do, or how they feel?) • How would having a prophylactic treatment available impact carers?	**Continuing from para 7.** Immune suppressed people tell us that if they had a reliable prophylactic treatment they would be able to phase a fuller and more normal life. Patients interviewed for this evaluation stated that a reliable therapy like this would make them confident in using public transport; going inside theatres, pubs and restaurants; and visiting friends' houses. We would be able to re-establish friendships and other relationships and get back to some sense of 'normality'. We would still be careful and most of us would wear masks in public places and practice social distancing. But, being vigilant in these ways is something we are used to doing as chronic lung disease patients. When they have been able to, carers have shielded with their IS partners. During 2020 and 2021 it was very difficult for households where the carer had to go out to work. But with widespread vaccinations and testing it became easier to stay safe while going out to work and for other reasons. Nevertheless, most carers recognise that even with vaccinations and testing there is a risk to their IS partner and they generally limit time outside the house and do things (for example shopping) which involve going into a shop to reduce the risk for their IS Partner. A prophylactic treatment would make things much easier for the carer since the IS patient would be better able to go out and do things as they used to do before Covid. It would also make them confident to use public transport and visit restaurants, theatres etc with there is Partners. Life would be fuller and more enjoyable.

Disadvantages of the technology

9. What do patients or carers think are the disadvantages of the technology?	None.

Patient population

10. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	The therapy should be made available to **ALL** immune suppressed people.

Equality

11. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	The main equality issues are that: • IS patients and their families still have to lead restricted lives, while the majority of the population are leading normal lives. Given this, it is disappointing that NICE is not appraising Evusheld on an accelerated pathway. • Some IS patients, who can afford it, are obtaining Evusheld in North America and Europe and we understand that the company is shortly to make the therapy available privately in the UK. There is growing inequality among those who can afford to buy the drug and those who cannot. • Action for Pulmonary Fibrosis thinks doctors should be able to prescribe Evusheld for all IS patents when they need it.

Other issues

12. Are there any other issues that you would like the committee to consider?	As stated above, the two groups of pulmonary fibrosis patients who are immune suppressed are either lung transplant recipients or those with auto-immune disorders linked to ILD. We would also like the Committee to consider whether Evusheld should be made available to all patients with progressive pulmonary fibrosis (not just those who are immune supressed) in light of evidence that: 1. Patients with ILD who are hospitalised are at 70%-80% higher risk of death from COVID-19, especially those with poor lung function and obesity. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7737581/pdf/rccm.202007-2794OC.pdf 2. Patients with idiopathic pulmonary fibrosis (IPF) do not mount appreciable anti-spike antibody responses to two doses of SARSCoV2 mRNA vaccine compared to the general population. https://openres.ersjournals.com/content/erjor/early/2022/03/17/23120541.00082-2022.full.pdf

Key messages

13. In up to 5 bullet points, please summarise the key messages of your submission.	• Many immune-suppressed people are still shielding 2.5 years after the start of Covid-19, with determinantal impacts on their mental health. • Post-covid therapies and lateral flow testing have made it possible for IS patients to get out more but their lives are still restricted. • UK patients are thus desperate for an effective prophylactic therapy, which will reduce the chance them catching covid in the first place. (Evusheld is available in most other western countries) • The high demand for Evusheld by IS patients can be seen in the increasing numbers of patients going to other countries to receive the therapy privately. • Action for Pulmonary Fibrosis believes that Evusheld should be made available to ALL IS patients, not just those able to pay for it privately.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

Please select YES if you would like to receive information about other NICE topics - YES or NO

For more information about how we process your personal data please see our privacy notice.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal
Tixagevimab–cilgavimab for preventing COVID-19 [ID6136]
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- Your response should not be longer than 10 pages.

About you

1.Your name	[redacted]
2. Name of organisation	Anthony Nolan
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	**Anthony Nolan** saves the lives of people with blood cancer and other blood disorders. Founded in 1974 as the world's first stem cell register, we're motivated by a mother's determination to save her son, Anthony. Now saving three lives every day, our charity is a lifesaving legacy. By growing our register of potential stem cell donors, conducting ground-breaking research into improving transplant outcomes, and providing outstanding support and clinical care for patients and their families, Anthony Nolan cures people's blood cancer and blood disorders. In this submission, we are representing the views and experiences of stem cell transplant recipients, CAR-T cell therapy recipients, blood cancer and blood disorder patients.
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.]	Anthony Nolan has not received funding from AstraZeneca in the last 12 months and there are no comparator products named in the scope. Anthony Nolan's Chief Medical & Scientific Advisor, Professor Antonio Pagliuca, has been nominated as a Clinical Expert representative to this appraisal by the manufacturer, AstraZeneca. Professor Pagliuca will not be involved in Anthony Nolan's submission to this appraisal and has not had any input into or involvement in this submission.

If so, please state the name of the company, amount, and purpose of funding.	
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	None
5. How did you gather information about the experiences of patients and carers to include in your submission?	Information for this appraisal was gathered from a range of sources, including: • Telephone interviews with stem cell transplant recipients, their carers and family members • Insight from the Anthony Nolan Patient Services Team • A survey of the experiences of blood cancer patients during the Covid-19 pandemic, with responses from over 600 people. • Clinical nurse specialists were also consulted to build our understanding of the experiences of patients and carers.

6. How has shielding from COVID-19 affected vulnerable people?	**Psychological impact** • Ongoing shielding from COVID-19 has had a profound impact on many stem cell transplant recipients. Many patients continue to shield to some extent despite the lack of official government support to do so. Those interviewed for this appraisal described the loneliness, anxiety and isolation that they and their family members feel as a result of ongoing shielding. '*I was climbing the walls, itching to get outside. I was losing my mind feeling locked in'* said one patient, who didn't leave the house at all for 9 weeks recently. Now, like many, they choose only to go for a walk in the very early hours of the morning, when the roads and parks are quiet, despite it being lonely and sometimes scary. • People vulnerable to COVID-19 experience poor mental health including depression as a result of isolation from friends and family. Many patients describe being '*terrified'* of catching COVID-19, contributing to their poor mental health. One patient commented *'it is really stressful, having spent so long in hospital already I want to avoid getting ill at all costs. Every time I leave the house I could catch something that I have been told that my body might not be able to deal with...it could kill me. That is frightening'.* • Many patients and family members are concerned that the threat of high COVID-19 cases in the coming winter months will mean that they need to self-impose increasingly strict restrictions. Stem cell transplant recipients and their families experience a particularly negative psychological impact due to requiring long periods of self-isolation after their treatment, as they are extremely vulnerable after transplant and have very little if any vaccine protection. The prospect of high rates of COVID-19 extending what is already an intense isolation period can be particularly difficult for this group. **Impact on daily life** • Many stem cell transplant recipients have adapted their life to a "new normal" that is highly unsustainable in the long-term, with significant additional precautions taken to protect themselves from exposure to COVID-19. • One patient spoke about their spouse having to leave their job due to the risk of COVID-19. '*There is a significant lack of understanding about just how at risk some people are to COVID-19',* they said. Despite support from their employer, their spouse was not able to return to work as a teacher due the continued risk of being exposed to COVID-19 for transplant recipients. '*After a period of being seriously unwell, you want to get your life back on track.* COVID-19 *has stopped us from doing that. My partner can't work in the job that they are trained to do and without additional protection I don't see that happening soon',* they said.

	• We also received concerning reports from some patients who have had access to treatment options removed that allow care to be delivered outside of the hospital setting. Patients have expressed significant concern, worry, anger and fear at the prospect of having to make more frequent or longer trips to the hospital to receive treatment, that in some cases, could be provided at home. The removal of special licences given to innovative treatments that could be administered at home during the pandemic has forced some patients who are otherwise shielding to make unnecessary trips to the hospital for treatment. Many feel that this is putting their life at risk. This causes added concern when considering the expected rise of COVID-19 cases during the winter months and the removal of non-pharmaceutical interventions in NHS settings, such as social distancing, mask wearing and regular handwashing. • Another patient described a serious adverse reaction to the vaccine and was told to delay further vaccination by their medical team. '*This meant I went back into full shielding*' they said, discussing '*dropping all of the things that makes life worth living'.* Often, patients report not seeing family members or friends and many are still exclusively socialising outdoors and infrequently. This becomes increasingly challenging during the winter months and some have expressed concern about loneliness and isolation. • This was well summarised by another patient who commented, '*I have not been to the shops in three years, the children and grandchildren have not been in the house. I have not had a hug from my child. I have not seen friends inside and I haven't been able to play team sports which keeps me fit and healthy. For immunocompromised people like me, the winter is a scary, lonely and isolating time'.* This person also felt unable to undertake their job, due to the risk of COVID-19 and has since stopped work. • These impacts are also felt by carers, partners and family members of those who are continuing to shield as a result of COVID-19. One person spoke about their condition impacting the ability of others in their family to work and the knock on impact of being at home 24/7. *'It has been tough on our household income, which is a real worry during the cost-of-living crisis. It has also stressed family connections, spending more time at home and less with friends'.* • The cost-of-living crisis was raised by a number of patients who were concerned about the additional cost of heating their homes during a long and tough winter. Staying warm, keeping fit and eating well are key to good post-transplant recovery and some worry about this being at risk. • Some patients also pay for private antibody tests to help them understand more about their own personal levels of immunity. While there is yet to be scientific consensus on the level of protection that antibody detection confers, some have said it allowed them to better manage risk. However, these tests are expensive and are not a feasible option for many patients.

7. Is there an unmet need for patients with this condition?	• Many blood cancer patients and stem cell transplant recipients remain at high risk from COVID-19 and are known to be comparatively less well protected by existing vaccines. • Numerous studies have shown that individuals with cancer have increased morbidity and mortality from COVID-19 infection and it has been reported that a significant proportion of individuals with haematological malignancies are unlikely to develop a protective immune response to COVID-19 vaccination.[1-9] This includes the CAPTURE clinical study, which showed that 50% of blood cancer patients elicited no antibody response following three COVID-19 vaccinations.[10] • Stem cell transplant recipients require full re-vaccination post stem-cell transplant. Patients may also be taking immunosuppressant drugs following their transplant, meaning for a period of several months (or years for patients who develop graft vs host disease after their transplant), re-vaccination against viruses including COVID-19 may not be possible or effective. • For this group there is a significant unmet need for effective treatment options, particularly pre-exposure prophylactic treatments which could provide additional protection from COVID-19 for people who are less likely to elicit a good level of protection from vaccination or who are not suitable for vaccination due to their immune status. • There is also an urgent need for additional pre- and post-exposure treatments that are effective against new and emerging variants of the virus that causes COVID-19. References 1. Lim, S. H. et al. Antibody responses after SARS-CoV-2 vaccination in patients with lymphoma. Lancet Haematol. 8, e542–e544 (2021). 2. Greenberger, L. M. et al. Antibody response to SARS-CoV-2 vaccines in patients with hematologic malignancies. Cancer Cell 39, 1031–1033 (2021). 3. Maneikis, K. et al. Immunogenicity of the BNT162b2 COVID-19 mRNA vaccine and early clinical outcomes in patients with haematological malignancies in Lithuania: a national prospective cohort study. Lancet Haematol. 8, e583–e592 (2021). 4. Parry, H. et al. Antibody responses after first and second COVID-19 vaccination in patients with chronic lymphocytic leukaemia. Blood Cancer J. 11, 136 (2021). 5. Herishanu, Y. et al. Efficacy of the BNT162b2 mRNA COVID-19 vaccine in patients with chronic lymphocytic leukemia. Blood 137, 3165–3173 (2021). 6. Van Oekelen, O. et al. Highly variable SARS-CoV-2 spike antibody responses to two doses of COVID-19 RNA vaccination in patients with multiple myeloma. Cancer Cell 39, 1028–1030 (2021).

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Advantages of the technology
 	
8. What do patients or carers think are the advantages of the technology?
 	
• How would having a prophylactic treatment available impact the day-to-day lives of vulnerable people? (for example, how would it change the activities people do, or how they feel?)
 	
• How would having a prophylactic treatment available impact carers?
	Prophylactic vs post exposure anti-viral treatments
	• Patients and carers contacted for this appraisal unanimously agreed that the availability of a pre-exposure prophylactic treatment, such as tixagevimab–cilgavimab, would have a positive impact on their day-to-day life.
	• We conducted a survey of blood cancer patients to assess views on the level of protection offered by existing post-exposure treatments, which has received over 600 responses. 106 patients (16% of those who responded to the survey) told us that they didn't receive existing post-exposure COVID-19 treatments due to access challenges, such as:
	  ○ Never being contacted after reporting a positive test result
	  ○ Delays in assessment for treatment, especially over the weekend, meaning people missed the treatment window of 5-days
	  ○ Patients not being able to get hold of GP or specialist nurse, with the phoneline constant engaged
	  ○ Antiviral treatments not being delivered in time
	  ○ Eligible patients not knowing how to access or being too ill to arrange access
	• Patients also reported being told they *'did not sound ill enough'* to access anti-viral treatments, while others reported not being able to access treatments in time, facing barriers that meant they were ineligible for treatment by the time they could access them. This causes significant worry as patients are aware that if their condition worsened, they may face further barriers to accessing treatment options.
	• One patient was told that he was *'hours from death'* had he not received lifesaving antiviral treatment. *'I am grateful for current antivirals'* he said, '*however, something that could stop me getting that ill and catching COVID-19 in the first place would be the real game changer'.* Many agreed with this sentiment and felt that the benefits of a pre-exposure prophylactic treatment could mitigate some of the challenges faced with access to antiviral treatments that are time sensitive and rely on self-advocation in a time of extreme need.
	• Speaking to one patient who faced challenges accessing post-exposure treatment options, they said having a preventative prophylactic treatment would provide '*significant additional peace of mind'*. Another referred to prophylactic treatments as '*empowering, enabling me to make the decisions I want to with confidence'.*
	• Some felt that the availability of prophylactic treatments could begin to enable them to return to work. Another commented that effective prophylaxis against COVID-19 was '*key to starting to get my life back'.*

	• Many spoke hopefully about the prospect of starting to return to seeing friends and family, socialising and returning to their hobbies. • A number of patients described being so desperate to access this treatment that they have explored options such as going abroad to receive tixagevimab–cilgavimab. '*I have seriously thought about it, anywhere I could safely go to get this treatment, I would'* commented CAR-T cell therapy recipient whose treatment has left them with chronic immune impairment. **Impact on carers** • Carers of immunocompromised people such as transplant recipients were also highly supportive of prophylactic treatments. Many described being able to consider the possibility of returning to work if prophylactic treatments were to become available. • Carers also noted that having effective prophylaxis available would enable them and their families to resume social contact and hobbies like playing sports, seeing live music and other activities, none of which they feel able to do

Disadvantages of the technology

9. What do patients or carers think are the disadvantages of the technology?	• Patients and carers did not raise any concerns or disadvantages of this technology. • When prompted about the level of protection that it may provide, patients and carers consulted understood that this technology could not provide absolute protection from COVID-19, but felt that it was important to have at least some additional protection, which it was felt this treatment could provide. • Most patients noted that the additional protection that the technology offered would provide some peace of mind. Some felt its availability may enable them to re-assess some self-imposed restrictions, depending on their health and the risk posed by the virus. • Most also acknowledged that as new variants prevail, the treatment may have limited effectiveness. However additional protection against at least some circulating variants was still considered to be a benefit to those consulted. • Concern was expressed by some related to supply and availability of the technology, with some patients and carers worried that access may be limited due to shortages.

Patient population

10. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	• No patient groups have been specifically identified who may benefit more or less from this technology than others, however many have raised concern over the treatment's availability. Potentially limited supply could lead to significant challenges around the prioritisation of treatment options for patients who may require access to tixagevimab–cilgavimab.

Equality

11. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	• None

Other issues

12. Are there any other issues that you would like the committee to consider?	• Many transplant recipients described feeling like the seriousness of their condition is not understood by both members of the public and some healthcare staff. People described feeling like others still question the measures they are forced to take to remain safe. '*When your healthcare team say that you could get very ill from* COVID-19*, you take that seriously*. *They weren't wrong, I was admitted to intensive care after catching the virus' said one patient.* Some worried that this lack of understanding may mean they are not prioritised for treatment, should it be available. • Patients also discussed their desire to see antibody testing rolled out routinely to patients. People felt that combining this with pre-exposure prophylactic treatments would enable them to make an informed decision about their own protection. • It was also commented by some clinicians who contributed to this appraisal delivery should take place in specialised services such as Bone Marrow Transplantation Units, easing pressures on primary care and ensuring treatment can be delivered safely and to patients of the highest clinical need first.

Key messages

13. In up to 5 bullet points, please summarise the key messages of your submission.	• Ongoing shielding has a significant impact on patients leading to feelings of isolation, worry and stress. The knock-on effect of this on people's employment and finances is also a significant challenge. • Blood cancer patients and stem cell transplant recipients feel strongly that the availability tixagevimab–cilgavimab would be a beneficial step in enabling them to return to a less restrictive life, including socialising and returning to work. • This treatment fills a significant gap in blood cancer and stem cell transplant patient need, as current vaccines against COVID-19 are much less likely to be effective or available to these patients. • Blood cancer and stem cell transplant patients are also at increased risk of morbidity and mortality from COVID-19. • It is not only the blood cancer patient or stem cell transplant recipient themselves who have had to change their lifestyle as a result of COVID-19, with carers and the wider family unit continuing to shield to protect the vulnerable person from exposure. Carers and family members experience isolation, lonleieness, and difficulties with their mental health as a result of shielding and struggle with still not being able to see friends a family. Carers and family members also experience a detraemental impact on their employment as a result of shielding with can strain the household income and cause stress at home.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

Please select YES if you would like to receive information about other NICE topics - YES or NO

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Single Technology Appraisal
Tixagevimab–cilgavimab for preventing COVID-19 [ID6136]
Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

NICE National Institute for Health and Care Excellence

About you

1.Your name	[redacted]
2. Name of organisation	Blood Cancer UK
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Blood Cancer UK is the UK's leading blood cancer research charity. We fund world-class research and provide information, support, and advocacy to anyone affected by the different types of blood cancer – from leukaemia, lymphoma, and myeloma to the rarest blood cancers that affect just a small group of patients. We also provide education and training to healthcare professionals including nurses who care for people with blood cancer. Blood Cancer UK has around 100 employees and is funded primarily through donations and legacies.
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant manufacturers are listed in the appraisal stakeholder list.] **If so, please state the name of manufacturer, amount, and purpose of funding.**	AstraZeneca – £15,000 to fund our COVID-19 policy work and £308 as payment for attending an advisory panel
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the	We gathered the information contained in this report through (1) pre-existing case studies and direct quotes from patients in contact with our support and advocacy service advisors, (2) contact with our network of

experiences of patients and carers to include in your submission?	healthcare professionals, (3) a survey conducted by Blood Cancer UK and disseminated to our patient community, and (4) interviews conducted with people affected by blood cancer. The survey had 779 responses from blood cancer patients. Since it was distributed by Blood Cancer UK, respondents were self-selecting and biased towards our existing networks. Their views, therefore, are less likely to reflect the views of groups who are underrepresented in our networks, some of whom may be marginalised due to e.g., ethnicity. For these groups, the impacts discussed below may be heightened or altered.
Living with the condition	
6. How has shielding from COVID-19 affected vulnerable people?	In our survey conducted with blood cancer patients, 23% of respondents reported being so concerned about Covid-19 that they only left home for essential trips, while over a third avoided meeting people unless necessary and stayed away from indoor places such as restaurants and shops. 82% of respondents reported feeling anxious about Covid-19. Patients tell our service advisors that they want the same opportunities as those who are not immunocompromised. Some of those who are still shielding have high and constant levels of anxiety and fear. One patient describes it as feeling like they're "being told to isolate or play Russian roulette," as they feel abandoned by both the Government and the general public and forced to shield in the absence of other robust, effective, and accessible protection mechanisms. Many feel that leaving their home for any reason is a deadly risk, a perception that has led to some patients refusing to get vaccinated for fear of contracting Covid-19 at the vaccine site. The experiences of one patient attests to this: he had been shielding since 2020 but left his home for the first time for a non-essential reason in October 2022. While in a public space, he contracted Covid-19. Another patient, who has been shielding since 2020 without their family, describes their desperation: "I would sell my home to get Evusheld if it meant I could see my family and live without fear." While Covid-19 prophylaxis, including Evusheld, would not eliminate the risk posed to patients (as is discussed in our response to question 9), it is a crucial component of the architecture of protection mechanisms available to patients. As one patient puts his shielding experience, "My diagnosis of Mantle Cell Lymphoma means that I have a potential lifespan of 5 – 10 years, so I would like to spend this time making memories with my family and friends. The fact that I am having to shield means that me and also my family are deprived of this valuable time together, this has a huge psychological impact. The fact I am unable to work [due to high risk in the workplace] means that we are put under a huge financial burden too, especially with the increasing cost of living. Having to shield also takes its toll on relationships, as it adds additional pressure due to the fact my daughter and wife cannot live a normal life either." For those who live with family members or loved ones, the effects of shielding

	extend to the entire household. Several patients who speak with our advisors cite significant relationship breakdowns as a result of the enormous mental and financial health impact of shielding. While the impacts of shielding are far-reaching, the committee must also consider the impact of Covid-19 on people who are in particular circumstances that bar them from shielding, or do not have the resources to shield. This includes those who are experiencing financial precarity and must work in public-facing jobs, those who do not have recourse to public funds, and those with school-age children. As the cost-of-living crisis worsens, this group of people will expand. People with blood cancer who cannot shield are at very high risk from Covid-19.
Unmet need	
7. Is there an unmet need for patients with this condition?	There is an overwhelming unmet need for people with blood cancer, who remain inadequately protected from Covid-19. As a result of weakened immune systems, people with blood cancer have always been at higher risk from infections than the general population. Yet Covid-19 remains an acute threat to life for this patient group: in the first 6 months of 2022 alone, more people with blood cancer died from Covid-19 than did as a direct result of flu and pneumonia in the past 10 years combined in Wales and England. From January to June 2022, 621 people with blood cancer died from Covid-19, while a combined total of 577 people died from flu/pneumonia between 2011 and 2021 (an average of 60 people per year), where blood cancer was a contributing factor according to ONS data. While the ONS uses differing death registration data to record these two datasets (the former including all people with blood cancer, and the latter including those for whom blood cancer was listed as a contributory cause), the stark difference in mortality rates underlines the risk from Covid-19 that remains despite the introduction of vaccines and post-exposure Covid-19 treatments. Indeed, the mortality rate from Covid-19 has not lowered at the same pace for people with blood cancer as it has for the general population, which demonstrates the inadequate protection afforded by vaccines for this patient group. In the first half of 2022, among the unvaccinated the immunocompromised made up 2.4% of Covid intensive care admissions according to an ICNARC analysis. Among those with 3 doses, this was 27.7%. Between January and October 2022, people with blood cancer made up 1 in 12 people (8.3%) admitted to intensive care where the primary reason was for Covid-19, despite making up less than 1% of the population at just under 580,000 people in the UK. Indeed, a recent publication by Greenberger et al., (2022) in Blood Cancer Cell shows that, in people with blood cancer, the Covid-19 vaccines predominantly induce CD4+ T cells (which merely regulate the immune

	response) rather than CD8+ T cells, which actively kill viruses. Greenberger and his colleagues also found that only 50% of people with blood cancer mounted a detectable T cell response to the vaccines, and that T cell response was correlated with antibody response. A growing body of literature also demonstrates that people with blood cancer and those on B-cell depleting treatment (including active cancer treatment) do not mount an adequate antibody/B-cell response to the vaccines, with 46% of blood cancer patients left without detectable antibodies following a third vaccine dose. The current Government approach to vaccination relies on T cell responses in the immunosuppressed cohort; it is now well-known that antibody immunity wanes relatively quickly among people with blood cancer, but they are offered vaccine doses only every 6 months based on the assumption that T cell response will protect them. The research above suggests, however, that patients with low or no detectable antibodies also have an impaired T cell response. For those who do mount a T cell response, they are not producing CD8+ T cells, or those needed to eliminate SARS-CoV-2. The failure of the vaccines programme to protect people with blood cancer is evidenced by their disproportionately high mortality and intensive care admission rates, listed above. While post-exposure Covid-19 treatments are available, there are serious barriers to accessing these treatments within the treatment window of 5 to 7 days post-symptom onset. OpenSafely data shows that only 24% of people who register a positive test and are referred for treatment actually receive it. While some of those referred may not be symptomatic, or may not be eligible according to their health condition, there is significant racial and socioeconomic disparity in access which suggests there are also operational failures that contribute to 76% of referred people not being treated. While 25% of those of white ethnicity receive treatment, the same can be said of only 13% of those in the Black or Black British ethnic group. Similarly, 28% of people in the least deprived areas are treated, while only 17% of those in the most deprived areas receive treatment – and those living in urban areas are less likely to be treated than those in rural areas. There is also significant regional variation, with 29% of people in the East of England treated, and only 18% treated in London and the North East, and 17% treated in Yorkshire and the Humber. Case studies gathered by our service advisors show common barriers to access: (1) there is a widespread misunderstanding and lack of knowledge of blood cancer as a condition, as well as the guidance and eligibility criteria for people with blood cancer among healthcare professionals working in Covid-19 Medicines Delivery Units and (2) the assessment system favours patients who 'perform' their illness and vulnerability in a way that is often incongruent with how cancer patients present themselves in their day to day lives. Taken together, these barriers mean that patients who have the resources to advocate for themselves and who can 'perform'

	their illness adequately are most likely to receive treatment – which has arguably contributed to the racial and socioeconomic disparity evidenced by the OpenSafely data. People with blood cancer are therefore inadequately protected both by vaccines, and by the post-exposure treatments available. Despite both of these programmes running throughout 2022, people with blood cancer are 12 times more likely to die from Covid-19 than members of the general population. This has led some people to shield, while forcing those who cannot shield (due to, e.g., the reasons outlined in answer to question 6 above) into unsafe environments, putting them at very high risk and leading to further disparity.
Advantages of the technology	
8. What do patients or carers think are the advantages of the technology? • How would having a prophylactic treatment available impact the day-to-day lives of vulnerable people? (for example, how would it change the activities people do, or how they feel?) How would having a prophylactic treatment available impact carers?	Nearly universally, people with blood cancer tell our service advisors that have an effective, safe, and accessible prophylactic treatment would "give [them their] life back", lessen their anxiety, and allow them to engage in public life in more meaningful ways than simply going to work or shielding. Many members of our community, even those who must put themselves at risk when going to work or welcoming their children home from school, have not engaged in non-essential trips or visits for over 2 years. They "want to hug and sit closely by family and friends without the worry of catching Covid and dying". As many households affected by blood cancer are practicing these restrictions together, the impacts of an effective preventative treatment would extend to carers and other household members. For one patient, it would "allow me to go back to work too, but also more importantly make me feel a lot safer when attending hospital appointments for my ongoing care." He continues, "I think it would also make my life a lot happier, as I can start to spend more time with my daughter too [who is at university]." People with blood cancer who are experiencing financial precarity are forced to work, often in public facing jobs, regardless of whether a preventative treatment is available. Such a treatment would drastically reduce the risks posed to them each day. People whose shielding has led them to financial precarity would also have their risk reduced, potentially to the extent it could be managed while also working. Prophylaxis would certainly allow them to have more informed conversations with their specialist teams about their risk levels as they incorporate risk management in their everyday lives. The vaccine and post-exposure treatment programmes have failed to adequately protect this patient group, as evidenced in response to question 7 above. An effective and accessible prophylactic treatment is vital to ensure that the risk from Covid-19 is reduced for people with blood cancer.

Disadvantages of the technology	
9. What do patients or carers think are the disadvantages of the technology?	The disadvantage of this technology is that its efficacy is dependent on the makeup of future variants, similarly to the Covid-19 and flu vaccines, and the already-available post-exposure monoclonal antibody treatments such as sotrovimab. Yet, patients often relay to our service advisors that they understand the technology does not eliminate their risk from both becoming infected with Covid-19, and adverse outcomes associated with infection. One patient says, if the technology to be made available, he would "still continue to take measures to protect myself, such as wearing filtered masks in public places and generally risk assess most situations." While Evusheld is ineffective against some variants (e.g., BA.4.6) it retains efficacy against others (e.g., BA.2.75), and it may or may not be effective against other variants in the future. Evusheld should therefore be monitored closely if it is made available (alongside sotrovimab, for example, by reviewing emerging evidence and considering input from international bodies and regulators).
Patient population	

10. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	The blood cancer cohort is heterogenous – due to the varying nature of blood cancer conditions and cancer treatments, some people within this cohort may benefit more from the technology than others. Those who do not mount an adequate cellular or humoral immune response from Covid-19 vaccines would benefit the most. While cellular immunity testing (T cell testing) is expensive and its accuracy is contested, serology testing would provide some insight into whether a humoral response has been elicited. It is important, however, that serology testing is not the sole indicator of who should receive this treatment; antibodies are but one component of the immune response, and those with cancers that affect their T cells may have seroconverted while still being at very high risk from Covid-19. Seronegativity could, however, be used as one key indicator of who might benefit and considered alongside a range of other factors when determining patient eligibility, and results from antibody testing would best be interpreted in light of the research cited in response to question 7 above which investigates the relationship between seroconversion and cellular response. A holistic assessment should be conducted to determine whether an individual would benefit from this treatment, using clinical markers and indicators beyond simply antibody response. Within the blood cancer cohort, Evusheld will likely be most beneficial in (1) those with evidence of clinically significant immune system failure (such as recurrent infections), (2) those whose treatment type and schedule are likely to cause or are causing clinically significant immune system failure, and (3) those for whom infection with Covid-19 would disrupt life-prolonging treatment (e.g., blood cancer patients receiving or about to receive induction therapy, chemotherapy, monoclonal antibody therapy, and stem cell transplants). Delays to these treatments can lead to disease progression and future treatments that would have not otherwise been necessary. Stem cell transplant patients also rely on donors, and delays can impact donor availability; starting conditioning for transplant and subsequently becoming infected with Covid-19 can be potentially catastrophic for these patients. This is a particularly acute risk for patient groups with historically low donor matches, including those from minoritised ethnic backgrounds. Further, some blood cancer patients may need treatments that require regular hospital visits, e.g., patients with Multiple Myeloma who need dialysis three times per week at a renal unit, or patients with MDS who require weekly transfusions where exposure to staff and other patients is unavoidable. The holistic assessment should also consider people with chronic blood cancers whose lives have been significantly disrupted by their high risk from Covid-19, such as being at risk of poverty and other forms of financial precarity and those with limited prognosis who wish to spend time with loved ones before death. There is also stark disparity in mortality rates from Covid-19, along ethnic and socioeconomic lines. A holistic assessment should take into account social and environmental factors that impact on risk from Covid-19. Over a quarter of intensive care admissions primarily for Covid-19 are from people living in the most deprived areas,

	and 48.6% of these intensive care admissions live in the two most deprived quintiles, according to ICNARC. People living in these areas are also the least likely to be treated for Covid-19 if they are infected. It is therefore imperative that, were the technology to be made available, it is rolled out in a way that ensures equitable access – with a focus on ensuring access for those living in the most deprived areas and without the resources to pay for this treatment through private channels.
Equality	
11. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	There are serious health inequalities in the Covid-19 protection programme for the immunocompromised, constituted by the vaccines and post-exposure treatment initiatives. People of Bangladeshi, Pakistani, Black Caribbean, and Black African backgrounds are less likely to be vaccinated than those of white backgrounds. People of all ethnic groups are less likely to receive post-exposure treatment than those of a white background – with people of Black backgrounds the least likely to receive treatment. Those living in the most deprived areas are both least likely to receive treatment, and most likely to be admitted to intensive care for Covid-19, as has been evidenced in response to questions above. This technology must therefore be rolled out in a way that ensures equitable access to those who are least likely to benefit from the other two components of the Covid-19 protection programme. A failure to do so risks increasing racial and socioeconomic disparity further.
Other issues	
12. Are there any other issues that you would like the committee to consider?	There is a wealth of evidence demonstrating that Covid infections in people with weakened immune systems are more likely to generate new variants, due to both the nature of their immune systems and the relatively longer length of infection. There is, therefore, a broader public health question around minimising the risk of new variants that must be considered when evaluating the effectiveness of Evusheld. Further, while people who are immunocompromised make up less than 1% of the population, they are overrepresented in intensive care admissions, making up more than 1 in 9 people admitted primarily for Covid-19. This figure, from an analysis conducted by ICNARC, is conservative. It includes only those who have had chemotherapy, radiotherapy or daily high dose steroid treatment in the previous six months, HIV/AIDS, or congenital immune deficiency. An evaluation of the cost-effectiveness of this technology must also consider the current costs associated with being at high risk from Covid-19. The evaluation should determine whether the costs of administering Evusheld are outweighed by potential savings made elsewhere.

Key messages

13. In up to 5 bullet points, please summarise the key messages of your submission.	• People with blood cancer remain inadequately protected from Covid-19, despite the vaccines and post-exposure treatment programmes. • Prophylaxis is a crucial way to address the unmet needs of this patient cohort. • This cohort's risk from Covid-19 has significant and far-reaching consequences including adverse outcomes and death from Covid-19, interruptions to life-saving treatments, and blood cancer disease progression. • Additional consequences of the risk from Covid-19 include financial precarity, social isolation, and psychological deterioration. • The current Covid-19 protection programme reflects and is productive of racial and socioeconomic health inequalities, and this technology must be rolled out in a way that ensures equitable access.

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NICE National Institute for Health and Care Excellence

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Tixagevimab–cilgavimab for preventing COVID-19 [ID6136]
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You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

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- Your response should not be longer than 10 pages.

NICE National Institute for Health and Care Excellence

About you

1.Your name	[redacted]
2. Name of organisation	Chronic Lymphocytic Leukaemia (CLL) Support
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	**CLL Support** is the only UK CLL specific support charity which was formed in 2005 and is run entirely by volunteers. The charity's remit is to provide support to people affected by CLL and its subtypes by keeping them informed of recent and relevant developments in CLL treatment and research and to provide opportunities for awareness raising and mutual support. This requires the association to support and aid empowerment through education while advocating for improving outcomes and access to better treatments. CLL Support provides support to the UK CLL community and CLLSA membership of 2,000+ association members who live with CLL or are carers and the 15,000+ CLLSA on-line community members on the Health Unlocked CLL Support platform (not all UK based). CLL Support provides up to 6 patient conferences a year including a regular Scottish patient's conference. Since 2020 the meetings have been via Webinars because of COVID19 and have been topical and more frequent. CLL Support supports patients through telephone and email, one to one at meetings, literature in the form of patient information packs, newsletters and the websites: http://www.cllsupport.org.uk and their online presence on Health Unlocked https://healthunlocked.com/cllsupport .

	The association is supported and generously funded by member's donations, legacies, members' fund raisers and unrestricted educational grants from various pharmaceutical companies.
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] **If so, please state the name of the company, amount, and purpose of funding.**	Yes, pharma funding: **CLL Support** (1) AstraZeneca – £15,000 Core funding of member services (2) Abbvie - £12,000 Core funding of member services (3) Roche – £16,000 Core funding of member services (4) Janssen - £7,500 Core funding of member services
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	We were not able to gather any UK information about patient experiences with Tixagevimab–cilgavimab for preventing COVID-19. Real life experiences and quotes were gathered from USA members on the Health Unlocked CLL Support social media platform. They are limited in number and relate only to immediate side effects.

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	In relation to COVID 19 and living with CLL, it means an increased susceptibility to serious illness and potentially death than other patients, primarily because CLL causes a dysregulated immune system even in the early watch and wait phase. For patients receiving treatment for their CLL, especially in combination with anti CD20 monoclonal antibodies, they are generally unable to mount any immune response and produce antibodies despite multiple covid vaccinations. The role of T cells in relation to covid immunity is not clear and many CLL patients have 'exhausted' T cells, reducing their effectiveness. Infection with covid often takes many weeks to clear and immunosuppressed patients have been known to act as a reservoir, enabling the virus to mutate into new strains. For both CLL patients, their family, colleagues and their carers, covid creates fear and worry of infection or passing on covid. The wider family often live restricted lives to avoid higher risk situations (essentially anything indoors with the wider public) and this ongoing situation is leading to mental health difficulties for most of them and CLL patients feel guilty for this, adding to their burden of anxiety. For those caring for someone with blood cancer who has COVID-19, their experience is often deeply traumatic. Dozens of people who lost loved ones to COVID-19 have contacted charity support lines for bereavement support. One person said the following: "My Dad died of COVID-19 and had blood cancer. He got through 2 and a half years of lockdowns, isolation, a diagnosis of blood cancer, chemotherapy, to then be in hospital and catch COVID-19 from someone, and die in 12 hours." Another told us, "I've been struggling a lot since we lost my Dad. In particular, I'm angry a lot of the time, mostly with anything surrounding COVID-19, and the lack of precautions the majority of people now take."

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	Patients who are immunosuppressed are very unhappy with the current treatments available for covid. Post exposure treatments such as Paxlovid are contra indicated to be taken at the same time as common CLL treatments such as steroids, chemotherapy and targeted treatments. This makes for a very difficult decision to stop treatment whilst receiving post exposure treatment for covid and taking the risk that the disease will flare or get worse. The alternative is to have no post exposure treatment which may mean that covid may become very severe and life threatening with admission to hospital a likely scenario. Patients have report difficulties with accessing the post exposure treatments via the NHS in a timely way, leaving them worried and frightened about how severe their case of covid will be. Many patients have reported 'rebound infections' of covid following Paxlovid which is worrying. Prevention of CLL with prior treatment with Tixagevimab–cilgavimab removes much of the worry of covid and the possibility of disruption of treatment schedules. Patients feel that they would be more confident to resume a more normal lifestyle. This reassurance and the improvements in quality of life would also ripple out to family members and carers.
8. Is there an unmet need for patients with this condition?	Most of society have now returned to 'normal' and are no longer taking precautionary measures to avoid covid. This places immunocompromised patients at high risk of catching covid and to avoid covid, most are excluding themselves from many aspects of normal society including weddings, travelling, eating in restaurants, theatre, even supermarkets. There is definitely an urgent unmet need for those patients that have not been able to make covid antibodies despite vaccinations in order to protect both their quality of life and mental well being.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	This treatment, was approved by MHRA in March 2022 to be used before being exposed to the risk of COVID-19 infection in order to prevent disease (known as 'pre-exposure prophylaxis'). It is a combination of two long-acting antibodies works by binding to the spike protein on the outside of the SARS-CoV-2 virus, the virus that causes COVID-19. This in turn prevents the virus from attaching to and entering human cells which offers a passively conferred immunity to patients who cannot make antibodies because they are immunosuppressed. In a clinical trial in adults, this treatment was found to reduce the risk of developing symptomatic COVID-19 by 77%, with protection from the virus continuing for at least 6 months following a single dose This treatment would give those patients the opportunity to return to a 'normal' life, possibly return to work for some, enjoy family gatherings with children and grandchildren. "Quotes from patients who had received the Tixagevimab–cilgavimab (Evusheld) treatment illustrate the dramatic difference it has made to their lives, general mental wellbeing and quality of life "I felt like I'd won the lottery after getting my first Evusheld and I had no side effects. I still mask etc but mentally, I felt a new freedom and have travelled and felt secure" "I got my Evusheld Wednesday and I've had absolutely no ill effects or pain afterwards" "Felt great after my Evusheld but very tired the next day, no other symptoms. I don't mind, I'm just so grateful to be able to have it" "I had my antibody levels measured following my Evusheld and I'm happy to report great levels" 'Had a phone call from a friend that I'd had dinner with to say he had covid and so had several others that we were with. I'd had Evusheld the month before and I was the only person from the group not to get covid. So happy and relieved!"

	Sources – Heath Unlocked CLL Support platform and Facebook Evusheld group.

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	The main disadvantages are that the treatment is given as two injections, possibly every 6 months. This may disadvantage those who have mobility issues and may struggle to get to a centre. There are uncertainties regarding the efficacy of the treatment with the currently prevalent strains of covid, particularly the new variants with converging mutations and with changes on the receptor binding domain.

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	Patients who are proven by laboratory testing to have none or very low levels of covid antibodies would benefit the most from this technology. If the treatment was approved for restricted use, this would be the group that should be targeted.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	none

Other issues

13. Are there any other issues that you would like the committee to consider?	

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• There is an urgent need to protect those immunocompromised patients who have few or no antibodies to covid. This technology can contribute to that. • Pre exposure prophylaxis treatment will drive a massive improvement in quality of life and mental health for both patients and families/carers. • Despite milder variants of covid, immunocompromised patients are as much at risk as ever, if not more, as the rest of the UK no longer takes precautionary measures to avoid covid (masks etc). • Winter cases of covid are likely to surge, putting more CLL immunocompromised patients at risk and increasing pressure on NHS bed capacity. • Immunocompromised patients can act as a reservoir and increase covid mutation rates.

Thank you for your time.

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- Your response should not be longer than 10 pages.

About you

1.Your name	[redacted]
2. Name of organisation	Crohn's & Colitis UK
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Crohn's & Colitis UK is the UK's leading charity for everyone affected by Crohn's and Colitis. We're working to improve diagnosis and treatment, and to fund research into a cure; to raise awareness and to give people hope, comfort, and confidence to live freer, fuller lives. We want: • To drive world-class research that improves lives today and brings us closer to a world free from Crohn's and Colitis tomorrow • Everyone to understand Crohn's and Colitis • To support and empower everyone to manage their conditions • To drive high-quality and sustainable clinical care • Early and accurate diagnosis for all. Founded as a patients' association in 1979, we now have over 47,000 members across the UK. Our members include people living with the conditions, their families and friends, health professionals and others who support our work. We have 50 Local Networks which arrange educational meetings, generate publicity and organise fundraising. Funding is through membership subscriptions and a wide range of fundraising activities, including events, grants, legacies and corporate partnerships. Full details are available in our annual accounts Crohn's & Colitis UK's annual reports and accounts (crohnsandColitis.org.uk)
4b. Has the organisation received any funding from	No

the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] **If so, please state the name of the company, amount, and purpose of funding.**	
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	We gather information about the experience of patients, carers and families through: • the Crohn's & Colitis UK helpline • local networks • calls for evidence via our website and social media • one to one discussion with people with IBD, clinicians, and the wider IBD community; and • research - our own and that of external organisations.

Living with the condition6. How has shielding from COVID-19 affected vulnerable people?	Over 500,000 people in the UK have Inflammatory Bowel Disease, the two main forms of which are Crohn's Disease and Ulcerative Colitis. These lifelong, incurable diseases of the gut can affect almost every part of the body and every aspect of life: from digestion and joints to energy levels, mental health, education and the ability to work. Crohn's and Colitis requires tight monitoring and management, often over several decades from the age of diagnosis. If left untreated, poorly managed or in cases of severe disease, Crohn's and Colitis can cause serious complications, which require emergency medical and/or surgical intervention. Crohn's and Colitis are conditions in which the gastrointestinal immune system responds inappropriately. It is therefore often treated with immune suppression medications to control inflammation and to prevent 'flares', a worsening in symptoms, which may be unpredictable. Early in the COVID 19 pandemic, the British Society of Gastroenterology (BSG) produced a risk grid to identify which people with Crohn's and Colitis were at highest risk of severe illness from COVID-19.[1] It categorised people as having high risk (clinically extremely vulnerable), moderate risk (clinically vulnerable) or lower risk (similar to the general population). This categorisation was based on several factors that were thought to increase a person's risk of severe illness if they got COVID-19. These included: • Current or recent Crohn's or Colitis medication. • Crohn's or Colitis disease activity (whether the person is in a flare-up). • Other conditions the person may have (such as lung disease, heart disease or diabetes). • Age over 70 years. Those categorised as 'high' risk were advised to follow shielding guidance. Shielding from COVID-19 had a profound physical and psychological impact of people living with Crohn's and Colitis. This included regular feelings of worry and isolation around trying to protect themselves from the virus, keep up to date with the latest health guidance and gain access to treatment in an overstretched health and care system. Our Life in Lockdown survey[2] found that 18% of patients reported that they had a flare of symptoms because they couldn't access the health services they needed. It is also likely that the stress of the pandemic and shielding contributed to an increase in flare symptoms.[3] Flares have a devastating impact on all aspects of a

	person's life, affecting the ability to work, study, socialise, participate in leisure activities and have intimate relationships.[4] The survey found that those patients who had delays to starting treatment were more likely to report that they needed mental health support. The survey also found that 1 in 5 people with Crohn's and Colitis did not receive the correct shielding information, which caused considerable anxiety and exposed them to avoidable and unacceptable risk. *"I have found that [shielding] has had a massive impact on my mental health where I withdraw into myself. This ends up in me missing medication as I find it really difficult to speak to anyone on the phone or face to face. I started with a flare-up as we went into lockdown and have found it extremely difficult to access help."* **Person living with Inflammatory Bowel Disease** People with Crohn's and Colitis are already at in increased risk of experiencing mental health issues such as anxiety, depression, suicidal ideation and self-harm.[5] [6] [7] This has been exacerbated by the need to shield. Research has also found that those in high-risk cohorts, such as the immunocompromised, have experienced significant psychological impacts from having to shied from Covid-19. A study found that a major cause of anxiety for high-risk individuals was living with others, particularly when those individuals were also in a high-risk category and shielding.[8] This anxiety was triggered by hospital attendance and a fear of transmitting the virus. Those surveyed who reported low mood and depression suggested that the main reasons included disease

[1] British Society of Gastroenterology, BSG COVID-19 Guidance on IBD patient risk groups, (2021) - BSG COVID-19 Guidance on IBD patient risk groups - The British Society of Gastroenterology

[2] Crohn's & Colitis UK, Life in Lockdown: What patients told us about their healthcare, (2020) - https://crohnsandcolitis.org.uk/our-work/healthcare-professionals/the-healthcare-professional-blog/the-healthcare-professional-blog/life-in-lockdown-what-patients-told-us-about-their-healthcare

[3] Sun, Y., Li, L., Xie, R., et al., (2019). Stress Triggers Flare of Inflammatory Bowel Disease in Children and Adults. Frontiers in pediatrics, 7, 432. https://doi.org/10.3389/fped.2019.00432

[4] Crohn's & Colitis UK (2018) Quality of Life Survey. Unpublished

[5] Irving, P., Barrett, K., Nijher, M., & de Lusignan, S. (2021). Prevalence of depression and anxiety in people with inflammatory bowel disease and associated healthcare use: population-based cohort study. Evidence-based mental health, 24(3), 102–109. Advance online publication. https://doi.org/10.1136/ebmental-2020-300223.

[6] Neuendorf, et al, (2016). Depression and anxiety in patients with Inflammatory Bowel Disease: A systematic review, Journal of Psychosomatic Research Volume 87, August 2016, Pages 70-80

[7] Hoogkamer et al (2021), Predicting the development of psychological morbidity in inflammatory bowel disease: a systematic review, Ssystrematic Review, 12(2): 137–144, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7873543/

[8] Kemp, et al, (2020), The psychological impact of COVID19 on a shielding high-risk cohort, Sage Journels, Vol64, Issue 4, https://journals.sagepub.com/doi/full/10.1177/0036933020951900

	relapse, progression, and limited exercise allowance. Other reasons included fear of lockdown ending, and subsequent plans for high-risk patients that would continue to limit their risk.

Unmet need **7. Is there an unmet need for patients with this condition?**	There is now reassuring evidence that most people with Crohn's or Colitis are not at higher risk of getting COVID-19[9] or having more severe COVID-19 because of their disease or treatment.[10] Due to this evidence, the risk grid developed by the BSG is no longer used as a tool for assessing the risk of severe complications from COVID-19 for people with Crohn's and Colitis. We have been working with the BSG to ensure that our information about risk reflects up-to-date evidence that we now have available.[11] Having said this, there is a cohort of people with Crohn's & Colitis – those in a flare-up or taking oral steroids where the risk from COVID-19 may be higher.[12] Furthermore, certain immunosuppressant medicines that people with Crohn's and Colitis take, may make the COVID-19 vaccine less effective. For example, evidence from CLARITY IBD[13] [14] and VIP[15] show that people who were taking an anti-TNF medicine, such as infliximab, an anti-TNF medicine plus a thiopurine or methotrexate, or tofacitinib around the time of their first vaccination may have a reduced response to vaccines.[16] The most recent round of CLARITY IBD results found that a third dose of a messenger RNA-based COVID-19 vaccine (either BNT162b2 (Pfizer-BioNTech) or mRNA-1273 (Moderna) substantially boosted COVID-19 antibody responses in patients receiving infliximab and vedolizumab treatment. However, participants treated with infliximab had antibody levels that were 5.5 times lower compared to vedolizumab-treated patients.[17] Furthermore, this response reduced faster over time in some people. COVID-19 infection after a third dose of COVID-19 vaccine occurred in approximately 15% of patients in the study, and most were due to the Omicron variant. Breakthrough infection was more common and occurred earlier in patients receiving infliximab treatment compared to patients receiving vedolizumab treatment. Re-infection occurred in 12.5% of patients and was mostly due to the Omicron variant. Hospitalisations remained uncommon, with 1.2% of patients requiring admission.[18] We therefore believe that there is a cohort of people with Crohn's or Colitis who would benefit from Tixagevimab–cilgavimab. Based on guidance from the Government's Green Book[19] and an independent report defining the highest-risk clinical subgroups[20] we believe that this cohort include people aged 18 years and over with Crohn's or colitis who are: • Currently taking steroids equivalent to 10mg or more of prednisolone.

[9] Corrias A, Cortes GM, Bardanzellu F, Marcialis MA, Melis A, Fanos V. Risk, Course, and Effect of SARS-CoV-2 Infection in Children and Adults with Chronic Inflammatory Bowel Diseases. *Children* 2021; **8**: 753.
[10] Ungaro RC, Brenner EJ, Agrawal M, *et al.* Impact of Medications on COVID-19 Outcomes in Inflammatory Bowel Disease: Analysis of More Than 6000 Patients From an International Registry. *Gastroenterology* 2022; **162**: 316.
[11] Lees CW, Ahmad T, Lamb CA, et al. (2022) Gut. Withdrawal of the British Society of Gastroenterology IBD risk grid for COVID-19 severity (bmj.com)
[12] Ricciuto A, Lamb CA, Benchimol EI, *et al.* Inflammatory Bowel Disease Clinical Activity is Associated with COVID-19 Severity Especially in Younger Patients. *Journal of Crohn's and Colitis* 2021; published online Sept 27. DOI:10.1093/ECCO-JCC/JJAB172.
[13] Kennedy NA, Janjua M, Chanchlani N, et al Vaccine escape, increased breakthrough and reinfection in infliximab-treated patients with IBD during the Omicron wave of the SARS-CoV-2 pandemic Gut Published Online First: 28 July 2022. doi: 10.1136/gutjnl-2022-327570
[14] Kennedy N, Goodhand J, Bewshea C, et al. Anti- SARS- CoV-2 antibody responses are attenuated in patients with IBD treated with infliximab. Gut 2021;70:865–875. doi:10.1136/gutjnl-2021-324388
[15] Alexander JL, Kennedy N, Ibraheim H, et al. COVID-19 vaccine-induced antibody responses in immunosuppressed patients with inflammatory bowel disease (VIP): a multicentre, prospective, case-control study. Lancet Gastroenterol Hepatol 2022; published online February 3, 2022 https://doi.org/10.1016/S2468-1253(22)00005-X
[16] Crohn's & Colitis UK, Clarity IBD (2020) - https://crohnsandcolitis.org.uk/our-work/research-and-evidence/covid-19-research-and-treatments/covid-19-research/clarity-ibd
[17] Exeter IBD Research Group, Clarity News, Participant Newsletter, Issue 5, 2022 - https://www.clarityibd.org/_files/ugd/56b269_1d7cc429fa96457985ba8d16c583d595.pdf
[18] Exeter IBD Research Group, Clarity News, Participant Newsletter, Issue 5, 2022 - https://www.clarityibd.org/_files/ugd/56b269_1d7cc429fa96457985ba8d16c583d595.pdf
[19]Gov website, Immunisation against infectious disease: the green book front cover and contents page (2021), https://www.gov.uk/government/collections/immunisation-against-infectious-disease-the-green-book
[20] Gov website, Defining the highest-risk clinical subgroups upon community infection with SARS-CoV-2 when considering the use of neutralising monoclonal antibodies (nMABs) and antiviral drugs: independent advisory group report (2022) - https://www.gov.uk/government/publications/higher-risk-patients-eligible-for-covid-19-treatments-independent-advisory-group-report/defining-the-highest-risk-clinical-subgroups-upon-community-infection-with-sars-cov-2-when-considering-the-use-of-neutralising-monoclonal-antibodies

	• Currently taking steroids equivalent to 7.5mg of prednisolone per day in combination with an immunosuppressant medicine
	• Currently taking a biologic medicine, tofacitinib or filgotinib.
	• Currently have, or have had in the last three months, active or unstable disease which required any of the following:
	  ○ An increase in dosage of immunosuppressive treatment such as azathioprine and mercaptopurine
	  ○ A new immunosuppressive treatment
	  ○ A steroid injection
	  ○ Oral steroids
	• Currently taking ciclosporin or methotrexate
	
	Furthermore, the pathways for the treatment of Crohn's and Colitis refer to a step-up approach to treatment, where patients whose symptoms do not improve with current medications can step up a level to the next medications and so on. These changes in treatment regimens can result in patients gaining or losing eligibility for Tixagevimab–cilgavimab. Currently, we know patients whose medication has recently changed have had difficulties in making the case for their eligibility for antiviral treatments, so we urge the committee to consider how all who should be eligible for Tixagevimab–cilgavimab will be coded, so that patients who have changed or stepped up their medication can access if they need.
	
	We also hear from people living with Crohn's and Colitis that COVID-19 Medicines Delivery Units are struggling to deliver antivirals to those who are eligible, due to staff shortages. Should Tixagevimab–cilgavimab be approved, it is paramount that people who are eligible will be able to gain access - at the pace COVID-19 vaccines were made available to the general public.

Advantages of the technology **8. What do patients or carers think are the advantages of the technology?** • How would having a prophylactic treatment available impact the day-to-day lives of vulnerable people? (for example, how would it change the activities people do, or how they feel?) • How would having a prophylactic treatment available impact carers?	We are hearing via our helplines from a cohort of people who continue to shield because they are taking immunosuppressant medicines or because they have concerns about vaccine efficacy. These individuals tell us that they feel vulnerable, let down and scared especially coming into the winter period and believe that the country has moved on, leaving them behind. Some still avoid seeing family and going to family events leaving them feeling lonely and isolated. They highlighted particular anxiety around going to face-to-face medical appointments and expressed worry that this situation will continue to dominate their future. Having access to a prophylactic treatment would enable this cohort of patients with Crohn's or Colitis to get their lives back by giving them more confidence to leave the house, attend medical appointments, go back to work, spend time with their friends and family. Currently, additional vaccines and other measures of protection are not being offered to family members or carers, despite the risk that if they become infected, they may infect the patient for whom they care. Family carers not being protected with the fourth vaccines is a huge worry for some, and just going shopping for food leaves them very guilty in case they bring COVID into the household.

Disadvantages of the technology

9. What do patients or carers think are the disadvantages of the technology?	Vaccines for COVID-19 are safe with no increased risk on gastroenterological side effects, including flare ups for Crohn's and Colitis. In their official statement on the coronavirus vaccine the BSG states: *"No serious gastrointestinal side-effects to SARS-CoV2 vaccinations have yet been reported. Furthermore, data from other commonly employed vaccination programs are reassuring, with no serious gastroenterological side effects and low rates of increased IBD disease activity reported."* However, it is essential that the new technology is monitored for its gastroenterological side effects through the MHRA Yellow card reporting site.

Patient population

10. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	Please see our response to question 7. Not all people with Crohn's and Colitis will need Tixagevimab–cilgavimab, only those receiving certain medications or their condition or in a flare up.

Equality

11. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	We know vaccine hesitancy is a huge problem. UK data (as of 11 March 2021) show lower vaccination rates (among those eligible for vaccination) in Black African and Black Caribbean (58.8% and 68.7%, respectively), Bangladeshi (72.7%), and Pakistani (74%) ethnic groups compared with White British (91.3%), and lower vaccination rates in people who live in more deprived areas (most deprived 87%, least deprived 92.1%).[21] We know vaccine hesitancy can be driven by multiple factors[22], including socio-economic and healthcare inequalities, structural racism, social disadvantages including lower levels of education and poor access to accurate information, misinformation, disinformation particularly on social media. Public health lessons must be learned in planning the roll out of Tixagevimab–cilgavimab and a strategy must be developed to ensure equity of access to Tixagevimab–cilgavimab.

Other issues

12. Are there any other issues that you would like the committee to consider?	No

[21] Office of National Statistics. Coronavirus and vaccination rates in people aged 70 years and over by socio-demographic characteristic, England: 8 December 2020 to 11 March 2021.
2021. https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/healthinequalities/bulletins/coronavirusandvaccinationratesinpeopleaged70yearsandoverbysociodemographiccharacteristicengland/8december2020to11march2021
[22] Razai et al (2021), Covid-19 vaccination hesitancy, British Medical Journal, 373:n1138- https://www.bmj.com/content/373/bmj.n1138

Key messages

13. In up to 5 bullet points, please summarise the key messages of your submission.	• Shielding from COVID-19 had a profound physical and psychological impact of people living with Crohn's and Colitis. This had included anxiety, depression, loneliness, isolation and increases reporting of flare-ups. • There is now reassuring evidence that most people with Crohn's or Colitis are not at higher risk of getting COVID-19 or having more severe COVID-19 because of their disease or treatment. However, the risk from COVID-19 may be higher for people in a flare-up or taking oral steroids. Furthermore, certain immunosuppressant medicines that people with Crohn's and Colitis take, such as anti-TNF medicine, such as infliximab, an anti-TNF medicine plus a thiopurine or methotrexate, or tofacitinib may make the COVID-19 vaccine less effective. Therefore specific cohort of people living with these conditions would therefore benefit from Tixagevimab–cilgavimab. • We know patients whose medication has recently changed have had difficulties in making the case for their eligibility for antiviral treatments, so we urge the committee to consider how all who should be eligible for Tixagevimab–cilgavimab will be coded, so that patients who have changed or stepped up their medication can access if they need. • Should Tixagevimab–cilgavimab be approved, it is paramount that people who are eligible will be able to gain access - at the pace COVID-19 vaccines were made available to the general public. • To understand the risk of Tixagevimab–cilgavimab triggering a flare-up in people with Crohn' or Colitis. It is essential that the new technology is monitored for its gastroenterological side effects through the MHRA Yellow card reporting site.

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Single Technology Appraisal

Tixagevimab–cilgavimab for preventing COVID-19 [ID6136]

Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

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- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you

1.Your name	[redacted]
2. Name of organisation	Clinically Vulnerable Families
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Clinically Vulnerable Families (CVF) was founded in August 2020 before children returned to schools for the first time following their closure towards the start of the pandemic in late March 2020. After shielding was paused in April 2021 and never resumed, CVF extended the offer of support to all clinically vulnerable persons and those who could be considered at high risk by living in clinically vulnerable households. CVF has multiple purposes and these are primarily to support, educate, assist, advocate and campaign for clinically vulnerable families in the United Kingdom due to the risks posed by SARS-COV2 ('COVID-19'). Current combined membership and following of CVF is approximately at 33,300 persons. The group have a significant online presence, through which most of their work is achieved and there are approximately 2,200 members of CVF's private Facebook group and around 8,900 Twitter followers. Each member tends to represent a family/household and we can therefore reasonably assume that CVF's reach is at least three times the number of actual members and followers to account for multiple occupancy households (8,900 + 2,200 x 3 = 33,300). We do not have any source of funding.
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.]	No

If so, please state the name of the company, amount, and purpose of funding.	
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	On the 6th October 2022 Clinically Vulnerable Families created a survey, which was pinned and published on their Facebook group. The survey was also announced on Twitter, the survey was open until the 12th October 2022. The survey introduction stated that it was only open for and applicable to households that include severely immunosuppressed individuals, or who are unable to be vaccinated due to severe adverse reaction. The survey commenced with an initial question confirming that respondents qualify as immunosuppressed. Individual answers were gathered anonymously to avoid GDPR issues. Members were asked not to share outside the Clinically Vulnerable Families group. Survey responders are self-selected and self-reported. It is acknowledged there may be CEV from outside the Clinically Vulnerable Families group with various perspectives on risk and impact. CVF believe that there is sufficient range in membership to garner useful information about the impact of COVID-19 and how Evusheld could make a difference. The CVF survey had 350 immunosuppressed households respond. Households can be categorised into immunosuppressed individuals in immunosuppressed household and non-immunosuppressed in immunosuppressed household.

	The CVF survey separated households into two categories. Those were “immunosuppressed individuals in immunosuppressed household” and “non immunosuppressed in immunosuppressed household”. Immunosuppressed individuals in immunosuppressed household: • 277 households have at least one immunosuppressed adult aged 18-64 years • 62 households have at least one immunosuppressed senior over 65 years • 21 households have at least one immunosuppressed child who is under 15 years • 17 households have an immunosuppressed young person aged 15 to 17 years Non immunosuppressed individuals in immunosuppressed household: • 326 have adults aged 18-64 years • 128 households have at least one child who is under 15 years • 91 households have at least one senior who is over 65 years • 76 households have at least one young person aged 15-17 years

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	**Shielding** The CVF survey identified that the percentage of people shielding has decreased over time: • 165 (45%) of all immunosuppressed respondents remain shielding • 72 (20.5%) of households with immunosuppressed and non-immunosuppressed individuals are shielding. This extended duration of time where people restricted their daily activities to keep themselves safe, has led to a tangible impact on mental health. **Mental Health** The CVF survey indicates: • 315 (93.6%) of immunosuppressed respondents experienced some form of anxiety. Of those individuals (327): o 139 (39.7%) experienced significant anxiety o and for 116 (33%) this has been extreme anxiety. • 75% of immunosuppressed households have non immunosuppressed individuals that have also experienced anxiety. • 27% of immunosuppressed households have sought counselling. **Masking** Masking is still an essential part of clinically vulnerable household daily life. The CVF survey highlights: • 293 (89.7%) of immunosuppressed adults still mask. Of those: o 97 (33.1%) mask indoors only o 84 (28.5%) mask indoors and outdoors only when in close contact or crowded spaces o 61 (20.8%) wear masks both indoors and outdoors in all situations o 21 (7.1%) mask only in healthcare settings. • 308 (88%) of immunosuppressed households have non immunosuppressed adults who still mask. Of those:

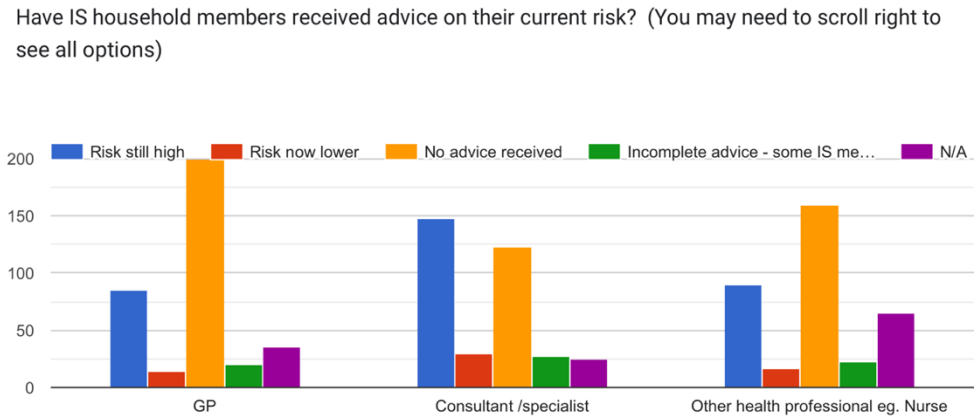
	○ 112 (32%) mask indoors only ○ 60 (17.1%) mask indoors and outdoors only when in close contact or crowded spaces ○ 45 (12.8%) wear masks just in healthcare settings ○ 42 (12%) wear masks both indoors and outdoors in all situations Masking is less prevalent in under 18 year olds, both in immunosuppressed and non-immunosuppressed children. **Victim of violence or aggression** The CVF survey highlights that most households have experienced some form of aggression, due to household immunosuppressed vulnerability, through wearing a mask that should enable them to remain safe. Out of the 350 immunosuppressed household respondents: • 197 (56.3%) faced in person subtle aggression • 108 (30.9%) experienced overt in person aggression • 102 (29.1%) encountered online aggression **Impact on working life and finances** Being part of an immunosuppressed household has significant impact on working life. The CVF survey identified: • 76 (50.2%) households have one or more adults work from home • 212 (60.5%) households have adults who work with others Of those who work with others: ○ 143 (67.5%) households have adults who feel unsafe in their workplace ○ 68 (32.1%) of immunosuppressed households had submitted a request to work from home, which had either been refused or were still awaiting a response. Households who had to give up work due to vulnerability: • 87 (24.8%) households had immunosuppressed individuals who had to give up work as a result of their vulnerability

	• 60 (17.1%) households had non immunosuppressed members who had had to give up work Households who had had to abstain from face-to-face settings: • 66 (18.8%) households had immunosuppressed individuals who had had to stop face-to-face activities on account of their vulnerability • 47 (13.4%) of households had non immunosuppressed members who had to cease face-to-face meetings. Financial loss: • 181 (51.7%) households had suffered some level of financial loss. Out of those: o 75 (41.6%) suffered a loss valued £10,000 or more. **Impact on Education** The CVF survey identified immunosuppressed households with children attending school, of those: • 133 (81%) had children who had lost schooling days over and above that of non-vulnerable peers • 34 (40.9%) of those going into further education had lost opportunities specifically due to the household's vulnerability • 88% of immunosuppressed households did not feel safe in schools o 80% of those who did not feel safe attended state schools o 8% of those who did did not feel safe attended private schools Of those immunosuppressed families that had raised concerns to school(s): • 93 (88.7%) were worried that the schools had not fully responded to their concerns • 12% of immunosuppressed households with school age children resorted to other education solutions, such as home education and online learning.

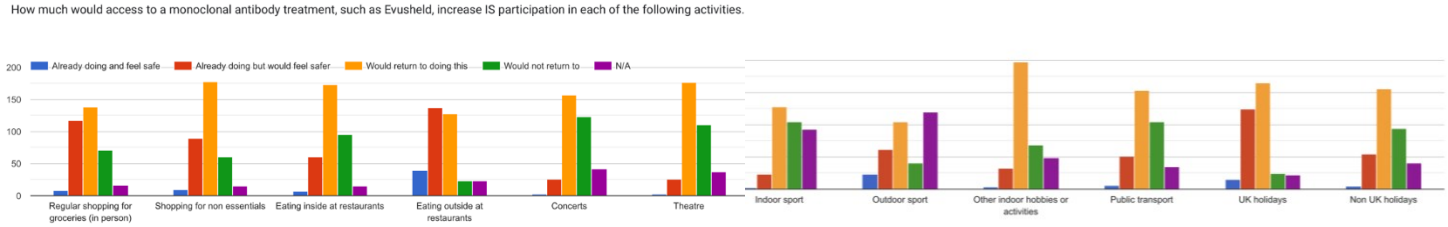
	Access to Healthcare The CVF survey found that: • 61% of households had immunosuppressed adults who had previously delayed a medical appointment on account of their vulnerability. • CVF polled the broader group in mid-October of 450 clinically vulnerable individuals (not specifically immunosuppressed). The poll concluded that 410 (91%) of clinically vulnerable individuals, have or would delay or cancel a medical appointment, due to the high risk of Covid-19.

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	Targeted interventions for immunocompromised patients have been unsatisfactory. Antivirals access can be a problem even for those who do qualify, particularly as it is crucial that antivirals are given early before the onset of severe disease. The disparate way in which data is held, maintained and accessed within the NHS means that immunosuppressed patients often find themselves liaising with individuals who do not fully understand their condition or associated risks and have limited time to investigate and respond to their case. This has been a particular problematic when cases are high and CMDUs are under more pressure. Immunosuppressed individuals would like to be free to travel like other people, not just for leisure but for business and personal family matters. There appears to be no process for accessing antivirals when not in the UK. Evusheld would provide some additional protection for immunosuppressed individuals when away from home. The CVF survey of 6th illustrated: • 184 (52.6%) households have not had Covid-19, almost certainly because they continue to restrict their lifestyle. • 30 (8.6%) caught Covid-19 before antivirals were available. Of those who had had Covid-19 and tried to access antivirals: • 27.8% had found it to be a slow or difficult process.

	Many have not received advice on their current risk and of those that have a significant percentage have been told that it is still high. The vast majority have not had antibody tests of any kind  fig.1
8. Is there an unmet need for patients with this condition?	There is an unmet need for immunosuppressed people. There is currently no prophylactic protective treatment available for immunosuppressed people in the UK, which leaves them dependent on timely diagnosis and access to antivirals should they catch Covid-19. In addition, the absence of protection from antibodies (which is the goal of vaccination for non-immune suppressed people) has led to the immune suppressed feeling the same level of fear of COVID they felt during the peak of the pandemic, and in many cases more. It is unjust that society has vaccinated without concern about whether vaccines fully work against newer variants and yet has held Evusheld which is essentially a form of passive vaccination to a much more stringent standard. As evidenced from our data, people who are immune compromised feel abandoned by society, experience very high levels of anxiety, and have in many cases altered their level of economic activity (both spending and, in some cases, giving up work). Traditional measures of the value of a treatment will fail to take into account the huge benefit to immune suppressed people of feeling they have at least some degree of protection allowing them to reassess the extent to which they wish to keep on isolating themselves. This feels to us like a basic issue of equity. It is perceived by many of our members to amount to discrimination against them on the grounds of their disability that they are not allowed to be given the available antibody protections. The benefits to our members and to society of them being able to return to at least some of their normal activities is incalculable.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	Approval of Evusheld would increase the confidence of patients and enable immunosuppressed individuals to be treated more inclusively at work and to engage in more social activities. The CVF survey queried how access to a monoclonal antibody treatment, such as Evusheld would impact their participation in face-to-face work meetings: • 90.7% would feel safer in face-to-face settings The CVF survey queried how access to a monoclonal antibody treatment, such as Evusheld would impact participation on compulsory school age children for in person education: • 96.3% would of families with children would feel safer and/or return to in person school settings In addition, households would be more willing to participate in activities that drive economic health, increasing interactions which would improve immunosuppressed mental well-being (fig. 2).  fig. 2

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	Members of the group do not really see any disadvantage in Evusheld being made available to them a primary concern is the availability of Evusheld and whether or not enough can be purchased for the relevant patient population. There is an acceptance that no treatment is 100% successful in preventing COVID19, but many patients feel that if they have antibodies in their system against the disease they are doing as much as they can to prevent it. There is a strong suggestion that even if you catch COVID having had the antibody preventatitve treatment it is likely to be less severe. And of course the hope would be that existing antiviral treatments remain available in the event of a patient

	who took Evusheld still catching COVID. Given the problems in accessing antivirals currently, the hope is that if Evusheld reduced the overall incidence of COVID infections in the immune compromised that access to the antivirals would be easier as the services would be less stretched. Our members can't understand why they cannot access antivirals in a much simpler way and why they cannot get emergency supply for example to take abroad with them if they choose to go on holiday.

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	We would expect patients to be prioritised based on clinical need. The clinical group would be expected to encompass both the severely immunocompromised and some others who continue to demonstrate high risk for severe Covid. We would expect that in making decisions on who would benefit from Evusheld that both IYTU and mortality data is taken into account. It is important to underline that we would expect any distribution of Evusheld to be equitable across both the country, communities and patient groups. We would like to see an update in risk information to enable groups to know their own risk. This has changed during the course of the pandemic as some groups were previously at high risk and are now largely protected by the vaccines. Other groups appear to be at higher risk now than ever. This is because behaviour has inevitably changed and so, for example, there is good evidence from the ONS that blood cancer patients (and by extension presumably other immuune compromised) are actually more likely to die from COVID as the pandemic progresses since vaccines are not working for them but measures to prevent infection have reduced meaning their risk of catching the disease has increased than at the beginning of the pandemic.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	As the answer to the previous questions, immunosuppressed and their families find themselves disadvantaged in the workplace and educationally as well as excluded from certain social settings. They have found friends to be unsympathetic and have been targets of aggression. All these issues indicate that this group is at a disadvantage in practically every area of their life. Access to Evusheld could lessen this disadvantage. The group strongly feels that approval of Evusheld has more obstacles placed in its way than approval of vaccines, And yet the issues for both technologies are similar. They therefore feel that there has been some discrimination against the clinically vulnerable. By definition immune suppressed are disabled and requite equity of access to all normal social actitivies in society. Evusheld being denied to them has effectively been discriminatory.

Other issues

13. Are there any other issues that you would like the committee to consider?	

Key messages

24. In up to 5 bullet points, please summarise the key messages of your submission.	1. People who are high risk from severe and the immune suppressed are currently restricted in their lives, and livelihoods; including loss of work, housing, educational opportunities, and social experiences. 2. The group understand they are high risk and that vaccination may not protect them. They feel unfairly left behind as they are aware of other countries using Evusheld. The UK is an international outlier. Why is this the case? 3. People who are high risk use mitigations such as masks and HEPA filtration, but they experience barriers in society to using these. This can even include aggression aimed at them. 4. People have been shielding for a long time and are being forced into unsafe scenarios, for example, sending their children to school. Some are making difficult decisions in order to allow their loved ones to continue with their lives. 5. People who are at increased risk and immune suppressed are still dying from Covid. We are constantly told that vaccines are the best way to prevent 'severe disease'. We are pleased this is the case but ask that people who remain high risk have the opportunity of some protection through Evusheld.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

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Tixagevimab–cilgavimab for preventing COVID-19 [ID6136]
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- Your response should not be longer than 10 pages.

About you

1.Your name	[redacted]
2. Name of organisation	Evusheld for the UK
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Evusheld for the UK is a patient-led campaigning group working for the availability of prophylactic monoclonal antibody therapies to prevent Covid in the immunocompromised in the United Kingdom. We accept no funding from anyone or any organisation and work entirely on a voluntary basis. We represent a patient body of approximately 500,000 people. We have an active group membership on Facebook of just under 2,000 members and a similar number on Twitter.
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.]	No. We have not received any funding from anywhere.
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No.

5. How did you gather information about the experiences of patients and carers to include in your submission?	We receive patient testimonials on a weekly basis – often desperate stories from members of the group asking for advice – and also have our own experiences on which to draw. We have distilled these into a set of essential types (e.g. cases where people are frightened of their workplace covid arrangements) that paint a powerful picture of the ongoing difficulties faced by our patients.

6. How has shielding from COVID-19 affected vulnerable people?	While, for most people, the restrictions of the pandemic are a distant memory, for a significant number of patients – estimated at around 500,000 – the ongoing nightmare of shielding has never ended. The immunocompromised, who remain at serious risk from Covid and who cannot respond as well to vaccines, are being forced to take desperate measures to protect themselves. Official NHS guidance at the time of writing recommends that this group "work from home if you can", "keep social distancing", and "avoid meeting with someone who has tested positive". Clearly, although all societal protections have been removed, the health service recognises that this group are *not* safe returning to "normal" and essentially advises shielding, while making this now, supposedly, a matter of "individual choice". **Mental Health** We receive approximately one email per fortnight from members that mentions suicide or the intolerable ongoing conditions under which they are living. The effects of prolonged isolation that this has entailed are causing serious mental health problems for our members. Length of time shielding/in quarantine is associated with poorer mental health outcomes (Brooks et al. 2020). Furthermore, rates of mental health in the clinically vulnerable group are already significantly higher than the general population (Rettie & Daniels, 2020; Daniels & Rettie, 2022). Length of time shielding during COVID-19 has been associated with poorer mental health (Daniels & Rettie, 2022) and with reported increased rates of mental health difficulties over time when comparing two samples (Rettie & Daniels, 2020; Daniels & Rettie, 2022). It is important that this group are recognised as being psychologically vulnerable due to the long-term effects of shielding because of their clinically vulnerable status (Daniels & Rettie, 2022; Rettie & Daniels, 2020). This has been well documented and provides important context for a NICE evaluation, with precedent in other NICE guidelines. The psychological impact of extensive behavioural measures directed at sustaining life has been pervasive, and should be considered when gaining a fuller understanding of the context of those who are clinically vulnerable. These additional behavioural measures have affected all aspects of life for this patient group, including coping, social interaction, family relationships, health, access to healthcare/medications and work. The impact of this long-term quarantine has been most recently reported in *The Lancet* (Brooks et al. 2020). A significant proportion of this population are experiencing mental health problems to a clinical level, with evidence suggesting that the mental health of those shielding others is also significantly affected (Daniels & Rettie, 2022).

	A body of research indicates that the mental health and psychological wellbeing of those who have been Clinically Extremely Vulnerable (CEV) and of those who are still shielding (due to following guidance to take additional precautions and known vulnerability) has been adversely affected (e.g. Rettie & Daniels, 2020; Daniels & Rettie, 2022) with 40% reporting clinical levels of health related anxiety. This is significantly higher than those in non-vulnerable groups (<5%). These mental health effects also go well beyond just the patient group. Many family members are also shielding and face the same mental pressures. Further, those that are not shielding nonetheless feel additional guilt and strain at the possibility of infecting their loved ones. The long-term cost of mental health problems in those with health problems is well documented. This aspect might be measured using a brief psychological measure such as the combined GAD-7 PHQ-9, or the DASS. The cost savings of reducing the (already established) mental health impact will be significant and should be taken into account in the economic analysis for cost-benefit analysis. **Work, Employment, Health and Safety, and Socialisation** Another recurring theme with which we have to deal is members who are being forced back into dangerous working conditions, with inadequate protection. With no formal restrictions on employers and no support for those who are shielding, we hear from members who have left their jobs and are living off savings. In one case, one of our members has had to sell her house as she could no longer safely work and had no other savings. We also know of a member who ran a successful carpentry business, employing three other people. He has had to close this down as he cannot work, in person, with other people given his ongoing clinical vulnerability. Our members are, essentially, not able fully to be full economic citizens at present. The limitations on their lives as a result of only partial protection from the pandemic through inadequate vaccine response has far-reaching employment and work consequences. Finally, we should note that our members are diverse. We span all ages, genders, sexualities, ethnicities, and socio-economic backgrounds. We have younger members whose prime of life has been reduced to Zoom calls and we have older members whose retirement is now effectively an isolation prison. The reduction in quality of life here is significant across an entire spectrum of people.

Unmet need

7. Is there an unmet need for patients with this condition?	Yes. We are very used to treating patients with primary and secondary immunodeficiencies using prophylactic IVIG therapies. Pre-exposure prophylaxis (PrEP) is also now widely used in HIV prevention. Indeed, as medical maxims go, “prevention is better than cure” has to be close to the number one spot. Evusheld (tixagevimab and cilgavimab) is the first pre-exposure prophylactic monoclonal antibody therapy available to protect those who do not mount an adequate response to vaccination. In several real-world Phase Four observational studies, this drug has been shown to be effective at reducing hospitalisation and death in vulnerable patients (e.g. Kertes et al., 2022; Nyguen et al., 2022). Despite some laboratory in-vitro results showing reduced neutralisation against more recent variant assays, every real-world study has demonstrated extremely strong protection from Evusheld (Al-Obaidi et al., 2022). 32 other countries are using Evusheld to great effect. The United Kingdom currently stands as an international outlier, acting against international clinical consensus as the only G7 nation not providing this treatment. As the recent clinical consensus letter from 125 clinicians, across 17 specialities, representing all four nations put it: “Patients who would derive meaningful benefit should be offered prophylactic antibody therapy […] there is strong emerging evidence that prophylactic measures using monoclonal antibodies is an effective strategy for immunocompromised individuals.”

8. What do patients or carers think are the advantages of the technology? • How would having a prophylactic treatment available impact the day-to-day lives of vulnerable people? (for example, how would it change the activities people do, or how they feel?) • How would having a prophylactic treatment available impact carers?	The availability of prophylactic antibody therapy for Covid would radically improve the lives of our patients. For close to three years now, many of our members have not been able to see family at Christmas; they have lived apart from their families (some sleeping in summer houses and sheds); and they have lost their livelihoods. Having the additional partial protection of a drug like Evusheld would transform these lives. Some of the key points that came from our patient body include: • **Safety of medical appointments**. At the moment, a significant number of our members feel unsafe in clinical settings, where mask mandates have been removed and where patients are forced into confined, poorly ventilated hospital spaces with potential infection risks. One of our members, for instance, was placed in a storage cupboard, waiting for eight hours, as this was the only way to keep him safe. Another vulnerable member was placed on an open ward next to a covid patient, separated only by plastic sheeting. Having an additional layer of protection with Evusheld would make it safer for people who require hospital treatments. • **Return to the workforce/employment**. Our members want to be full economic citizens, but at present struggle safely to participate in the workplace. Evusheld would allow those who work “in person” to have additional protection and safety, without worrying about whether their employer will protect them. • **Basic sociality**. Some of our patients have never held newborn family members, cannot see any family members who do not isolate or cannot meet outdoors, and all of our members face a third winter in cruel isolation. One of our members is even living apart from her husband and daughter for safety reasons and sees them only by Skype/Zoom. This is an intolerable standard of life. Evusheld would give some of this life back and improve the mental health situation. • **Reduction of pressure on the NHS**. Recent statistics showed that approximately 1/3 of seriously ill Covid patients admitted to hospital ICUs were immunocompromised. Given the pressure on ICU bed space, Evusheld could reduce the need for hospitalisation in this cohort, thereby alleviating pressure on the health service. • **Impact on family and carers.** While the figure for the number of vulnerable patients is given as 500,000, the impacts of *not* providing Evusheld are felt much more widely. Families and carers are also living under the same conditions of isolation as the vulnerable as they cannot risk becoming a transmission vector. Again, Evusheld could help to free this group. • **Making the most of treatments.** Many of our patients have had expensive previous treatments (chemotherapy, radiotherapy, organ transplants). Some have a limited life expectancy. However, at present they are not able to make the most of their remaining time or to benefit from the richness of life,

	because they remain shielding. Evusheld would allow this group to have a much higher quality of life and to reap the rewards of their other treatments.

Disadvantages of the technology

9. What do patients or carers think are the disadvantages of the technology?	• **Level of protection.** Patients are (and should be) well informed about the level of protection that Evusheld confers. Nobody believes that the technology is a silver bullet. However, the message for this group with vaccines has been that “some protection is better than nothing”. We think that the same should apply to Evusheld, as part of a multi-layer protection programme.

Patient population

10. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	The cohort who should be given the drug are specified in 'Defining the Highest-Risk Clinical Subgroups upon Community Infection with SARS-CoV-2 When Considering the Use of Neutralising Monoclonal Antibodies (NMABs) and Antiviral Drugs: Independent Advisory Group Report'. GOV.UK. 30 May 2022. All members of this group are "unlikely to mount an adequate immune response to COVID-19 vaccination", the terms of Evusheld's MHRA authorisation. We note that we are <u>strongly opposed</u> to serum antibody testing to identify beneficiaries of this treatment, for several reasons: • There is no internationally recognised threshold for understanding how a level of serum antibodies correlates with actual protection against Covid (hence the US's FDA recommends against its use) • Adding an antibody test creates significant additional logistical challenges for implementation • Antibody testing may deter patients, particularly those from ethnic backgrounds who have been shown to exhibit healthcare/vaccine hesitancy • The MHRA authorisation is for those "unlikely" to mount an adequate vaccine response, not those definitively shown not to have

Equality

11. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	Yes. Evidently many of those who will be most affected will be those covered under the equality act due to long-term health problems and disabilities. These groups are known to be most physically and psychologically vulnerable over the pandemic, and it is important that charities and patient representatives are involved in the decision making process so the impact can be fully considered. It is also more likely that those with long-term health problems and/or multiple morbidities will also be more likely to be experiencing socioeconomic deprivation. Thus this should be considered if the prophylactic is distributed outside of a trial (e.g. travel to treatment centres presenting additional costs to those immunocompromised should not lead to economic disadvantage to those most vulnerable, for reasons beyond their control). Those eligible are also more likely to experience mobility difficulties, or be homed in health and social care settings (learning disability, older people, mental health) treatment must be accessible for all groups. It is important that any roll out of this medication is well publicised among both patient groups and clinicians. Those from BAME background and immunocompromised are likely to be at higher risk, more likely to be from low socioeconomic background, and less likely to be engaged with health services when these aspects are present. Therefore it is vital that a roll out also targets those from under-represented groups to achieve equity of care.

12. Are there any other issues that you would like the committee to consider?	**Randomized Control Trials** • **Not guinea pigs.** Our patients have been concerned by the calls for additional randomized control trials of Evusheld at this point. When there is such compelling evidence from overseas of real-world efficacy, testing by randomization to placebo is unethical and not acceptable to our group. 86% of respondents said that if they were offered such a trial, they would not feel safe enough to abandon their current shielding practices, meaning that any such study would remain flawed anyway with altered behavioural profiles. We feel that such an approach would be akin to testing parachutes that have been shown to work 80%-90% of the time in the real world by giving them only to 50% of jumpers from a plane. **Bibliography** • Al-Obaidi, Mohanad M., Ahmet B. Gungor, Sandra E. Kurtin, Ann E. Mathias, Bekir Tanriover, and Tirdad T. Zangeneh, 'The Prevention of COVID-19 in High-Risk Patients Using Tixagevimab–Cilgavimab (Evusheld): Real-World Experience at a Large Academic Center', The American Journal of Medicine, 2022 <https://doi.org/10.1016/j.amjmed.2022.08.019> • Brooks, Samantha K., Rebecca K. Webster, Louise E. Smith, Lisa Woodland, Simon Wessely, Neil Greenberg, and others, 'The Psychological Impact of Quarantine and How to Reduce It: Rapid Review of the Evidence', The Lancet, 395.10227 (2020), 912–20 <https://doi.org/10.1016/S0140-6736(20)30460-8> • Daniels, Jo, and Hannah Rettie, 'The Mental Health Impact of the COVID-19 Pandemic Second Wave on Shielders and Their Family Members', International Journal of Environmental Research and Public Health, 19.12 (2022), 7333 <https://doi.org/10.3390/ijerph19127333> • Kertes, Jennifer, Shirley Shapiro Ben David, Noya Engel-Zohar, Keren Rosen, Beatriz Hemo, Avner Kantor, and others, 'Association between AZD7442 (Tixagevimab-Cilgavimab) Administration and SARS-CoV-2 Infection, Hospitalization and Mortality', Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America, 2022, ciac625 <https://doi.org/10.1093/cid/ciac625> • Nguyen, Yann, Adrien Flahault, Nathalie Chavarot, Cléa Melenotte, Morgane Cheminant, Paul Deschamps, and others, 'Pre-Exposure Prophylaxis with Tixagevimab and Cilgavimab (Evusheld©) for COVID-19 among 1112 Severely Immunocompromised Patients', Clinical Microbiology and Infection: The Official Publication of the European Society of Clinical Microbiology and Infectious Diseases, 2022, S1198-743X(22)00383-4 <https://doi.org/10.1016/j.cmi.2022.07.015> • Rettie, Hannah, and Jo Daniels, 'Coping and Tolerance of Uncertainty: Predictors and Mediators of

	Mental Health during the COVID-19 Pandemic', The American Psychologist, 76.3 (2021), 427–37 <https://doi.org/10.1037/amp0000710> We note, for reasons of acknowledgment, that these comments have been jointly prepared by [redacted] with input from [redacted], [redacted], and [redacted].

Key messages

13. In up to 5 bullet points, please summarise the key messages of your submission.	• Many of our patients are still living under intolerable life conditions in order to protect themselves from Covid. They are not able to participate in work or social events and are sometimes living away from their families. They face incredible economic hardship as a consequence, with some having sold their houses just to survive. Others have abandoned successful businesses and laid off employees. Finally, many have been unable safely to access medical treatments. • Evusheld could alleviate this situation and has been shown to provide good protection in every real-world study. • Adding antibody testing to the process complicates the logistics significantly and is not necessary given the report identifying patients who should receive this therapy. • Evusheld does not need to provide 100% protection to be of value. As part of a multi-layered strategy, combined with vaccines, it would provide stronger levels of reassurance to this patient body. • The benefits to the NHS in alleviating both long-term mental health problems in this group and in freeing Covid ICU bed space are many.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal
Tixagevimab–cilgavimab for preventing COVID-19 [ID6136]
Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you

1.Your name	[redacted]
2. Name of organisation	Immunodeficiency UK
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Immunodeficiency UK (previously known as PID UK) supports people affected by primary and secondary immuno-deficiency (PID and SID). We help give advice on managing their condition, their treatment; promote awareness and understanding of PID and SID within the general public and medical profession to promote better understanding of these conditions and their impact. We provide a helpline service, events and practical help and advice and advocate for improved healthcare. Our funding comes from public donations, events, legacies, pharmaceutical companies and trusts and foundations (Immunodeficiency UK - Sponsors). We currently have over 1000 members.
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months?	No
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	Immunodeficiency UK carried out a survey of its members with questions addressing the issues of this consultation. The survey was a mixture of quantitative and qualitative (free text) questions. Access to the survey was via a link sent by a membership mailing. We received 516 responses: 254 from people directly affected by PID; 194 affected by SID and 68 responses from carers of those affected. Responses were collected from 11 - 27 August 2022. **Numbers of people testing positive:** Of 254 PID respondees 101 (39.76%) had tested positive for COVID. For 194 SID patients 62 (32%) had tested positive for COVID.
6. How has shielding from COVID-19 affected vulnerable people?	Shielding has had a severe adverse effect on the mental health and quality of life of people affected by primary and secondary immunodeficiency. Anxiety, worry, fear, depression, isolation, lack of social interaction, panic attacks, and PTSD (from having had a COVID infection) were mentioned in our survey responses group. There is

	a constant fear from infections brought home by others in the family unit and this fear is likely to increase further as case rates of COVID increase over the coming winter period. Shielding has also affected people's income and ability to earn a living and in some cases led to loss of their job and businesses. This impact is not only on the person who has been shielding but also on the family unit. Through our helpline and survey responses we have heard of broken relationships caused by the strain of shielding, people with immunodeficiency living away from their loved ones so that the unaffected members of the family can get on with their lives. Many carers are still shielding and leading very restrictive lives, in order to protect their relatives. For some of our members shielding has resulted in not being able to invite children to birthday parties for their children, missed celebrations of family events, lack of contact with grandchildren. There remains considerable anxiety and distress within the community about getting COVID and profound fear about the health consequences of having a COVID-19 infection. **Our survey found that a significantly high proportion of our community are effectively continuing to shield.** Of 439 respondents, in our survey, affected with either SID or PID, 30% were not going out at all, 43% had little confidence in going out; 16% (71) were moderately confident; with only 6% mostly confident and 5% very confident. **Our survey data shows that the quality of life (QoL) for those affected by PID and SID is continuing to be severely affected by COVID.** When asked to rate their quality of life (QoL) on a scale of 1 -100 (poor to excellent) pre-pandemic and now, PID and SID patients reported an average rating pre-pandemic QoL rating of 79 (430 responses) compared to a QoL rating of 30 (426 responses) at the time of the survey. **Carer data on shielding:** Of 43 carers who responded to this question, 17 were not going out at all, 18 had little confidence in going out; 5 were moderately confident; with 2 mostly confident and 1 very confident. When asked to rate their quality of life (QoL) on a scale of 1 -100 (poor to excellent) pre-pandemic and now, carers reported an average rating pre-pandemic QoL rating of 81 (43 responses) compared to a QoL rating of 25 (43 responses) at the time of the survey. **Survey data below showed that despite the 'safety net' of access to *COVID medicines if people test positive, confidence in entering society. Confidence of living with COVID in those people with PID/SID who had tested positive and had accessed *COVID_19 therapies:** Of 105 respondents (affected by PID or SID) 20% were not going out at all, 38% had little confidence in going out; 21% were moderately confident; 13% were mostly confident and 8% very confident indicating there remains considerable concern about getting COVID again.

	***Please note that only a proportion of people who are eligible for anti-COVID medicines actually get them.** **Data from the COVAD study** shows that since the deployment of CMDUs, 61.4% (n=70/114) of treatment eligible patients actually got treatment from a CMDU. The study found significantly lower rates of hospitalisation (4.3% vs 15.9%, p=0.03) amongst individuals treated by CMDU but overall mortality was not affected (2.8% vs 4.5%, p=0.63). **Our survey data** showed that of 154 people who had tested positive for COVID -19 and were on the COVID medicines eligibility list, 46 (30%) were not offered any form of treatment. This uncertainty in accessing COVID-19 treatments, despite being listed on the eligibility list, adds further to the anxiety and uncertainty that people are facing in the context of living with the threat of COVID. **Patient quote:** 'I do not currently feel safe with the treatments available in the UK. At the moment, if we contract Covid we are given post-exposure therapies. This then relies on us taking the risk of becoming infected and then seeking help. This feels incredibly risky and, as a result, we are still shielding with incredibly limited lives'. **Carer quote:** 'Despite 5 Pfizer vaccine doses my wife has no antibodies (test paid privately as told not available under NHS) she has no protection to covid and thus our lives are now so different. I've had to stop work to protect her and we have no social life merely living an existence at home and going nowhere.' **Carer quote: '**My husband has a PID which, according to recent statistics, would result in a high chance of death if he contracted it. As these are risks we are not prepared to take we therefore remain shielded, and this has had a huge impact on our mental and physical wellbeing as well as the company that we run locally which is a major employer for the area'. **Carer quote:** The immuno suppressed are expected to live a normal life like everyone else who has been vaccinated, and hope that if they catch Covid (which is highly probable, as the vaccines are not effective for them) they can access the antivirals in time for them to be at their most effective. As a result they are not living a " normal " life, and most are actually still shielding, or living a very restricted and isolated existence. This is having a massive knock-on effect to their physical and, in particular, mental health. **It has left my wife suicidal and needing 12 months of counselling and cognitive behavioural therapy.** Whilst the initial impact is on the 500,000 immunosuppressed, there is also the impact this has on their families and friends. There is the fact that some people have felt the need to give up their jobs or lost them as a result of not feeling safe in the place of work. I go to work in a hospital every day worried that I will bring the virus home, as does our son, to my wife

who is immunosuppressed. We are unable to eat in restaurants, go to the theatre or cinema. We do not have family/friends in the house , nor any workmen.'

Carer quote: 'My husband has not caught it due to continued careful shielding, however the shielding itself has had a significant impact on the mental health of all our family. For example our teenage daughter has been diagnosed by CAMHS with moderate depression and is now on antidepressants.'

Shielding from the fear of getting COVID is also affecting people wanting to access healthcare. 169 of 437 respondents (38%) were < 20% confident; only 86 of 437 respondents (20%) had > 60% confidence in accessing healthcare in a hospital setting. Some free text responses indicated that people were NOT willing to access ANY healthcare in hospital due to the risk of getting Covid, especially as many COVID restrictions have been lifted.

Patient quotes: 'Since freedom day in 2021 I have not been able to safely visit NHS sites. Worried about catching covid whilst travelling to the appointment or in the NHS venue'. 'Attending hospital environment is so traumatic and stressful'. 'Many safeguards have been removed that would help protect me'.

7. Is there an unmet need for patients with this condition?

COVID continues to pose a significant risk to subgroups of patients with PID and SID who have been unable to produce a protective response after repeated vaccination and there is an unmet need. Evidence for this is included in the following publications:

- Fendler et al., Nat.Rev.Clin. Oncol 2022:19 (6):385-401
- Lee at al., Lancet Oncol 23. 748-757 (2022)
- Shields et al., J Clin Immunol 2022 Apr 14;1-12.

Data from CO-VAD study (antibody deficient patients) indicates that inpatient mortality has remained high (19% for PID, 42.8% for SID) suggesting if you are sick enough to end up in hospital then that is a poor prognostic sign. CO-VAD data is available on 155 individuals with SARS-CoV-2 infection since the deployment of vaccination (January 2021). Hospitalisation rate with Omicron was 9.9% vs 2.2% for the general population and mortality was 2.7% vs 0.2% for the general population. As of August 2022, the cumulative incidence of infection in this longitudinal cohort is 28.6% which is much, much lower than the ONS cumulative incidence of infection in the general population which was 70% back in February 2022 indicating that many people in this group have not

	yet been exposed to the virus. This is probably due to a large proportion of the community continuing to shield. Our survey data concerning patient views on unmet need: 79.67% (341/428 responses) from people affected by SID or PID indicated an unmet need. Only 3.5% (15/428) of respondents said there was no unmet need; 4.4% (19/428) stated they didn't know. Of those people who said there was an unmet need, 40% (139/341) specifically mentioned the need for Evusheld and 12% (41/341) stated the need for prophylaxis/prevent infection therapies, indicating that people recognise that although COVID-19 medicines may be available via CMDUs if they test positive for COVID-19 they desperately want a protective strategy. **Patient views:** 'I do not generate memory antibodies – so DoH banging on repeatedly about the success of the vaccine program is very frustrating. Vaccines might be good enough for some vulnerable patients, but vaccination alone is not enough for my needs.' 'Yes, there is prophylactic options available such as Evusheld which is being used in other countries. This has not been made available so consequently life is still anything but normal for me and I am having to be incredibly careful still. If I keep contracting covid and needing months off work then I will lose my job. I still cannot go to the shops or a restaurant or meet friends and family in their homes because I do not want to experience the terrifying experience I have already had once with covid. I think much, much more needs to be done to support the immune compromised in getting back to normal life and being able to function in society and prophylactic medicines would facilitate us being able to take steps to do this.' 'Yes, absolutely. There are many thousands of primary and secondary immune deficient people still living their lives under shielding conditions - removed from society and from 'normal' life, unable to go into public contact situations without fear - people with children, jobs, family, dependents, etc - who still cannot participate in everyday activities because of the lack of protection available. There is an enormous unmet need. None of the therapeutic options currently on offer give any protection for these vulnerable people, and Evusheld is the only option available for these people to be able to return to some kind of 'normal' life.' It is also noteworthy that the APPG on Vulnerable Groups to Pandemics has produced a 'National Clinical Expert Consensus Statement 'Coronavirus monoclonal antibodies as a prophylactic therapy against COVID-19 for

	immunocompromised groups'. This was produced and endorsed by over 120 clinicians indicating that the **medical profession is also of the opinion that there is an unmet need.** https://bit.ly/3bpE6oO . Continued below – problems in formatting the pages - apologies

8. What do patients or carers think are the advantages of the technology?	**Benefits of access would include:** • Helping people to re-enter their workplace and carry out normal activities of daily family life and social interaction • Reduce the fear of getting infection from family members or in work-related environment following lifting of all restrictions • Socio/economic benefits as people can contribute more fully as members of society • Psychological benefits - improved mental health and relief of strong feelings of anxiousness and isolation and increased confidence to reduce shielding. • Prevention of new pathogenic escape variants due to inability of the immunocompromised to clear COVID-19 infection, even after treatment with anti-viral therapies. COVID infections in the immunocompromised are a possible driver of mutations (https://www.nature.com/articles/s41467-022-30163-4) and can cause the subsequent creation of new variants that escape immunity from vaccines and previous infections. This adds to the argument that protections for people who have immunodeficiency should be bolstered, as part of a wider public health strategy of permanently reducing overall Covid cases. • Improvement in health as people who are immunocompromised will feel more comfortable in accessing healthcare (see our survey data above) – noting that NHS England ceased to enforce the mandatory use of face coverings in hospitals and GP practices, based on guidance from the UK Health Security Agency. • Reduced clinical demand overall – GPs, A&E, hospitalisations, ICU costs • Demonstrating that the health system is supporting **all** members of society going forward in the living with COVID-19 plan • Reduced call on CMDU services and use of anti-virals It is noteworthy from our survey that in patients who had tested positive for COVID and accessed anti-virals, 37% of respondents reported that the COVID-19 medications offered did not clear their infection, resulting in COVID rebound, recurrence of symptoms and in some cases, people required 2nd courses of treatment. This inability to clear infection resulted in time off from work and in some cases long periods of illness and hospitalisation.

	Patient experience: 'It [Paxlovid] definitely improved my condition and I believe I would have ended up in hospital very poorly without it. However I was still positive on day 18, ended up in A&E on day 20, was very poorly for weeks to come and still suffering after effects now'; 'tested positive for ten weeks after taking paxlovid'; 'I continued to develop different symptoms and remained very unwell signed off work for 3 weeks. I tested positive continually for 17 days'; 'I was still testing positive at 21 days but had to return to work on day 19 whilst still feeling terrible.'; 'Admitted to hospital with a very high viral load 10 days after finishing outpatient treatment'. 'Molnupiravir did not clear the infection needed to have Sotromivab as a follow-up treatment'. 'The first course of Paxlovid failed to clear the virus and so I got COVID rebound, recurrence of symptoms and I needed a 2nd course of Paxlovid before I was consistently COVID-free.' • Reduced cases of chronic coronavirus infections and consequent health costs of long COVID: From our survey data 59% (93/157) of PID + SID respondents who had tested positive for COVID reported long-term effects of having had COVID. 70% (64 of 92 respondents) reported effects lasting several months. **Physical impacts reported included**: reduced breathing capacity for several months, lung pain, constant coughing, exacerbation of previous health problems, increased susceptibility to infection, mobility issues, fatigue and exhaustion, anosmia, gastrointestinal problems; joint pain, cognitive difficulties with memory/attention /concentration/word finding difficulties (brain fog), dizziness, fainting, headaches & migraines, post exertion symptom exacerbation (PESE/PEM), diarrhoea, neurological symptoms such as vertigo, spells of deafness in one or both ears, spells of agonising headaches, vision problems, heart problems. **The mental health impact,** in this group, was mentioned in 21% (20/93) of responses. Anxiety, worry, fear, depression, isolation, panic attacks, PTSD, frustration at losing previous relatively fit lifestyles were reported. **Impact on ability to work** was mentioned in 13% (12/93) responses and included loss of employment, bedbound/unable to work – on disability benefits, need to take several months off work, taking reduced hours/ inability to work full-time, phased returns to work, occupational health support and reasonable adjustments at work, need to take early retirement and expectation to lose jobs due to continuing health problems. These problems have led to people losing income with resulting financial instability. There was also mention of the on-going need to depend on other people for care and support. There should also be consideration of the psychological impact of **NOT** having access to this therapy when it is available to immunocompromised groups in other countries see - Rettie, H. & Daniels, J. Coping and tolerance of uncertainty: Predictors and mediators of mental health during the COVID-19 pandemic. Am. Psychol. 76, 427–437 (2021). This is especially harmful since there is no alterative therapeutic prevent strategy for

	subgroups of people with primary and secondary immunodeficiency who have not been able to benefit from vaccination. **View from a carer:** 'Despite all of our best efforts, our immunosuppressed daughter contracted Covid because she had to go into work one day, and despite her wearing high quality masks, because there are no longer any mitigations in place, she was infected. It was absolutely terrifying, our worst nightmare. Fortunately her specialist team accessed Sotrovimab for her really quickly, but it didn't seem to neutralise anything. She was very poorly, dropping SATs which we constantly monitored, isolated her at home and double masking in the house. She tested positive for 15 days, had to come off all of her other disease modifying medications to give her immune system a chance to recover, and has now had to go on a high dose of steroids to help get her back on track before resuming her usual treatments. All because of the position this government is taking that despite all of the real world wide data there is regarding effectiveness, it will not procure Evusheld. She leads a virtually non-existent life, she is a young woman whose life has shrunk to nothing. I have seen her change form a strong person who dealt with her underlying condition as best she could and led as full a life as possible to a shadow of her former self, frightened of contact with people and who I now not only fear for physically, but mentally as well. She used to have a life, she used to socialise, travel, do normal things all of which meant putting money into the economy. She doesn't do any of that now so if we dispassionately take out the physical and mental effects of not being able to live with Covid, the economical impact is significant. Because this doesn't only affect her, it affects us as her carers as well. Our lives have shrunk too, we are in our 60s and cannot enjoy a full life because we have to weigh up everything in the context of what risk might we bring home to her. We only socialise now in a limited way, we have only travelled once and I am reluctant to do so again. So we too aren't putting money into the economy.'
9. Disadvantages of the technology?	It is an intramuscular injection and will hurt.
10. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	We absolutely recognise that not all people affected by PID and SID will benefit from Evusheld or are in equal need of Evusheld. People with PID and SID represent an extremely diverse range of patients many of whom will have mounted a good protective response against COVID through the vaccination programme (although there is no routine testing of antibody levels, T cell function in this group). Therefore, there needs to be expert clinical judgement as to which patients would benefit most based on individual vaccine response data and knowledge of the underlying condition and co-morbidities, and subsequent risk level from COVID.

	Evusheld would certainly provide an extra layer of protection for those patients with primary antibody failure and secondary antibody failure who will not recover B cell function and for those patients who have had B-cell depleting agents and even more important for those who are older/have co-morbidities e.g. major organ involvement such as significant kidney, liver or lung inflammation or significantly impaired renal, liver and/or lung function. These are common complications of having a PID or a SID. X-linked Agammaglobulinemia and other PID conditions with very low/absent B-cells appear to be specifically associated with inability to clear SARS-CoV-2 virus leading to prolonged infection (Brown et al., J Allergy Clin Immunol. 2022 Feb;149(2):557-561.e1; reviewed in Ponsford et al., Curr Opin Allergy Clin Immunol. 2021 Dec 1;21(6):525-534.). Patients with the PID APS1/APECED have been reported to have had life-threatening COVID-**19** (Meisel et al., J Clin Invest. 2021 Jul 15;131(14):e150867 and Bastard et al., J Exp Med. 2021 Jul 5; 218(7):e20210554). Common variable immunodeficiency (CVID the most type of PID) is associated with variable outcomes regarding COVID, likely reflecting the clinical heterogeneity of this group of patients. Co-morbidities known to be associated with worse COVID outcome in the general population, such as pre-existing lung and liver disease have higher prevalence in CVID and are also associated with worse outcome in this group (Shields et al, J Allergy Clin Immunol. 2021 Mar;147(3):870-875.e). Other subgroups that would benefit include people with combined immunodeficiencies which affect T and B cell function, patients with 22q11 have had particularly bad outcomes following COVID infection, people with immune mediated inflammatory disease patients e.g. individuals with stable rheumatoid arthritis, but have terrible lungs with poor pulmonary function, people on rituximab, CD19 CAR-T, BTK inhibitors treatment patients and patients after HSCT who are still considered to be immunosuppressed.
11. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	Evidence indicates there has been considerable inequality in mortality rates, vaccine uptake and indeed access to COVID medicines amongst different ethnic groups and socioeconomic backgrounds (Antivirals and nMABs for non-hospitalised COVID-19 patients: coverage report | OpenSAFELY: Reports; section: Key demographic and clinical characteristics of treated patients). This means that **one** measure of cost effectiveness isn't representative of everybody's circumstances and both clinical and non-clinical parameters need to be considered in the NICE analysis. Equitable access is needed via secondary care settings (specialist centres) and not via a CMDU due to reported problems with this delivery system – see below. Treating clinicians are the people that know their patients best. They are specialists in the underlying health condition and have access to all relevant clinical details, including

	co-morbidities, and are best able to do a comprehensive clinical assessment and make a clinical judgement regarding access to Evusheld.

Key messages

13. In up to 5 bullet points, please summarise the key messages of your submission.	• For people with primary and secondary immunodeficiency shielding has had a severe adverse effect on their mental health, quality of life, ability to earn a living and their confidence in accessing healthcare and a significant proportion of people affected by these conditions, and their carers are continuing to shield because of fear of getting COVID and the serious health complications it could bring. • There are specific subgroups of people with primary and secondary immunodeficiency who would benefit from access to Evusheld as a protect strategy because of an inability, due to their underlying condition, to mount an adequate protective response through vaccination. • Access to COVID medicines (antivirals, Mab therapy) for those people who test COVID positive and are on the eligibility list can be challenging and access is not guaranteed. COVID rebound, lack of access due to contraindications to anti-virals, existing health problems compounded by long-COVID are major problems. • Our patient survey data highlights a major unmet need - an additional strategy based on providing protective therapies such as Evusheld to help people re-enter society and live more normal lives. • People in our community continue to feel that their specific needs are being marginalised and forgotten in the 'living with COVID' planning by the UK Government. This feeling of injustice and inequality is further underlined by UK being the only G7 country where Evusheld is not available. Evusheld should be made available to the subgroups of patients that would benefit most as soon as possible.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal
Tixagevimab–cilgavimab for preventing COVID-19 [ID6136]
Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

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- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you

1.Your name	[redacted]
2. Name of organisation	Kidney Care UK
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Kidney Care UK is the UK's leading kidney patient support charity providing advice, support and financial assistance to thousands every year. It is not a membership organisation, but it is in touch with thousands of kidney patients through its direct patient services (eg advocacy, counselling, facebook support group, patient grants), social media channels, telephone helpline and website. The organisation is funded by voluntary donations and interest on its investments.
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] **If so, please state the name of the company, amount, and purpose of funding.**	December 2021, AstraZeneca - £657.20 honorarium and expenses for attending a CKD roundtable December 2021, £250 – honorarium for meeting attendance December 2021, AstraZeneca - £20,000 donation to support patient information March 2022, £325 – honorarium for meeting attendance July 2022, £350 – honorarium for meeting attendance August 2022, £45,000 to support development of Kidney Kitchen
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	n/a
5. How did you gather information about the experiences of patients and	The information and views represented in this submission has been gathered through a range of sources:

carers to include in your submission?	Kidney Care UK advocacy services and Facebook support group, the views of Kidney Care Staff who are kidney patients, our Patient Advisory Group. We have also run regular surveys throughout the Covid pandemic to capture the experience and challenges faced by people with kidney disease. These have collected over 2,500 responses in total. Our series of 10 Covid Question Time webinar has also provided a significant insight into people's experiences and concerns. Throughout the pandemic people with kidney disease have turned to the charity for advice, information and guidance and to share their experiences. This has provided a very deep and broad understanding of the experience of this group. We also ran a survey to inform this submission, asking about the impact of living with Covid when immunosuppressed and views on the advantages and disadvantages of the technology. We invited responses via our e-newsletter, social media channels and website and gathered responses from 181 people who are severely immunosuppressed or carers/family members.

Living with the condition **6. How has shielding from COVID-19 affected vulnerable people?**	Covid continues to have a major impact on the lives of people who remain at higher risk and are likely to be less well protected by the vaccine: • **93% of survey respondents said Covid had affected their day-to-day activities in the past month. 93% said it had affected their family or social life**. • **59% of respondents said they were extremely worried about their risk from Covid, 31% very worried, 6% moderately, 1% slightly and 1% not at all**. • **When asked how their risk from Covid had increased their levels of stress and anxiety over the past month, 40% said it had extremely, 36% very much, 14% moderately, 7% slightly and 2% not at all.** Many people at higher risk who may not describe themselves as shielding are carefully following current Government guidance on how to reduce their risk. These behaviours can have very similar negative affects to shielding but people feel they have no choice but to follow them in order to keep safe. Shielding and other restrictions are severely affecting the quality of life, mental and physical health, financial security, ability to maintain social connections and achieve personal goals of many immunocompromised people. Impacts are felt also by family members. We have grouped impacts into themes, with illustrative quotes from respondents to the survey run to inform this response: **Impact on mental health** Many people reported struggling with feelings of anxiety and low mood, following an extended period of shielding and living with heightened risk of Covid. Our survey of kidney patients (343 responses received) carried out in Feb/Mar 2021 when restrictions were starting to ease found 68% of respondents would like continued mental health support to help them cope as restrictions ease (Kidney Care UK, 2021). The survey to inform this response found impact on mental health continues, quotes include: *Simple tasks such as going to the dentist, hospital, hairdressers are all filled with fear* *Constantly risk assessing situations that healthy people take for granted is exhausting and stressful. You never know your own level of exposure to Covid, and it leaves you doubting, fretting and regretful if you go somewhere that felt too busy. It basically saps all the fun and ease from life* *These restrictions have definitely affected my mental health, and I am much more anxious. I also see myself differently; before 2020 I had an active life, now I feel unable to do most things I used to enjoy outside the home.* *I've been shielding for 30 months. I only go to clinic appointments. I fight depression everyday, everyday feels wasted as my life is on hold. Have lost fitness, am lonely, despairing. The thought of the winter and increased risk through having to close windows really frightens me - in addition to kidney transplant I have asthma. I think I'm clinically depressed due to 30 months of essentially lockdown.*

	I am shielding still and don't leave the house, my husband has to turn down face to face work and shields with me. My mental health is very poor and I often think about suicide
	Physical health
	Respondents reported problems with maintaining physical health. Reasons include being fearful of attending in-person medical appointments, unable to continue with physical activity due to shielding/avoiding crowds, difficulty sleeping due to reduced levels of activity as well as heightened anxiety, challenges to following a healthy and varied diet when shopping online only:
	Not able to go swimming which was my main form of exercise before Covid.
	We had a good social life going to ballroom dances which is physically and mentally important but have not been able to do this for the past 2.5 years. We are existing rather than living. *My sleep pattern has been altered due to anxiety and the need for constant hypervigilance.*
	Before the pandemic I never missed a health appointment - now far too risky to go to the opticians, dentist, GP's and hospital because the rules have been relaxed.
	I have to have everything delivered, unable to access all the deals in store (making it more expensive during a time when money is getting tighter) reliant on what is in stock on the day (which often leads to key ingredients missing making healthy food prep difficult)
	Financial health/employment
	Throughout the pandemic we have heard from vulnerable people who have missed out on opportunities because of having to work from home or had to give up their jobs entirely. Survey responses included:
	I had to stop my wedding photography business as the risk of mixing with large groups is very high. I have lost a lot of income. Trying to build a new business so I can work from home - it is very difficult to get new business up and running as I can't meet people in person.
	I continue to work at home so am missing interaction with work colleagues and missing opportunities
	I don't socialise anymore. I am unable to perform my job (self-employed cafe owner) as I feel uncomfortable/ at risk being in close proximity to attend who may or may not have Covid
	Impact on daily activities
	Respondents to our survey reported that shielding and trying to reduce their risk from Covid meant they had had to give up activities that had brought fulfilment and richness to their lives pre-Covid, including hobbies and interests, attending church, voluntary activities, helping in children's school activities:
	I am a scout leader but have not attended scouts since February 2020 except for online events. I have missed many social and family events because of the need to minimise risk

	Our lives have been affected by: No working, normal family visits, going out socialising eg restaurants, pubs, concerts, theatre, football & NO holidays. Everything in our lives as been destroyed. Life is now about survival. *I'm still anxious about travelling on buses and being around people in general. I go to a few shops at quiet times, but I have barely left my hometown since 2020, and have missed many many events and chances to catch up with friends. I don't drive and have to rely on others for getting anywhere including hospital appointments. I am back at my volunteering but only a couple of hours a week because I can get a lift and Sunday mornings are quiet.* **As a number of these quotes have shown, the impact of shielding and anxiety caused by being at higher risk of Covid often extends beyond the person with kidney disease to their carers and family**. They may be shielding or restricting their activities to reduce the risk of passing on Covid, and the anxiety they feel about their loved one being at high risk can be difficult to deal with: *My family's lives circumscribed along with mine, to keep me safe. At first lockdown husband decided to shield with me, had no idea we would still be effectively doing so this long. Mentally, living with 'living with Covid' takes its toll on such a sociable and outgoing person. And I mind for him, as well as for me.* *He follows the guidance, as do all the rest of the family to protect him, but it curtails all normal social activities and isolates not only himself, but his wife who is his carer too.* *I'm distant from my children when they're back at school, …, strain on my relationship due to my not wanting to 'live with Covid', my adopted children have missed out on opportunities because I can longer provide the opportunities I once could.* *It affects every single day. I cannot do anything without thinking of the risk of catching it or bringing it to my twin sister who already had her kidney transplant.*

Unmet need
7. Is there an unmet need for patients with this condition?
	Yes, effective protection from Covid that does not have the profound impact of shielding or restrictions is an unmet need for patients less likely to be protected by Covid vaccines.
	People who are immunocompromised are arguably in a *worse* situation now than during wave 1 of the pandemic. Although Covid is still circulating, shielding is no longer an option for most. There are currently no alternative methods of protection.
	• There are no vaccines that work for many who are immunocompromised – a study of kidney transplant recipients without prior natural infection found 24% and 19% do not have any detectable spike protein antibody in response to 3rd and 4th doses of vaccine respectively. T cell responses are poor following fourth dose vaccination regardless of prior infection status. (https://doi.org/10.1016/j.eclinm.2022.101642)
	• Many immunosuppressed people have a reduced response. We do not yet know what level of antibody response confers adequate protection against Covid and there is no policy for the clinical testing of vaccine response.
	• Many Covid antiviral treatments are not suitable for people with CKD, and they have proved impossible to access in the 5-day window for many people. The short window also deters people from going abroad on holiday or for work.
	• Shielding can reduce the risk of catching Covid, but there are important practical and ethical reasons why this is not an appropriate alternative to prophylactic treatment for people at highest risk:
	  ○ There is no longer income support for immunocompromised people who are shielding, so shielding is not an option for people who cannot work from home:
	  ▪ Almost half (47%) of kidney patients are in the two most deprived quintiles of the population and cannot afford to quit their jobs. Many won't be trained in jobs that cannot be done from home, and can't afford training to change career
	  ▪ The cost of living crisis exacerbates this. Kidney patients risk worsening health if they turn off their heating to save money so giving up their jobs to shield at home is now even less affordable.
	  ○ Kidney patients who receive in-centre dialysis cannot shield – they travel to hospital 3 times per week, putting themselves at risk. The cost-of-living crisis makes at home dialysis unaffordable, since many trusts are not reimbursing patients for the additional utility costs of running dialysis machines at home.
	  ○ There is no mental health support for people who need to shield, and the mental health impact is considerable.
	  ▪ Kidney patients with poor mental health are more likely to suffer disease progression and death (Tsai, Y., Chiu, Y., Hung, C., Hwang, S., Tsai, J., Wang, S., Lin, M., & Chen. H. (2012). Association of symptoms of depression with progression of CKD. American Journal of Kidney Diseases, 60(1), 54-61. https://doi.org/10.1053/j.ajkd.2012.02.325)
	  ▪ The heavy burden on shielders' mental health has been underscored by recent research from the University of Bath.

Advantages of the technology **8. What do patients or carers think are the advantages of the technology?** • How would having a prophylactic treatment available impact the day-to-day lives of vulnerable people? (for example, how would it change the activities people do, or how they feel?) • How would having a prophylactic treatment available impact carers?	• Having a prophylactic treatment available would be life changing for many people who remain at higher risk of Covid. A very common phrase in response to this question is '*I would get my life back*'. • Advantages described by kidney patients include; significantly reducing the constant anxiety and hypervigilance created by the ongoing risk from Covid; resuming activities that give life meaning and purpose with resulting improvements in mental and physical health; financial benefits through enabling a fuller return to employment; feeling a sense of greater equality with the rest of society. • Kidney patients report to us that even if prophylactic treatments may not be a magic bullet, a safe and effective protective drug offers another layer of protection. This may reduce anxiety enough to enable a more normal life. Compared to how many have been living, even small adjustments could be life changing. ***Patient quotes:*** *It would build my confidence to go out more, reduce anxiety and improve my mental health. Without this I do not see an end to my continuing to shield myself due to the risks* *Life changing. Less anxiety, more life living with my precious gift that was supposed to give me my life back!!* *Feeling more protected would encourage me to try buses again, which would change my life, to be honest - no more relying on my elderly mother for lifts, and I'd be able to visit friends again. Also I'd feel confident enough to volunteer more hours which definitely improves my mental well-being.* *Evusheld represents a "safety net" that gives confidence to all immunosuppressed individuals to try to get back to "normal". To shop, eat out, go to work, have a drink with friends without fearing grave illness or even death. It's as much preventing a mental health crisis in this group of people as it is potentially reducing the medical crisis* *It's not a magic bullet, but would reduce the overall risk from infection (of death, hospitalisation and/or serious illness leading to reduced quantity of life) to a level where moderate activity could be resumed. I would not run around the world yet or meet up in an enclosed space when rates were high, but when rates are moderate to low I would be able to commute to work with only my mitigations in place in relative safety, and could regain a small social life. I would also be less concerned about visiting a medical setting when needed but not essential, ensuring my overall health was maintained and would feel less of a potential drain for the NHS* *It would give me freedom to do more things, even if I still wore a mask, I'd feel more able to participate in society* *Life changing. It would rescue me, and help my physical, emotional and severely worsening mental health. Hosp appts would be safer. I could see people, make a cautious return to living, go home. The list is endless.*

Disadvantages of the technology

9. What do patients or carers think are the disadvantages of the technology?	Respondents to our survey were not aware of potential disadvantages. As highlighted in the previous answer, many respondents reflected that it may not removal all risk from Covid, the additional protection it did offer would change the balance of risks and benefits when considering how they lived their daily lives. *It's not a silver bullet but it would provide a better quality of life and protect against most variants. At the moment I have no protection and most antivirals clash with meds.*
10. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	People who are immunosuppressed and do not respond well to the Covid vaccines may benefit from the technology more than people who do respond to the vaccines. However, as we understand it research has not yet been able to ascertain what level of response is needed for protection, making it difficult to clearly define this group. Within our survey respondents: 68% of people had had an antibody test (this will include privately bought tests as well as NHS provided) 28% had not had a test, 4% were not sure if they had. Of the people who had had an antibody test: • 49% reported no antibodies detected • 39% had some antibodies (this included low positives and uncertainty whether any protection provided) • 11% were not sure of result (some people had had multiple tests with varying results depending on timeframe)

11. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	**The current unmet need for effective protection from Covid for the severely immunosuppressed should be taken into account as it places that group at significant disadvantage:** The restrictions that people must follow to reduce their risk puts them at disadvantage compared to people who are protected from Covid by vaccination on many counts; • access to employment opportunities • normal participation in family and community life • leisure and opportunities for physical activity. Responses to our survey reflected these experiences of exclusion: *I feel that I do not matter as much as other citizens and I cannot live my life as others do. I am not protected against Covid and feel discriminated against because the government has refused to buy Evusheld to help protect the immunosuppressed. Please help us, we are desperate to return to normal life along with the rest of the population* *Despite living a normal life before Covid my life has completely changed and my family, relationships and well being have been compromised. We do not live with Covid in the true sense of the word. We exist on parole in a world with little empathy.* **The current unmet need for effective protection against Covid for immunocompromised people is likely to impact differently on different groups in society:** • CKD is more common amongst people from lower socio-economic groups. Almost half (47%) of kidney patients are in the two most deprived quintiles of the population (UKRR data) • Ability to reduce risk by working from home varies across groups - people in lower socio economic groups and of black ethnicity are less able to work from home (Blundell, R. *et al.* (2020). COVID-19 and Inequalities*. *Fiscal Studies*, Vol 41, 291–319.) • People from Black or South Asian communities are more likely to have CKD risk factors such as high blood pressure or diabetes – which are also risk factors for COVID-19 hospitalisation and death – and are five times more likely to be accepted for renal replacement therapy than other groups (Roderick PJ et al, 1996, The need and demand for renal replacement therapy in ethnic minorities in England, J Epidemiol Community Health, 50(3): 334-9 https://www.ncbi.nlm.nih.gov/pubmed/8935467)

Other issues

12. Are there any other issues that you would like the committee to consider?	n/a

Key messages

13. In up to 5 bullet points, please summarise the key messages of your submission.	• Shielding and other restrictions are severely affecting the quality of life, mental and physical health, financial security, social connections and achievement of personal goals of people who remain at much higher risk from Covid and are less protected by the Covid vaccine. Impacts are felt also by family members. • As well as the impact of shielding/behavioural restrictions the anxiety and constant vigilance engendered by immunosuppressed people's ongoing risk from Covid is having a grave impact on mental health and quality of life. • The extra layer of protection provided by a prophylactic treatment would enable people to start to resume a normal life. Even if individuals choose to retain some restrictions, small steps towards normality would be life changing for many. • A prophylactic treatment is an opportunity to move towards equality for what's become a marginalised group in society. • The lack of effective protection that does not have the huge mental, physical, economic health impact of shielding or restricting behaviour is a clear unmet need.

Thank you for your time. Please log in to your NICE Docs account to upload your completed submission.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

Please select YES if you would like to receive information about other NICE topics - YES

NICE National Institute for Health and Care Excellence

Single Technology Appraisal
Tixagevimab–cilgavimab for preventing COVID-19 [ID6136]
Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

NICE National Institute for Health and Care Excellence

About you

1.Your name	[redacted]
2. Name of organisation	Kidney Research UK
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Kidney Research UK is the leading kidney research charity in the UK. We fund and promote research into kidney disease and related topics; bring together patients and researchers in networks and clinical study groups; campaign for the adoption of best practice by the NHS and improved health outcomes for patients. Our latest annual report 2020/21 shows the majority of our income is from donations, gifts, and legacies (78%). The remainder is from trusts, partnerships, investments, trading, and government funding. We are not a membership organisation but have an extensive supporter base and a significant number of active volunteers, many of whom are kidney patients.
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] **If so, please state the name of the company, amount, and purpose of funding.**	Funding from manufacturer: AstraZeneca - £150,000 for research projects
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	We regularly engage with patients and carers through formal mechanisms, such as our Lay Advisory Group and our Kidney Voices Facebook Group, and through informal mechanisms such as social media, meetings, and events. We work with other patient-facing kidney charities which allows us to see a wider picture of patient experience in relation to Covid-19.

Living with the condition

6. How has shielding from COVID-19 affected vulnerable people?	Shielding has taken a significant toll on the physical, emotional, and financial well-being of kidney patients. Some kidney patients have been shielding for more than 2 ½ years due to the significant threat to life posed by Covid-19. This is particularly true for people who have had a kidney transplant and those on B cell-depleting therapies such as Rituximab, as they remain at increased risk from the virus. There are around 40,000 people in the UK living with a kidney transplant, so the number of people affected is significant. Kidney disease can affect anyone at any age - children and young people have been shielding, as well as adults. Kidney patients who have been shielding have become socially isolated, missing out on meeting up with family and friends, including significant life events such as family birthdays, weddings, and funerals. Many have suffered from a lack of physical contact and human touch, fearing to hug their loved ones in case they catch Covid. Simple pleasures which are now possible for the rest of the population, are denied to clinically vulnerable kidney patients, such as meeting friends in a café or pub, going to the shops or the cinema, or taking their children on trips out to a local museum or library. It has also affected their working lives. Many do not feel safe travelling to work on public transport and have become reliant on their cars (if they have one), at great financial cost with the current increases in fuel costs. Others have given up their jobs or careers where accommodations cannot be made, or they cannot work from home. Children and young people have missed out on school and college, affecting not only their educational attainment but also their social lives. Children and young people's life chances have been curtailed due to shielding. Another key problem for those shielding is the issue of hospital visits. For many kidney patients, these are an essential part of maintaining their wellbeing and even those shielding cannot avoid them without a cost to their health. Lack of masking in many areas of hospitals is a risk and some people are missing hospital appointments for fear of contracting Covid-19. It's not only those shielding whose lives are affected. Those living in the same household as a clinically vulnerable kidney patient also have to restrict their lives and fear contaminating their loved ones. Some have to live separately in the same house, to minimise contact, but with resulting increased tensions. Rettie and Daniels (2022) [Daniels, J.; Rettie, H. The Mental Health Impact of the COVID-19 Pandemic Second Wave on Shielders and Their Family Members. *Int. J. Environ. Res. Public Health* 2022, *19*, 7333.

	https://doi.org/10.3390/ijerph19127333] reported on the mental health impact of shielding and stated that health-related anxieties in this group had grown, in contrast to the rest of the population where they have reduced. Kidney disease is known to be associated with an increased risk of mental ill-health. In a survey of 1,000 adult kidney patients carried out by Kidney Research UK in January 2022, 67% reported symptoms of depression and 27% had considered self-harm or suicide. Knowing there is a treatment available which could allow them to live a more normal life, but being denied access to that treatment, has taken a further toll on patients' mental wellbeing. It has been particularly hard for patients to see their contemporaries with kidney disease in other countries given access to the prophylactic treatment, while they remain unprotected. Shielding also has a physical impact on kidney patients who are already at increased risk of cardiovascular disease. The effect of lockdown behaviours has been shown to increase sedentary behaviour (Stockwell S, Trott M, Tully M, et al. Changes in physical activity and sedentary behaviours from before to during the COVID-19 pandemic lockdown: a systematic review. BMJ Open Sport & Exercise Medicine 2021;7:e000960. doi: 10.1136/bmjsem-2020-000960). Kidney patients who are shielding are likely to display more sedentary behaviours due to being more home-based with fewer opportunities for physical activity. Over the long period of time of the pandemic, this reduces fitness and stamina, leading to other health issues. [redacted], who is living with a kidney transplant, described the impact of shielding on her wellbeing ""*For those of us facing our third winter of avoiding Covid-19, it feels desperate. As a kidney patient I had a full, active life, until Covid arrived. I would never have described myself as 'vulnerable'. I miss my old life: face to face meetings with work colleagues, exercising at the gym, going out with friends and family, browsing for a gift in a department store, being at a birthday celebration in a restaurant, going to events, taking a holiday abroad. Living in Greater London, I often travelled on rail, tube, and bus but it no longer feels safe, especially as no-one is masked, and most people don't test for Covid now tests are no longer free. Mostly I just stay at home now, living my life remotely. I feel like I've shut down a part of myself in order to cope, trying not to think about everything I've lost*."

Unmet need

7. Is there an unmet need for patients with this condition?	There remains a significant amount of unmet need of protections form Covid for kidney patients. The Government's response to the pandemic has been a huge nationwide and continuing vaccination programme, to protect individuals from the worse effects of Covid – serious illness, hospitalisation, and death. Prevention is seen as the best route for individuals as well as for the NHS. Although vaccines do not prevent infection with Covid, are effective for an unknown duration and may not be effective against variants which might exist in the future, vaccination is encouraged and there is widespread promotion of the autumn booster programme to protect the NHS for the winter. Those for whom vaccines are effective are able to 'live with Covid' and go about unmasked and largely unconcerned about the effects of Covid, other than a slight inconvenience if they become unwell. An entirely different strategy is in place for the clinically vulnerable, arguably those who would most benefit from a preventative strategy which significantly reduces the risk that they become seriously ill with Covid. Instead, they are left at risk of being unprotected. There is widespread evidence that vaccination is less effective in transplant recipients. Pre-print research by Imperial College London found that 38% of kidney transplant patients had no antibodies after two doses of the vaccine (New results highlight the need for immunosuppressed patients to remain cautious - Kidney Research UK). In addition, the OCTAVE study showed 11% immunocompromised patients had no immune response after two doses (OCTAVE trial: Initial data on vaccine responses in patients with impaired immune systems | NIHR). In 2021 Kidney Research UK initiated and part-funded a clinical trial called the MELODY study (Mass evaluation of lateral flow immunoassays for the detection of SARS-CoV-2 antibody responses in immunocompromised patients). The study is looking at the impact of fourth doses on immunocompromised patients and the results are due to be published shortly. The choices available for the clinically vulnerable are either to continue to shield to minimise the likelihood of catching Covid, or to risk becoming ill or dying A recent study showed that the hazard ratio of death for transplant recipients compared to the non-transplanted population was 26.33 in the third wave of Covid (Changes in COVID-19-related mortality across key demographic and clinical subgroups: an observational cohort study using the OpenSAFELY platform on 18 million adults in England The OpenSAFELY Collaborative. medRxiv 2022.07.30.22278161; doi: https://doi.org/10.1101/2022.07.30.22278161). This was supported by ONS data which also showed that kidney transplant patients were 26 times more likely to die from Covid than the general population in late 2021, despite access to vaccines. Any treatment which would allow the

	immunocompromised similar benefits to those of vaccination in the non-vulnerable population would represent a sea change for those still living in fear of Covid.

Advantages of the technology

8. What do patients or carers think are the advantages of the technology? • How would having a prophylactic treatment available impact the day-to-day lives of vulnerable people? (for example, how would it change the activities people do, or how they feel?) • How would having a prophylactic treatment available impact carers?	Having access to tixagevimab–cilgavimab would have a significant positive impact on the lives of many kidney patients. It would allow many of them to resume a more normal life again, after shielding for so long. Kidney patients told us they continue to limit their social activities and their employment activities to avoid the risk of contracting Covid-19, leading restricted lives and not able to take part in an active life which the rest of the population can now take for granted. The ability to fully participate in their work lives, to join in with significant life occasions such as birthdays, weddings, and funerals, not to have to decline invitation after invitation, not to have to continue to explain to others why they can't take part, would be a huge weight lifted from the shoulders of vulnerable kidney patients. Access to tixagevimab–cilgavimab could give them the confidence to stop feeling like social outcasts but to resume more of these everyday activities and re-join the rest of society living more safely with Covid. Many kidney patients feel the Government has invested considerable sums of money into a vaccination programme without a cost-effective analysis or evidence of benefit for them but chooses to delay procurement of a prophylactic treatment which is likely to benefit them and for which there is a large amount of real-world evidence. They feel abandoned by the Government and that their life is seen as having less value than healthy individuals, in contrast to 32 other countries where the treatment has been made available to vulnerable people. The treatment has had conditional approval from the MHRA since March 2022, and this is seen by kidney patients and others who would benefit as more than six months of precious lives unlived. Carers report the positive impact having a prophylactic treatment would have on them. They say they live in fear of their loved one catching Covid-19 and the possible serious impact on the person's health. Carers have also missed out on social occasions due to their loved one shielding. If they do go out, they feel guilty that their loved one is unable to, and they live in fear of bringing the virus back into the home. Having access to a prophylactic treatment could enable carers to resume a more normal life.

Disadvantages of the technology

9. What do patients or carers think are the disadvantages of the technology?	The reasons given for why it has not been made available include the fact that it is not 100% effective at preventing Covid-19 infection, its effects are of unknown duration or that it might not be fully effective against future variants. However, this is also the case for vaccinations, and everyone is encouraged to receive a booster on the basis that some protection is better than no protection. No patients or carers have reported this as a disadvantage to tixagevimab–cilgavimab to us, nor any other disadvantages. Their view is that they would prefer to receive some protection in the same way that the general population receive protection from vaccinations.

Patient population

10. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	The MELODY study has recruited 30,000 patients and will correlate antibody responses with outcome in the most at-risk population, such as kidney, lupus, and vasculitis patients. The study will also be able to report on socio-demographic details, mental health wellbeing and health economics study. It will identify the types of patients who are likely to have mounted a reduced antibody response to vaccination. These patients might benefit the most from tixagevimab–cilgavimab and routine antibody testing should be offered to these patients, so that those at highest risk (i.e. those without antibodies) can be offered the drug as prophylaxis. In addition, kidney disease disproportionally affects people from deprived communities and ethnic minority groups*. People in these cohorts also progress faster to end stage renal failure and are therefore more likely to require dialysis or a kidney transplant and be immunocompromised. They might therefore benefit more from tixagevimab–cilgavimab. * Kidney Health Inequalities in the UK: Reflecting on the past, reducing in the future. Kidney Research UK 2018

Equality

11. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	See above – people from ethnic minority groups and deprived communities may be more likely to benefit from this treatment as they are more likely to live with kidney disease and therefore less likely to mount a response to vaccines. The UK Renal Registry 2020 report found that the median age of new patients requiring kidney replacement therapy (KRT), eg dialysis/transplant, was 63.7 years, but this was dependent on ethnicity (White 65.4 years, Asian 62.3 years and Black 57.2 years). This suggests that kidney patients from ethnic minorities reach renal failure at a younger age and might therefore experience increased financial hardship if they shield to protect themselves from Covid-19. Tixagevimab–cilgavimab might disproportionally benefit this cohort of patients.

Other issues

12. Are there any other issues that you would like the committee to consider?	The NICE appraisal of tixagevimab-cilgavimab is welcomed but in addition we believe that this treatment should be made available on an emergency basis immediately and before the publication of the guidance, in the same way that post-Covid treatments have been made available in advance of their NICE appraisal. The winter is a time of risk both to individuals and to the NHS and the more provision for protection against Covid the better. Winter is a particular difficult time for those avoiding Covid as safer outdoor activities are curtailed, and ventilation is reduced due to inclement weather. Access to tixagevimab-cilgavimab now would have a dramatic and positive effect on the lives of the clinically vulnerable.

Key messages

13. In up to 5 bullet points, please summarise the key messages of your submission.	• Some people with kidney disease have been shielding for 2 ½ years to protect themselves from Covid-19 • This has taken a significant toll on their mental and physical well-being and that of their families. It has affected their social lives, employment, and education • Access to a prophylactic treatment could enable them to resume a more normal life • Kidney patients from deprived communities and ethnic minority groups are proportionately more likely to benefit from tixagevimab–cilgavimab as they make up a disproportionate percentage of patients requiring KRT • There is an existing and growing body of evidence of a lack of protection from vaccination for a significant proportion of immunocompromised patients and therefore significant unmet need.

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Single Technology Appraisal

Tixagevimab–cilgavimab for preventing COVID-19 [ID6136]

Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.
You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.
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3. Your response should not be longer than 10 pages.

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About you

1.Your name	[redacted]
2. Name of organisation	Leukaemia Care
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Leukaemia Care is a national blood cancer charity, founded in 1969. We are dedicated to ensuring that anyone affected by blood cancer receives the right information, advice and support. Approximately 85-90% of our income comes from fundraising activities – such as legacies, community events, marathons etc. Leukaemia Care also receives funding from a wide range of pharmaceutical companies, but in total those funds are less than 15% of our annual income. Leukaemia Care has undertaken a voluntary commitment to adhere to specific policies that regulate our involvement with the pharmaceutical industry set out in our code of practice here: https://media.leukaemiacare.org.uk/wp-content/uploads/Leukaemia-CARE-Code-of-Practice-pdf.pdf.
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] **If so, please state the name of the company,**	AstraZeneca: 2021 - £15,000 core funding 2022 - £25,000 core funding plus £550 for an employee of Leukaemia Care attending a global CLL advisory board

amount, and purpose of funding.	
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	Information on patient and carer experience in this submission came from the following sources: **1.** Leukaemia Care's internal progress report (January-December 2020) **2.** A survey of blood cancer patients (mostly leukaemia, MPN and MDS) in April 2022 on the removal of COVID-19 protection measures. This survey had 288 respondents **3.** A survey of blood cancer patients (mostly leukaemia, MPN and MDS) on Evusheld for the purpose of this submission in September 2022. This survey had 78 respondents. **4.** Conversations with patients via our advocacy service and our helpline

Living with the condition

6. How has shielding from COVID-19 affected vulnerable people?	Shielding from COVID-19 started for many immunocompromised leukaemia patients at the start of the pandemic. Some patients even began shielding before they were declared as clinically extremely vulnerable (CEV) and instructed to do so, as patients often know they are at risk to viruses due to their compromised immune systems. The general public, alongside immunocompromised people, suffered negative impact on their mental health and wellbeing and some people faced serious health crises and lost loved ones. For leukaemia patients and their families this impact was strong, as they were more likely to face serious illness and death from COVID-19 than the general public. In terms of Leukaemia Care's support services, in 2020 overall the helpline was dominated by calls regarding shielding, general COVID-19 support in lockdown and vaccines. In January 2020, before the pandemic, our helpline received 148 calls in the month, whereas in March when the first lockdown was announced in the UK we received 240. This was an increase of 62.2%, showing the significant increase in the need for support. Similarly, our advocacy service, which advises people on their rights, advocates for them and gives guidance related to their condition and COVID-19, saw a similar increased demand in COVID-19 related queries between 2020 and 2021. In April 2022, just over 2 years after the first lockdown in the UK was announced, we surveyed blood cancer patients, majority of whom were leukaemia, MDS or MPN patients, to understand their views on the removal of COVID-19 protection measures and the re-opening of society. From this point on the difference in the lives and experiences of many leukaemia patients compared to the general public grew; while many in the general public resumed day-to-day activities as they had before the pandemic, this was not a reality for many leukaemia patients, who were aware they might still be at risk or have reduced protection from vaccines, as per scientific studies conducted. As such, many patients and their families continued to shield and missed out on special family occasions e.g., weddings and graduations. Below are some of the responses to this survey (in April 2022) which illustrate that many leukaemia patients and sometimes their families continue to shield, and the mental health toll this takes: "*My actions are the same as when the strictest restrictions were in force. I meet only my bubble, I shop once a week at the quietest time while wearing a mask - other than that, I remain at home."* *"I go out of my apartment very little as I do not feel other people respect my needs."*

	"We have shielded for well over two years, only going out to medical appointments. We have been unable to see our children and grandchildren." *"I feel very conflicted about the lifting of restrictions. It's great that the world is opening up especially for my kids and their generation but the more it opens up the greater the gap between me and everyone else. And it's really awkward finding ways to turn down invites to weddings and other celebrations. My general rule is to avoid situations where people are 'unmasked and milling'. It's really stressful negotiating this."* ***"****Continued shielding is having a really negative effect on our mental health."* *"Feel more isolated from healthy friends who are socialising heavily now and less likely to do lateral flow before meeting me. Feel unable to go to my daughter's graduation which is gutting."* *"To all intents and purposes I have continued shielding but friends and even family don't understand. They tell me shielding has finished and I'm beginning to feel that people think I'm a hypochondriac."* *"I cannot attend indoor events of any description now restrictions have been lifted. I'm even frightened to be in hospital. I am not elderly. The winter months are very difficult and isolating. The impact is huge on my family household."* One patient told us about the knock-on impact of her vulnerability and shielding on her family members: *"My daughter didn't go to secondary and we are paying for an online school as we feel we can't risk me going through that and her bringing covid home and my partner will likely have to give up his job that he's been in for 25 years for the same reason as no mitigations have been made in school or work."* Some respondents to the survey in April 2020 also described how through continuing to shield they are missing out on medical appointments, including appointments to monitor their bloods, which are essential to adequately manage, treat, and care for patients with leukaemia. Alongside experiencing feelings of loneliness, isolation, fear, and hopelessness, this poses additional risk to their physical health:

	"I feel unable to visit my dentist, optician and hairdresser, all of which are sorely needed and impossible to manage with any reliable assurance of safety. I am equally anxious about outpatient hospital appointments, and using any kind of public transport… This is in addition to the loneliness of isolation from family and friends". *"The general public has no idea about what we, the immune compromised and extremely vulnerable have been and still are going through…I haven't seen my adult son and daughter and two tiny grandchildren for nearly a year now and it hurts. I watch people out and about through my window, as I am too afraid to go out. There are too many people round and now I know just how many blood cancer patients have died, I'm even more afraid...So I see others going to shops, the cinema, etc. but I can't go anywhere.* ***I won't even go to the hospital for bloods*** *as I fear Covid is all over the hospitals too. I feel it's hopeless and I'm tired of having to explain my situation and fighting to be heard."* The financial impact of shielding can be significant for many leukaemia patients and their carers, friends and/or family. This is because some people have had to quit their jobs in order to protect their health or their loved ones. *"My life has changed so much that I feel I've lost my identity. My business of 23 years has had to be closed down and I've gone from being a higher rate tax payer to a recipient of Universal Credit. I am lonely and stressed. Evusheld is my only hope now." (September survey)* *"As a carer I have had to remain resolutely covid free. This has meant that since mask wearing is no longer required I have had to give up my job as a massage therapist and now have no income and am not entitled to benefits. I'm very worried."* We conducted another survey in September 2022 for the purpose of this submission, which indicates that the experiences shared in April haven't improved. We asked in late September how different, if at all, patients' activities and actions are now compared to before the pandemic. On a sliding scale of 1 being the same as before the pandemic and 5 being vastly different (e.g., shielding) and the most common answer, as voted for by 50% of patients, was option 5 (vastly different e.g., shielding). Together options 4 and 5 had a combined response of 74.4%.

	When we asked in September to what extent the pandemic still has an impact on patients' mental wellbeing, e.g., anxiety and fear, the most common response (on a 5-point scale) was option 5 (39.7%), indicating the pandemic still has a significant negative impact on mental wellbeing.

Unmet need

7. Is there an unmet need for patients with this condition?	When we asked blood cancer patients, particularly leukaemia, MDS and MPN patients, as well as their carers whether they thought current COVID-19 prevention/treatments are sufficient to protect people with leukaemia, 94.9% said no or not sure. Many leukaemia patients do not respond in the same way someone with a normal functioning immune system would to the COVID-19 vaccines. This means that many leukaemia patients are unable to build antibody responses from the vaccines and that the vaccines therefore offer little or in some cases no protection for this group. This is still the case despite having additional boosters and primary courses of vaccination. In addition, there is a small group of immunocompromised patients who cannot have the vaccine due to a history of severe adverse reaction to a COVID-19 vaccine or COVID-19 active ingredients. With the often sub-optimal response that immunocompromised people have to the COVID-19 vaccines, the antiviral treatment programme is relied on by many leukaemia patients should they contract COVID-19. However, there have been multiple issues with accessing antivirals and we've heard of several patients who are on the eligibility list be turned away for treatment. This has created a feeling of distrust in the programme in the community, meaning antivirals aren't providing the hope that people thought they would, and patients are continuing to shield. Not only are eligible patients being turned away, but issues with the patient communications after a patient has tested positive have also created problems. For example, many patients who register their positive tests online don't hear back from the NHS within 24 hours. Not all patients know how to or are able to follow up of their own accord meaning antivirals are missing people who might really need them. In addition, CMDU closures on weekends has meant that the tight turnaround for receiving treatment from symptom onset (5 days) has not always been met. Alongside issues in the courier delivering antivirals on time and communications between CMDU staff and NHS staff at all points of the process, the fear of contracting COVID-19 and the resulting threat of severe illness and death remains in the patient community and therefore creates a significant unmet need. Patients have told us: "*I can't rely on antivirals if I catch Covid as so many patients with CLL are being refused them. So, I have no safety net and having avoided the virus for over two years, I don't want to risk catching it now.*"

	"I know I have had poor response to the vaccines. The access to the antivirals is Russian roulette and people have died because they were considered not ill enough. The CMDU have been overwhelmed during periods of high infection rates." *"I am somewhat immunocompromised already with having a B cell leukaemic type lymphoma (MCL) and have been trying to shield. But life is getting impossible as everyone, including clinicians, has moved on and just expect us to get covid. However, access to antivirals seems patchy and totally dependent on who is in charge and what day they work. I am told that I'll need chemo and a stem cell transplant soon and I am absolutely TERRIFIED of life during and after that with the backdrop of covid. I am also going to have rituximab for two years after and many people who have been through all this still don't make any antibodies to the vaccines. It feels like people like me have been utterly abandoned."*

Advantages of the technology

8. What do patients or carers think are the advantages of the technology? ● How would having a prophylactic treatment available impact the day-to-day lives of vulnerable people? (for example, how would it change the activities people do, or how they feel?) ● How would having a prophylactic treatment available impact carers?	The survey conducted for the purpose of this submission revealed that many of those who are shielding currently would no longer feel they had to shield if Evusheld was available. As such the impact on the day-to-day lives of those people would be significant. Patients report not being able to see loved ones and missing out on special occasions, such as weddings, so for many Evusheld would give them the protection and the confidence to resume these vital activities, essential for maintaining a good quality of life and mental wellbeing. *"I feel my chance of a more normal life has been taken from me. I have no visitors in my home ,rarely get to cuddle my grandchildren , Only visit places that are outside .For everyone else life goes on but I feel left behind and as if I don't count .Also restricts my husband's life .He was allowed to work from home for 2 years to protect me .He is now having to go back out to work but because his job would put me at high risk we isolate from each other within our home for 3 weeks out of 4 .Basically I exist not live. Evusheld would give me some of my old life back."* *"With Evusheld I would have as much protection as the healthy population with vaccines. I could go back to my previous activities and visit my 94 year old mum with dementia in a care home 3 hours away. I could see friends without them needing to do a lateral flow test."* *"I've been shielding since the start of the pandemic and am being forced to continue to shield. Evusheld was the one beacon of hope that I could start to return to some sort of normal. I was absolutely devastated to hear that the government had decided not to purchase it - especially as it's being used in over 30 countries. I feel like the immunocompromised, and the people they live with, are being totally ignored. The decision not to purchase it has has significantly adversely affected my mental health."* *"Not having a drug that can prevent me from getting COVID means I basically have to continue shielding with an impact not only on my mental health, but also that of my wife. If Evusheld was approved and available, I believe my life and that of my family could return to something resembling normality, notwithstanding I would have to continue to be more vigilant than ordinary people."* *"I feel so upset at Evusheld not being available to clinically vulnerable people. It would give us confidence knowing we would have protection to have some sort of normal life again. I so miss the closeness of my family and grandchildren."* The impact of shielding also affects carers and family members who are worried about passing COVID-19 on to those they care for or live with. As the quotes alluded to, some carers quit their job and one family member is attending

	school online rather than going in person. As such the freedom that Evusheld would grant immunocompromised people would be extended to those carers and family members and would therefore improve quality of like for these people too.

Disadvantages of the technology

9. What do patients or carers think are the disadvantages of the technology?	One patient shared their concern about Evusheld keeping up with variants as they change and mutate. They said, *"I think that as Covid 19 evolves evusheld will need to evolve to keep up with the variants we are seeing, I'm not saying I wouldn't have it but how long will it remain effective?"* However, some research indicates that people who are immunocompromised are more likely to spread new variants of COVID-19 (through viral shedding for example), so approving Evusheld for this cohort and preventing them from contracting COVID-19 might help to reduce the number of variants in circulation.

Patient population

10. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	Those who are vulnerable with sub-optimal response to the COVID-19 vaccine. This includes many with leukaemia due to their diagnosis and/or treatment. When the eligibility criteria were set for COVID-19 antiviral treatments, lack of sufficient data on the rarer leukaemia types meant that some vulnerable people were missed out. For example, LGLL patients. As such we would like to see this mitigated against when defining the eligibility criteria for Tixagevimab–cilgavimab.

Equality

11. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	Many other countries around the world have approved Evusheld for use and have rolled it out. As such patients feel they have been given unequal access to this treatment in comparison to these other countries. Granting access would solve this equality issue. Patients feel forgotten about, they feel discriminated against and do not feel equal to the rest of society due to their immunocompromised status and the impact this has on their day-to-day lives, e.g., shielding. Evusheld would enable many to resume normal day-to-day activities as pre-pandemic which would make them feel more equal to the rest of society.

Other issues

12. Are there any other issues that you would like the committee to consider?	N/a

Key messages

13. In up to 5 bullet points, please summarise the key messages of your submission.	● Shielding continues to have a significant mental, physical (through missed appointments) and financial impact on leukaemia patients and also on their families/carers. ● Vaccines have a sub-optimal response in many immunocompromised leukaemia patients and therefore provide little or no protection. Similarly, issues with accessing antivirals has meant that patients do not feel they can rely on them. This creates a strong unmet need. ● Many leukaemia patients said having access to Evusheld would mean they can stop shielding, which would have a significant positive impact on patients' quality of life, their finances and their mental and physical wellbeing and on their family, friends and carers. ● There are inequality issues between leukaemia patients and the general public (immunocompetent people), which Evusheld would help to solve. ● Other countries around the world have approved this treatment for use, and patients in England deserve equitable access.

Thank you for your time.

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About you

1.Your name	[redacted]
2. Name of organisation	Long Covid SOS
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Registered charity funded to date by donations from the general public Trustees: 4 Volunteers: 6
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] **If so, please state the name of the company, amount, and purpose of funding.**	No

4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	Through advocacy, membership of support groups, social media, research

Living with the condition

6. How has shielding from COVID-19 affected vulnerable people?	Many people with Long Covid are unwilling to risk reinfection and potential deterioration of their symptoms or a return of symptoms after a previous resolution, and so find it difficult to mix in public places now that there are no mitigations against COVID infection; they are not classified currently as clinically vulnerable but are nevertheless effectively forced to shield. A significant minority of people living with this condition have had an adverse reaction to COVID vaccination or suffered worsening illness as a result. They are more vulnerable to infection given that they are unable or unwilling to risk taking further vaccinations. This is impacting their ability to work, live, parent and take part in normal social activities, and has a negative effect on quality of life and mental health as well as sense of self and identity.

Unmet need

7. Is there an unmet need for patients with this condition?	Yes. COVID vaccination may not be advised for some people with this condition if they have experienced a worsening of symptoms after previous vaccination. Our own published research https://www.mdpi.com/2076-393X/10/5/652 demonstrated that 17.9% of those surveyed (n=812) reported deterioration of their symptoms after vaccination. 'Breakthrough' infections after vaccination lead to cases of Long Covid - estimates vary, but studies suggest the risk of getting Long Covid after vaccination compared to the risk in non-vaccinated people is 50%-85% (https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(21)00460-6/fulltext, https://www.nature.com/articles/s41591-022-01840-0). This suggests that vaccination is not protecting people from developing sequelae from COVID and research into the effectiveness of this technology in reducing the risk of Long Covid is very welcome.

Advantages of the technology

8. What do patients or carers think are the advantages of the technology? • How would having a prophylactic treatment available impact the day-to-day lives of vulnerable people? (for example, how would it change the activities people do, or how they feel?) • How would having a prophylactic treatment available impact carers?	The availability of this technology would enable those with Long Covid who are at risk from further vaccination, or who worsen with each COVID infection, to feel more confident about mixing in public: using public transport, working away from home if they are able to, and meeting up with friends and family, thereby representing a QALY gain. This could in many cases have a significant impact on their ability to interact with others. Many people with Long Covid are effectively isolated. For those who are housebound or disabled by their illness, the risks posed by infection means that they are unwilling to welcome visitors into their homes, and attending doctor or hospital appointments can cause a great deal of anxiety. This is exacerbated for those who have had, or who fear, a worsening of symptom burden after vaccination. If their protection against infection can be increased this anxiety could be alleviated to a greater extent, enabling them to rejoin society. This would also impact on their carers, who are usually similarly isolated as they cannot risk bringing an infection to the person they are caring for, especially if they are not fully vaccinated.

Disadvantages of the technology

9. What do patients or carers think are the disadvantages of the technology?	The disadvantages are linked to any uncertainty as to the effectiveness of the intervention with current or future SARS-CoV-2 variants, however this equally relates to vaccines. Any research into the impact of Tixagevimab–cilgavimab on those with Long Covid would be welcome - especially on its impact on the trajectory of Long Covid symptoms, if any, and prevention of Long Covid.

Patient population

10. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	Those who have had an adverse reaction to a Covid vaccine or who have seen their symptoms deteriorate after a Covid vaccination or who have a prior sensitivity to any vaccine If it is established that the technology is less likely to impact negatively on Long Covid symptoms compared to vaccination it could be beneficial for those with Long Covid who fear vaccination because of the possible consequences (having heard negative reports on social media, in the press or through family and friends) and who are therefore unwilling to take it up Additionally, there is a subgroup of people (numbers not yet established due to lack of published research) who have developed Long Covid symptoms after vaccination without having had a Covid-19 infection. This group will be very unwilling to risk further vaccinations and are therefore vulnerable to infection

Equality

11. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	How will people who meet the criteria find out about the drug? How will those who lack transport or support networks obtain medication, especially those with Long Covid/who are clinically vulnerable, who are unable to travel themselves to obtain it without worsening symptoms or putting themselves at further risk?

Other issues

12. Are there any other issues that you would like the committee to consider?	What is the risk of further COVID-19 infections to those people who are already in a clinically vulnerable, shielding group, especially those likely to mount a poor response to vaccine, who have developed Long Covid? COVID-19 infection has left them with ongoing health issues and would therefore put them in a 'known to be at risk from Covid-19' category, should they be considered in a higher risk group, if risk stratification is done?

Key messages

13. In up to 5 bullet points, please summarise the key messages of your submission.	• Many people with Long Covid are shielding in order to avoid a re-infection which carries a risk of worsening their symptoms: this has a negative impact on their quality of life and mental health • Those with Long Covid whose symptoms deteriorate after vaccination (estimated as approx 18%) should be considered for prophylaxis to enable them to live life as normally as possible • The subset of people who have developed Long Covid type symptoms after vaccination and for whom further vaccination is contraindicated would also benefit from this intervention • Some people with Long Covid remain unvaccinated as they fear the possible consequences •

Thank you for your time.

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- Your response should not be longer than 10 pages.

About you

1.Your name	[redacted]
2. Name of organisation	LUPUS UK
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	LUPUS UK is the only national registered charity supporting people affected by lupus. The charity produces high-quality information for patients, carers, employers and clinicians. Through volunteer-led regional groups the charity provides support group meetings and raises awareness of the disease within local communities. LUPUS UK also funds medical research and Specialist Lupus Nurses in UK hospitals. LUPUS UK receives most of its income from public donations, fundraising events, and legacies. Additional funds are secured as grants from charitable trusts and foundations, with a small amount from companies. The charity has approximately 3,500 subscribed members; however, we are here for all people affected by lupus and therefore engage with many more people with the disease in the UK.
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] **If so, please state the name of the company,**	LUPUS UK has received the following funding from pharmaceutical companies in the past 12 months: • £5,000 of restricted funding from Janssen Pharmaceuticals in January 2022. This funding was to assist LUPUS UK in the development of an initiative to engage more patients in research, particularly covering the costs of a new CRM database and staff time.

amount, and purpose of funding.	
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

5. How did you gather information about the experiences of patients and carers to include in your submission?	• LUPUS UK conducted an online survey about experiences during the COVID-19 pandemic which was shared with members and supporters of the charity from 16/08/2022 to 23/08/2022. The survey received a total of 204 responses.
	• LUPUS UK conducted an online survey about shielding and tixagevimab–cilgavimab (Evusheld) which was shared with members and supporters of the charity from 04/10/2022 to 09/10/2022. The survey received a total of 126 responses.
	• RAIRDA conducted an online survey between 23/03/2022 and 07/04/2022 about access to COVID-19 vaccines and treatments. The survey received a total of 526 responses. We have used the summary of findings in preparing our submission. https://rairda.org/2022/06/21/survey-shows-poor-communication-around-covid-19-vaccine-and-treatments-for-people-with-rheumatic-conditions/
	• The RECORDER Project studied COVID-19 infection, hospital admission and death amongst people with rare autoimmune rheumatic diseases in England from 01/03/2020 to 31/07/2020. We referred to their findings in preparing our submission. https://www.medrxiv.org/content/10.1101/2021.08.17.21260846v3
	• Three papers published by Melanie Sloan and her research group were also referred to;
	  ○ COVID-19 and shielding: experiences of UK patients with lupus and related diseases – Published Jan 2021
	  ○ The impact of the COVID-19 pandemic on the medical care and health-care behaviour of patients with lupus and other systemic autoimmune diseases: a mixed methods longitudinal study – Published Dec 2020
	  ○ Will 'the feeling of abandonment' remain? Persisting impacts of the COVID-19 pandemic on rheumatology patients and clinicians – Published Jan 2022
	
	The final draft of the submission was circulated to LUPUS UK's Board of Trustees and a small selection of Expert Patients to review and provide additional comments.

Living with the condition

6. How has shielding from COVID-19 affected vulnerable people?	*"Shielding has had a negative impact on all aspects of my life - apart from the fact that I've succeeded so far in avoiding catching Covid"* Sloan et al. (Jan 2021) found shielding has a negative influence on mental health. The changes included: ○ **Increased isolation** - feeling isolated and depressed from reduced social interaction; especially severe among those fully following shielding guidance and living alone. • *"I was so, so lonely. I haven't been shielding for months now but I still haven't mentally recovered from the isolation. I felt like the people shielding were often an afterthought for the government and it made me feel like I wasn't valuable compared to others. I am so scared of needing to shield again in the future."* ○ **Fear** – many estimated their mortality risk from COVID-19 as very high and expressed great anxiety. Additional risk factors, such as being from a Black, Asian and minority ethnic group, also increase anxiety. • *"As time has gone on it is much more stressful. I am still being very cautious, no planes, holidays, restaurants, cinemas etc. only meeting others outside. I feel isolated in winter. I have missed funerals, weddings, and milestone birthdays. It has caused friction with some family members and friends who act like covid is over and no longer a risk (as per government spin). I now have issues with my employer who thinks as some 'clinically vulnerable' people have returned, we all should."* ○ **Identity** - for many, the shielding classification provided medical and societal acknowledgement, and validation of the severity of their disease. However, the term 'clinically extremely vulnerable' was sometimes reported to have negative impacts on social and self-identity, with some perceiving their disease to have greater control over their lives than before the pandemic. • *I was lucky enough to have a husband to support me in shielding, but I was unable to work as a nurse. This was very distressing, watching the circumstances that my colleagues and friends were working in. Because I was unable to work for about 2 years my registration has lapsed, and I am now not able to work as a nurse after almost 40 years. I am still grieving this loss* Healthcare seeking behaviour has been impacted for those who fear contracting the virus. 71% agreed that they had not wanted to go to hospital for fear of catching COVID-19. ○ *"I have not reached out for medical attention when I've needed it as I'm so scared I'll be sent to hospital and catch coronavirus."* Many people who shielded/are shielding have experienced decreased medical support. Fewer than 30% of survey respondents agreed that they felt medically supported during the pandemic. Most reported cancellations of appointments, and some received no communications or response to requests for help from rheumatology departments. There were many

	reports of adverse impacts on physical and mental health from this reduction in care, including participants reporting attendance at A&E departments or being admitted, owing to untreated and/or uncontrolled disease activity or infections. Several participants felt this might have been avoidable and had tried unsuccessfully to contact rheumatology departments before deteriorating to the point of requiring admission. Others considered that the stress and lack of medical and/or government support had directly caused a flare. LUPUS UK's online survey from 4th to 9th October revealed that 47 respondents (approx. 41%) are still shielding. The respondents reported that the areas of their lives most impacted by shielding were hobbies and social activities, mental and emotional wellbeing, and relationships with friends and family. It should be noted that families of vulnerable people frequently shield with them or isolate themselves to reduce the risk of introducing the virus into the household. • *When I started shielding, my three children were 8, 10 & 12. We took them out of school the week before the first national lockdown. Since then, my husband has had to work from home or isolate from the family in our caravan. I have home schooled the children whenever the rates have been high - and had to fight schools for this to avoid being fined or taken to court and treated like a criminal. This has affected my physical and mental health. I am now on antidepressants and started having anxiety attacks. My three children also have restricted lives and now go to school, after having vaccines, but only with masks on and eat only outside. They do not go to friend's houses or social venues and nor do we. It affects the children's mental health and greatly impacts on our lives.* • *"Having teenage children who returned to school and to activities I was limited in the extent I could effectively shield. However, they did their best to protect me; so, my shielding also adversely affected them as they limited their social contacts."* • *"I've been living separately to my husband and daughter for 18 months so my daughter can attend school."* • *"It was bad enough when most people were also shielding, but at least we were 'in the same boat' as most people during lockdown. Over the 14+ month period since it has been really hard. Almost everyone who has no-one close who is shielding has NO empathy. So that on top of the impacts listed above we are seen as 'weirdos' when wearing masks in crowded places on the occasions when we do go out. It is isolating and depressing."*

Unmet need

7. Is there an unmet need for patients with this condition?	Systemic lupus erythematosus (SLE) is a chronic, potentially life-threatening autoimmune disease. Management of the disease typically involves treatment with a range of immunosuppressive therapies and corticosteroids. Biologic therapies such as rituximab and belimumab may also be used in more severe and/or refractory cases. A RECORDER analysis (**HERE**) found that, between 01/03/2020 and 31/07/2020, the age-sex-standardised mortality rate for COVID-19-related death was 2.41 times higher than in the general population for those with rare autoimmune rheumatic diseases (including lupus). There was no evidence of an increase in deaths from other causes in this population at the time. This analysis was for a large patient cohort representing significant variation in individual risk. It is expected that risk of mortality would be higher for patients on strong immunosuppressant therapy and those with additional risk factors such as lupus nephritis. This data is from before the implementation of the COVID-19 vaccinations, which will likely have reduced risk of severe illness and death for many in this cohort. **However, there is a significant unmet need for the people treated with strong immunosuppressants who have not had adequate protection from the vaccines.** The OCTAVE study showed that a significant proportion of immunosuppressed people have a low or undetectable immune response after two doses of the vaccines (**HERE**). It has also been shown (**HERE**) that antibody responses were completely undetectable in 33% of patients with rare autoimmune rheumatic diseases (RAIRDs) and insufficient in a further 24% after two doses of vaccines compared to healthy controls. Importantly it has also been revealed that RAIRD patients with low/no antibody response had significantly lower T cell response which is essential in coordinating and regulating antiviral immunity. Other studies have shown that additional doses increase the proportion of immunosuppressed people with a measurable response, but some remain refractory to COVID-19 vaccination, particularly those treated with rituximab. **Thus, it is imperative to explore additional protective strategies that can be used alongside vaccination.** There is a further group of patients who were unable to complete their course of COVID-19 vaccine doses. Some people could not complete their COVID-19 vaccination doses due to history of anaphylaxis or a significant adverse reaction to an early dose. Without the protection of vaccines, these people remain at a high risk from COVID-19. A further unmet need relates to the post-exposure COVID-19 therapeutics. Unfortunately, there have been many reports of difficulties in accessing these treatments within the necessary timeframe for people at high risk from COVID-19. Many people with rare autoimmune rheumatic diseases (including lupus) have been missed when the NHS has been identifying individuals who may be eligible for the COVID-19 therapies. From 23/03/22 to 07/04/22, RAIRDA found that approximately 40% of respondents to their online survey who identified as meeting eligibility criteria had received no correspondence from the NHS to notify them of their eligibility, give instructions on accessing treatments, or provide COVID-19 tests. Of these people, 50% who had contracted COVID-19 reported the process to get referred to a COVID-19 Medicines Delivery Unit (CMDU) to be ‘very difficult’ (**HERE**).

	• *"I recently tested positive for COVID and having been classed as CEV I have been very anxious about catching it but have felt reassured knowing that there are antiviral treatments available. So far (I am now on day five) accessing those antivirals is proving almost impossible. I keep being told by the COVID-19 Medicines Delivery Unit that I am on the list for a doctor assessment, but it is a very long list and I am not yet near the top."* • *"I was very unwell with COVID-19. I registered my test result in order to access anti-viral treatment but did not receive it due to a late response from the NHS. I developed a chest infection and sinusitis."* Post-exposure COVID-19 therapeutics are contraindicated for some individuals. As such, Evusheld could fulfil a vital unmet need for those people who are not protected by vaccines and cannot be offered COVID-19 treatments following a positive test. Paxlovid is typically the primary choice of post-exposure COVID-19 treatments but it has many contraindications including many medications and those with severe kidney or liver disease. It is important to note that lupus nephritis affects approximately 30-50% of people with SLE and therefore could exclude them from Paxlovid. There are also concerns that some of the post-exposure COVID-19 therapeutics may be less effective for people with SLE. A UK population-based study of more than one million people eligible for treatment with sotrovimab in England found that, when slitting the 28-days risk period for hospitalisation into narrower periods, there was an increased risk of hospital admission for systematic lupus erythematosus in the 2-3 days following the treatment (**HERE**).

Advantages of the technology

8. What do patients or carers think are the advantages of the technology? • How would having a prophylactic treatment available impact the day-to-day lives of vulnerable people? (for example, how would it change the activities people do, or how they feel?) • How would having a prophylactic treatment available impact carers?	Many respondents to our survey indicated that a preventative treatment is preferable to managing the illness after contracting the virus. This would be seen as a particular advantage because people with lupus are not only at higher risk of severe illness from COVID-19 but contracting viruses is often a trigger for flares of lupus disease activity. In our online survey, 96 respondents reported having COVID-19. Of these, approximately 44% said that COVID-19 had affected their lupus with a further 34% saying they were unsure whether the virus had impacted their lupus. Many reported worsened symptoms or flares of their lupus and this frequently required additional treatment, such as increased corticosteroids. • *"Evusheld would give me greater confidence that I do indeed have some protection. It is also important that I am protected against any illness, not just serious illness, as infections can cause my lupus to flare up."* • *"Prevention is always better than treatment. I am especially concerned about the risk of Long Covid as I already struggle with chronic fatigue. Additional fatigue and any other long-term consequences of covid would likely destroy my quality of life."* • *"Living with multiple autoimmune diseases is hard enough… I should not have to risk getting even more Ill when there is a solution. Evusheld would decrease the risk of getting C19 as opposed to getting C19, which could then possibly kill me even with treatments. The likelihood of my health problems worsening is not acceptable when a solution is available."* In many cases, when someone with lupus has COVID-19, they are instructed to pause their immunosuppressive treatments to help their body fight the infection. This can further increase the risk of lupus flares, resulting in a prolonged period of ill-health. • *"By preventing covid infections it would mean I can remain active, which helps my condition, and prevent taking time off work. I currently have covid and have had to take 10 days off work. I have had to stop my immunosuppressants which I had only just started, so it is delaying getting established on them."* Some people with lupus commented that, even if Evusheld does not effectively prevent them from contracting SARS-Cov-2, it should provide additional protection to that given by the vaccines. • *"As a prophylactic, it is a proactive step to give protection where the vaccines have been unable to. Whilst it may not be a guarantee of protection, it would likely reduce the impact/severity of contracting covid. Ultimately, it would be more cost effective to provide this rather than wait to treat once a person has covid and is likely to need antivirals and/or significant hospital intervention, resulting in extensive cost."* There is some concern that the currently available post-exposure treatments could not be reliably accessed in a timely manner and would not be suitable for all patients. Evusheld would provide another option for those who have contraindications to other COVID-19 treatment. • *"Sotrovimab is the only treatment I can take as antivirals are contraindicated with my other meds. The World Health Organisation (WHO) has recommended that sotrovimab stop being used as it is no longer effective. Against current variants I have no antibodies. I have lung and heart damage from first covid. I can't get it again. I live in fear of getting it again. It nearly killed me. Post-exposure treatment that does not work is no good."* • *"I was eligible for the antivirals and called immediately, but molnupirivir only arrived on the last day of the useful 'window'. Paxlovid was the preferred option, but the window had closed. I had an 'antiviral rebound' after finishing the course and a*

	worsening of symptoms for around 10 days. I was too afraid of hospitals and the possibility of getting another infection to be admitted. I now have scarred lungs and after three months have no idea if my breathing problems are permanent. I can't afford to get covid again." We received a lot of comments from people with lupus who were uncertain how much protection (if any) they may have from COVID-19 vaccines and would feel reassured by the additional protection Evusheld could offer. Many commented that this could enable them to have a more "normal" life, returning to social activities and reducing problems with their employment. • *"Knowing that I had preventative protection would allow me to freely exercise in gym/pool without worry and allow me to socialise more confidently. I would be happier knowing that my family could be more relaxed going to school/work."* A prophylactic treatment could significantly benefit family and household contacts of people with lupus. This extra protection could help reduce the anxiety experienced by many people who do not want to risk exposing their vulnerable loved-one to SARS-Cov-2. • *"My daughter and I would be free to pursue normal lives. The children's fears of their mother dying would be significantly reduced. We would have our own Freedom Day and get our lives back."*

Disadvantages of the technology

9. What do patients or carers think are the disadvantages of the technology?	The most expressed concern about this treatment was the unknown risk of side-effects for people living with lupus. Some respondents were unsure whether it may be contraindicated with their medications and whether the treatment could cause adverse effects. A few respondents reported side-effects and lupus flares from the COVID-19 vaccines and asked whether these would also be a similar risk with Evusheld. • *"Having had bad reaction to CV19 vaccinations…I am very wary. I am on rituximab which has not worked when given 6 weeks post vaccination. I'm plodding along OKish…. I have no antibodies so would only accept Evusheld if I was able to personally consult a specialist who could advise me."* • *"I'm unsure if taking this would contradict with some of my medications, infusions and/or past vaccines. I also don't know if it would cause a flare up or give me new symptoms."* Another concern was related to uncertainty of Evusheld's efficacy against newer variants of COVID-19. A couple of people made comments suggesting that reassurance from the treatment could change behaviours and put someone at a greater risk of exposure to SARS-Cov-2. • *"Maybe it would give a false sense of security to those of us who have not yet experienced Covid infection."* However, this should be considered within the current environment. In many cases, vulnerable people are already at risk of exposure to SARS-Cov-2 because public health measures to reduce the spread have been removed, including in many healthcare settings where they must attend for treatment and monitoring.

Patient population

10. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	The patients who would benefit most from this treatment are those who have the poorest immune response to COVID-19 vaccinations. Several research studies and trials have investigated how patients respond to COVID-19 vaccines and have shown some treatments are associated with lower likelihood of response. Treatments associated with poor response to COVID-19 vaccines include rituximab (HERE), glucocorticoids (HERE), mycophenolate mofetil and methotrexate (HERE). Additionally, patients who were unable to complete their course of COVID-19 vaccine doses would also benefit more from access to this treatment. Some people could not complete their COVID-19 vaccination doses due to history of anaphylaxis or a significant adverse reaction to an early dose. Another group who would benefit more are those who may not benefit from post-exposure COVID-19 therapeutics. These treatments may not be suitable for some people due to contraindications. There is also evidence suggesting that sotrovimab may be less effective for reducing risk of hospitalisation for people with SLE (**HERE**).

Equality

11. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	Access to Evusheld could potentially address an inequality experienced by this patient group. Most of the population have benefitted from COVID-19 vaccinations and/or previous infection to protect them and reduce their risk of severe COVID-19. Society has withdrawn most of the measures to reduce spread of COVID-19, aimed at protecting the most vulnerable. This imposes further risk and inequality upon people who are severely immunosuppressed. If this treatment is made available, the NHS will need to carefully consider how to select patients. From 23/03/22 to 07/04/22, RAIRDA found that approximately 40% of respondents to their online survey who identified as meeting eligibility criteria for COVID-19 treatments had received no correspondence from the NHS to notify them of their eligibility, give instructions on accessing treatments, or provide COVID-19 tests (**HERE**). Some people who might be eligible for Evusheld may not be invited for the treatment. This could disproportionately impact patients who are less engaged with their healthcare due to language or education barriers. There is evidence indicating that uptake of sotrovimab to treat COVID-19 has differed across ethnic groups with higher update in White, Indian, Bangladeshi and other Asian groups and lower in Black Caribbean and Black African groups (**HERE**). Efforts must be made to address possible reasons for this and enable equal access.

Other issues

12. Are there any other issues that you would like the committee to consider?	NICE should consider adopting a condensed timeline for this appraisal due to the urgent need. A faster, more flexible approach was adopted for the Multiple Technology Appraisal for COVID-19 therapeutics [ID4038]. The need is more urgent for Evusheld because it is not currently being used by the NHS and we are entering winter when airborne viruses like COVID-19 spread more readily. The eligibility criteria for this treatment must be very carefully considered. The subgroup within the draft scope included people who have received anti-CD20 monoclonal antibody therapy (such as rituximab) in the last 12-months. It should be considered whether the time since last treatment should be increased. The B-cell depleting effects of these therapies can be significantly longer than 12-months and if this was used as an eligibility criterion it could leave some people at high risk from COVID-19. This assessment must take a broad approach to considering what factors to include within 'health-related quality of life'. An important outcome to consider is psychological impact of having some protection against COVID-19 for some people who may have been shielding since March 2020. These people have forgone social activities, travel and, in some cases, lived separately from family. As such, a comparison of many aspects of quality of life before and after the treatment is needed to measure potential improvements. The evaluation should also consider the costs of post-exposure COVID-19 therapeutics if Evusheld is not administered. The population for this treatment will largely be eligible for community-delivered COVID-19 therapeutics such as sotrovimab if they contract the virus. Would these post-exposure treatments be required in someone successfully treated with Evusheld?

Key messages

13. In up to 5 bullet points, please summarise the key messages of your submission.	• Some people with lupus, particularly those treated with strong immunosuppressive therapies, remain at high risk of severe disease from COVID-19 infection despite repeated vaccination. • An additional sub-set of people with lupus remain at high risk from COVID-19 because they could not complete their course of vaccination due to allergies and/or severe adverse events. • The threat of COVID-19 infection is still significant for many people with lupus who are immunosuppressed and their families. Behaviours to reduce risk of exposure to COVID-19, such as shielding, continue to have a profound negative impact on quality of life. • This prophylactic treatment could provide protection against infection and/or severe COVID-19 disease for this high-risk patient group. • The need for this treatment is urgent. NICE should consider adopting a condensed appraisal process to allow for faster access, if it is recommended.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal
Tixagevimab–cilgavimab for preventing COVID-19 [ID6136]
Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you

1.Your name	[redacted]
2. Name of organisation	Lymphoma Action
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Lymphoma Action is a national charity, established in 1986, registered in England and Wales and in Scotland. We provide high quality (PIF Tick accredited) information, advice and support to people affected by lymphoma – the 5th most common cancer in the UK. We also provide education, training and support to healthcare practitioners caring for lymphoma patients. In addition, we engage in policy and lobbying work at government level and within the National Health Service with the aim of improving the patient journey and experience of people affected by lymphoma. We are the only charity in the UK dedicated to lymphoma. Our mission is to make sure no one faces lymphoma alone. Lymphoma Action is not a membership organisation. We are funded from a variety of sources predominantly fundraising activity with some limited sponsorship and commercial activity. We have a policy for working with healthcare and pharmaceutical companies – those that provide products, drugs or services to patients on a commercial or profit-making basis. The total amount of financial support from healthcare companies will not exceed 20% of our total budgeted income for the financial year (this includes donations, gifts in kind, sponsorship etc) and a financial cap of £50,000 of support from individual healthcare companies per annum (excluding employee fundraising), unless approval to accept a higher amount is granted by the Board of Trustees. The policy and approach ensure that under no circumstances will these companies influence our strategic direction, activities or the content of the information we provide to people affected by lymphoma. https://lymphoma-action.org.uk/about-us-how-we-work-policies-and-terms-use/working-healthcare-and-pharmaceutical-companies
4b. Has the organisation received any funding from the company bringing the	AstraZeneca 2021 £40,000 and 2022 £6,000

treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] **If so, please state the name of the company, amount, and purpose of funding.**	
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	NO
5. How did you gather information about the experiences of patients and carers to include in your submission?	We sent a survey to patients affected by lymphoma and their carers asking about their experience of living with lymphoma during the pandemic, the care and vaccinations they received, any antiviral treatment given on contracting Covid, and specifically to elicit their views on Tixagevimab–cilgavimab for preventing COVID-19. We also draw on our experience from supporting and giving information to people affected by lymphoma over the past 2 years: through our helpline services, online support meetings, general enquiries, use of relevant webpages, and patient groups. We have also gathered evidence from Lymphoma Coalition member organisations including Israel and France, where Evusheld is currently used, to corroborate our submission.

Living with the condition

6. How has shielding from COVID-19 affected vulnerable people?	For this submission we spoke to people affected by a range of lymphomas. Every point made applies to all lymphoma types unless otherwise stated. To fully understand the impact of the pandemic, it is also important to understand the challenges that those affected by lymphoma faced before. Both the lymphoma and its treatment can significantly affect quality of life. Fatigue is a particularly common – and disabling – symptom reported by the majority of patients. Around 8 in 10 lymphoma patients rate it as the symptom that affects them the most, and stops them doing things that other people their age can do. Patients find it affects all aspects of their life: work, social activities, mood, relationships, exercise and ability to focus or concentrate. Many people need to take time off work or studies, or even stop work completely. Over 4 in 10 people with lymphoma report being unable to work or changing their work pattern because of their illness. This can be very difficult financially. The uncertainty of relapse and the need for repeated courses of treatment is also physically and psychologically challenging for many patients. Other psychological effects of lymphoma include isolation, depression, anxiety and loss of self-esteem. "*A diagnosis of cancer is absolutely life-changing and living with the long-term impact of treatable but incurable lymphoma takes a lot of getting used to … the endless active monitoring is tricky, the knowledge of probable relapse and more treatment repeated and repeated plus the expectations of others is hard to manage, the interminable 'being careful' is tough."* Caring for someone with lymphoma can be challenging emotionally, practically, and financially. Carers often provide transport to-and-from hospital appointments and treatment sessions, requiring time off work. They also provide emotional support, whilst trying to deal with an emotionally difficult situation themselves. Most also take on more chores and household tasks. Over 3 in 4 caregivers report feeling anxious and physically and emotionally worn out. Some carers and family members report needing counselling. Others feel that it puts a serious strain on relationships. Around 3 in 10 patients with lymphoma feel that their illness creates problems with partners, close friends or relatives. **The Covid pandemic** has impacted hugely on the lives of people affected by lymphoma. We are told "*It can be difficult to live with lymphoma at the best of times…and then Covid! At the beginning of the pandemic, I locked myself away and saw no-one. The letter I received saying I was extremely vulnerable and the advice it gave felt very threatening, but I followed the recommendations."* Another states "*The pandemic has made living with Lymphoma much harder. I have effectively been shielding since March 2020". "The pandemic has severely*

	impacted family life. Obviously, there is the constant worry associated with bringing the virus in to the home. And, as our young adult children go out to work, and live a social life, we are no longer able to eat together as a family, with the children having to eat on their own, in a different room." While the individual risk of becoming seriously ill after contracting Covid can depend on the type of lymphoma, the treatment received, when the treatment was received, and having other medical conditions, for example: • People who have had a splenectomy. • People who have low-grade non-Hodgkin lymphoma even if you have not required treatment for many years. • People who have received a stem cell transplant, radiotherapy or chemotherapy in the last 12 months. • People who have received a donor (allogeneic) stem cell transplant with active graft versus host disease, regardless of the time from transplant. • People who have received CAR T-cell therapy in the last 24 months. we know that this does not stop many people affected by lymphoma being anxious, especially now the national restrictions and pre-cautions have been lifted. "*To everyone else, Covid is just a mild condition. For people with lymphoma (as well as other people in the risk groups), we do not know how we will react to catching the virus… the vaccination programme did not alleviate this worry because it became known that some types of lymphoma would not mount an appropriate response."* Patients are telling us they are not able to 'return to normal' as they feel the Government demands "*Having to risk assess every action, being frightened when amongst the public, having to think for the public as they think everyone is able to return to "normal".* People with lymphoma are often unable to *"meet family or friends, shopping, work, volunteer, attend theatre/concerts/sporting events, go out for a meal or coffee, holidaying,''* One patient said that *"there is no return to normal for anyone in a high-risk group."* We are also told that making adaptations to normal daily life is a financial burden for some "…*have made one train journey in nearly three years, going first class as there is less movement around the carriage. We walked or taxied rather than use public transport. These adaptations are not financially viable for some people."* The pandemic, and the continued presence of Covid, has greatly impacted the carer role. The need to protect the patient is paramount for them and heightened by the stopping of restrictions. One patient told us "*during the*

	pandemic, one friend basically put his life on hold to help me out. I have spoken to people where their partner has basically adopted the same extreme care as them, and this has changed their lifestyles enormously." As with the patient, carers report life to be a constant balancing of risks and benefits in order to achieve anything like a 'normal' life-style, and the constant fear of bringing Covid into the house as a strain on relationships. "*Carers have an additional burden of worry and concern as they might be the vector for giving the immune-compromised a virus – a particular worry during a pandemic – and could be devastating to a relationship."* Particular of recent, as many people have returned to living their 'normal lives', those who are immunocompromised feel left behind and forgotten about. One patient stated that "*Although I felt well cared for in terms of shielding and extra support at the start of the pandemic, I now feel a little forgotten as the risks for us are still there and show no sign of diminishing yet."* They continue, quite reasonably, to feel very unsafe and fear death or grave illness from Covid infection. This can mean that many patients continue to live very 'locked down' lives in fear of these things.

Unmet need

7. Is there an unmet need for patients with this condition?	There is currently no pre-exposure prophylaxis treatment available on the NHS that is used in the same way as Tixagevimab–cilgavimab. Current treatments and care available on the NHS include vaccinations against COVID-19 and antivirals to hopefully reduce symptom burden, which are available once an eligible individual has contracted COVID-19. Tests for eligible individuals are also available through the NHS. However, some Lymphoma patients do not mount a response to vaccines and therefore there remains an unmet need for them as they have a greater risk of catching COVID-19 and becoming ill, compared to the general population. One patient summarised that "*especially the group very unlikely to have adequate antibodies against Covid-19, feel very much that the drug should be made available to people in these groups, such as people on 'B' cell inhibitors, people after stem cell transplants and many others to be defined by relevant clinical experts."* Another patient said that vaccines are fine for a *"normal person*" however not for those who *"have not produced any Covid antibodies."* Similarly, another patient stated that the *"the available vaccines don't appear to give any B Cell protection to someone with my condition."* Additionally, Lymphoma patients are amongst those who still have anxieties around catching COVID-19 and who do not yet feel like the pandemic is over. Patients feel they are being left behind as there is not yet a treatment available for them. "*I would like the world at large to understand that there are still some people who can be badly affected, or may even die, if they get Covid. It seems as if everyone feels we are free of Covid, or its effects are only mild. There is a real lack of awareness. For most people, yes, it's mild; but not everyone. And there is a huge feeling of being left behind. What about people working in unsafe environments because they have no option but to go to work to bring in an income?"* Some patients we spoke to also expressed concerns about the antiviral treatments and noted they would rather have preventative treatments than cures. One patient who has used antivirals stated that they *"did mean I recovered from Covid but I would rather be in the position that I had greater protection to start with, rather than (having to) treat the virus."* Similarly, another patient noted that they would rather have Evusheld than rely on antivirals, saying that *"receiving the two tablets by post is unnecessarily worrying due to the timescales involved and the success rate is less than Evusheld."*

Advantages of the technology

8. What do patients or carers think are the advantages of the technology? • How would having a prophylactic treatment available impact the day-to-day lives of vulnerable people? (for example, how would it change the activities people do, or how they feel?) • How would having a prophylactic treatment available impact carers?	Patients see Tixagevimab–cilgavimab as an opportunity for immunocompromised people to return to living their normal life, making a difference to their quality of life. One patient stated that it would allow *"immunocompromised people (to be) on the same footing as everyone else."* Another patient said that *"there are no lengths I wouldn't go to for peace of mind and a drug like Evusheld would be such a huge step towards this."* Tixagevimab–cilgavimab *is "an opportunity to go back to living their life normally, as many others have done already."* Many patients acknowledged the benefit that Tixagevimab–cilgavimab being made available would have on not only their physical health, but their mental health too. One patient said that "*"anyone with a severely compromised immune system is potentially feeling very vulnerable still and their mental health will not be good"* and another acknowledged that "*mental health will improve, anxiety and frustration will be eased"* if Tixagevimab–cilgavimab was to be made available. It was also acknowledged that the availability of Tixagevimab–cilgavimab would benefit carers, as well as patients, with one patient saying that it would *"relieve my family of a huge burden potentially associated with bringing the virus into our home; allow us to have something resembling a family life; and allow me to reconnect with extended family and friends."* Furthermore, patients and carers recognise not only the benefits for themselves, but also for the NHS. Respondents of the survey praised the NHS but acknowledged the strain it has been under because of the pandemic. Patients and carers believe that Tixagevimab–cilgavimab would help reduce burdens on the NHS by ensuring less immuncompromsied people are hospitalised with COVID-19. One patient stated that Tixagevimab–cilgavimab would *"reduce the risk of future infections overwhelming the NHS in a needless way."* Another patient stated that *"with the NHS likely to be under immense stress in the winter, I wouldn't like to depend on the current system."*

Disadvantages of the technology

9. What do patients or carers think are the disadvantages of the technology?	Patients acknowledged that while *"Evusheld is not perfect" "none of the current vaccines and treatments are"* either.

Patient population

10. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	A sub-set of patients for whom the fear of catching Covid remains a real concern are those who have not, or do not know whether they have, produced antibodies as a result of vaccination. Many lymphoma patients are immunocompromised, meaning that they either know they haven't produced antibodies or are not aware. One patient said*, "Those who don't produce a necessary antibody response to the current vaccines, and are at risk if they catch Covid, should be seriously considered as a beneficiary"* and another that they are *"worried for those that have no antibodies which from the studies, is the majority of patients."* As a result, many people still leave in fear and feel they can not live their lives as normal. *"Now Covid is here, and knowing that my vaccines have not worked means life is lived in fear, loss of confidence and running away from the general public…"*

Equality

11. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	

Other issues

12. Are there any other issues that you would like the committee to consider?	Comprehensive testing for antibodies amongst the patient population to learn who has antibodies and who doesn't so that help can be targeted more. The pandemic has had a disproportionate impact on those with compromised immune systems - partly health-based and partly political (i.e. the government's decision about shielding). Preventative methods and treatments are essential to ensure that the vulnerable are treated justly and can continue to live and work as others can. Evusheld is already available in countries such as France, Israel, the USA and Canada. A study in Israel, where Evusheld has been made available, concluded that "AZD7442 (Tixagevimab-Cilgavimab) administration among persons with severe immunosuppression appears to provide protection against Omicron variant infection and severe disease sequelae. These findings have broad implications on public health policy and health service provision for the immunocompromised individual and encourage physicians to recommend AZD7442 for highly immunosuppressed patients." Study here: Association Between AZD7442 (Tixagevimab-Cilgavimab) Administration and Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infection, Hospitalization, and Mortality | Clinical Infectious Diseases | Oxford Academic (oup.com)

Key messages

13. In up to 5 bullet points, please summarise the key messages of your submission.	• The COVID-19 pandemic is not over for those who are immunocompromised, including some lymphoma patients. Taking steps to ensure these people feel protected and can live as normal life as possible is crucial. • The current care available on the NHS is not sufficient for all lymphoma patients. Some lymphoma patients do not mount a response to vaccines, and some see antivirals as unreliable. Neither are a better solution to a possible preventative treatment. • Evusheld would benefit both the physical and mental health of immunocompromised individuals, including some lymphoma patients. • Many lymphoma patients aren't aware whether they mount a good response to vaccines or what their antibody levels are. This might help targeted treatments for the right people. • Evusheld is already available in other countries across the world, with real world data and studies proving it is effective, even against new variants.

Thank you for your time.

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Your privacy

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- Your response should not be longer than 10 pages.

About you

1.Your name	[redacted]
2. Name of organisation	The MS Trust
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	The MS Trust is a UK charity dedicated to making life better for anyone affected by MS. Last year we supported **827,000** people with our expert MS information and helpline. (This covers our online and print information content, podcasts, video and webinar views and enquiries answered by our helpline). Our core belief is that the best outcomes will come from well-informed people with MS making decisions in partnership with their specialist health professionals, and our aim is to support both sides of this partnership as much as we can. We provide expert information to help people with MS manage their own condition, and, uniquely, we inform and educate the health and social care professionals who work with them about best practice in MS treatment and care. We receive no government funding. We are not a membership organisation. We rely on donations, fundraising and gifts in wills to fund our services.
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] **If so, please state the name of the company,**	None.

amount, and purpose of funding.	
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	None.
5. How did you gather information about the experiences of patients and carers to include in your submission?	We have prepared this submission based on our experience of supporting people affected by MS at all stages of the condition. We speak daily to people who are dealing with issues relating to MS: coping with the impact of diagnosis, coping with physical, emotional and financial consequences of MS. To gain further insight for our submission we spoke to people living with MS who have been shielding due to concerns around exposure to Covid infection. We have also asked health professionals for their views on Evusheld as a treatment for people with MS whereby treatment prevents adequate vaccine response.

Living with the condition

6. How has shielding from COVID-19 affected vulnerable people?	We asked people with MS how shielding from COVID-19 has affected their lives. People with multiple sclerosis who remain concerned about exposure to Covid infections have continued to follow a restricted lifestyle in order to maintain social distancing. These quotes demonstrate that long-term shielding has had a negative impact on quality of life, affecting physical and emotional wellbeing, key relationships and employment. "I don't go to shops; I haven't been to work. I am now retired on the grounds of ill health. I had been in the same job for twenty-two years and it was a big shock to stop working. I absolutely loved my job,". "I feel I have missed out a lot these past few years [due to shielding]. We are being denied a freedom that people who aren't vulnerable have. People are going to parties, festivals, crowded places, to drinks. I've lost all my friends. There are only so many times you are asked for a drink before they stop asking. All my colleagues who I was friendly with are gone." "I need the same protection as everyone else. I don't want to spend the rest of my life like this. I'm not living a normal life, I'm young, not in my 90's, I don't want to be sat at home like an old lady. Having access to Evusheld would mean we can get some of our lives back." We have also heard from health professionals about the impact of shielding on the mental health of people living with MS and on the impact on physical health and in particular deconditioning.

Unmet need

7. Is there an unmet need for patients with this condition?	Yes, Evusheld offers an alternative to the existing vaccines which may be ineffective or unsuited for some people with MS. People with MS have welcomed the introduction of Covid-19 vaccinations and take-up has been equivalent if not better than the general population. The vaccines have also proved to be effective and safe for most people with MS. Many people with MS take NICE-approved disease modifying treatments (DMTs) to slow down the progression of the disease. However, several DMTs prevent development of an adequate antibody response to the Covid-19 vaccine. Without adequate vaccine protection, people taking these DMTs have little alternative but to shield. Several NICE approved treatments for multiple sclerosis are known to blunt the Covid vaccine response: • Sphingosine 1-phosphate receptor modulators (fingolimod, siponimod, ponesimod) • Alemtuzumab treatment within the past 24 months • Anti-CD20 monoclonal antibodies (ocrelizumab, ofatumumab) Furthermore, evidence suggests that people treated with ocrelizumab may be more likely to be hospitalised and need intensive care if they're infected with Covid-19, although the risk appears to be small. People with multiple sclerosis taking these treatments are concerned about exposure to Covid infections and continue to follow a restricted lifestyle to maintain social distancing. “I started taking my DMT Ocrevus [ocrelizumab] in March 2020. Ocrevus has been the most effective treatment I have tried as it enables me to walk. Before I took Ocrevus, I had frequent relapses of multiple sclerosis and I had to use a wheelchair. Three previous DMTs I took didn’t work.” We are also aware that concerns about a blunted vaccine response deter some neurologists from prescribing and some patients from starting treatment with one of these highly effective multiple sclerosis treatments. Multiple sclerosis which is untreated or inadequately treated can lead to long-term disability. There is significant unmet need for a treatment that provides effective protection from Covid for those who do not respond to the vaccine.

Advantages of the technology

8. What do patients or carers think are the advantages of the technology? • How would having a prophylactic treatment available impact the day-to-day lives of vulnerable people? (for example, how would it change the activities people do, or how they feel?) • How would having a prophylactic treatment available impact carers?	People living with MS told us: "The benefits of Evusheld include having the ability to feel safe to go outside. I have panic attacks when I go anywhere, I go into fight or flight mode if someone comes towards me. I would be able to shop for myself, I would feel safe around my granddaughter who is now in nursery, I'd be able to spend normal time with my partner and his children." "I just want to live a normal life. I want to return to physio and the things I was doing before. I want to keep myself healthier and if I had access to Evusheld, my mental health would improve too." "Having access to Evusheld would make a huge difference to my life. I could live again, spend time and feel safe around people. I could go to hospital to access medical care without it being an emergency. I could live the life that people that aren't vulnerable can live now – being outside, and not worrying if people are coughing as they walk past." In terms of the impact on carers, partners and family members will be concerned about infecting the person who has MS, and may also have continued to shield or take extra precautions when returning home from outside activities or work. "My partner is a teacher, but we live separately. Living together would be too risky because he is exposed to Covid-19 through is work and his children, and he has had Covid several times. He and I only meet for walks in the woods keeping our distance from each other,".

Disadvantages of the technology

9. What do patients or carers think are the disadvantages of the technology?	People with MS struggled to think of disadvantages of the technology. One person we spoke to said “In my view, the downsides of Evusheld include pain from injection and the unknown long-term risk that it may have. But the benefits outweigh the disadvantages”.

Patient population

10. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	People with MS who take NICE approved treatments for multiple sclerosis which are known to blunt the vaccine response would benefit most from this technology. As outlined above, these are: • Sphingosine 1-phosphate receptor modulators (fingolimod, siponimod, ponesimod) • Alemtuzumab treatment within the past 24 months • Anti-CD20 monoclonal antibodies (ocrelizumab, ofatumumab) Furthermore, evidence suggests that people treated with ocrelizumab may be more likely to be hospitalised and need intensive care if they're infected with Covid-19, although the risk appears to be small. Concerning people living with multiple sclerosis, current evidence also suggests that certain factors may increase the risk of serious illness from Covid-19. These include higher disability levels; progressive disease with longer disease duration; older age (above 65); obesity; black, Asian and minority ethnicity (BAME); and other health conditions, particularly diabetes and cardiorespiratory disease.

Equality

11. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	Yes. It could be argued that someone taking one of the DMTs listed above is being discriminated against because the Covid vaccine doesn't work for them. Furthermore, people with greater levels of disability, older age, from an ethnic minority community, comorbidities, obesity and progressive MS may be at increased risk of serious illness if they contract Covid-19. Disability, age and race are protected characteristics under the Equality Act 2010. However, it could be argued that having no access to Evusheld is indirect discrimination towards people with these characteristics. It is deeply unfair that people with increased risk of severe illness from COVID-19 are prevented from accessing Evusheld, which may prevent this.

Other issues

12. Are there any other issues that you would like the committee to consider?	Feedback from health professionals who support people living with MS is that if this treatment is approved there needs to be clear guidance provided to ensure effective use of the treatment with targeting to those who will most benefit.

Key messages

13. In up to 5 bullet points, please summarise the key messages of your submission.	• Many people with MS take NICE-approved treatments to slow disease progression, however some treatments prevent adequate antibody response to COVID-19 vaccines. • Some people with MS on the aforementioned treatments have been long-term shielding to avoid acquiring Covid. However, this negatively affects quality of life, emotional and physical wellbeing, relationships and employment. In particular, for people with MS, avoidance of public spaces such as hospitals prevents management of MS symptoms leading to greater burden of disease. • It could be argued that having no access to Evusheld is indirect discrimination towards people with characteristics that enhance their vulnerability to risk of severe illness from COVID-19. • Health professionals who support people with MS state that if Evusheld is approved, clear guidance is required to ensure treatment targets people who would most benefit. • •

Thank you for your time.

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- Your response should not be longer than 10 pages.

About you

1.Your name	[redacted]
2. Name of organisation	Myeloma UK
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Myeloma UK is the only organisation in the UK dealing exclusively with myeloma and its associated conditions. Our broad and innovative range of services cover every aspect of myeloma from providing information and support, to improving standards of treatment and care through research and campaigning. We are not a membership organisation and rely almost entirely on the fundraising efforts of our supporters. We also receive some unrestricted educational grants and restricted project funding from a range of pharmaceutical companies.
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] **If so, please state the name of the company, amount, and purpose of funding.**	No
4c. Do you have any direct or indirect links	No

with, or funding from, the tobacco industry?	
5. How did you gather information about the experiences of patients and carers to include in your submission?	Myeloma UK carried out four COVID-19 surveys to collect information on the impact of the pandemic on patients and their families and friends. Our first survey launched in May 2020, was open for two weeks and had 1,165 responses: 871 from patients; and 294 from family and friends. Our second survey launched after shielding measures had been paused and was open from 28 August 2020 – 16 September 2020. There were 815 responses: 621 from patients and 194 from family and friends (68% of these respondents had completed our first survey). Our third survey was launched on 7 May 2021 after shielding ended and most patients and their families had received one or both of their COVID-19 vaccinations. When this survey closed on 7 June 2021, lockdown had eased in many parts of the UK. 690 people took part in this survey: 528 of respondents were patients. Our final survey was launched during a key transition point for myeloma patients, their families and friends, when the government confirmed the removal of social distancing measures across the UK. Within 48 hours, 1,733 people responded to our survey.

Living with the condition

6. How has shielding from COVID-19 affected vulnerable people?	Myeloma patients and their families and friends have been one of the most significantly affected groups during the COVID-19 pandemic, with patients at all stages of treatment being asked to shield. From our first survey, more than half (54%) of patients found it harder to manage their physical health and a third (33%) found it harder to manage their mental health while shielding. 86% of patients and 93% of family and friends were concerned about the impact of shielding for a prolonged period of time. Despite this, 60% of patients felt shielding was necessary. Only 3% did not think they had to shield or considered themselves not to be shielding. While shielding has been hard, most patients saw it as necessary and low numbers of myeloma patients testing positive indicates that shielding has worked. ***I am missing family but understand the need to stay protected.*** When shielding measures were paused in 2020, 16% of patients still consider themselves to be shielding. 55% stated they were either somewhat or very concerned about shielding being paused. A smaller proportion of patients found their physical health more difficult to manage than in our previous survey. The same number of patients (33%) in both Survey 1 and Survey 2 stated that they found their mental health more difficult to manage during the COVID-19 pandemic, compared to usual. ***Pausing shielding is not relevant because I am continuing to shield until I feel safe.*** When shielding ended in May 2021, myeloma patients, their families and friends continued to follow many shielding measures despite the lifting of restrictions. 90% of myeloma patients continued to follow some or all of the previous guidance after shielding ended with over 80% continuing to wear a facemask. After social distancing measures were relaxed in July 2021, myeloma patients continued to have a consistent approach to safeguarding themselves against COVID-19: 93% continued to wear a face mask outside of their home, in enclosed spaces and indoors; 90% continued to follow the guidance on handwashing; 84% avoided crowded places; 78% would carefully consider who they were meeting and weigh up the risks; and 78% would physically distance themselves from others. ***I am avoiding crowded places. I do have 'sensible' friends to visit and maintain social distancing.***

	We have continued to shield; it has not felt safe to stop.

Unmet need

7. Is there an unmet need for patients with this condition?	If approved for use, this will be the first treatment available to prevent COVID-19 infection. The National Clinical Expert Consensus Statement[1] outlines the strong emerging evidence that this treatment would be an effective strategy for immunocompromised individuals. We believe that this evidence supports the treatment to be part of the clinician's toolkit, in addition to vaccinations, to provide patients with the highest possible level of protection from COVID-19 infection. [1] Lee LYW, Agrawal S et al. (2022) National Clinical Expert Consensus Statement: Coronavirus monoclonal antibodies as a prophylactic therapy against COVID-19 for immunocompromised groups. Available at: https://getevusheld.uk/assets/downloads/consensusstatement.pdf

Advantages of the technology

8. What do patients or carers think are the advantages of the technology? • How would having a prophylactic treatment available impact the day-to-day lives of vulnerable people? (for example, how would it change the activities people do, or how they feel?) • How would having a prophylactic treatment available impact carers?	Vulnerable people such as myeloma patients and their carers remain highly anxious about contracting COVID-19. Myeloma patients tend to receive intensive drug treatments and/or stem cell transplants in order to control their illness and this can leave them with severely depleted immunity against infections at various stages of their treatment journey. This means that they are likely to struggle to mount an effective immune response to COVID-19, even after a full course of vaccinations. Awareness of this risk creates significant worry for patients as well as their carers and families and leads them to adapt how they live their day-to-day lives, as evidenced by the above findings of Myeloma UK's COVID-19 surveys. In this respect, access to a prophylactic treatment would be beneficial in alleviating the anxiety experienced by myeloma patients and their carers. Tixagevimab–cilgavimab provides added protection against COVID-19 and reduces the chance of vulnerable patient populations of becoming seriously ill. In AstraZeneca's PROVENT phase III trial, one dose of Evusheld granted 83% efficacy against symptomatic COVID-19 for six months in a population where 75% of trial participants had one or more risk factors for severe illness.[1] As research continues to explore the clinical efficacy of the treatment, this finding remains an important baseline for understanding the potential advantage for myeloma patients given their immunological risk. Patients and their carers believe that clinicians should have access to as broad a range of tools as possible in order to provide them with the highest level of protection against COVID-19 infection. Prophylactic treatments are perceived as an essential complement to vaccinations and antiviral treatments and provide extra reassurance to myeloma patients and their carers as they navigate life after the roll-back of social distancing measures. This is particularly the case for patients whose immunity has been severely compromised following a recent stem cell transplant or period of intensive treatment for their myeloma.

[1] Evusheld significantly protected against symptomatic COVID-19 for at least six months in PROVENT Phase III trial in high-risk populations: https://www.astrazeneca.com/media-centre/press-releases/2022/evusheld-significantly-protected-against-symptomatic-covid-19-for-at-least-six-months-in-provent-phase-iii-trial-in-high-risk-populations1.html#!

Disadvantages of the technology

9. What do patients or carers think are the disadvantages of the technology?	It is impossible to predict how the COVID-19 virus will mutate in the future, hence there remains a certain degree of uncertainty regarding how long treatment with tixagevimab–cilgavimab can be effective in protecting against infection. Patients consider this uncertainty as a potential drawback. However, they understand that this is equally the case for antiviral treatments and vaccinations and accept that it is part of the wider challenge of living with COVID-19. Overall, they do not feel that that this uncertainty justifies reticence about the addition of effective prophylactic treatments, such as tixagevimab–cilgavimab, to the clinician's toolkit for mitigating the risks of COVID-19.

Patient population

10. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	There are over 20,000 patients living with myeloma in England.[1] Clearly there are a much larger number who have been identified as clinically extremely vulnerable, with 561,630 people in England identified as severely immunosuppressed in March 2022.[2] There remain clinical uncertainties about which patients mount an immune response and further, what level of protection immune response, particularly antibodies provide. Further work and clinical input are needed to ascertain the best way to identify those most at risk based on the data we have. To identify myeloma patients that have not mounted an adequate immune response to COVID-19 vaccination would require data collection of laboratory-ascertained absent (or low) SARS-CoV-2 spike protein antibody response following vaccination. [1] Cancer Prevalence UK Data Tables (2015) National Cancer Registration and Analysis Service. Available at: http://www.ncin.org.uk/about_ncin/segmentation [2] COVID-19 vaccinations of severely immunosuppressed individuals (March 2022) NHS England. Available at: https://www.england.nhs.uk/statistics/statistical-work-areas/covid-19-vaccinations/

Equality

11. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	No

Other issues

12. Are there any other issues that you would like the committee to consider?	No

Key messages

13. In up to 5 bullet points, please summarise the key messages of your submission.	• Myeloma patients and their families and friends have been one of the most significantly affected groups during the COVID-19 pandemic, with patients at all stages of treatment being asked to shield. • Following the end of shielding and the relaxation of social distancing measures, our COVID-19 survey findings show that patients and their carers remain highly anxious and vigilant about safeguarding themselves against COVID-19 infection. • There is strong emerging evidence that tixagevimab–cilgavimab would be an effective strategy for immunocompromised individuals. • Patients consider a prophylactic treatment like tixagevimab–cilgavimab an essential complement to vaccinations and antiviral treatments. • Patients and their carers believe that clinicians should have access to as broad a range of tools as possible in order to provide them with the highest level of protection against COVID-19 infection.

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- Your response should not be longer than 10 pages.

About you

1.Your name	[redacted]
2. Name of organisation	Scleroderma and Raynaud's UK
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	SRUK's mission is to improve the lives of everyone affected by Scleroderma and Raynaud's. We do this by investing in research, improving awareness and understanding of the conditions and providing information and support to all those affected. We are the only UK based charity which serves this population. We have 9,900 members and supporters who are signed up to receive charity communications.
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] **If so, please state the name of the company, amount, and purpose of funding.**	No

4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	None
5. How did you gather information about the experiences of patients and carers to include in your submission?	At SRUK, we have close ties and a longstanding dialogue with our patient community. To gather information on the specific experiences of living with scleroderma who may benefit from Evusheld SRUK conducted a survey which was promoted via our website and social media channels. The survey was directed towards members of our community living with systemic sclerosis, the most severe form of scleroderma, who are most likely to be taking immunosuppressive medications and B cell depleting therapeutics. The survey combined a combination of check box questions, and longer form free text questions. We also engaged with our community through our local support groups.

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Systemic sclerosis (scleroderma) is an rare rheumatic autoimmune disease and is a progressive, fibrosing and life limiting condition. The effects of this condition on patients are far reaching and affect the skin along with vital organs such as the heart, lungs and kidneys. Systemic sclerosis can be grouped into two main subtypes: diffuse or limited systemic sclerosis. The diffuse form of the condition is thought to be the most severe in terms of organ involvement but complications such as interstitial lung disease (SSc-ILD) can occur in both forms of the disease. The nature of the disease along with the often-severe organ complications mean that patients are treated with immunosuppressive drugs such as high dose oral steroids, methotrexate, cyclophosphamide, and increasingly for those with ILD, the B cell depleting therapy rituximab. It is likely that for this latter category that this NICE HTA is most relevant. At present around 20% of patients with SSc-ILD receive rituximab, this is likely to increase due to emerging evidence from the DESIRE and RECITAL studies. Our patient community has suffered great fear and anxiety during the pandemic. Research has shown that people with rare autoimmune rheumatic conditions are at greater risk of COVID-19, being more than twice as likely to die from the virus or a complication related to it compared to the general population.[1] With life returning to normalcy for the majority, some of our community feel very much left behind with fear and anxiety persisting among the most severely immunosuppressed. Our survey has shown that this anxiety continues largely due to uncertainty over their risks to their already poor health from infection along with the effectiveness of the COVID-19 vaccination in our community due to their immunocompromised status: • Over 90% of respondents reported that they had received the full primary course of vaccinations and were up to date with boosters offered through the booster programme. The remainder stated that they had received the full primary course of vaccinations as a minimum. • Around 85% of those surveyed reported that a medical professional had told them that their immune system was weakened through the medications that they take to manage their scleroderma and 55% of respondents had been told by a doctor that they may not make effective responses to the COVID-19 vaccine owing to these medications.

	• Patients still exhibit an extreme level of anxiety in relation to social interactions for fear of catching COVID-19. Only a third of patients surveyed reported that they had resumed normal life, professional and social activities following the pandemic. This anxiety is not limited to patients, it also effects their loved ones whose lives are also limited by the virus. "They worry and have also limited their social activities to reduce risk to me becoming infected" "They are extra careful with their own exposure so as to lessen the risk to me!" "Nothing like a normal life has resumed for myself and my household. We still work from home and avoid any indoor contact with people as far as is possible. We used to be very social people and spent a lot of money on hospitality! This is no longer the case." "They are constantly aware of the risk to me and are unable to live a normal life because of it" "For over two years I'm living my life in constant fear that I will get infected and what the consequences will bring, my son stopped seeing his friends, and no ppl allowed to come over for visiting me, no life, and feels social anxiety." "I feel at risk, rheumatology nurse agrees. Have one daughter in secondary school (travels 1 hour there, 1 hour back on a coach) and one daughter at University - the girls worry incredibly. They both wear masks but still worry they will bring covid home and both have been subject to abuse. I caught flu December 2019 and was ill for several weeks, both girls therefore worry about covid. Their worry is something that they should not have to bear and it has affected their lives emotionally, socially etc." 1] Rutter, M. et al. (2021) COVID-19 infection, admission and death among people with rare autoimmune rheumatic disease in England: results from the RECORDER project, Rheumatology.

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	Half of those surveyed stated that they did not feel adequately protected through the NHS vaccination and booster programme and the post-exposure antiviral drugs/ antibody treatments available. Some patients justified their response through the following comments: “Following each vaccination I became unwell and still got COVID after taking all doses. Since then have had repeated respiratory infections.” “Despite shielding, then limiting contact and being up to date with boosters I caught Covid; I feel very vulnerable as my job is in a school, who want me to return full time” “Because despite 5 vaccines I have made no antibodies. I am scared of catching covid.” “Infection rates are still high and it does not feel safe to mix with people given my weakened immune system. This is getting increasingly more challenging as most other people have resumed normal activities and are not taking precautions for others.”
8. Is there an unmet need for patients with this condition?	As mentioned above, around half of those surveyed feel that the current available options (vaccination and post-exposure anti-virals) are not sufficient to manage their COVID-19 risk. This indicates that there is an ‘unmet need’ for patients with weakened immune systems (i.e. those taking strong immunosuppressant/ B cell depleting therapies) to be proactively identified and offered pre-exposure prophylactic treatments like Evusheld if effective against variants in circulation.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	Information such as the mode of administration, the number of injections per dose and the duration of effect of the therapy was provided to the participants. Based on this, 78% of those surveyed responded that they believed Evusheld could offer benefit to them. Patients who have low immune systems see the main advantages of this technology as protecting them against COVID-19 infection, reducing fear and uncertainty over how this infection will affect them given their low immune system and pre-existing health condition. They believe that a therapeutic such as Evusheld could be instrumental in restoring their (and their close families) pre-COVID-19 lives.

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	Some patients expressed concern regarding the potential severe side effects noting that they had already experienced side effects from COVID-19 vaccination. There was an awareness that all medications come with a risk of side effects, and these are likely to be rarer and less severe than the risks posed by COVID-19 infection. Patients commented that if this treatment were to be approved by NICE that they would like to receive more information through discussion with a medical professional to find out more about their potential for benefit along with their risk of side effects.

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	We believe that those who are most severely immunosuppressed are likely to benefit most from this treatment. Ideally, patients receiving immunosuppressants likely to most benefit should be identified based on the evidence from studies such as OCTAVE and OCTAVE DUO (or in the absence of robust evidence individuals who are likely to be immunocompromised and hence have low immunity to immunisation should be proactively identified through blood antibody testing).

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	None of which we are aware at present.

Other issues

13. Are there any other issues that you would like the committee to consider?	None

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• The threat of COVID-19 infection is still causing anxiety to/further limiting the lives of a subset of systemic sclerosis patients who are immunosuppressed and their families. • People living with rare autoimmune rheumatic conditions like systemic sclerosis may not generate sufficient immune responses to protect from COVID-19 infection – for these people this treatment is not an extra layer of protection it is their only protection making access to these treatments even more important! • The prospect of a new prophylactic therapy to protect those who need it most from COVID-19 along with clear guidance on access to this therapy based on pre-existing immunosuppressant usage (blood antibody titres following vaccination) would be welcome. • Side effects are the main concerns, but this could be easily alleviated with more information/ education. •

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal
Tixagevimab–cilgavimab for preventing COVID-19 [ID6136]
Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

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- Your response should not be longer than 10 pages.

About you

1.Your name	[redacted]
2. Name of organisation	Vasculitis UK
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Vasculitis UK is a registered charity supporting vasculitis patients, their families and raising awareness about the full range of vasculitis diseases among medical professionals and the general population. Vasculitis UK represents a variety of rare diseases which affect all ages and have a major impact on quality of life and survival. We collaborate with healthcare professional groups in particular UKIVAS and support original research into cause and treatment for these diseases. One important study we have supported is the MELODY study whose findings are of direct relevance to this assessment. Vasculitis UK's income comes entirely from voluntary donations from members and supporters. We run a telephone helpline and also virtual support groups on Facebook, the main group has more than 5,000 members and is very active. We have also a community in HealthUnlocked with around 7,000 members.
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] **If so, please state the name of the company,**	No

amount, and purpose of funding.	
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	Our members have been experiencing challenging times since March 2020 and while most of the population have returned to normality, our members are immunosuppressed and so concerned about exposure to the virus despite immunisation. Evusheld has been discussed in our online groups many times, and many vasculitis patients calling our helpline have enquired about it (we receive around 900 calls annually and 3,000 emails). We have formed our view from this spontaneous and loud discussion and furthermore, we posted a few open questions in our group to receive feedback from our members.

6. How has shielding from COVID-19 affected vulnerable people?	Shielding for a prolonged time since March 2020 has affected vulnerable (and in particular CEV) people physically, emotionally, and mentally. A whirlwind of emotions, fear, anger, hopelessness, bitterness, loneliness is still taking over their life. Furthermore, they feel abandoned. The biggest impact is on their mental health. Most of our members still semi-shield, many are still shielding. They feel even more isolated and socially remote now as the rest of the populations has returned to normal living. Many of them don't have any close contact with their loved ones, they haven't hugged a person since March 2020. These who try hard to reintegrate into society suffer from anxiety and panic attacks. Our members feel even more insecure about going out now as Covid-19 is just part of everyday life for most of people. However, for the vulnerable people it is more dangerous now that it is so endemic in the population and this variant is so transmissible. With all precautions taken away the risk has increased for immunocompromised patients. Most of the public don't really understand the risk to those who are CEV and patience is running out. Unfortunately, this makes vulnerable people to be extremely selective of where to go or who to meet. They are forced to isolate and try to calculate the risk of doing anything publicly. Our members are from a range of ages including many young people and people who still work – shielding is detrimental to their long-term employment prospects and many worry over the cost of living crisis. Many of our members had to reduce their physical activity to avoid the risk of getting covid-19 and that has impacted on their mobility. Going to the doctor is done by necessity and consequently their health can decline. Indeed, clinic visits may be substituted by remote consultations but this has a deleterious impact on overall clinical care for people living with vasculitis.

Unmet need

7. Is there an unmet need for patients with this condition?	Yes, there are high unmet needs. Many of the vulnerable people are left to deal with a pandemic that is still here, while the rest of the public acts like it is gone. Our members continue to follow the UK Government advice on this topic COVID-19: guidance for people whose immune system means they are at higher risk - GOV.UK (www.gov.uk) although the guidance is increasingly hard to follow since COVID is increasingly prevalent again. This means that our members are effectively house bound once again unless they take clinical risks and go to work, hospital clinics for care or even to see family and friends. Many of our members have participated in the MELODY study and their antibody test came back showing that they do not mount an immune response to vaccination even after three or four doses, and therefore remain at high risk of serious outcomes from COVID-19 infection. These people are at particular risk and are often those very same people who are of working age. This group must be identified and could form the first segment for antibody therapy. Furthermore, getting antiviral treatment after registering their positive Covid-19 lateral flow test hasn't been straightforward for many immunosuppressed patients. Many had to advocate for themselves to get them, others got them as late as the 7th day, some never got them. The stress of this in addition to their body fighting the infection is a trigger for relapse of their vasculitis. Our members report high unmet need and poor patient experience.

Advantages of the technology

8. What do patients or carers think are the advantages of the technology? • How would having a prophylactic treatment available impact the day-to-day lives of vulnerable people? (for example, how would it change the activities people do, or how they feel?) • How would having a prophylactic treatment available impact carers?	Our members are well informed around their disease, risk of COVID and response to vaccination so understand and operate risk benefit decisions every day of their lives still. We have seen the FDA, MHRA and EMA approvals of Evusheld and are bewildered by the delay until next year for decision making. Other countries have been using for some time and we see the real world evidence of benefit from studies in Europe (Nguyen et al https://doi.org/10.1016/j.cmi.2022.07.015) and Israel (Kentes et al https://doi.org/10.1093/cid/ciac625) as well as the decision by the FDA to increase the dose in response to changing virus types. Our members do not understand why UK patients are not allowed to receive despite regulatory approval. It would transform the quality of life for severely immunosuppressed people and reduce the gap between vulnerable patients and the rest of the public – this gap is widening and will widen further as winter comes. Almost all patients discussing the advantages of Evusheld say that it would give them the confidence to start living again, to meet people indoors, to go to the supermarket, to go back to work in a workplace, to go to medical appointments without fear, to use the public transport again, to have a cultural social life. They would be able to start doing all things other people are starting to take for granted again. It would provide protection to Covid 19 that their immune system does not generate from vaccines due to their immunosuppressive medication. Therefore, it would reduce their perception of risk of Covid 19 infection and significant outcome if they were to catch it. Having Evusheld would substantially lower their anxiety, fear, and uncertainty for mixing with other people. The carers' lives are affected as the patient's, sometimes the responsibility of having to keep their person safe is a very heavy burden so a medication that will decrease the risk of Covid-19 is more than welcome. Many carers have been shielding as well, asking to work for home, not having a social life as it would put their loved ones lives in risk. Evusheld would reduce the concern the families have when they go out to work, to school etc with the fear that they will bring covid back to a person they love and may result in them becoming really unwell. Here are some quotes from patients and carers: [redacted]: *'' I would be delighted to get evusheld, the normal vaccines don't work as well for me because of rituximab and I have had a very minimal antibody resp''onse even after having covid and five vaccines. I would feel happier going out to the shop some days or socialising. Too nervous to go to the cinema for example and the children being back at school makes me nervous.''*

	[redacted]: *'' If I had Evusheld it would enable-me to do my work without constant worry. At the moment I can't visit any services as the asymptotic testing of staff and service users has stopped.''* [redacted]: *'' it would give me hope and at least a little bit of protection would be so amazing.''* [redacted]: *'' I would be happy to go into coffee shops or restaurants as a special treat. I have not felt safe to do that since March 2020. I would also feel happier to go into a supermarket. The first would improve my quality of life immensely. My husband (healthy = my carer) and I have been shielding permanently since March 2020''* [redacted]*: '' If I had Evusheld then I could see more of my friends, family without being petrified for the next five days. I'm dreading the winter as I tend to spend most of my time in the house. It has seriously affected my mental health and I get incredibly anxious all the time. If I had Evusheld my husband could also live a relatively normal life.''* [redacted]: *'' EVUSHELD would allow us to undertake various activities that we don't currently enjoy, more visits to places with people - restaurants, cinemas, theatres, hotels, maybe even flights to holiday abroad. I think as carers we suffer the same as our spouses, we don't take risks as we don't want to harm them. I feel at times as though I'm on guard if we go out, and I'm scanning for risks to be avoided.''* [redacted]: '' *I would feel that I was participating fully in life and contributing.I am a social person and I feel my personality is being stilted and I will die of boredom if vasculitis or Covid doesn't get me first!''* [redacted]: *'' Evusheld would make me feel more confident about using public transport and going indoors where mask wearing is not enforced, such as the vets, dentists and other health facilities when restrictions are lifted more often than not. I do these things but not without serious consideration about whether it is worth the risk. I had to sit all day on the infusion ward when the mask mandate was lifted in*

	June and it seemed so unfair to people like me. The advantage of Evusheld is that it offers protection from COVID to people like me, who have not made a response to the existing vaccines. I am much more likely to be admitted with serious illness with COVID without it, even with antivirals.'' Anonymous: *'' With evusheld I would feel a lot more confident about where I could go and what I could do. My family would feel more confident around me at the moment I think they are confused/frustrated about what I feel I can/can't do.''* Anonymous: *'' I am living with a partner who due to medication has no antibodies despite 6 vaccines! I am much more anxious and careful than he is as I would hate to be the person who brought Covid into our home. I gave up my profession as it was in a high risk area. Receiving Evusheld would enable us to have more confidence in mixing with others.''* [redacted]: *'' Evusheld will hopefully reduce the mental stress of the thought of catching Covid… at times I feel I'm screaming inside''*

Disadvantages of the technology

9. What do patients or carers think are the disadvantages of the technology?	As with all medications our members know it won't provide 100% protection from Covid-19 and it seems additional doses will be needed to be covered long term. The biggest disadvantage vulnerable people have pointed out is people may think it is 100% effective and becoming overconfident and truly go back to normal. Good education will be needed to avoid this, and Vasculitis UK would do our part to ensure patients and carers are still assessing risk carefully. They do not see additional disadvantages from the clinical data which has been reviewed and our members assume the MHRA would keep side effects under careful review with the manufacturer.

Patient population

10. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	Vulnerable people who are highly immunosuppressed would probably benefit the most. These people have poor response to the covid-19 vaccines and are still at high risk. This includes many of our members and it is possible that those without any identified immune response to vaccination would benefit the most. We would strongly advise against any other limitations on the basis of for example age or working status.

Equality

11. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	We believe that all patients should be considered – we appreciate that some patient groups e.g., those of Asian descent and those in deprived areas have been shown to be at high risk from COVID 19 and poor outcomes. These aspects should be considered carefully by NICE bearing in mind available trial and real-world data.

Other issues

12. Are there any other issues that you would like the committee to consider?	The unfairness of leaving people behind. It is not by choice they have severe chronic illnesses and must be on such medication. Vulnerable patients are trying to do the best they can under the circumstances. It has been traumatic loosing members of our community because of Covid-19 and it hasn't stopped. Every time someone tests positive in one of our virtual groups, we all hold our breath. Vulnerable people don't want to be invisible; they want to be contributing members of the community.

Key messages

13. In up to 5 bullet points, please summarise the key messages of your submission.	• Shielding has affected vulnerable people physically, emotionally, and mentally. • A big proportion of vulnerable people are still shielding or semi-shielding. • Many immunosuppressed patients have not responded to the Covid-19 vaccination and are still in high risk. • The pandemic is not over for those who have to be extremely careful, their cares and their families. • Evusheld may not be panacea, but it will certainly improve the quality of life of the vulnerable patients. It will boost their confidence and will allow them to slowly reintegrate to the community. It will give people the chance to live a more normal life and contribute to the society.

Thank you for your time.

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Tixagevimab–cilgavimab for preventing COVID-19 [ID6136]
Professional organisation submission

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You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

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- Your response should not be longer than 13 pages.

About you

1. Your name	CLL forum committee
2. Name of organisation	UK CLL forum
3. Job title or position	
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? Yes A specialist in the treatment of people with this condition? Yes A specialist in the clinical evidence base for this condition or technology? Yes Other (please specify):
5a. Brief description of the organisation (including who funds it).	CLL support association is an umbrella organisation for CLL in the UK. Its aims were, and remain, to bring together everyone with an interest in CLL and in particular to bridge the gap between the clinical and scientific aspects of the disease. In doing so, the Forum provides an ideal framework within which the entire UK CLL community can input into issues such as guidelines, clinical trials and translational science
5b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] **If so, please state the name of manufacturer, amount, and purpose of funding.**	Astra Zeneca supported organisation of educational meetings in March 2022 and October 2021, £10,000
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

The aim of treatment for this condition

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	To prevent COVID-19 infection and the severity of COVID-19 disease
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Reduction in the rates of hospitalisation with COVID-19 or mortality from COVID-19
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes in a proportion of patients with the condition.

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	Once COVID-19 infection is confirmed access to monoclonal antibody therapy or anti-virals can be received.
9a. Are any clinical guidelines used in the	BSH CLL guidelines.

treatment of the condition, and if so, which?	
9b. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Yes. Currently patients are to notify NHS direct or 119 if they test positive for COVID-19 and access therapy via CMDU
9c. What impact would the technology have on the current pathway of care?	It may reduce the number of patients that need to access CMDU.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	There is no prophylactic medication currently available for COVID-19 in patients at risk in the UK.
10a. How does healthcare resource use differ between the technology and current care?	Prophylactic antibody would be delivered as an infusion that last months and could provide some antibody protection to patients who do not mount adequate immune responses.
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Specialist clinics – CMDU or within secondary care if capacity on day units.
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Capacity mainly - chair time and nurses to deliver the monoclonal.

11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	This is difficult to assess as no meaningful comparison is available to compare monoclonal Ab therapy at the point of testing positive for COVID-19 compared with receiving it as a prophylactic drug.
11a. Do you expect the technology to increase length of life more than current care?	As above it is unclear how prophylaxis will compare with receiving treatment at the point of testing positive. Data from real world data from EPICOVIDEHA survey, suggests reduced mortality during previous variants (https://doi.org/10.1182/blood.2022017257).
11b. Do you expect the technology to increase health-related quality of life more than current care?	Yes, patients feel isolated and vulnerable. Many continue to shield and avoid mixing. Evusheld is likely to improve this for patients (but this must be weighed up against future variants and the potential for being less cautious/ changing behaviour and increasing social mixing.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Amongst patients with CLL, those who have immunoglobulin replacement therapy, prophylactic antibiotics for recurrent infection and those with profound hypogammaglobulinaemia or taking BTKi would be the groups most likely to benefit. There are additional haematology patient groups that are likely to benefit including those who have received recent anti-CD20 therapy, those who have undergone alloSCT and CAR-T therapy or intense chemotherapy.

The use of the technology

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors	Monoclonal antibody therapies are well tolerated. Anti-viral treatments are available with similar reduction in hospitalisation rates (paxlovid) but these can be unsuitable for patients due to co-morbidities and drug interactions. Health care professional time and capacity would be need to be accounted for.

affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Patients with no antibody responses following COVID-19 could be used as a means to stratify which immunocompromised patients are eligible.
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	No
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	It may reduce mortality and allow patients to feel more confident at social mixing.
16a. Is the technology a 'step-change' in the management of the condition?	For subgroups of patients with CLL, it may be.

16b. Does the use of the technology address any particular unmet need of the patient population?	Patients feel vulnerable and 'left behind'. Providing Evusheld is likely to help with this.
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Evusheld has little side effects and is well tolerated.

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	The Provent trial shows efficacy in a vaccine naïve vulnerable population as a prophylactic therapy.
18a. If not, how could the results be extrapolated to the UK setting?	
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	Reduced hospitalisation and reduced mortality have been shown in pre-vaccinated population and with the viral variants that were present at the time of the trial.
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	n/a
18d. Are there any adverse effects that were not apparent in clinical	no

trials but have come to light subsequently?	
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	no
20. How do data on real-world experience compare with the trial data?	https://doi.org/10.1182/blood.2022017257; Young-Xu et al. https://www.medrxiv.org/content/10.1101/2022.05.28.22275716v1.full 2. Kertes et al. Clin Infect Dis 2022; https://doi.org/10.1093/cid/ciac625. Nguyen Y et al. Clin Microbiol Infect 2022 doi: 10.1016/j.cmi.2022.07.015

Equality

21a. Are there any potential equality issues that should be taken into account when considering this treatment?	No
21b. Consider whether these issues are different from issues with current care and why.	

Key messages

22. In up to 5 bullet points, please summarise the key messages of your submission.	• Evusheld could be useful for selected patients within the CLL community based on disease and patient characteristics. • Careful observation of real world data and neutralisation data would be needed. • Participants need to be aware that it is unlikely to prevent COVID-19 infection.

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- Your response should not be longer than 13 pages.

About you

1. Your name	[redacted]
2. Name of organisation	UK Renal Pharmacy Group
3. Job title or position	[redacted]
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? Yes A specialist in the treatment of people with this condition? Yes A specialist in the clinical evidence base for this condition or technology? No Other (please specify):
5a. Brief description of the organisation (including who funds it).	The Renal Pharmacy Group is a group of pharmacists and technicians with an interest in renal. We are a charity and part of the UK Kidney Association. We are sponsored by industry partners to enable a yearly conference.
5b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] **If so, please state the name of manufacturer, amount, and purpose of funding.**	AstraZeneca – RPG national conference funding for 2022 = £5000
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

The aim of treatment for this condition

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	The aim is to reduce severity of disease and prevent hospital admission in those who have not mounted an adequate response, or had no response, to vaccines and who are at highest risk of adverse COVID-19 outcomes. Many renal / transplant patients are on systemic immunosuppression which attenuates vaccine response.
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Treatment response - Reduced hospital admissions with serious COVID infection / mortality in renal / transplant patients with previous inadequate vaccine response
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes there is. For immunosuppressed renal / transplant patients who have not mounted a response to the vaccines., Many renal patients are still shielding and unable to live normal lives due to fear of catching covid and becoming severely unwell. This is impacting mental health too. Potentially this drug would allow people to stop shielding and return to normal lifestyle.

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	Vaccination is first line for prevention as the Green book (chapter 14a). The OCTAVE trial showed 40% of patients with specific immunocompromised or immunosuppressed conditions generate lower levels of antibody reactivity compared to healthy people after 2 Covid-19 vaccines. The MELODY study has looked at response to 3 or more doses of vaccine and preprint details are that many patients still do not generate antibodies. Covid-19 disease is then treated as per NICE guidance, CAS alerts

9a. Are any clinical guidelines used in the treatment of the condition, and if so, which?	NICE guidance, CAS alerts
9b. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Yes well defined, however there can be differences of opinion on when to use the treatments and treatment delivery.
9c. What impact would the technology have on the current pathway of care?	It would potentially result in fewer people being admitted to hospital and treated for severe covid as was seen following the vaccination program. Fewer patients being triaged to CMDU units.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	It could be used in the same way as vaccinations, but targeting those patients who are known to have generated lower levels of antibody reactivity
10a. How does healthcare resource use differ between the technology and current care?	At present, antibody levels are not tested routinely. In order to ascertain eligibility patients would need to be identified to have their antibody status checked, targeting patients in the cohort of specific immunocompromised or immunosuppressed conditions and those already known to have low levels of antibodies.. There would need to be agreement regards frequency of /need for antibody testing.
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	It could be administered via specialist clinics in primary or secondary care
10c. What investment is needed to introduce the technology? (For example,	Costs associated with additional antibody testing of patients in order to identify those at risk due to inadequate response to vaccines.

for facilities, equipment, or training.)	
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes this is expectation.
11a. Do you expect the technology to increase length of life more than current care?	Yes this is the expectation if the patient were to catch covid.
11b. Do you expect the technology to increase health-related quality of life more than current care?	Yes with the expectation this technology would give patients the confidence to stop shielding and thus improve their quality of life/mental health/return to work.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	More effective for patients with specific immunocompromised or immunosuppressed conditions who have generated lower levels of antibody reactivity. Would not be needed for those who have generated an antibody response to vaccines or being infected with covid-19.

The use of the technology

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant	Patients will need an antibody test and where applicable would need an IM injection possibly every 6 months. This test could be performed with other standard blood surveillance tests for their underlying renal condition / solid organ transplant.

treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	To start technology - Patients would need to be tested to see if they have low antibody levels and again before any subsequent doses.
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Benefits include – reducing severity of covid disease if contracted. Further benefits include being able to stop shielding, return to work, mental health etc.
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Yes we do
16a. Is the technology a 'step-change' in the	Yes it is

management of the condition?	
16b. Does the use of the technology address any particular unmet need of the patient population?	There is an unmet need for any patients who have not generated an antibody response to vaccines. These patients are continuing to shield as they are living in fear of contracting covid and associated morbidity/mortality.
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Reported side effects are injection site and hypersensitivity reactions, from the PROVENT study most common adverse reactions were headache 6% and fatigue 4%

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	Evusheld is not used in the UK at present. It is not available. The PROVENT study enrolled patients who had an increased risk of an inadequate response to vaccination who are the precise cohort we believe it should be available for. The licensed recommended dose is 300mg Evusheld. However, given the ever changing circulating variants of COVID-19 higher doses may be needed. Eg Omicron BA1, BA 1.1 – in vitro neutralisation data suggested 600mg Evusheld dose more efficacious. Current circulating strain as per UKHSA is BA.5 (July 2022)

18a. If not, how could the results be extrapolated to the UK setting?	N/A
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	A single 300mg dose had efficacy for the prevention of Covid-19 without evident safety concerns. However dominant circulating covid strains in the UK are now different.
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	N/A
18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Not that we are aware of.
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No as not aware it is being used in UK. Not aware of any actively recruiting trial or compassionate use. However published on the 6th October 2022:- WHO's Therapeutics and COVID-19 Living Guideline on mAbs needs to be reassessed - The Lancet. [Online reference, accessed 6/10/2022: https://doi.org/10.1016/ S0140-6736(22)01938-9] This paper found that sotrovimab, imdevimab (component of Ronapreve), and cilgavimab (component of Evusheld) neutralised omicron BA.2, BA.2.12.1, BA.4, and BA.5 and the cilgavimab (component of Evusheld), showed strong neutralisation against all omicron variants tested.

20. How do data on real-world experience compare with the trial data?	Trial data is from a time with a different circulating covid variant. There was also a paucity of immunosuppressed/immunocompromised patients entered into the trial. Both therefore suggest a likely difference to real world data

Equality

21a. Are there any potential equality issues that should be taken into account when considering this treatment?	Access to blood tests for antibodies to Covid-19 in a timely manner to identify those at most risk who would benefit from Evusheld.
21b. Consider whether these issues are different from issues with current care and why.	Current care doesn't require routine antibody testing. Current care does not provide options for patients who have not generated a response to vaccination. Current care is only vaccination and treatment of patients with progressive covid infection.

Key messages

22. In up to 5 bullet points, please summarise the key messages of your submission.	• Reduced hospital admissions with serious COVID infection / mortality in renal / transplant patients with previous inadequate vaccine response • Fewer patients being triaged to CMDU units. • Provide confidence to patients to stop shielding and thus improve their quality of life/mental health/return to work. • Standardise antibody testing of immunosuppressed/immunocompromised patients in order to identify those at risk due to inadequate response to vaccines

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

Your privacy

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Please select YES if you would like to receive information about other NICE topics - YES or NO

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal
Tixagevimab–cilgavimab for preventing COVID-19 [ID6136]
NHS organisation submission (ICBs and NHS England)

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you

1. Your name	Miranda (Mandy) Matthews
2. Name of organisation	NHS England
3. Job title or position	Medicines Lead (Specialised Commissioning)

4. Are you (please select Yes or No):	Commissioning services for an ICB or NHS England in general? Yes Commissioning services for an ICB or NHS England for the condition for which NICE is considering this technology? No Responsible for quality of service delivery in an ICB (for example, medical director, public health director, director of nursing)? No An expert in treating the condition for which NICE is considering this technology? No An expert in the clinical evidence base supporting the technology (for example, an investigator in clinical trials for the technology)? No Other (please specify):
5a. Brief description of the organisation (including who funds it).	NHS England leads the National Health Service (NHS) in England. We set the priorities and direction of the NHS and encourage and inform the national debate to improve health and care. NHS England shares out more than £100 billion in funds and holds organisations to account for spending this money effectively for patients and efficiently for the taxpayer. During the pandemic, NHS England has been a decision-making member of the RAPID C-19 collaboration and also led on the development of UK wide clinical access policies for COVID-19 therapeutics, for subsequent approval by the Chief Medical Officers.
5b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

Current treatment of the condition in the NHS

6. Are any clinical guidelines used in the treatment of the condition, and if so, which?	Vaccination is currently the primary pharmaceutical intervention for preventing COVID-19, as detailed in the Green Book (Chapter 14a). Tixagevimab–cilgavimab has been granted conditional marketing authorisation by the MHRA, for the pre-exposure prophylaxis of COVID-19 in adults who are not currently infected with SARS-CoV-2 and who have not had a known recent exposure to an individual infected with SARS-CoV-2 and: • Who are unlikely to mount an adequate immune response to COVID-19 vaccination or • For whom COVID-19 vaccination is not recommended There are no clinical guidelines currently in use for tixagevimab–cilgavimab as pre-exposure prophylaxis.
7. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	The pathway of care is not yet defined in England.
8. What impact would the technology have on the current pathway of care?	If tixagevimab–cilgavimab is recommended, and as a therapy which isn't currently used, the pathway will need defining. Impact will be dependent on various elements within the context of an evolving pandemic, including the eligible population, identification of eligible individuals, effectiveness against current and future variants, vaccination rates and the operating model for administration.

The use of the technology

9. To what extent and in which population(s) is the technology being	Tixagevimab–cilgavimab is not currently used in England.

used in your local health economy?	
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	How the technology will be used is to be determined. A process to identify appropriate patients will be required, which may include the use of digital technology. Models for administration will also need to be agreed; these may include access in primary care, for example via General Practices (GPs) and community pharmacies; secondary care; homecare providers.
10a. How does healthcare resource use differ between the technology and current care?	There will be additional resources required: • To identify eligible patients (for example, a proactive model using digital cohorting. If antibody testing is required, further resource will be required) • Administration of the therapy • Cost of the therapy
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	A variety of models may be used to administer this therapy, including primary care (via GPs and community pharmacies, specific delivery units) and secondary care. Homecare provision, with supply and administration, may also be an option.
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Investment is likely to be needed for: • Patient identification • Administration of the therapy • Cost of the therapy
10d. If there are any rules (informal or formal) for starting and stopping treatment with the technology, does this include any additional testing?	There are currently no starting or stopping rules as the treatment is not used. Testing may be required if patients require antibody testing to identify them as eligible for the therapy.
11. What is the outcome of any evaluations or	N/A

audits of the use of the technology?	

Equality

12a. Are there any potential equality issues that should be taken into account when considering this treatment?	A review of access to COVID medicines, when used to treat COVID-19, to highest risk patients in community settings has highlighted areas of potential inequality of access common to some other areas of healthcare access (including COVID vaccination). For example, access is lower than expected for those in younger or older age groups, for those in more deprived groups, and for those with black African, black Caribbean or mixed-race ethnicity. Similar issues may occur with access to prophylaxis with tixagevimab–cilgavimab.
12b. Consider whether these issues are different from issues with current care and why.	An inequalities impact assessment would need to properly consider whether these identified risks were likely to be mitigated or extended under NICE's STA recommendations, once available.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

Your privacy

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Tixagevimab–cilgavimab (Evusheld) for preventing COVID-19 [ID6136]

Clinical expert statement

Thank you for providing your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature. The External Assessment Report and stakeholder submissions are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

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In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

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Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

NICE National Institute for Health and Care Excellence

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See the NICE health technology evaluation guidance development manual (sections 5.4.1 to 5.4.10) for more information.

The deadline for your response is **5pm** on **Friday 13 January 2023.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

NICE National Institute for Health and Care Excellence

Part 1: Current options for preventing COVID-19 in high-risk groups

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	ANTONIO PAGLIUCA
2. Name of organisation	ANTHONY NOLAN & KINGS COLLEGE HOSPITAL
3. Job title or position	CHIEF MEDICAL AND SCIENTIFIC ADVISOR & PROFESSOR OF STEM CELL TRANSPLANTATION
4. Are you (please tick all that apply)	☒ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with conditions that put them at high risk of severe COVID-19? ☐ A specialist in the clinical evidence base for COVID-19 or this technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.):
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	NONE

8. What are the main aims of treatment with Evusheld?	The aim of Evusheld is to provide pre-exposure prophylaxis in individuals who are immunocompromised and have a poor response to vaccination or who cannot receive vaccination for other reasons
9. What do you consider a clinically significant treatment response?	In many studies including the Lee et al paper in JAMA Oncology, December 2022 there are significant numbers of patients, in this case cancer cases, who have no response to vaccination and the aim of Evusheld is to protect them from getting Covid 19 and the ensuing clinical issues, including hospitilisation (G&A and ITU), death and also long Covid. It would also allow patients on active therapy to continue having therapy on schedule. Patients would also be able to rejoin society as many are taking extreme precautions and have been isolating or reducing social contact for nearly 3 years.The psychological impact is significant and this treatment has shown both physical and psychological benefit.
10. In your view, is there an unmet need for patients at high risk of severe COVID-19?	There is an unmet need. In the high risk populations as defined in the McInnes report some patients have no antibody or T cell response despite full vaccination. They have been shown to have increased morbidity and mortality despite vaccination and attempted treatment once infection starts. The current anti-viral treatments are precluded in patients with liver disorders as well as patients on calcineurin inhibitors. They do not have equitable access to effective therapies and pre-exposure prophylaxis will reduce the risk for treatment
11. How are patients at high risk of severe COVID-19 currently treated in the NHS? • What are your thoughts on the care already available on the NHS for COVID-19 for high-risk groups? (e.g. vaccines and post-exposure treatments) • How do the COVID-19 treatments being offered interact with your community's disease area? Are there any contra-indications? • Are there any issues with accessing these treatments?	They have all received vaccines and boosters but in some cohorts especially haematological cancers, BMT and CART patients anything from 20-40% have no useful antibody and cellular response and these patients have increased mortality rates as shown in several US, EU and UK cohorts. Indeed in some of these cases continued viral persistence has created the risk of viral mutation in vivo with patients still positive weeks after infection. This jeopardises their treatments and is a risk to all other patients and their carers. Many patients with cancer and blood disorders cannot receive some of the viral medications due to drug interactions (Paxlovid). Molnupiravir data was in immune competent patients and therefore may not be helpful in the immunocompromised group.

	Charity data suggests that patients have had difficulty accessing treatment through the hubs with knowledge of the specific issues needing improvement. Less than 40% accessed treatment in a timely manner.
12. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	Pre exposure prophylaxis should be considered in the same light as vaccination for the immunocompromised cohort who are not able to produce an antibody response due to their disease or treatment. It provides and short and long term bridge for patients until their own immune response normalises. Immuno-suppressed patients are over-represented in ICNARC admission to ITU and despite improvements in management continue to have increased mortality and therefore preventing COVID would allow safe and effective treatment for their disease and therefore improve survival. Quality of life has been impacted for both patients and their families. Many have lost their jobs and business. Significant depression due to shielding and a sense that they have been forgotten. Evusheld will increase HR QoL.
13a. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than those who are unlikely to mount an adequate immune response to COVID-19? **13b. How could patients who would most benefit from treatment be identified? Are there any groups outside of the McInnes report that need further consideration?**	The McInnes report is very broad. It would be more appropriate to consider a targeted approach based on antibody levels in the different cohorts. There are many US,EU and UK studies showing patients below a certain Ab threshold have increased risk of hospitalisation and death. The recent Lee et al paper in Jama oncology highlights the haematological malignancies as very high risk due to inadequate vaccine response. An antibody assessment and then guided therapy would be the most appropriate management plan nationally
14. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, potential for roll out in the CMDU framework, any concomitant treatments needed, additional	CMDU's have struggled to manage the numbers of cases when there have been significant COVID surges. Evusheld is an IM injection x 2 and will require training to deliver. For some patient cohorts this would be better delivered by the local hospital facilities so that patients did not need to travel to the CMDU where there would be infected patients.

clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	In some groups concomitant therapy may need to be modified to deliver the IM injections eg warfarin, NOAC's, aspirin, platelet support etc. This would require local disease expertise and clear monitoring
15a. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing? **15b. How should Evusheld be used in clinical practice? (e.g. dosing, frequency, setting)**	The current data suggests 6 months of coverage and treatment may need to be repeated if the risk is maintained. Some US centres advocate an Ab level and if below a set threshold these patients may require Ab prior to the 6 month schedule. In highly specialised cases treatment should be done within the clinical services and will need support to deliver this. Unlikely that GP's would be able to manage the additional workload to deliver this.
16. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	This is a 6 monthly treatment allowing normalisation or equivalence for this group of patients. It would allow return to a more normal lifestyle and return to work. The societal costs are never well considered in QALY analysis. The psychological impact needs to be considered too. Furthermore the risk of Long COVID and the multisystem sequalae of COVID can be reduced eg cardiac, stroke, thrombo-embolism etc
17. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	This therapy is a step change for the immune-compromised population in the UK who have not received equitable therapy compared to their immune-competent population. The other treatments are not as effective and for some vaccine response has been poor. Pre-exposure prophylaxis provides levelling up for this immune compromised population who have effectively been forgotten and have had a much higher morbidity and mortality compared to age matched controls.

18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Side effects are immediate from receiving 2 IM injections but morbidity is considered low and treatment will improve QoL
19. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Patients in studies where Evusheld has been compared show a risk reduction in COVID – Provent study and other ODB from the US. Reduction in risk, hospitalisation, morbidity and mortality. All studies are always behind the Covid curve as the virus has been allowed to mutate at pace due to the lack of controls (ie Living with the virus). Therefore study data may not represent the current VOC environment and never will whilst virus evolution is maintained and accelerated. Real world data has shown that Evusheld is effective in the Omicron era but it remains unclear how the virus evolves.
20. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	A systematic review has been submitted to a UK journal
21. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could	There has been poor uptake of vaccine in certain communities in the UK and these patients have seen higher morbidity and mortality from COVID. Minority ethnic groups are typically poorly represented in studies and may have poor access to treatment options including Evusheld.

• exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Immunocompromised patients have poor response to vaccination
Immunocompromised patients have higher morbidity and mortality with COVID 19
Anti-viral therapy through CMDU has not been as accessible and may not be feasible due to drug interactions
The immunocompromised population feel left behind and have not been prioritised despite their high risk
Evusheld would provide the equitable levelling up for this group of at risk patients

Thank you for your time.

Your privacy

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Tixagevimab–cilgavimab (Evusheld) for preventing COVID-19 [ID6136]

Patient expert statement

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments and feedback on the key issues below are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources. The external assessment report (EAR) and stakeholder submissions are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

In part 1 we are asking you about living with, or caring for a patient with a condition that puts them at high risk of severe COVID-19.

The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

NICE National Institute for Health and Care Excellence

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Your response should not be longer than 15 pages.

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NICE National Institute for Health and Care Excellence

Part 1: Living with, or caring for a patient with a condition that puts them at high risk of severe COVID-19

Table 1 About you, the condition, current treatments and equality

1. Your name	Jill Nicholson
2. Are you (please tick all that apply)	**TICK**☐A patient at high risk of severe COVID-19? **TICK**☐A patient with experience of the treatment being evaluated? ☐ A carer of a patient with a high risk of severe COVID-19? ☐ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	Blood Cancer UK
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐No (please review all the questions and provide answers when possible) **TICK** ☐Yes, my nominating organisation has provided a submission and: **TICK**☐ I agree with it ☐ I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.):
5. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes

6. How did you gather the information included in your statement? (please tick all that apply)	**TICK**☐ I am drawing from personal experience **TICK**☐ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: I have included a couple of points in statements 7 from comments made by other Lymphoma acquaintances (if this is relevant)
7a. How has COVID-19 impacted the lives of people at high risk and their families?	One needs to comprehend and remember the fear in which WE ALL LIVED when covid was first encountered - lockdown, hospitisation, death and no vaccine. I still have that fear, it is wearing, ageing and mentally utterly draining to still assess how dangerous a situation may be. Vulnerable people are still in that isolated position. Evusheld would relieve some of those fears. These are some of the "normal" things that I CURRENTLY FEEL UNABLE TO DO, because I know that I have no Covid antibodies, and I have been told to make informed decisions and carry out the necessary risk assessments as I see them, realising that everyone else is `living with Covid`. • Visit or invite close family indoors – see below • Meet friends indoors (coffee shop or at home) • Food shop – see below • Walk in busy places (ie. the streets of my nearest town) • Clothes shop • Work, unless it is online • Visit a library, museum, further education class, exercise class, etc • Go to the Doctors without full risk assessment • Go to the Dentist without full risk assessment • Long distance hospital appointments require a full risk assessment (timings, how many people will I need to interact, toilet facilities avoiding busy service stations on a 150 miles round trip, etc) • Go to the hairdressers

	• Visit a restaurant • Go to the theatre, cinema or concert • Enter a hotel room without deep cleaning upon entry • Use of public transport • Attend parties, gatherings, get togethers, weddings or funerals • Accept car lifts from family, friends or neighbours (we live in a rural area) • Easily upgrade home interior, undertake routine maintenance work, etc without having to ask the work person to wear a mask and take care in what they touch • Holiday abroad • Look forward with happy anticipation to planning even outside social with family/friends events (we are in the Lakes – rainfall is high) From the above list the 2 most difficult and what I miss the most are people and shopping, one being an emotional difficulty and the other practical. Maintaining relationships with family/friends is challenging on a virtual platform. Meeting elderly (deaf) relations like my 85 years old parents-in-law and asking them to wear masks for a brief inside visit in their own home. Or meeting friends outside and them wearing 2 coats and bringing rugs or/and long johns. I listen to the weather forecast obsessively to double check if any opportunities may arise so that social meetings can be planned. I feel, after all this time, I am now imposing upon their good nature, and, quite frankly, even though I try to laugh things off, I am a bit of a burden and somewhat a freak. People have even stopped inviting me to things as they know I can`t/won`t come as I am no longer able to ask them to make unnecessary sacrifices. Mentally, it's incredibly draining, isolating and depressing.

	On a practical note, shopping poses numerous problems. Without doubt, online shopping has been invaluable, but it's definitely more expensive and the quality of fresh fruit and vegetables is noticeably inferior (something which is unhelpful if you want to keep your health in the best order possible) and the choice is smaller. At certain intervals I do now go shopping, either at the crack of dawn or just before the shop shuts. It's a mad trolley dash, made difficult, obviously at those times of day by hardly anything on supermarket shelves. There is no time to browse as one is constantly on edge. Buying clothing, particularly shoes, is challenging due to self-imposed time restraints in order that I don't encounter too many people. There is no pleasure in buying anything and large purchases (for the home) are deferred. Other less obvious things occur due to my situation - my husband`s colleagues ring on occasions, telling him a household member of theirs has Covid so the rota has to be changed so that he can avoid them. He still wears a mask and a lanyard plus he has screens to help. I use this example to demonstrate how many people are affected by one immuno-suppressed person. Additionally, heating and lighting costs are higher, I cannot work away from the house, I cannot go into a ` warm space` therefore more energy is consumed – double whammy. Very few people now wear masks and some people affected by lymphoma who have gone to do essential shopping, etc, have had comments made to or about them by others who don't realise their vulnerability. I have been sworn at and pointed at, even photographed, I am an adult, I should not allow these things to affect my mental health, but I am human and it is really distressing. Obviously as an individual knowing that without Evusheld I currently have no immunity at all, I have to consider self care (PPE in this case) and continually think for others to pre-empt what their movements may be. In addition to the emotional toll of diagnosis and treatment for a cancer that is little understood among the general population, many people living with lymphoma are also experiencing the stress of a constant threat to their health and recovery from a

	known cause, for which there is a solution but one which the UK government refuses to fund. Imagine, needing to leave the house for something essential, but ALWAYS having to think: is it Friday, can I leave early enough to avoid people ie 7.30 ish, is it the month end, is it the run up to Christmas, school holidays, is it a suitably wet, cold, miserable day when there are less people about, what is the current local infection rate. Obviously, the mental health of the immuno supressed is fragile and exhausted, with self hate that one does not dare to leave home at more convenient, pleasant times of the day/week. This is leading to the expression of additional feelings of abandonment and worthlessness (very much along the lines that those in care homes felt during the height of the pandemic - that they were expendable) by many in our support meetings. If good mental health and a positive outlook are important factors in good recovery from cancer, the conditions under which many people with lymphoma are existing (many would not describe it as 'living' because of the continued threat of Covid for them) are having a deleterious effect. Of course, for many people, lymphoma is a chronic form of cancer from which they do not make a full remission. Instead, they are living with cancer for the rest of their lives, never knowing when they might need treatment or further treatment, or whether or not that line of treatment would be successful. That is a chronic stressor, which so many find very difficult to live with. They see no end to the threat from Covid, every time they venture out, they could contract an infection that could hasten the end of their life. As a result, many weigh every social interaction carefully, taking various precautions, including drastically limiting contact with family and friends, let alone the wider population. This compounds their isolation and makes an already difficult life miserable. People who are in employment may be staying away from work for longer and, in some cases, are not getting the support needed from employers, bring additional stress, including the fear of losing their job altogether.

8a. What do you think of the current treatments and care available for COVID-19 on the NHS? (e.g. vaccines and post-exposure treatments) **8b. How do the COVID-19 treatments being offered interact with your community's disease area? Are there any contra-indications?** **8c. Are there any issues in accessing these treatments?** **If there are disadvantages for patients of current NHS treatments for people at high risk of severe COVID-19 please describe these**	I have had 6 Covid vaccinations in 21 months as recommended by the Government, this being the answer to "returning to normal". However, I am fully aware that none of these have worked. Others in a similar situation to myself have either not responded or have had little response to the multiple Covid vaccinations they have been given. Obvious worsening of mental health and quality of life is connected to this. Fortunately I am passed these stages, but those that are having treatment need to wait until after it has finished before vaccination would have any effect at all. Those on maintenance therapy have to time vaccinations to the mid-point between bi-monthly infusions, if they are to have any hope of being effective; some people have had their maintenance therapy curtailed so they can have the vaccinations or to reduce their immediate vulnerability, which could mean their lymphoma relapses more quickly than it otherwise would. Covid vaccinations have little effect on transmission, so having the rest of the population vaccinated doesn't really reduce our risk. Additionally, being a cell transplant patient, I was fortunate enough to be offered the services of a NHS clinical phycologist – we both agree that these costly and time consuming sessions for the professional would have ended in summer 2020 had a suitable vaccine been offered to people like myself. Antivirals should be an excellent backstop if I were unfortunate to catch Covid, but recent press has advised that 2 of those antivirals have minimal efficacy (WHO). I am also unaware on how the current Postal strike would affect obtaining these, or how they would be obtained and administered should an immuno-suppressed person decide to go abroad. Reports have also led me to believe that some people who are eligible for antivirals have not been able to procure them when needed. Paxlovid has contra indications for many types of chemotherapy, forcing patients to make the agonising decision between Covid and cancer treatment.
9a. If there are advantages of Evusheld over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability	Covid vaccinations – 0% protection for me and plenty of others (are we using the same formula given to me in Jan '21 with that given in Oct '22?). Antivirals – success rate unknown to me on a personal level. As mentioned previously, two have minimal efficacy.

to continue work, education, self-care, and care for others? **9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?** **9c. Does Evusheld help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these**	Evusheld – up to 80% efficacy against 50% of the current Covid variants Evusheld would give me more confidence to have a more “normal” life and do most, but not all, of the listed activities mentioned in Section 7. It would not allow me to do everything exactly the same as I did prior to Covid, I would still need to evaluate the situation, but it would result in a more meaningful life in which to live, a better quality of life. For example, we are a one car family living in a rural area and to look after myself I pick up monthly prescription from the chemist. If my husband has our car for work I cannot accept a lift with neighbours, jump on a bus, etc., therefore, whilst I am not disabled, I do have mobility issues with just getting from `a to b`. Additionally, I have to consider the timing of the visit, this again takes its toll mentally as everything has to be over thought. Any protection is better than none at all
10. If there are disadvantages of Evusheld over current treatments on the NHS please describe these. For example, are there any risks with Evusheld? If you are concerned about any potential side effects you have heard about, please describe them and explain why	I have spoken with a several consultants in various hospitals, Blood Cancer and Lymphoma Action since Evusheld was authorised by MHRA in March 2022 and no one has advised me of any disadvantages of Evusheld.
11a. Are there any groups of patients who might benefit more from Evusheld or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments **11b. How could the patients who would most benefit from Evusheld be identified?**	The most vulnerable to definitely receive would be:-. non solid cancers eg blood and lymph haematological diseases and recipients of haematological stem cell transplant (HSCT) renal conditions liver conditions immune-mediated inflammatory diseases (IMIDs) primary and acquired immune deficiencies

	Thereafter, if affordability allowed, on a secondary level, visually impaired people, the elderly and maybe even people in care homes may eventually benefit from Evusheld. All identified from the list that was provided to the Government when it was decided who should receive the first vaccination. GPs/consultants could also nominate certain cohorts. Initially experts have suggested only a relatively small number of patients (10000) would be vaccinated.
12. Are there any potential equality issues that should be taken into account when considering people at high risk of severe COVID-19 and Evusheld? Please explain if you think any groups of people with this condition are particularly disadvantaged Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	Whilst I have no direct experience, I have been led to believe by the media and my own limited web research that certain demographic groups have not undertaken the Covid 19 vaccinations as they consider the product not to be safe, religious reasons, effect on fertility, etc. Therefore, my concern would be that they possibly would not actively procure other alternative treatments such as Evusheld?
13. Are there any other issues that you would like the committee to consider?	Evusheld, I realise will not solve all these problems and I am completely aware it cannot work against all the new variants and strains any more than the regular mainstream vaccines that we are all encouraged to take. However, after 6 vaccinations knowing (thru testing) that I have no immunity, something like Evusheld that gives some immunity would stop me wandering around like a ticking time bomb. Any immuno-suppressed person would not behave wrecklessly after being given Evusheld, having been cautious after all these months. I am also fully

	aware that the longevity of Evusheld is not infinite, the exact same as the existing Covid vaccinations that have been encouraged to be taken by the rest of the nation. However, the possibility of the opportunity to have a more fulfilling, mentally, physically, emotionally and balanced life, whilst still using some caution, is too large to adequately convey. It is beyond my comprehension that a stretched NHS may have to provide a bed for somebody in the immuno-suppressed community, which must cost more than Evusheld. Again, fear and frustration ride high with the `get jabbed` message just rubbing salt in the wounds (due to, in my case, inefficacy) and the Government requesting my age group to return to work (impossible at present). Additionally, I am now aware that 2 anti virals are less effective than first considered. This alone is yet another psychological hurdle to overcome. It has been a fight and a triumph to still be alive and have a life, I realise with all my treatment my life expectancy will have lessened, therefore it is utterly cruel not to permit people like me live a more fulfilled better quality of life, being part of and contributing to society and to see the people I love knowing that that love is reciprocated.

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- There is a specifically designed alternative treatment for this group which has a better efficacy than the recommended vaccines that are used worldwide and is available to the UK to ease the continual mental and emotional strain on the immuno-suppressed and their immediate friends and family.
- With the current situation, it is hard to see any light at the end of this increasing 2 years 10 months tunnel of living in fear after having any other human interaction.
- Under Article 2, `the right to life`, surely the lack of accessibility of Evusheld is discriminatory, at the very least, and cruel to leave this vulnerable part of society so abandoned when we are your contemporaries, trying to balance life, work, pay bills and even occasionally have the opportunity to enjoy life,
- The usual formula adopted by NICE cannot in this instance be used when there are hourly reports of a `stretched NHS` and that prevention should always be better than cure, utilising a proactive approach ultimately saving the NHS, lives and money.
- If I were a person of colour, non hetrosexual or mentally/physically impaired, the lack of availability of Evusheld would be labelled as discrimatory, the abandonment and isolation of the immuno supressed could thus be significantly reduced by permitting us some form of immunity.

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Single Technology Appraisal

Tixagevimab–cilgavimab (Evusheld) for preventing COVID-19 [ID6136]

Patient expert statement

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments and feedback on the key issues below are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources. The external assessment report (EAR) and stakeholder submissions are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

In part 1 we are asking you about living with, or caring for a patient with a condition that puts them at high risk of severe COVID-19.

The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

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We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Your response should not be longer than 15 pages.

The deadline for your response is **5pm** on **<insert deadline>.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

NICE National Institute for Health and Care Excellence

Part 1: Living with, or caring for a patient with a condition that puts them at high risk of severe COVID-19

Table 1 About you, the condition, current treatments and equality

1. Your name	Stephen Jones
2. Are you (please tick all that apply)	☒ A patient at high risk of severe COVID-19? ☒ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with a high risk of severe COVID-19? ☒ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	Action for Pulmonary Fibrosis
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☒ Yes, my nominating organisation has provided a submission and: ☒ I agree with it ☐ I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.):
5. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes

6. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience ☒ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: **I am in frequent contact with immune suppressed patients living with pulmonary fibrosis. Additionally, for the purposes of this submission, I talked to immune-suppressed people living with other diseases, including blood cancer and kidney failure.**
7a. How has COVID-19 impacted the lives of people at high risk and their families?	COVID-19 has had a profound impact on the lives of people at high risk and their families. For the first 15 months, we shielded along with everyone else but when Boris Johnson relaxed national safeguards and declared 'Freedom Day' for the country in July 2021, the 500,000 people who were immune suppressed in the UK had to remain locked down and become even more vigilant. By removing safety measures like mask wearing in public places, the government had increased the risk of us catching COVID-19. Shielding has seriously affected the quality of life and psychological well-being of the hundreds of thousands of immune-suppressed people. We live in constant fear of catching COVID-19 and have to isolate from friends and families. This together with the need for constant vigilance, can cause anxiety and other mental health issues. Many of us have also had to give up work and volunteering outside the home, which heightens our feeling of isolation and reduces the contribution we make to society. There are many heart-breaking cases I could have presented. Here are two: ***Man in his 40's with lymphoma*** *I was diagnosed with Mantle Cell Lymphoma, an incurable blood cancer, in March 2021. Despite having a life expectancy of only 5-10 years I recovered well from*

	chemotherapy and an Autologous Stem Cell Transplant in 2022 and, am currently fit and otherwise healthy. However, because I have Rituximab injections every 8 weeks, I am immunocompromised and have to shield because I have no protection from Covid. *This has had serious impacts on our family. Since, I cannot mix with others, I have not been able to work for 2 years which means we are living on savings meant for our pension. I am also unable to mix with family and friends, which is exactly what you want to do when you have had such a shocking prognosis. This is beyond cruel, not just for me, but also the other members of our family, as they want to also make the most of the limited time we have left together.* *My daughter has also had to move into student accommodation in Sheffield, so we see her very little. She was planning to commute, but that would be too risky for me. When we do see her, she has to isolate for a few days before coming and then test and wear a mask when she is in the house.* *I am up to date with my vaccinations and paid privately to have Evusheld. As a result, we were able to have a great family Christmas, whilst still being careful. We know Evusheld is not 100% effective, but it gives us that extra confidence to begin to get our lives back to 'normal'. In my view, Evusheld should be available on the NHS to ALL immune suppressed people in the UK, as is the case in other western countries.* ***Man in his 40s with sarcoidosis*** *I have been shielding since March 2020 because I have fibrotic sarcoidosis of the lung and take immune suppressants. Since I cannot go outside the house and mix with other people, I have had to shut down my successful business and lay off 3 full time staff. Shutting down the business has had a severe impact on family income.* *I am married with 3 children, 2 living at home. Since they each have to get on with their lives, I move into the summer house in the garden, whenever the COVID-19*

	risk is high. In total, I have spent 9 months living away from my family when children at school are 'pinged' as covid contacts or the prevalence of the disease is high in our area. *Although the family agrees on this strategy, it places a heavy burden of guilt on my wife and children. They don't want to see me isolated away from the family but, feel guilty because they may bring COVID-19 into house and risking my health.* *The impact of COVID-19 and shielding on my family's mental health has been marked and has strained relationships in the family. One of my children is undergoing counselling and on medication. She is suffering from anxiety, which has severely affected her education, and has limited her options for further education. I have been unable to hold our eldest child for nearly 3 years. We seem to be constantly assessing risks, which itself causes anxiety for the whole family.* *I have recently paid for Evusheld and am beginning to mix more with others, while still being very cautious. But it's going to take a lot to repair the damage shielding has done to our family.*
8a. What do you think of the current treatments and care available for COVID-19 on the NHS? (e.g. vaccines and post-exposure treatments) **8b. How do the COVID-19 treatments being offered interact with your community's disease area? Are there any contra-indications?** **8c. Are there any issues in accessing these treatments?**	The vaccination programme is good. Although immune-suppressed people may not benefit directly from vaccinations, the government programme reduces the number of people in society catching COVID-19 and reduces the severity of the disease for them. For immune-suppressed people, the lower the levels of COVID-19 circulating in the community, the better for us because it reduces our chance of catching the disease. The COVID-19 treatments, which have been offered to lung transplant and pulmonary fibrosis patients since December 2021 have been helpful. Some immune suppressed people, while still being extremely careful (e.g., wearing masks, asking friends to do lateral flow tests, social distancing), have taken the risk and attended important events such as funerals and weddings.

If there are disadvantages for patients of current NHS treatments for people at high risk of severe COVID-19 please describe these	In general, the NHS has made treatments available in a timely way. I know of 12 immune suppressed people who caught COVID-19, including myself. All received treatment with 72 hours of reporting their positive test and none required hospitalisation. This said, our community is very concerned about NICE's proposed Consultation Paper for COVID-19 treatments, which would limit the treatments available and mean some patients are denied treatment, because the only ones available are contra-indicated for them. See Action for Pulmonary Fibrosis' submission on ID4038.
9a. If there are advantages of Evusheld over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? **9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?** **9c. Does Evusheld help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these**	Evusheld is a prophylactic treatment designed to stop immune-suppressed people catching COVID-19. Since COVID-19 vaccines do not provide adequate protection for immune suppressed people, Evusheld would reduce the risk of catching COVID and make it possible for us cautiously to restart our lives, after shielding for nearly three years. A few immune suppressed people who could afford it, including me, have paid for Evusheld at a cost of over £2,000 each. We are aware that the effectiveness of the treatment is probably now below 50%, due to the rise of new COVID-19 variants. Nevertheless, when you are told vaccinations do not work for you, Evusheld offers a possible game-changer. When combined with other measures (for example wearing FFP2 masks, asking friends and colleagues to do lateral flow tests before meeting you, maintain social distancing and avoiding public transport, where possible), Evusheld would be an important way of helping us re-establish our normal lives. Although I manged to maintain my physical fitness over the last three years, I suffered from periods of low mood (something I had not known prior to the pandemic). I saw very little of family and friends and could not continue many of my earlier hobbies. Since receiving Evusheld, I have started to hold face-to-face professional meetings again, have been inside a few pubs and restaurants, for the first time in three years, and have had many face-to-face gatherings with family and grandchildren. I have been cautious in the ways outlined above but Evusheld has given me the

	confidence to start getting back to normal. This winter is immeasurably better than the last (2021-22). The importance of Evusheld to immune suppressed people was recognised by all other G7 governments, who made the drug available within a few months of approval by their regulator. Disappointingly, after MHRA approval in early 2022, the UK government decided further lab tests were needed followed by this lengthy NICE TA. The immune-suppressed community cannot understand why the government did not use an accelerated appraisal process, more suited to an urgent COVID-19 medicine? The UK government's decision not to institute a more rapid process made the immune suppressed community angry. Had the government made Evusheld available soon after MHRA approval, immune-suppressed people would have been able to take steps to re-establish a normal life starting in early summer 2022. The government missed the opportunity to reduce the isolation and physical and mental health problems of the immune suppressed community.
10. If there are disadvantages of Evusheld over current treatments on the NHS please describe these. For example, are there any risks with Evusheld? If you are concerned about any potential side effects you have heard about, please describe them and explain why	No
11a. Are there any groups of patients who might benefit more from Evusheld or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	Evusheld would benefit all immune suppressed people.

11b. How could the patients who would most benefit from Evusheld be identified?	
12. Are there any potential equality issues that should be taken into account when considering people at high risk of severe COVID-19 and Evusheld? Please explain if you think any groups of people with this condition are particularly disadvantaged Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	The over-riding equality issue is that immune-suppressed patients and their families still have to lead highly restricted lives, while the majority of the population are leading normal lives.
13. Are there any other issues that you would like the committee to consider?	No

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Most immune-suppressed people are still shielding nearly three years after the start of Covid-19, with determinantal impacts on their mental health and adverse impact on family incomes.
- Immune-suppressed patients are desperate for an effective prophylactic therapy, which will reduce the chance them catching covid in the first place. Evusheld linked to lateral flow testing and other measures (for example masking, social distancing) would make it possible for immune-suppressed people to cautiously restart their lives.
- Evusheld is available in over 30 other countries, including all G7 countries. Why nor in the UK?
- The high demand for Evusheld by IS patients can be seen in the increasing numbers of people, who can afford it, obtaining the therapy privately.
- Evusheld should be made available to ALL IS patients, not just those able to pay for it privately.

Thank you for your time.

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NHS England comment on the NICE Single Technology Appraisal of Tixagevimab-cilgavimab (Evusheld) for preventing COVID-19 [ID6136]

1. NHS England (NHSE) recognises that there are a large group of people who are at high risk of an adverse COVID outcome if they become infected with the SARS-CoV-2 virus, either because they cannot have a COVID-19 vaccine or have known or anticipated failure of response to COVID-19 vaccination.

2. The COVID-19 neutralising monoclonal antibody combination, tixagevimab and cilgavimab (Evusheld) is indicated for the pre-exposure prophylaxis of COVID-19 in adults who are not currently infected with SARS-CoV-2 and who have not had a known recent exposure to an individual infected with SARS-CoV-2 and: who are unlikely to mount an adequate immune response to COVID-19 vaccination, or for whom COVID-19 vaccination is not recommended

3. The authorization for this monoclonal antibody combination was based on data from a randomized trial (PROVENT) of over 5000 adults, aged 18 years or older who had not received COVID-19 vaccination and had no history of prior SARS-CoV-2 infection using a lower dose (300mg of Evusheld) than in the Company Submission.

4. Whilst positive benefits were seen in terms of reduction in symptomatic infection and other outcomes, the PROVENT trial was carried out when the circulating SARS-Cov-2 variants were Alpha, Beta, Delta, and Epsilon.

5. The generalisability of the results from PROVENT to the current, and future, UK scenario is therefore questionable, as the Omicron sub-variant of COVID-19 is the dominant lineage in the UK, and there is increasing concern and evidence that Evusheld is ineffective against Omicron sub-lineages such as BA.2.75.2, BQ.1/BQ.1.1 and XBB/XBB.1/XBB.1.5

6. NHSE notes that this is highly relevant as “Since the end of June 2022, most COVID-19 infections in the UK have been Omicron variant BA.5 or its sub-lineages. One of these BA.5 sub-lineages, BQ.1, has been increasing in recent months. In the week ending 18 December 2022, BQ.1 comprised 56.2%, and other BA.5 variants (and sub-lineages, excluding BQ.1) comprised 12.3% of all sequenced COVID-19 infections. The variant BA.2.75 and its sub-lineages (that include XBB and its sub-lineages, and CH.1.1 and its sub-lineages) comprised 29.7%, with the sub-lineage CH.1.1 and its sub-lineages comprising 11.3%, and the sub-lineage XBB and its sub-lineages comprising 9.3% of sequenced infections in the week ending 18 December 2022. In the same week, BA.4 and its sub-lineages comprised 1.0% of sequenced infections” [source: Coronavirus (COVID-19) Infection Survey, Office for National Statistics, UK: 6 January 2023]

7. NHSE notes that whilst the Company Submission includes evidence of Evusheld effectiveness against Omicron subvariants, these data are not fully generalisable to the currently circulating Omicron subvariants in the UK

8. NHSE notes that the EAG has explored this uncertainty by reducing the relative risk reduction for Evusheld from 66% to 30% (lower effectiveness) resulting in a higher ICER for the corrected company's base case. However even a relative risk reduction of 30% may be optimistic and the impact on the ICER of relative risk reductions less than 30% should be calculated

9. NHSE also notes that the Company Submission states that many immunocompromised people are taking extra precautions to protect themselves from SARS-CoV-2 infection. There is therefore a potential that these people may be reassured by Evusheld treatment, but not protected and remove these precautions, resulting in a higher risk of poor COVID-19 outcomes

10. In summary whilst there is a very high unmet need in this group of people, Evusheld does not appear to be effective against currently circulating SARS-CoV-2 variants, which makes the cost-effectiveness analyses and ICERs highly uncertain

Dr Sanjeev Patel
Consultant Rheumatologist
NHS England Clinical Advisor (Non-oncology)
13th January 2023

NICE National Institute for Health and Care Excellence

NHS commissioning expert statement

Tixagevimab–cilgavimab (Evusheld) for preventing COVID-19 [ID6136]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1. Your name	**Mohammed Asghar**
2. Name of organisation	**Frimley Health and Care ICS**

3. Job title or position	**Associate Director of Pharmacy: Medicines Optimisation**
4. Are you (please tick all that apply):	☐ √ commissioning services for an ICB or NHS England in general? ☐ √ commissioning services for an ICB or NHS England for the condition for which NICE is considering this technology? ☐ responsible for quality of service delivery in an ICB (for example, medical director, public health director, director of nursing)? ☐ √ an expert in treating the condition for which NICE is considering this technology? ☐ an expert in the clinical evidence base supporting the technology (for example, an investigator in clinical trials for the technology)? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ √ other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation submission and/ or do not have anything to add, tick	☐ √ yes

here. (If you tick this box, the rest of this form will be deleted after submission.)	
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**
Current treatment of the condition in the NHS	
8. Are any clinical guidelines used in the treatment of people at high risk of severe COVID-19, and if so, which?	Yes currently follow national commissioning policies for different patient cohorts
9. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your	Pathways are largely well defined but do have questions around elligibility for some groups of immunosuppressed patients, also in instances of patients not being appropriate to receive 1st,2nd and 3rd line options again there is some occasional ambiguity in clinicians minds around when to employ the use of nMAB therapy

experience is from outside England.)	
10. What impact would the technology have on the current pathway of care?	Would result in a significant cohort of high risk patients no longer needing treatment post exposure to Covid19
The use of the technology	
11. How will the technology be used in NHS clinical practice?	
• How is healthcare resource use expected to differ between the technology and current care?	Will allow for more planned management for eligible patients as opposed to the time sensitive post exposure management that is undertaken for highest risk patients currently. Would allow significant scaling back of CMDU services
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Would suggest this is deployed in primary care, GPs should already be aware of the highest risk patients within their practices and as the technology involves IM as opposed to IV administration should be something that is manageable at practice level. Appreciate there will be questions raised about workload and resource to do this.
• What investment is needed to introduce the technology? (For	Need to ensure data on vulnerable patients is accurate and easily available down to practice level. May need some work between NHS Digital and GP clinical systems to support this.

example, for facilities, equipment, or training.)	
• If there are any rules (informal or formal) for starting and stopping treatment with the technology, does this include any additional testing?	
Equality	
12a. Are there any potential equality issues that should be taken into account when considering this treatment?	Throughout pandemic have seen disparities in uptake of therapies with minority groups encountering greater morbidity/mortality and also lesser uptake of Vaccination and of CMDU services. Need to ensure that the potential for this occurring with this new intervention is recognised and active actions taken to ensure widespread uptake by all demographics within the highest risk cohort.
12b. Consider whether these issues are different from issues with current care and why.	This may be somewhat easier in comparison to CMDU services if the technology is deployed at GP practice level, could possibly result in greater trust and therefore uptake of the service but this is largely conjecture.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

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Tixagevimab–cilgavimab for preventing COVID-19: A Single Technology Appraisal

Produced by School of Health and Related Research (ScHARR), The University of Sheffield

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Declared competing interests of the authors

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Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

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Contributions of authors

Sarah Davis and Andrew Metry critiqued the health economic analysis submitted by the company. Abdullah Pandor summarised and critiqued the clinical effectiveness data reported within the company's submission. Rebecca Harvey critiqued the statistical aspects of the submission. Ruth Wong critiqued the company's search strategy. All authors were involved in drafting and commenting on the final report.

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Abbreviations

Adverse events	Adverse events
AIDS	Acquired immune deficiency syndrome
CEAC	Cost-Effectiveness Acceptability Curve
CI	Confidence Interval
CMDU	COVID Medicine Delivery Unit
CS	Company Submission
DHSC	Department of Health and Social Care
DiD	Difference-in-difference
EAG	External assessment group
EMA	European Medicines Agency
EQ-5D-3L	EuroQol 5 dimensions 3 level
EQ-5D-5L	EuroQol 5 dimensions 5 level
EAG	External Assessment Group
FDA	Food and Drug Administration
HIV	Human immunodeficiency virus
HR	Hazard Ratio
HRG	Healthcare resource group
HRQoL	Health-Related Quality of Life
IC50	Half-maximal inhibitory concentration
ICER	Incremental Cost-Effectiveness Ratio
ICU	Intensive care unit
IFR	Infection fatality rate
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
LYs	Life-years
MHRA	Medicines and Healthcare products Regulatory Agency
MHS	Maccabi HealthCare Services
MTA	Multiple Technology Appraisal
IMV	Invasive mechanical ventilation
NG188	The NICE COVID-19 rapid guideline on managing the long-term effects of COVID-19
NHS EED	National Health Service Economic Evaluation Database
NICE	National Institute for Health and Care Excellence
NIV	Non-invasive ventilation
nMAB	Neutralising monoclonal antibodies

NR	Not Reported
ONS	Office for National Statistics
OR	Odds ratio
PAS	Patient Access Scheme
PCR	Polymerase-chain-reaction
PEER	Prior event rate ratio
PH	Proportional Hazards
PIN	Primary Immunodeficiency Network
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALY	Quality-Adjusted Life Year
RCT	Randomised Controlled Trial
RT-PCR	Reverse-transcriptase-polymerase-chain-reaction
RWE	Real-world evidence
ScHARR	School of Health and Related Research
SLR	Systematic Literature Review
SMD	Standardised mean difference
SMS	Short Message Service
SoC	Standard of care
VA	Veteran Affairs
WHO	World Health Organization
WTP	Willingness-to-pay

1. EXECUTIVE SUMMARY

This summary provides a brief overview of the key issues identified by the external assessment group (EAG) as being potentially important for decision making. It also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Sections 1.3 to 1.6 explain the key issues in more detail. Background information on the condition, technology and evidence and information on non-key issues are in the main EAG report.

All issues identified represent the EAG's view, not the opinion of NICE.

1.1 Overview of the EAG's key issues

Key issues identified by the EAG that impact on the incremental costs and quality-adjusted life years (QALYs) for tixagevimab and cilgavimab (referred to in this report as Evusheld) compared to standard of care (SoC) in the absence of pre-exposure prophylaxis for COVID-19 are summarised in **Table 1**

Table 1: Overview of the EAG's key issues

ID	Summary of issues	Report section
Issue 1	The company's economic analysis assumes two doses of Evusheld are administered 6 months apart but the Summary of Product Characteristics (SPC) for Evusheld states that there are no safety or efficacy data available for repeat dosing with Evusheld.	2.3.2 & 4.3.4.1
Issue 2	The PROVENT randomised controlled trial (RCT) was conducted using a lower dose, in an unvaccinated population and prior to the emergence of the Omicron variants.	3.8.2 & 4.4.2.13
Issue 3	The clinical effectiveness review described in the company submission (CS) excluded some studies which recruited specific subgroups of patients such as solid organ transplant recipients	3.2 & 4.3.4.3
Issue 4	The company's economic analysis uses historical risks for COVID-19 that may not reflect the risk of COVID-19 in the year after guidance on Evusheld is published.	4.2.6.3, 4.3.4.5 & 4.4.2.14
Issue 5	There were errors identified in the company's adjustments to incorporate the impact of post year one cases of COVID-19.	4.2.6.20, 4.3.4.18 & 4.4.2.1
Issue 6	The company has applied a direct utility gain, which aims to reflect the impact of Evusheld on continued shielding behaviours, to all patients receiving Evusheld and not only to those patients continuing to follow shielding advice.	4.2.6.7, 4.3.4.4, 4.4.2.2 & 4.4.2.3
Issue 7	There is uncertainty in the risk of long COVID for patients with COVID-19 who do not require hospitalisation	4.2.6.16, 4.3.4.13 & 4.4.2.4

Issue 8	The EAG believes that the costs of administering Evusheld to the large eligible cohort have not been properly estimated.	4.2.6.2, 4.3.4.2 & 4.4.2.5
Issue 9	The company's estimate of the duration of long COVID does not reflect the most recent Office for National Statistics (ONS) data and assumes a longer duration for patients having COVID-19 that did not require hospitalisation that those that did require hospitalisation.	4.2.6.17, 4.3.4.14 & 4.4.2.6
Issue 10	The company's estimate of the cost of long COVID is not evidence-based and has been taken from an exploratory analysis conducted by ScHARR for the Multiple Technology Appraisal (MTA) of COVID-19 therapeutics rather than the value used in the ScHARR COVID-19 MTA base case.	4.2.6.19, 4.3.4.16 & 4.4.2.7
Issue 11	The EAG does not agree with the method used by the company to estimate the utility decrements for long COVID from the PHOS-COVID cohort study or the fact that they are assumed to be constant for the duration of long COVID.	4.2.6.18, 4.3.4.15 & 4.4.2.8
Issue 12	The risk of hospitalisation for COVID-19 applied in the company's model does not reflect the fact that the risk of hospitalisation is lower for infections occurring when Omicron was the dominant variant and vaccination levels were higher.	4.2.6.4, 4.3.4.6 & 4.4.2.9
Issue 13	The company's analysis does allow for patients having COVID-19 infections in the second year and beyond to experience long COVID.	4.2.6.20, 4.3.4.18 & 4.4.4.12
Issue 14	The company's economic analysis assumes a constant treatment effect across 6 months following each dose based on an estimate obtained from a study with a maximum follow-up of 4 months.	2.3.2, 3.3.2.1, 4.3.4.1 & 4.4.2.13
Issue 15	The target population for Evusheld is likely to be heterogeneous in terms of their age and the impact of their comorbidities on life expectancy and health-related quality of life (HRQoL) and this may impact the ICER estimates.	4.2.6.1 & 4.3.4.3, 4.4.2.13

The key differences between the company's preferred assumptions and the EAG's preferred assumptions are as follows:

- The EAG has corrected several errors in the company's modelling of post year one cases of COVID-19.

- The EAG has applied the direct utility gain attributable to Evusheld only to the proportion of patients who are continuing to follow shielding advice (13%), whereas the company's base case applies it to 100% of the population receiving Evusheld.

- The EAG has applied the direct utility gain for 1 year in those who do not have COVID-19 in the year after receiving Evusheld and for 6 months in those having COVID-19, whereas the company has applied it for one year in all patients surviving the first year.

- The EAG has applied a lower risk of long COVID in non-hospitalised patients (12.7% versus 34.8%) using data from a study that accounted for the prevalence of long COVID symptoms in people not reporting COVID-19.

- The EAG has assumed that the administration costs for Evusheld will be similar to those required for administration of COVID-19 therapeutics in COVID Medicine Delivery Units (CMDUs), whilst the company applies only the cost for 30 minutes of GP Practice Nurse time.

- The EAG has used alternative estimates for the rate of recovery for patients experiencing long COVID using the latest data from the ONS without any calibration or adjustment, whereas the company used the estimates from the ScHARR COVID-19 MTA model which were based on an earlier ONS data release, which they then calibrated against data from the PHOSP-COVID cohort (Evans 2022).

- The EAG has applied the cost of chronic fatigue which was used in the ScHARR MTA COVID-19 model as a proxy for long COVID, whereas the company has applied a higher cost used in the MTA model only for an exploratory analysis.

- The EAG has adjusted the utility values applied for long COVID taken from the PHOSP-COVID UK cohort (Evans 2022), so that they reflect the weighted average across patients stating either that they were not recovered or that they were unsure if they were recovered. This was to reflect the fact that half of the 'unsure' group were considered in the company's model to have ongoing long COVID, but the company used only the utility estimates from those stating they had not recovered.

- The EAG assumed that the utility decrements for long COVID linearly decline over 5 years to 50% of their starting value, whereas the company's base case assumed a constant utility decrement for the duration of long COVID.

- The EAG has applied a lower estimate for the risk of hospitalisation in immunocompromised patients (15.9% versus 18%, both from Shields 2022) to reflect the reduced risk of hospitalisation for patients infected when the Omicron variant was dominant, and vaccination levels were higher, compared with those infected during earlier waves, whilst excluding the impact of COVID-19 therapeutics.

- The EAG incorporated newly available COVID-19 specific reference costs when estimating the costs of hospitalisation for COVID-19, whereas the company applied estimates from an earlier set of reference costs in which no COVID-19 specific costs were available.

- The EAG assumed that the data on the proportion of patients requiring different types of hospital care (e.g., proportion requiring mechanical ventilation beds) should be based on estimates on the proportion of patients requiring mechanical ventilation beds using UK government statistics over the previous year (up to 5th October 2022) whereas the company used estimates averaged over the first and second waves of COVID-19 (January 2020 to March 2021).

- The EAG has also estimated the impact of allowing post year one cases of COVID-19 to result in new cases of long COVID, which the company's model did not allow.

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Overall, the technology is modelled to affect QALYs by:

- Direct utility gain from feeling protected enough from SARS-Cov-2 infection to be able to resume normal activities and participate fully in society
- Reducing the risk of COVID-19 leading to the prevention of health-related quality of life (HRQoL) reductions during non-fatal acute COVID-19 in the year of Evusheld treatment (risk of COVID-19 occurring after the first year is not affected by Evusheld treatment)
- Reducing the severity of COVID-19 leading to a lower proportion of cases requiring hospitalisation and fewer fatal cases of COVID-19 in the year of Evusheld treatment
- Preventing excess deaths in the years after hospital discharge for patients requiring high-flow oxygen, non-invasive ventilation (NIV) or invasive mechanical ventilation (IMV) for COVID-19 by reducing the number of patients with severe COVID-19
- Preventing long COVID, which is a chronic illness with associated reductions in HRQoL, by preventing cases of COVID-19 in the year of Evusheld treatment

Overall, the technology is modelled to affect costs by:

- Incurring costs for drug acquisition and administration for Evusheld
- Prevention of resource use for acute hospital management of COVID-19 in the year of Evusheld treatment
- Prevention of chronic ill health with associated health resource use due to long COVID
- Resource use related to and routine monitoring following COVID-19 requiring hospital management.

The modelling assumptions that have the greatest effect on the ICER are:

- The risk of COVID-19 in the year after guidance on Evusheld is published
- The effectiveness of Evusheld against variants circulating in the year after guidance on Evusheld is published
- The adjustments made to incorporate the cost and QALY losses from COVID-19 cases occurring after year one, including whether the model allows these cases to cause long COVID
- The proportion of patients experiencing direct utility gain from stopping shielding behaviours and the duration of direct utility gain in patients experiencing COVID-19
- The risk of long COVID in non-hospitalised patients
- The costs assumed for administering Evusheld
- The data used to estimate the duration of long COVID
- The costs applied for long COVID
- The utility decrements applied for long COVID

1.3 The decision problem: summary of the EAG's key issues

Issue 1 Economic analysis assumes two doses of Evusheld are administered 6 months apart

Report section	2.3.2 and 4.3.4.1
Description of issue and why the EAG has identified it as important	The intervention is Evusheld (tixagevimab and cilgavimab administered by two consecutive intramuscular injections) as listed in the NICE scope. However, the EAG notes that the economic analysis assumes one year of Evusheld treatment consisting of an initial 600mg dose, followed 6 months later by a second 600mg dose. The SPC for Evusheld states that there are no safety or efficacy data available for repeat dosing with Evusheld. (See also Issue 14 which discusses the company's assumption that efficacy is the same for both doses in the economic analysis)
What alternative approach has the EAG suggested?	The EAG suggests that the committee should consider whether a repeat dose of Evusheld should be given at 6 months given that the SPC indicates that there is no data on the safety and efficacy of repeat dosing with Evusheld.
What is the expected effect on the cost-effectiveness estimates?	The company has provided an exploratory analysis which suggests that the cost effectiveness estimates when they assumed a single dose with a 6-month treatment effect are relatively consistent with the company's base case. However, the company's analysis assumes that the risk is constant across time whereas experience would suggest that the infection risk tends to peak and wane. The company's' exploratory analysis therefore does not explore whether a single dose would need to be timed to coincide with the period of greatest risk (see Section 4.3.4.1).

What additional evidence or analyses might help to resolve this key issue?	The company could provide a threshold analysis to explore the range of risk of COVID-19 in the SoC arm that results in an ICER under the range of £20,000 to £30,000 per QALY when assuming a single dose of Evusheld. There will be additional information available in [redacted] from ongoing studies to assess the efficacy and safety of repeat doses.

1.4 The clinical effectiveness evidence: summary of the EAG's key issues

Issue 2 Uncertainty regarding the efficacy of Evusheld against current and future variants

Report section	3.8.2
Description of issue and why the EAG has identified it as important	The key RCT for Evusheld (PROVENT) was conducted during a period in which the Alpha and Delta variants of SARS-CoV-2 were dominant and in an unvaccinated population and using a lower dose (300 mg) than is assumed in the company's economic analysis (600mg). Although real-world evidence (RWE) evidence studies are available which were conducted in more widely vaccinated populations and using mainly the 600 mg dose, these studies were conducted when early Omicron variants were dominant (BA.1 or BA.2) and may not reflect the efficacy of Evusheld against the current dominant variant (BA.5). In addition, while the EAG considers the propensity matching approach applied by the company's key RWE study (Young-Xu 2022) to be reasonable, data quality issues and methodological limitations may have impacted the estimates of effectiveness.
What alternative approach has the EAG suggested?	In the absence of any anticipated additional information regarding the efficacy of Evusheld against current variants, the EAG would advise that the company's estimates of cost-effectiveness are uncertain.
What is the expected effect on the cost-effectiveness estimates?	The EAG's exploratory analyses identified that a reduction in the RRR from 66% to 30% would result in an ICER of [redacted] when using the EAG corrected company base case and keeping the annual risk of COVID-19 at the base case value of 22.58%. However, if the annual risk of COVID-19 was reduced to 17.5% then a reduction in the RRR to 30% would result in an ICER of [redacted]. This reflects the combined impact of uncertainty around the efficacy of Evusheld against future variants and the future risk of COVID-19 which is uncertain and dependent on many factors.
What additional evidence or analyses might help to resolve this key issue?	[redacted]

Issue 3 Exclusion of studies for specific subpopulations with the target population for Evusheld

Report section	3.2
Description of issue and why the EAG has identified it as important	The clinical effectiveness review described in the CS excluded some studies which recruited specific subgroups such as solid organ transplant recipients. The EAG and their clinical advisors consider solid organ transplant recipients to be an important high-risk clinical subgroup within the overall immunocompromised population.
What alternative approach has the EAG suggested?	The EAG suggests that any studies conducted in groups that fall within the marketing authorisation for Evusheld should have been included in the CS
What is the expected effect on the cost-effectiveness estimates?	The impact of estimating the cost-effectiveness for specific subgroups of patients is not known.
What additional evidence or analyses might help to resolve this key issue?	The company could provide a cost-effectiveness analysis using any RWE studies available for specific subgroups of patients such as those having solid organ transplant.

1.5 The cost-effectiveness evidence: summary of the EAG's key issues

In addition to the issues described below, the EAG also made changes in their exploratory analyses to the reference costs for admission with COVID-19 and the proportion of hospitalised patients with COVID-19 requiring IMV (see Section 1.6), but these are not described in this section as they had a small impact on the ICER.

Issue 4 Risk of COVID-19 in the target population without Evusheld

Report section	4.3.4.5
Description of issue and why the EAG has identified it as important	The company's economic analysis uses the average risk of reporting a positive test for SARS-CoV-2 in the general public between August 2021 to August 2022 as the estimate of risk in the model. This may overestimate the risk of COVID-19 because not all patients reporting a positive SARS-CoV-2 test will have been symptomatic. This is especially true in periods where asymptomatic testing was widespread in educational and other settings. Equally it may underestimate the risk during periods when free access to testing for the general public was restricted (i.e., post 1st April 2022). In addition, there is an inherent uncertainty regarding the risks of COVID-19 in the future as it may depend on the circulating variant, the degree of protection offered by existing vaccines to that variant, the degree of non-pharmacological measures to prevent transmission in the general public and the degree of infection avoidance behaviours in the target population.
What alternative approach has the EAG suggested?	The EAG has conducted scenario analysis using the EAG's corrected company base case to test how sensitive the cost-effectiveness estimates are to uncertainty regarding the risk of infection.
What is the expected effect on the cost-effectiveness estimates?	It is not possible to predict the size and direction of the effect due to the inherent uncertainty in the future risk of COVID-19 infection in the target population. However, the EAG's exploratory analysis demonstrates that a decrease in the risk of COVID-19 from 22.58% to 10% per annum would increase the EAG's corrected company base case from [redacted] to [redacted].
What additional evidence or analyses might help to resolve this key issue?	This uncertainty could be addressed through expert elicitation to provide a range of plausible risks that the committee may wish to consider, although this will not reduce the inherent uncertainty of trying to predict future risks.

Issue 5 The implementation of adjustments to capture post year one cases of COVID-19

Report section	4.3.4.18
Description of issue and why the EAG has identified it as important	The company's model structure does not structurally capture cases of COVID-19 occurring beyond the first year. Therefore, the company has attempted to incorporate the impact of post year one cases of COVID-19 using simple adjustments to its existing model structure. The EAG identified several errors in the way these adjustments were implemented. In particular, the EAG identified that the company's method for adjusting for fatal cases of COVID-19 occurring after the first year did not allow for deaths to accrue over time and was therefore equivalent to deaths only occurring for COVID-19 infections in year 2 of the model.
What alternative approach has the EAG suggested?	The EAG has corrected the errors identified. In particular, a correction was made to ensure that the QALYs lost from deaths allowed for deaths to accrue over time for post year one COVID-19 cases. In addition, two smaller corrections were made to the estimation of acute costs and QALYs losses for post year one cases of COVID-19.
What is the expected effect on the cost-effectiveness estimates?	The company's base case ICER increased from [redacted] to [redacted] when these corrections were applied [EAG's corrected company base case]
What additional evidence or analyses might help to resolve this key issue?	No additional evidence is required as the EAG believes this issue has been resolved by their corrections.

Issue 6 Estimation of the direct utility gain attributable to Evusheld

Report section	4.3.4.4
Description of issue and why the EAG has identified it as important	The company has applied a direct utility gain to patients receiving Evusheld with the intention of capturing the impact of Evusheld on shielding and other infection avoidance behaviours. The company has applied this to all patients who either do not experience COVID-19 or who have non-fatal COVID-19 in the year after receiving Evusheld. However, the company states that only 13% of patients in the target population are continuing to follow shielding advice.
What alternative approach has the EAG suggested?	The EAG suggests that the direct utility gain should only apply to the 13% of patients in the target population who are currently continuing to follow shielding advice. The EAG would also argue that it should apply only for 6 months in patients who experience COVID-19 after receiving Evusheld on the basis that they will not feel protected after experiencing a treatment failure.
What is the expected effect on the cost-effectiveness estimates?	Reducing the duration of proportion to which the direct utility is applied to 13% increased the ICER from [redacted] to [redacted] when applied in isolation to the EAG's corrected company base case. [EA1] Applying the direct utility gain only for 6 months to patients experiencing COVID-19 increased the ICER from [redacted] to [redacted] when applied in isolation to the EAG's corrected company base case. [EA2]
What additional evidence or analyses might help to resolve this key issue?	The company has not provided any health utility data directly measured in patients receiving Evusheld. A RWE study measuring EQ-5D-5L prospectively in patients receiving Evusheld might reduce this uncertainty.

Issue 7 Risk of long COVID in non-hospitalised patients

Report section	4.3.4.13
Description of issue and why the EAG has identified it as important	The company has estimated the risk of long COVID from a study that did not compare the prevalence of long COVID symptoms in patients who have had COVID-19 versus controls who have not COVID-19. This may have overestimated the risk of long COVID as other studies have identified that a proportion of people not experiencing COVID-19 will report symptoms consistent with long COVID. There is also evidence to suggest that long COVID risk is dependent on both vaccination status and the dominant circulating variant.
What alternative approach has the EAG suggested?	The EAG has used an alternative source for the risk of long COVID which included a control cohort. This estimate (12.7%) is used in the EAG's base case. However, this was conducted in the Netherlands at a time when the Alpha variant was dominant and when vaccination rates were low. A lower risk (4.2%) estimated from ONS data in triple-vaccinated adults having long COVID 12 to 16 weeks after a confirmed positive SARS-CoV-2 test with the Omicron BA.2 is explored as the lower end of the plausible range, on the basis that immunocompromised individuals may not have the same protection from triple vaccination as the general population.
What is the expected effect on the cost-effectiveness estimates?	The EAG's exploratory analysis suggest that implementing a lower risk for long COVID in the non-hospitalised patient group (12.7%) increases the ICER from [redacted] to [redacted] when applied in isolation to the EAG's corrected company base case. [EA3] In the EAG's exploratory analysis which examined a lower limit of 4.2% for long COVID in the non-hospitalised patient group the ICER for the EAG's preferred base case increased from [redacted] to [redacted]. However, using the company's preferred estimate of long COVID risk (34.8%) in the EAG's preferred base case scenario reduced the ICER from [redacted] to [redacted].
What additional evidence or analyses might help to resolve this key issue?	The EAG is not aware of any additional studies that might better quantify the risk of long COVID in the population eligible to receive Evusheld.

Issue 8 Administration costs for Evusheld

Report section	4.3.4.2
Description of issue and why the EAG has identified it as important	The company has assumed that the only resources required to administer Evusheld will be 30 minutes of GP Practice Nurse time per patient receiving Evusheld. This does not take into account the fact that patients need to be observed for 1 hour after treatment. It also does not capture the logistical resources required to set up clinics that would allow multiple patients to be observed in order to achieve the efficiency savings required to reduce the resource use down to 30 minutes of nursing time per patient. In addition, the EAG expects that some form of coordinated provision would need to be set up for the administration of Evusheld, to the 1.8 million patients that the company estimates would be eligible, and this would fall outside of any existing agreements for routine care by primary care providers, or routine vaccinations within primary care.
What alternative approach has the EAG suggested?	The EAG has used the costs of administering COVID-19 therapeutics through CMDUs as a proxy for the costs required to administer Evusheld.
What is the expected effect on the cost-effectiveness estimates?	The EAG's exploratory analysis which applied the administration costs from CMDUs increased the ICER from [redacted] to [redacted] when applied in isolation to the EAG's corrected company base case. [EA4]
What additional evidence or analyses might help to resolve this key issue?	A more detailed assessment of the likely costs for a large-scale programme of Evusheld administration may be useful. This could be informed by professionals with experience of delivering COVID-19 therapeutics through CMDU or COVID-19 vaccinations within community and primary care settings.

Issue 9 Duration of long COVID for hospitalised and non-hospitalised patients

Report section	4.3.4.14
Description of issue and why the EAG has identified it as important	The company used the log normal time to recovery curve from the ScHARR COVID-19 MTA but then calibrated it to adjust for a lower proportion recovering between 5 months and 1 year in the PHOSP-COVID cohort than would be predicted from the log normal extrapolation. The company also set the proportion of hospitalised patients with long COVID at 6 months equal to the proportion reporting long COVID at 5 months in the PHOS-COVID cohort. However, the calibrated log normal curve for time to recovery was applied without manual adjustment at 6 months for the non-hospitalised group experiencing long COVID. The EAG did not believe that it was reasonable that the proportion recovering from long COVID in the first 6 month was higher for patients hospitalised with COVID-19 than for patients with COVID-19 who were not hospitalised. The EAG also noted that the company's approach resulted in a longer duration of long COVID than would be expected based on the latest ONS data on self-reported long COVID.
What alternative approach has the EAG suggested?	The EAG preferred to use the company scenario analysis which incorporated more recent ONS data to estimate the duration of long COVID without the calibration to adjust for the 1-year data from the PHOSP-COVID cohort. The EAG also removed the adjustment at 6 months in the hospitalised group in their base case scenario. In an exploratory scenario analysis, the EAG used the updated ONS data with calibration and set the proportion who have recovered at 6 months equal to the proportion recovered in the PHOSP-COVID cohort at 5 months for both hospitalised and non-hospitalised patients.
What is the expected effect on the cost-effectiveness estimates?	The EAG's exploratory analysis suggest that implementing a shorter duration of long COVID has a substantial impact on the ICERs as the increased the ICER from [redacted] to [redacted] when the unadjusted ONS data was applied in isolation to the EAG's corrected company base case. [EA5]
What additional evidence or analyses might help to resolve this key issue?	The long-term trajectory of recovery (i.e., > 2 years) is inherently uncertain because long COVID is a condition which has only been diagnosed since 2020. The COVID-19 Infection Survey, used to generate the ONS estimates of self-reported long COVID, is ongoing and is reporting updated results monthly. The EAG is not aware of any other additional or ongoing studies that would better quantify the duration of long COVID in either hospitalised or non-hospitalised patients with COVID-19.

Issue 10 Long COVID costs

Report section	4.3.4.16
Description of issue and why the EAG has identified it as important	The company's updated post clarification base case analysis applied a cost for long COVID (£2,500) that was used in an exploratory analysis in the ScHARR COVID-19 MTA model, instead of the cost used in the ScHARR COVID-19 MTA base case which was a cost estimate for chronic fatigue syndrome (£1128). The figure used by the company in their base case was arbitrarily selected by the MTA's EAG to measure the sensitivity of the results to the change in the costs of long COVID. This sensitivity analysis intended to explore the impact of attempting to account for additional costs resulting from possible organ damage. It was not informed by any specific evidence and was not included in the EAG's base case analysis for the COVID-19 MTA.
What alternative approach has the EAG suggested?	The EAG's preference is to use the estimate for the cost of chronic fatigue (£1128) as a proxy for the cost of long COVID, as assumed in the ScHARR COVID-19 MTA base case analysis. [EA6]
What is the expected effect on the cost-effectiveness estimates?	Decreasing the cost of long COVID to the value used in the base case analysis increased the ICER from [redacted] to [redacted] when applied in isolation to the EAG's corrected company base case.
What additional evidence or analyses might help to resolve this key issue?	The cost of managing long COVID is currently uncertain as it is a new condition. The EAG is not aware of any additional or ongoing studies that will provide a better estimate than those applied in the ScHARR COVID-19 MTA model.

Issue 11 Long COVID utilities

Report section	4.3.4.15
Description of issue and why the EAG has identified it as important	The company estimated utility decrements for long COVID by comparing 5-month EQ-5D utility scores in the PHOS-COVID cohort (Evans 2021 and Evans 2022) with retrospectively estimated pre-COVID EQ-5D utility scores. These estimates were available at 5 months for patients stratified by disease severity allowing the disutilities to be estimated according to the level of hospital care required. The company then uplifted these estimates by a factor of 1.71 to reflect what if believed to be an increase in the utility decrements between 5 months and 1 year in the PHOS-COVID cohort. The EAG did not agree with the method used to calculate this uplift factor as it did not compare two like-for-like figures. In addition, the company used the disutility for patients reporting that they were not recovered at 1 year to estimate the uplift, but when estimating the proportion experiencing long COVID at 5 months and 1 year they also included half of the patients who responded that they were unsure if they were recovered. The company's analysis also assumes that the disutility estimates for patients having long COVID after COVID-19 requiring hospitalisation without oxygen therapy are applicable to those having long COVID after COVID-19 not requiring hospitalisation. The company assumes that the disutilities for long COVID are constant for the duration of long COVID.
What alternative approach has the EAG suggested?	The EAG has adjusted the disutility values applied for long COVID taken from the PHOSP-COVID UK cohort (Evans 2022), so that they reflect the weighted average across patients stating either that they were not recovered or that they are unsure if they were recovered at 1 year. This was to reflect the fact that half of the 'unsure' group were considered in the company's model to have ongoing long COVID. The EAG has then used the 5-month estimates of disutility vs pre-COVID which were stratified by COVID-19 severity to estimate disutilities for long COVID stratified by COVID-19 severity from the 1-year disutility estimates. The EAG has also assumed that the utility decrements for long COVID linearly decline over 5 years to 50% of their starting value based on the approach used in a company scenario analysis.
What is the expected effect on the cost-effectiveness estimates?	Incorporating the EAG's preferred disutilities for long COVID increased the ICER from [redacted] to [redacted] when applied in isolation to the EAG's corrected company base case.[EA7]
What additional evidence or analyses might help to resolve this key issue?	Estimates of the impact of long COVID on health utility measured in patients who did not require hospitalisation for their COVID-19 would be useful, but none were identified in the CS.

Issue 12 Hospitalisation risk for patients with COVID-19

Report section	4.3.4.6
Description of issue and why the EAG has identified it as important	The company has estimated the risk of hospitalisation (18%) in patients having COVID-19 from an immunocompromised cohort reported by Shield *et al.* However, Shields *et al.* also reported that the risk of hospitalisation was lower for patients infected during the period when Omicron was dominant compared to those infected in earlier waves (9.9% vs 41.5% for prior variants) but higher in those not receiving COVID-19 therapeutics (15.9% vs 4.3%).
What alternative approach has the EAG suggested?	The EAG has applied a lower estimate for the risk of hospitalisation in immunocompromised patients (15.9%) to reflect the reduced risk of hospitalisation for patients with COVID-19 during the period when the Omicron variant was dominant compared with those infected during earlier waves, whilst excluding the impact of COVID-19 therapeutics.
What is the expected effect on the cost-effectiveness estimates?	Applying a 15.9% risk of hospitalisation for COVID-19 increased the ICER from [redacted] to [redacted] when applied in isolation to the EAG's corrected company base case. [EA8]
What additional evidence or analyses might help to resolve this key issue?	The EAG is not aware of any additional or ongoing studies that may provide further evidence to resolve this issue. The proportion of patients with COVID-19 requiring hospitalisation may change in the future if the dominant variant changes and therefore this model parameter is inherently uncertain.

Issue 13 Risk of long COVID for patients experiencing post year one cases of COVID

Report section	4.3.4.18
Description of issue and why the EAG has identified it as important	The EAG identified that the company's model, which includes adjustments for post year one cases of COVID-19, does not allow for incidences of long COVID occurring after the post year one cases of COVID-19. This means that patients who avoid a year one case of COVID-19 by receiving Evusheld are then protected from long COVID during all subsequent years. This overestimates the benefit of Evusheld as in reality patients not experiencing COVID-19 in year one may experience a post year one case of COVID-19 and then go on to develop long COVID. In these patients the protection provided by Evusheld in the first-year delays rather than eliminates the risk of long COVID, but the company's model assumes that the risk of long COVID is eliminated by avoiding COVID-19 in year one.
What alternative approach has the EAG suggested?	The EAG has attempted to estimate the impact of including a risk of long COVID for cases of COVID-19 occurring after the first year
What is the expected effect on the cost-effectiveness estimates?	The impact of the EAG's model amendments depends on whether the other changes related to long COVID risks, costs and utilities have been implemented. However, adding this change in isolation to the EAG's corrected company base case increases the ICER from [redacted] to [redacted].
What additional evidence or analyses might help to resolve this key issue?	The EAG believes that it would be better if the company attempted to model post year one cases of COVID-19 using a model structure that accounts for the number of patients who remain at risk of long COVID over time.

Issue 14 Assumption of a constant treatment effect for 6 months after each dose of Evusheld

Report section	4.3.4.1
Description of issue and why the EAG has identified it as important	The company's economic analysis assumes one year of Evusheld treatment consisting of an initial 600mg dose, followed 6 months later by a second 600mg dose (see also Issue 1). The economic analysis applies the treatment effect estimated in the RWE study by Young-Xu *et al*. as a constant relative risk reduction (RRR) over a 6-month period following each dose. However, the maximum duration of follow-up in this study was 4 months meaning that it is not possible to assess if the proportional hazard assumption would hold over a 6-month period. The company has provided some information to assess the proportional hazards assumption during the 6-month follow-up of the PROVENT study, but further information would be useful (see below). The company's analysis also assumes identical efficacy for the second dose but there is currently no data on the efficacy of repeat dosing (see also Issue 1).
What alternative approach has the EAG suggested?	The EAG has explored a scenario in which the RRR is reduced to two-thirds of its base case value to explore the impact of a worst-case assumption of zero treatment effect from 4 to 6 months. However, this was not incorporated in the EAG's preferred base case.
What is the expected effect on the cost-effectiveness estimates?	Reducing the RRR by a third for both COVID-19 and hospitalisation risks increased the ICER from [redacted] to [redacted] when applied in isolation to the EAG's corrected company base case. [EA12] This scenario was not conducted for the EAG's preferred base case scenario but any reduction in the RRRs would be expected to increase this ICER further.
What additional evidence or analyses might help to resolve this key issue?	The company could provide further assessment of the proportional hazard assumption from the PROVENT study such as a quantitative test of the proportional hazard's assumption, and an assessment of the Schoenfeld residuals. Data from ongoing studies exploring the impact of redosing at 6 months is expected in [redacted] (see Issue 1) and this may help confirm the company's assumption regarding the efficacy of the second dose.

Issue 15 Heterogeneity with the target population for Evusheld

Report section	4.3.4.3
Description of issue and why the EAG has identified it as important	The company's model has used average patient characteristics from the PROVENT study in their base case. However, the EAG notes that the subset of patients classified as immunocompromised within the PROVENT study had a higher mean age. The EAG also notes that the company has included adjustments for all-cause mortality and utility in patients not experiencing COVID-19 or long COVID to account for the prevalence of comorbidities in the target population for Evusheld. The EAG believes that the target population for Evusheld is likely to be heterogeneous in terms of age, and whether the individual has a reduced life expectancy or reduced quality of life due to the health condition that means that they are eligible for Evusheld.
What alternative approach has the EAG suggested?	The EAG has conducted a scenario analysis in which the patient characteristics for the immunocompromised group from PROVENT are used. The EAG has also conducted an exploratory analysis removing the adjustments for all-cause mortality and utility to explore whether the cost-effectiveness estimates are likely to vary depending on the characteristics of the patients within the target population. None of these changes were included in the EAG's preferred base case.
What is the expected effect on the cost-effectiveness estimates?	Changing the patient characteristics to reflect the characteristics of the immunocompromised group from PROVENT increased the EAG's preferred base case ICER from [redacted] to [redacted] [EAG scenario 2]. However, this analysis did not fully explore the potential for heterogeneity in patients' characteristics within the target population.
What additional evidence or analyses might help to resolve this key issue?	Further analyses exploring the cost-effectiveness of Evusheld in specific groups could be provided by the company as suggested in Issue 3

1.6 Other key issues: summary of the EAG's view

The EAG did not identify any other key issues that are anticipated to have a significant impact on the ICER.

1.7 Summary of EAG's preferred assumptions and resulting ICER

Table 2: Summary of results of EAG exploratory analyses, deterministic (unless otherwise stated)

Scenario	Incremental cost	Incremental QALYs	ICER (change from company base case)
Company base case (Deterministic)	[redacted]	[redacted]	[redacted]
EAG's corrected company base case: correcting implementation errors in the company's economic model [included in all subsequent rows]	[redacted]	[redacted]	[redacted]
EA1: Varying size of direct utility gain or size of group it is applied for to 13%	[redacted]	[redacted]	[redacted]
EA2: Halving the duration of direct utility gain for those infected while on Evusheld	[redacted]	[redacted]	[redacted]
EA3: Assuming 12.7% of the non-hospitalised cohort would develop long COVID	[redacted]	[redacted]	[redacted]
EA4: Assuming cost of administration for Evusheld of £410 based on CMDU costing exercise	[redacted]	[redacted]	[redacted]
EA5: Using the October 2022 update of the ONS data to estimate the duration for long COVID without the Evans 2022 adjustment	[redacted]	[redacted]	[redacted]
EA6: Using the long COVID annual costs of £1128 assuming chronic fatigue as proxy	[redacted]	[redacted]	[redacted]
EA7: Recalculating disutility values due to long COVID and assuming linear HRQoL improvement by time for 5 years	[redacted]	[redacted]	[redacted]
EA8: Using 15.9% as the risk estimate of hospitalisation for infected patients	[redacted]	[redacted]	[redacted]
EA9: Updating hospitalisation reference costs associated with acute admissions	[redacted]	[redacted]	[redacted]
EA10: Reducing proportion of hospitalised patients requiring IMV	[redacted]	[redacted]	[redacted]
EA11: Applying long COVID to new infections after 1 year	[redacted]	[redacted]	[redacted]
EA12: Assuming reduction in relative efficacy by one-third	[redacted]	[redacted]	[redacted]
EAG's preferred base case applying analyses EA1 to EA11 - deterministic	[redacted]	[redacted]	[redacted]
EAG's preferred base case applying analyses EA1 to EA11 - probabilistic	[redacted]	[redacted]	[redacted]

Modelling errors identified and corrected by the EAG are described in 4.4.2.1. For further details of the exploratory and sensitivity analyses done by the EAG, see Section 4.4.

2 BACKGROUND

This section presents a brief summary and critique of the company's definition of the decision problem for the appraisal of tixagevimab–cilgavimab (hereafter referred to as Evusheld) for preventing COVID-19. A brief description of the underlying health problem and current service provision is also provided as background to the decision problem.

2.1 Critique of company's description of underlying health problem

The company submission (CS) describes severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), as a highly contagious coronavirus which can cause the respiratory disease known as COVID-19. The NICE COVID-19 rapid guideline on managing the long-term effects of COVID-19 (NG188), uses the terms 'acute COVID-19' to describe signs and symptoms of COVID-19 experienced for up to 4 weeks, 'ongoing symptomatic COVID-19' to describe signs and symptoms of COVID-19 from 4 weeks to 12 weeks and 'post-COVID-19 syndrome' to describe signs and symptoms that develop during or after an infection consistent with COVID-19, which continue for more than 12 weeks and are not explained by an alternative diagnosis (from 12 weeks or more).[1] NG188 describes 'long COVID' as the commonly used term which encompasses both ongoing symptomatic COVID-19 and post-COVID 19 syndrome.[1] The CS appears to use the term COVID-19 interchangeably with the terms 'acute COVID-19' and 'symptomatic COVID-19' and sometimes incorrectly uses the term COVID-19 to refer to situations where people have a positive diagnostic test for SARS-CoV-2 but they may or may not have symptoms. In contrast, the EAG has in this report used the term COVID-19 to refer only to symptomatic SARS-CoV-2 infection. The CS has defined long COVID as *"long-term clinical sequalae and new comorbidities"* (CS, pB1.3.3, p20). For the purposes of this report the EAG uses the term long COVID as defined in NG188.[1]

The CS describes the ongoing burden of SARS-CoV-2 in terms of the ongoing rate of infection, which the CS states as ranging from 1.29% to 7.6% of people in England being infected per week during the course of 2022.[2] It notes that there had been 177,977 deaths in the UK within 28 days of a positive SARS-CoV-2 test (data up to May 2022).[3] It also reports that 2.0 million people in the UK have reported long COVID symptoms which have a significant detrimental impact on quality of life, citing a government press release.[4] However, the EAG notes that the source cited to support this statement is describing estimates generated from the REACT study and whilst the aim of the study was to obtain prevalence estimates representative of the population of England as a whole (not the UK), it was based on self-reported data from approximately 500,000 patients. Furthermore, whilst the REACT study paper itself does state that it estimates that 2 million are reported as having one or more persistent symptom, it reports a lower estimate for the number experiencing severe symptoms (just under a million adults had three or more persistent symptoms).[5] The CS also reports that SARS-CoV-2 is continuing to have

a high burden within the NHS. Using the source cited in the CS, the EAG notes that admissions have varied significantly across the previous year will a low of around 440 admission per day in May 2022 and a high of around 2,100 per day at the end of March 2022.[6] However, a cumulative incidence of around 396,000 admissions occurred in the year up to 1st Sept 2022, which is in keeping with the company's statement around the continuing burden of SARS-CoV-2 on the NHS.[6]

The CS describes the prevailing epidemiology in terms of 1.29% of people in England being infected in the week ending 5th September 2022,[3] with the current dominant variant being the Omicron (B.1.1.529) sub-lineage BA.5, with other variants of concern detected in the UK being Omicron (B.1.1.529) sub-lineages BA.1, BA.2 and BA.4.[7]

The CS describes how the risk of poor COVID-19 outcomes, such as hospitalisation and death, are increased in immunocompromised individuals. The CS describes how the population at highest risk of poor outcomes were identified in the McInnes report with the aim of providing a target population for patients who should be prioritised for COVID-19 treatments such as antivirals and neutralising monoclonal antibodies (nMABs).[8] The definition of this group is further discussion in Section 2.3.1 but broadly speaking the report aimed to identify those people whose immune system means they are at higher risk of serious illness from SARS-CoV-2.

The CS describes the high clinical burden of COVID-19 in this high-risk population. The CS (page 23) notes that immunocompromised individuals make up a disproportionately high number of hospitalisations, intensive care unit (ICU) admissions and death as a result of 'breakthrough' COVID-19 (i.e., COVID-19 infection following vaccination), given that they account for only a small proportion of the UK general population. The EAG were able to verify the figures in CS, Figure 1 which support the statement that immunocompromised patients made up a higher proportion of fully vaccinated (2 doses) and boosted (3 doses) patients admitted to ICU than would be expected, given that they account for only a small proportion of the UK general population.[9] To support the higher rate of breakthrough hospitalisations and breakthrough deaths, the CS cites data from the UK Primary Immunodeficiency Network (PIN) (Shields *et al*. 2021).[10] However, the EAG did not find anything in the cited paper that described data specifically for vaccinated patients and therefore, does not believe that this paper provides information specifically on breakthrough COVID-19. In particular, the paper reports data from infections occurring between March 2020 and July 2021 and will therefore include a mix of infection pre- and post-vaccination roll-out. It does however report a high rate of hospital admission (45.8%) and death (17.7%) in patients with primary or secondary immunodeficiency who have COVID-19, which was higher than reported for the general population.[11] The EAG note that a later publication reporting data from the UK PIN dataset does report a significant improvement in morbidity and mortality in later waves due to the widespread availability of vaccinations, COVID-19 specific treatments and possibly

the emergence of new variants.[10] This study also notes that immunocompromised groups remain at increased risk compared to the general public.[10] Overall, the EAG would agree that immunocompromised patients are at increased risk of adverse clinical outcomes, including hospitalisation, ICU admission and death, but that care is needed when estimating the absolute risk of these outcomes as this may change over time depending on the impact of vaccination, improvements in care over time and changing variants.

The CS also describes the humanistic burden of SARS-CoV-2 in terms of the lifestyle changes adopted by people who do not feel adequately protected from vaccination. The CS describes how 82% of clinically extremely vulnerable individuals are still taking extra precautions to protect themselves from infection and 13% are continuing to follow previous shielding advice.[12] They also describe the impact that shielding and other infection avoidance behaviours have on the ability of people to work, use public transport and participate in social gatherings. They also describe the fear and anxiety experienced by individuals who are at the highest risk of severe outcomes. In some cases, the impact of shielding extends to families' members and carers who adopt lifestyle modification themselves in order to avoid bringing the infection home. Further information on the humanistic burden of SARS-CoV-2 in the various groups of individuals that falls within the company's target population for Evusheld is given in the submissions provided by patient and carer organisations and professional organisations, which are not summarised in the EAG report.

2.2 Critique of company's overview of current service provision

The CS describes the current NHS care pathway in terms of strategies to prevent SARS-CoV-2 infection and strategies to treat COVID-19 infection. The EAG believes only the former is relevant for this appraisal because the scope of this appraisal specifies a population not currently infected with SARS-CoV-2.[13]

The CS describes how the detrimental impact of COVID-19 has been substantially reduced for people who do not have an underlying health condition by the high uptake of vaccinations to prevent SARS-CoV-2 within the general UK population. However, it also highlights that the groups identified by McInnes *et al*.[8] are those considered to remain at the highest risk of severe COVID-19 despite full adherence with vaccination. Therefore, the company claims that there is considerable unmet need in this group. The CS also highlights that a small proportion of the UK population (0.00067%) are not able to be fully vaccinated with any available COVID-19 vaccines, and therefore, are also considered at high-risk with an unmet need for protection against SARS-CoV-2 (CS, page 21).

The EAG agrees that there is an unmet need in the population specified as being at highest risk of an adverse outcome from SARS-CoV-2 infection. A preprint publication reporting early results from the

OCTAVE trial found that 11% of immunocompromised patients failed to generate antibodies to the SARS-CoV-2 spike protein 4 weeks after two doses of vaccine, and 40% of those who did generate antibodies generated lower levels of antibodies compared to healthy subjects.[14] However, the EAG notes that the relationship between an individual being immunocompromised and vaccination response as determined by the presence of antibodies, and the likelihood of severe infection after vaccination, is still under investigation in various studies; the OCTAVE-DUO and the MELODY studies aim to improve the understanding of responses to COVID-19 vaccination in individuals who are immunocompromised or receiving immunosuppressive treatments respectively.[15, 16] It is also possible that the degree of unmet need will vary considerably within the overall group defined as being at highest risk of an adverse outcome by McInnes, but the degree of variation is poorly understood at this time.

2.3 Critique of company's definition of the decision problem

2.3.1 Population

Evusheld has a conditional marketing authorisation for the pre-exposure prophylaxis of COVID-19 in adults who are not currently infected with SARS-CoV-2 and who have not had a known recent exposure to an individual infected with SARS-CoV-2 and:

- who are unlikely to mount an adequate immune response to COVID-19 vaccination, or
- for whom COVID-19 vaccination is not recommended.

However, the CS focuses on a specific target population described as adults who are not currently infected with SARS-CoV-2 and who have not had a known recent exposure to a person infected with SARS-CoV-2 and:

- are at the highest risk of an adverse COVID-19 outcome, namely hospitalisation and death, or
- for whom COVID-19 vaccination is not recommended

The CS acknowledges that this is a subgroup of the licensed indication and therefore they are targeting those at the highest risk of an adverse COVID-19 outcome from within the group unlikely to mount an adequate immune response to COVID-19 vaccination. The company states that this subgroup should be aligned with the population identified in the report by McInnes *et al*.[8] which defines the highest-risk clinical subgroups upon community infection with SARS-CoV-2 when considering the use of nMABs and antiviral drugs. McInnes *et al*. state that when identifying the highest-risk clinical subgroups upon community infection, they mean those people whose immune systems means they are at higher risk of serious illness from COVID-19.[8] CS Table 4, summarises the groups identified by McInnes *et al*. using 10 broad categories as follows:

- Down's syndrome and other genetic disorders
- Solid cancer
- Haematological diseases and haematopoietic stem-cell transplantation recipients
- Renal disease
- Liver diseases
- Solid organ transplant recipients
- Immune-mediated inflammatory disorders
- Immune deficiencies
- Human immunodeficiency virus (HIV) / Acquired immune deficiency syndrome (AIDS)
- Rare neurological and severe complex life-limiting neuro-disability conditions

However, the EAG notes that the McInnes report details which patients within these broad categories are considered to be at the highest-risk and therefore the full detail provided in Figure 1 of the McInnes report should be referred to when defining the population proposed by the company.[8] The CS also states that the McInnes report identified a highest risk population of approximately 1.8 million people in England.

The EAG's clinical advisors were satisfied that the McInnes report would identify the groups mostly likely to benefit from Evusheld provided that the specific criteria within the McInnes report were adhered to. The EAG's clinical advisors were also satisfied that the group identified by McInnes *et al*.[8] as being at highest risk from SARS-CoV-2 infection would fall within the marketing authorisation, as those who are unlikely to mount an adequate immune response to SARS-CoV-2 infection are also unlikely to mount an adequate immune response to vaccination.

The McInnes report also discusses the potential for serology to support decision making by allowing clinicians to identify those with the least robust response to vaccination.[8] However, the consensus at that time was that community serology monitoring would not be useful as there was no given level of antibody levels that could correlate sufficiently with levels of protection for general clinical use and there was a lack of access for serology monitoring in the community.[8] The EAG's clinical advisors agreed that whilst using serology levels to target treatment at those with the poorest response to vaccination was an attractive proposition, it was not practical at this time. However, the clinical implications of various serology levels are being investigated in current ongoing studies.[14-16]

The EAG also asked their clinical advisors whether they would want to prioritise treatment to those individuals who had not previously been infected with COVID-19 on the basis that recovery from a prior infection might be protective of a future severe infection. However, the clinical advisors were not

confident that recovery from a prior infection was sufficient to predict that patients would not be at risk of a future severe infection in the context of newly emerging variants.

The CS does not present an economic analysis for any of the specific subgroups that make up the population at highest risk of an adverse COVID-19 outcome, as defined by McInnes *et al*.[8] The clinical effectiveness review excluded some real-world evidence (RWE) studies which recruited specific subgroups, such as solid organ transplant recipients, on the basis that they had 'restricted populations' (see Section 3.2). The EAG and their clinical advisors consider solid organ transplant recipients to be an important high-risk clinical subgroup within the overall immunocompromised population. The inclusion and analysis of evidence from specific subgroups at highest risk in the CS would have been helpful.

2.3.2 Intervention

Evusheld is a combination of two recombinant human IgG1k monoclonal antibodies (tixagevimab and cilgavimab). Evusheld is approved at both a 300mg and 600mg dose and is administered as sequential intramuscular injections, one of tixagevimab and one of cilgavimab, given at two different injection sites. The 300mg dose constitutes one injection of 1 vial (1.5mL) of 150mg tixagevimab and one injection of 1 vial (1.5mL) of 150mg cilgavimab. The 600mg dose requires 2 vials of each drug per injection. The list price is £800 per 300mg and £1,600 per 600mg, but an application for a simple patient access scheme (PAS) price has been submitted which reduces the cost of the 600mg dose to [redacted], although this proposed PAS has not yet been approved by the Patient Access Schemes Liaison Unit (PASLU). The company states that, [redacted]

The company's economic analysis assumes that Evusheld dosing is one 600 mg dose at start of the model, followed by another 600 mg dose at 6 months. The summary of product characteristics (SPC) states (as accessed on 25th October 2022) that, "*Evusheld may be effective for pre-exposure prophylaxis for six months post administration."* This would appear to support the need for repeat dosing to maintain efficacy beyond 6 months. However, the SPC for Evusheld states that there are no safety or efficacy data available for repeat dosing with Evusheld.[17] The EAG notes that there is an ongoing sub-study examining repeat dosing within the PROVENT[18] cohort and an ongoing phase II study (ENDURE)[19] examining the safety, immunogenicity, pharmacokinetic, and pharmacodynamic profiles of repeat dosing regimens with Evusheld. Therefore, whilst not available able this time, data on the safety and efficacy of repeat dosing with Evusheld is likely to be available in the future ([redacted] for PROVENT sub-study and ENDURE respectively). The company has provided a scenario analysis exploring a shorter treatment course of one 600mg dose, but no analysis is provided of a longer treatment course (i.e., 3 or more doses).

2.3.3 Comparators

The comparator specified in the scope is no prophylaxis and the EAG and their clinical advisors are not aware of any other relevant comparators. The EAG notes that the SPC states that "*Pre-exposure prophylaxis with Evusheld is not a substitute for vaccination in individuals for whom COVID-19 vaccination is recommended."*[17] Therefore, vaccination is not a comparator for Evusheld as Evusheld would be offered in addition to vaccination in individuals where vaccination is recommended.

2.3.4 Outcomes

The outcomes listed in the NICE scope are summarised in Table 3. The EAG notes that the outcomes primarily addressed in the key clinical studies are incidence of SARS-CoV-2 infection, incidence of symptomatic COVID-19, hospitalisation, mortality and adverse events (AEs). Although symptomatic COVID-19 was specified as the outcome of interest in the final NICE scope, only the key study (PROVENT) reported this outcome. The two RWE studies included in the CS, reported the incidence of SARS-CoV-2 infection, defined as any person with a recorded positive reverse-transcriptase-polymerase-chain-reaction (RT-PCR) or positive antigen test result. Therefore, these RWE studies did not require patients to have symptoms at the time of their positive SARS-CoV-2 test. The EAG's clinical advisors commented that symptomatic COVID-19 was more clinically relevant than any SARS-CoV-2 infection detected with or without symptoms. They also advised that studies reporting hospitalisations and deaths were more useful from a clinical perspective than those that focused purely on symptom severity. It should be noted that some studies reported composite outcomes combining either COVID-19 hospitalisation or severe COVID-19 with death and other reported deaths separately. Hospitalisation was not a pre-specified outcome for the key clinical study (PROVENT[20]), which instead reported the incidence of severe or critical illness and the incidence of emergency department visits. The definition of severe or critical illness used in PROVENT was a World Health Organization (WHO) Clinical Progression Score of $\geq$5 where 4 would indicate that a patient was hospitalised but did not require oxygen and a score of 5 would indicate hospitalisation requiring oxygen.[20] However, a post hoc analysis of the number of participants hospitalised due to COVID-19 was performed for the PROVENT study (see clarification response to A21).

The EAG notes that not all outcomes specified in the scope are addressed in the CS, with none of the included studies reporting outcomes for HRQoL, depression or anxiety. In addition, the outcome of time to return to normal activities post COVID-19 was not reported The TACKLE study is described in CS Table 9 as reporting time to return to usual health but this outcome was not reported in the CS. The EAG would agree with this outcome not being included as TACKLE was a therapeutic study included only for the purposes of assessing the safety of the 600mg dose and therefore information on

this outcome is unlikely to be relevant to the population receiving Evusheld as pre-exposure prophylaxis.

2.3.5 Other relevant factors

There is currently an ongoing MTA of COVID-19 therapeutics [ID4038]. Under the reference case, the economic modelling for a NICE TA should include all downstream treatments that may be affected by the use of the treatment being appraised and would therefore be expected in this case to include the cost savings from avoiding treatments for COVID-19 that are not needed either due to infections being avoided by pre-exposure prophylaxis or infections being less severe meaning that treatments indicated for severe COVID-19 are avoided. However, downstream treatments for COVID-19 included within the scope of the ongoing MTA have not been included in the company's economic analysis as they are not currently routinely commissioned in England and Wales; they are instead currently covered by NHS England's Interim Clinical Commissioning.[21] This is problematic as many of these treatments have been available within the NHS through NHS England's Interim Clinical Commissioning and their effect on COVID-19 outcomes may be captured within recent data on hospitalisation and mortality rates.[21] Furthermore, the economic analysis conducted by the company to inform this appraisal may become rapidly out of date once the outcome of the on-going MTA is known which increases the uncertainty associated with the company's estimate of future costs and benefits associated with the possible introduction of Evusheld.

Table 3: The decision problem (reproduced from CS, Table 1 with minor amendments and comments from the EAG)

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comments
Population	Adults who are not currently infected with SARS-CoV-2 and who have not had a known recent exposure to a person infected with SARS-CoV-2 and: • who are unlikely to mount an adequate immune response to COVID-19 vaccination, or • for whom COVID-19 vaccination is not recommended	Adults who are not currently infected with SARS-CoV-2 and who have not had a known recent exposure to a person infected with SARS-CoV-2 and: • are at the highest risk of an adverse COVID-19 outcome, namely hospitalisation and death, or • for whom COVID-19 vaccination is not recommended	The target population represents a subgroup of the licenced indication since it focuses on the highest risk patients within those who are unlikely to mount an adequate immune response to COVID-19 vaccination. An independent report commissioned by the UK Department of Health and Social Care (DHSC) identified patient subgroups, as defined by their underlying health conditions, who are deemed to be at the highest risk of adverse clinical outcomes due to COVID-19.[8] These patients predominately comprise of those who are immunocompromised and therefore often do not mount a sufficient immune response to COVID-19 vaccinations. AstraZeneca has consulted with 60 clinical experts across 19 specialities who consistently advised that the populations identified in the DHSC report represents those at highest risk of adverse clinical outcomes and are at the greatest need for prophylaxis. Therefore, UK clinical experts advised that the anticipated positioning of Evusheld should be in this clearly defined highest risk subgroup, as well as for adults for whom COVID-19 vaccination is not recommended – and as such inadequate protection is provided.	The EAG's clinical advisors were broadly happy with the target population for Evusheld being based on the groups deemed to be at the highest risk of adverse clinical outcomes due to COVID-19 as defined by McInnes *et al*. in the report commissioned by the DHSC.[8] However, they noted that this should be interpreted as including only those in the detailed list provided by McInnes *et al*. rather than all patients covered by the broad headings provided in CS, Table 4. They also noted that these groups had broadly been selected as people whose immune system means they are at higher risk of serious illness from COVID-19 either due to their primary disease or the need for immune suppressant treatments. However, within the eligible population defined by McInnes *et al*. there would be a spectrum of immunocompromised individuals. The EAG also noted that the key clinical trial (PROVENT)[20] was conducted in a broader population and included those at increased risk of infection rather than increased risk of an adverse outcome following infection. Examples of these groups included, amongst other groups,

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comments
				healthcare workers and students living in dormitories. Furthermore, these groups would not fall within the marketing authorisation. Therefore, the overall population of the PROVENT trial is broader than both the marketing authorisation and the target population specified in the CS.
Intervention	Tixagevimab and cilgavimab (Evusheld)	As per scope	NA	None
Comparator(s)	No prophylaxis	As per scope	NA	None
Outcomes	The outcome measures to be considered include: • incidence of symptomatic COVID-19 • mortality • requirement for respiratory support • hospitalisation (requirement and duration) • symptoms of post COVID-19 syndrome • anxiety and depression	As per scope	NA	The EAG's clinical advisors commented that COVID-19 (i.e., symptomatic SARS-CoV-2 infection) was more a clinically relevant outcome than any SARS-CoV-2 infection detected with or without symptoms. They also advised that studies reporting hospitalisations and deaths were more clinically relevant than those that focused purely on symptom severity. The EAG noted that none of the studies included in the CS reported HRQoL, anxiety or depression in patients who received Evusheld.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comments
	• time to return to normal activities post COVID-19 • adverse effects of treatment • health-related quality of life (HRQoL)			The only study reporting time to return to usual health was TACKLE but this outcome was not reported in the CS. The EAG would agree with this outcome not being included as TACKLE was a treatment study included only for the purposes of assessing the safety of the 600mg dose.
Economic analysis	Outcomes expressed as incremental cost per QALY. Time horizon for estimating clinical and cost-effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator, and subsequent treatment technologies will be taken into account.	As per scope	NA	None
Subgroups to be considered	If the evidence allows the following subgroups will be considered:	Captured as part of the target population for this submission.	NA	The subgroup of adults at highest risk of adverse COVID-19 outcomes is the main focus of the CS as discussed

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comments
	• adults at highest risk of adverse COVID-19 outcomes			above under the heading 'population'. The EAG notes that there is relatively little information presented for the other subgroup covered by the marketing authorisation which is those for whom COVID-19 vaccination is not recommended. The CS does not provide any evidence for specific subgroups within the target population and excluded some studies which recruited specific subgroups such as solid organ transplant recipients. The EAG and their clinical advisors consider solid organ transplant recipients to be an important high-risk clinical subgroup within the overall immunocompromised population.
Special considerations including issues related to equity or equality	Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.	As per scope	NA	None

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comments
	The impact of vaccination status or SARS-CoV-2 seropositivity on the clinical evidence base of each intervention, generalisability to clinical practice and interaction with other risk factors will be considered in the context of the appraisal. The impact of different variants of concern of COVID-19 on the clinical evidence base of each intervention will be considered in the context of the appraisal.			

Abbreviations: DHSC – Department of Health and Social Care; EAG - External Assessment Group; NA – Not applicable; NHS – National health service; NICE – National Institute for Health and Care Excellence; SARS-CoV-2 – severe acute respiratory syndrome coronavirus 2; CS - company submission.

3 CLINICAL EFFECTIVENESS

This chapter presents a summary and critique of the clinical effectiveness evidence contained within the CS for Evusheld for preventing COVID-19. Section 3.1 provides a critique of the company's systematic review of clinical effectiveness and safety evidence. Section 3.2 to 3.3 provides a summary of the clinical effectiveness and safety results, together with a critique of the included studies. Section 3.4 provides a summary of the neutralisation effect of Evusheld. Sections 3.5 and 3.6 provide a summary of any indirect treatment comparisons; whilst Section 3.7 clarifies that no additional work on the clinical effectiveness was undertaken by the EAG. Finally, Section 3.8 provides the conclusions of the clinical effectiveness chapter.

3.1 Critique of the methods of review(s)

In general, the clinical evidence submitted by the company comprises a systematic literature review (SLR) with targeted updates. However, the presentation of the SLR in the CS is complex due to the lack of clarity and extensive cross-referencing between (and within) the main document, its appendices and the company's clarification response. Further details are provided in the sections below.

3.1.1 Searches

The company performed one clinical effectiveness search to identify all effectiveness and safety studies (RCT & non-RCT evidence) of Evusheld or comparator preventative/prophylaxes for COVID-19 (Appendix D.1 Identification and selection of relevant studies).

Several clarification questions were raised with the company (CS A25-31) that were related to:

- Field-restricted searching for the population (title only)
- Population search terms (COVID-19) compared to NICE's COVID-19 search filter
- Reporting of targeted literature searches and retrieval of non-RCT and observational evidence
- Restricted AEs searching
- Inconsistent application of search terms in the original non-traditional database searches (missing intervention terms for 'Evusheld' and utilization of the COVID specialist databases).

The company searched several electronic bibliographic databases in October 2021 (Appendix D.1 Identification and selection of relevant studies): MEDLINE (via Ovid), MEDLINE in Process (via Ovid), EMBASE (via Ovid), and EconLit (via Ovid). Three living databases were searched: COVID-19 L-OVE; COVID-NMA; WHO COVID-19 Research Database. The company searched several key conference abstracts via websites or EMBASE searches (via Ovid) in the last two years (2021 and

2022): the International Society for Health Economics and Outcomes Research, the European Respiratory Society International Congress, the Infectious Diseases Society of America, the Society for Healthcare Epidemiology of America, the Human Immunodeficiency Virus Medical Association, Paediatric Infectious Diseases Society, and the Society of Infectious Diseases Pharmacists (via IDWeek), and the Academy of Managed Care Pharmacy.

In all the traditional database searches, limited terms for the population COVID-19 were applied, including field-restricted searching to titles only (CS, Appendix Tables 2 [p7], Tables 11-15 [p29-31], and Table 30 [p118]). Whilst the company has used a limited but relevant set of keywords for "COVID-19", the EAG also notes that there is a living COVID search filter by NICE (Levay & Finnegan, 2021)[22] where multiple field searching is carried out (title, abstract, keyword heading, and keyword heading word) and MeSH headings are included (SARS-COV-2/ and COVID-19/). The company acknowledged that title field searching was not a form of high-sensitivity search but that this would be mitigated by citation searches (CS clarification response to A25). Indeed, the EAG explored the impact of this approach on the number of records retrieved, showing that the different strategies result in > 322K compared to ~249K results.

It was unclear to the EAG, how non-RCT and observational evidence (prophylactic) of Evusheld were retrieved and identified, given that the database searches were restricted by applying an RCT filter to find only RCT evidence (statements 18-19 of CS Appendix D.1 Table 2 [p7]). The company clarification response (A5) describes daily searches being undertaken in PubMed, via preprint servers (including MedRxiv, SSRN and Research Square), and hand searching of key journals (e.g., The Lancet, The Lancet Infectious Diseases, The Lancet Respiratory Medicine, The Lancet Microbe, eClinicalMed, eBioMed, Science, Cell, Nature, and Nature Med). While daily searches for the most recent studies are feasible, the EAG believes that this would be difficult to document (using PRISMA), and thus it is unclear where studies originated.

In CS B2.1.2., the CS [p32] conducted bi-monthly targeted literature review searches from October 2021 onwards to monitor published clinical studies (CS, Appendix D.1.4. [p17]) e.g. the PROVENT trial.[20] The company reported a further five RWE comparative studies that have evaluated prophylaxis in immunocompromised patients, although only two studies informed both the clinical effectiveness review and the economic modelling (Young-Xu *et al*.[23] and Kertes *et al*.[24]). The EAG questioned the company about the reason for replacing the original SLR searches with targeted searches. The company chose to search fewer database sources because the L-OVE COVID database covered multiple databases, including PubMed and Embase (clarification response A25). Following the EAG request,

the company provided comprehensive tables of all search terms applied to targeted updated database searches (A25, Tables 15-22).

The EAG review of the company's applied search terms shows inconsistent application and reporting of the intervention and comparator search terms (see CS Appendix D.1. Table 3 [page 8]). The key terms that are missing from the searches include "Evusheld," "tixagevimab", or "cilgavimab." The EAG also notes that the application of search terms was not sufficient to search the COVID L-OVE database and that the drop-down search functionality of intervention names should have also been applied. The company provided a satisfactory response (A30) that the brand name and substance name were not available on the date of the searches in October 2021, and thus keywords for "AZD7442" and "long-acting antibody" were used instead.

The EAG reviewed the targeted search strategies in the L-OVE COVID database (covering 43 databases) and grey literature sources (clinical trials registries, pre-print databases, Food and Drug Administration [FDA], European Medicines Agency [EMA], and NICE databases), and that the company's applied keywords were comprehensive (clarification response A26). Whilst there are studies to suggest that this database is the most comprehensive in terms of source and content coverage (Verdugo-Paiva *et al*., 2022)[25], there are no studies to assess the performance and usability of the search interface and functions, i.e. via the 'advanced search' interface, classification platform. The company had only searched the 'advanced search' interface and not the classification platform so the impact of this is unclear.

In response to the EAG request, the company provided full search strategies (clarification response A26) to the databases searched in CS Appendix D Table 6 for COVID L-OVE: three clinical trials registries (WHO International Clinical Trials Registry Platform, Clinicaltrials.gov, and EU Clinical Trials Register); preprint searches in MedRxiv and BioRxiv combined; NICE's Rapid Guideline and Summaries on COVID-19; EMA COVID-19 Database; and the FDA COVID-19 Database. The terms in the targeted searches are comprehensive and consistently applied across the sources listed in CS Appendix D Table 6.

The EAG questioned the company (clarification response A27) about whether additional studies have been found since the last reported searches in May 2022, given the high publication output rates. The company's clarification response confirmed that a non-relevant publication had been published by

Herman *et al*.,[26] which was a secondary publication to NCT04452318, a post-exposure prophylaxis study of casirivimab and imdevimab.

In the original SLR, the company did not separately search clinical trial registries (clarification response A28) such as clinictrials.gov and/or the WHO ICTRP but instead searched through the COVID-NMA website. The company did, however, search these sources in the targeted updated database searches. The COVID-NMA static list of preventative treatments website was reviewed by the company. However, trials are only included up to October 2021. Because the COVID-NMA database search interface has not been formally evaluated, the EAG cannot comment on whether this approach is more sensitive and whether no studies were missed.

The technology is marketed for pre-exposure prophylaxis; the intended population is in those not infected with SARS-COV-2 who are unlikely to mount an adequate immune response to COVID-19 vaccination. The company has conducted searches for AEs in PubMed and EMBASE for Evusheld (CS Section B2.10 and Appendix F). According to the Cochrane Handbook,[27] searches in a few databases may not be adequate, and a breadth of sources is required. The EAG questioned the sources searched for AEs, such as the Web of Science Citation Index, BIOSIS Previews. Unpublished sources were recommended by the EAG, such as the Medicines and Healthcare products Regulatory Agency (MHRA) Yellow Card Scheme (https://yellowcard.mhra.gov.uk/), the European Medicines Agency's EduraVigilance database (https://www.ema.europa.eu/en/human-regulatory/research-development/pharmacovigilance/eudravigilance), trials registers and regulatory agency websites. However, after searching these additional sources, no further studies were found by the company (clarification response A31).

The EAG had reviewed the company's further searches for AE (CS Appendix F [p24]) and identified several search limitations that are contrary to Cochrane guidance on searching for these studies: i) restricted term searching; ii) restricted free-text terms for AE searching iii) a lack of generic index terms search for AEs iii) a lack of floating heading searching.[27]

EAG's additional searches for safety

Given that the evidence base for Evusheld is less than 300 references, the EAG expanded the Evusheld search to multiple-purpose searching (.mp. which will search 11 fields). In Appendix 1, Table 32, the Evusheld terms are combined with generic drug reaction terms (Statement 6), AE indexed headings (Statement 8), and floating subheadings (Statement 10). However, the EAG did not attempt to identify

studies from the search results, so it was not possible to confirm the effect of these search approaches on the number of relevant studies retrieved.

EAG comparison of NICE's COVID-19 search filter versus company searches

The EAG compared the published COVID-19 search filter with the company's COVID-19 search terms. These can be found in Appendix 1, Table 33, NICE's COVID-19 search statements are 1-4, whereas the company's terms are found in statement 10. The EAG concluded that NICE's filter was more sensitive because of the multiple field searching (73K more records) and broader term variants (21K more records). However, the EAG is unable to confirm the effect of this difference on the number of relevant studies retrieved if the filter is combined with the intervention/comparator terms and study design filters,

In summary, although the EAG is confident that all relevant controlled trials (published and unpublished) would have been identified by the company including ongoing/planned trials; the EAG is not confident that all relevant non-controlled studies would have been identified (also see section 3.1.2). Whilst it was not possible for the EAG to undertake a rapid review of Evusheld for COVID-19, a recent SLR (available as a preprint)[28] on the clinical effectiveness of Evusheld for prophylaxis of COVID-19 in immunocompromised patients included 17 studies (ten retrospective cohort studies,[23, 24, 29-36] six prospective, observational cohort studies[37-42] and one RCT).[43] Nine of these 17 studies[23, 24, 29, 32, 34-36, 39, 43] were included and or cited within the CS, its appendices or clarification responses. However, it is unclear if the remaining (all non-comparative RWE) studies were identified by the company searches or excluded at the study selection stage.[30, 31, 33, 37, 38, 40-42] The EAG also notes that a study by Bertrand *et al*., was identified in the company's SLR but not in the SLR conducted by Suribhatla *et al.*[28]. Both SLRs failed to identify Goulenok *et al.,*[44] a non-comparative RWE study which was identified in the Rapid C-19 Oversight Group report.[45]

3.1.2 Inclusion criteria

The CS describes an adequate method of identifying and screening references for inclusion in the SLR of clinical effectiveness. Two independent reviewers applied pre-specified inclusion and exclusion criteria (via a two-stage sifting process) to citations identified by the searches. Any disagreements were resolved by discussion with a third reviewer (see clarification response to question A9, p38 and A13 p42). A summary of the inclusion and exclusion criteria, as reported in the CS (Appendix D1.1, Table 4) and the company's clarification response (question A8), is reproduced (with minor changes) in Table 4.

Table 4: Inclusion/exclusion criteria used to select studies of Evusheld in the CS (reproduced with minor changes from CS, Appendix D1.1, Table 4 and company's clarification response, Table 6)

Criteria	Inclusion	Exclusion
Population	• Pre-exposure: people who had not been exposed to coronavirus and had not tested positive • Post-exposure: people who had had a positive polymerase-chain-reaction (PCR) test and are asymptomatic (i.e., do not present any symptoms) • All ages included	• Non-human studies • People diagnosed with COVID-19 and with symptoms
Interventions*	• Evusheld® (combination of tixagevimab [AZD8895] and cilgavimab [AZD1061]) • Bamlanivimab (also known as LY-CoV555 and LY3819253) • Etesevimab (also known as LY-CoV016 and LY3832479) • Casirivimab (also known as REGN10933) • Imdevimab (also known as REGN10987) • Casirivimab + imdevimab (the brand name for the combination of both is REGEN-COV®) • ADG20 • Molnupiravir (Lagevrio® [also known as MK-4482 and EIDD-2801])	• Any other treatments
Comparators*	• Any of the above interventions • Vaccine booster (i.e., third dose of any vaccine) • Standard of care / best practice • Placebo	• Any other treatments
Outcomes	• Efficacy outcomes o Incidence of SARS-CoV-2 RT-PCR-positive symptomatic illness o Incidence of patients with post-treatment response o Hospitalisations after treatment (general ward or ICU) o Incidence of COVID-19-related death after treatment o Incidence of all-cause mortality after treatment, with detail about case of death if reported • Safety outcomes o Adverse events (AEs) (total and grade ≥3), up to 10 AEs from the categories below o Serious AEs (total), up to 10 AEs from the categories below o Safety categories:	• Studies that do not report any of these outcomes will be excluded due to lack of outcomes of interest • Studies reporting solely outcomes not related to clinical efficacy or safety of preventative/prophylactic treatment, for example epidemiological data, healthcare resource use data, mental health outcomes, will be excluded

Criteria	Inclusion	Exclusion
	▪ Blood and lymphatic system disorders (total n, %) ▪ Metabolism and nutrition disorders (total n, %) ▪ Nervous system disorders (total n, %) ▪ Gastrointestinal disorders (total n, %) ▪ Skin and subcutaneous disorders (total n, %) ▪ Musculoskeletal and connective tissue disorders (total n, %) ▪ General disorders and administration site conditions (total n, %)	
Study design	• Clinical trials, including early stage (phase I and II) and clinical stage (phase III and IV)**	• Pooled analyses • Ad-hoc analyses • Single-arm clinical trials • Observational studies (e.g., prospective or retrospective cohort studies) • RWE studies (e.g., clinical registry studies, reviews of medical records) • Pharmacodynamic/pharmacokinetic studies • Genetic studies • Cellular/molecular studies • Case reports or case series • Narrative reviews • Qualitative studies • In vitro, ex vivo studies • SLRs and NMAs***
Additional limits	• Time limit: 2020 to 7th October 2021 • Geographical limits: no limits • Language: only abstracts published in English language will be included	• Conference abstracts • Letters to the editor • Editorials • Comments • Notes • Erratum • Trial protocol • Guidelines

* Criteria updated for greater clarity following a clarification request to question A8 (Table 6, p37)
**When publications were identified reporting on different trial stages for a single product (i.e., phase II and phase III for the same product), only the latest trial stage was extracted
***Relevant SLRs were excluded but flagged

Abbreviations: AE, adverse event; COVID-19, coronavirus disease 2019; HIV, human immunodeficiency virus; ICU, intensive care unit; IFN, Interferon; LAAB, long-acting antibody; NMA, network meta-analysis; NSAID, non-steroidal anti-inflammatory drug; PCR, polymerase chain reaction; rSIFN-co, Recombinant super-compound interferon; RT, reverse transcription; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SLR, systematic literature review

The specified inclusion and exclusion criteria were mostly appropriate and generally reflected the decision problem. It is noteworthy that the CS (Section B2.1. p31-35) initially considered a wider remit

to capture the entire evidence base as part of the inclusion criteria for the SLR (i.e., all potentially relevant preventative/prophylactic treatments for COVID-19) but then restricted the SLR only to those studies which were directly relevant to the decision problem (i.e., Evusheld only [see CS, Section B.2.1.2]). In addition, the company's systematic review was originally planned to exclude all non-trial evidence including RWE and observational evidence (CS, Table 4, Appendix D.1.1, p8-11). However, the CS (see Section B2.1.2, p33) states that "*As of 30th May 2022, five comparative real-world evidence (RWE) studies of Evusheld were identified (2,72–75) These studies evaluated prophylaxis in immunocompromised populations who were predominantly vaccinated, during a period when Omicron sub-lineages were dominant*". The CS (including the company's clarification response to questions A9 and A5) did not provide sufficient detail on how this non-trial evidence was identified and which inclusion/exclusion criteria were applied during the study selection process. For example, it is unclear why a potentially relevant unpublished RWE study by Chen *et al*.,[34] which investigated COVID-19 cases and clinical outcomes in a cohort of immunocompromised patients who received Evusheld for pre-exposure prophylaxis within a single health system in the US during a period when Omicron was the predominant circulating variant, was excluded from the CS. The company's clarification response to question A10 suggest this study was excluded as it '*did not use authentic Evusheld'.* The EAG and their clinical advisors are not aware of the manufacturers and availability of generic Evusheld in the US health system. Ideally, SLRs should have clearly focused research questions and inclusion/exclusion criteria at the outset.

The company's SLR excluded studies which were reported only as abstracts (CS, Table 4, Appendix D.1.1, p8-11); however, no justification for this exclusion was provided. In order to avoid publication bias, a SLR should aim to include all relevant studies, regardless of publication status. Although differences often occur between data reported in conference abstracts and their corresponding full reports, differences in results are usually not very large.[46] However, the EAG notes that it can be difficult to appraise study quality from limited details provided in an abstract. As a result, sensitivity analyses may be carried out to examine the effect of including data from conference abstracts.[47] Furthermore, limiting a systematic review by language (as reported in the CS, Appendix D.1.1, p7 and p10) can lead to language bias.[27, 48]

3.1.3 Critique of data extraction

The data extracted and presented in the CS for the SLR of clinical evidence appear to be appropriate and comprehensive. As noted in the company's clarification response (questions A13 and A26), all relevant data were extracted by a single reviewer and checked for accuracy by a second independent reviewer. Any discrepancies were resolved through discussion with a third reviewer. Further to section 3.1.1, neither the EAG nor its clinical advisors are aware of any additional relevant completed studies within the scope of this appraisal.

3.1.4 Quality assessment

The company used various tools to assess the quality of each key source of evidence (CS, Section B2.7 and Appendix D1.3). As noted in the company's clarification response (questions A13 and A15), assessment of the methodological quality of key included studies was performed by one reviewer and checked by a second reviewer. In general, the EAG considers the quality assessment tools used by the company to be acceptable.

The methodological quality of RCTs (the PROVENT trial),[20] was assessed using the minimum criteria for assessment of risk of bias and generalisability, as recommended in the current NICE user guide template for company evidence submissions.[49] The methodological quality of RWE studies (i.e., Young-Xu *et al*.,[23] and Kertes *et al*.,[24]) was assessed using the criteria recommended in the current NICE user guide template for company evidence submissions for non-randomised and non-controlled evidence.[49] However, the EAG believes that this tool is less appropriate for assessing the quality of RWE studies. Following a request for clarification from the EAG (see clarification response, question A16), the company critically appraised the observational RWE discussed in the CS using the recently developed ArRoWS critical appraisal tool[50] (see Section 3.2.2.1 for further details).

The EAG notes that the company did not quality assess all key studies included in the CS. As noted in the CS (p35), the TACKLE study[51] was part of the evidence base (albeit additional) that informed the safety of the higher 600mg dose of Evusheld. Owing to time constraints, the EAG was unable to undertake any additional quality assessments.

3.1.5 Evidence synthesis

The company undertook a narrative synthesis of the evidence for Evusheld; however, no explicit details were provided in the CS on how this approach was undertaken. Ideally, a narrative synthesis approach should be justified, rigorous (i.e. describe results without being selective or emphasising some findings over others) and transparent to reduce potential bias.[27, 46] Despite the lack of transparency regarding the methods adopted, the EAG acknowledges that the narrative synthesis approach undertaken by the company was acceptable.

3.2 Critique of trials of the technology of interest, the company's analysis, and interpretation

The key clinical studies identified by the company (PROVENT trial)[20] along with RWE studies (Young-Xu *et al*.[23] and Kertes *et al*.[24]) and the main study used by the company to estimate safety of the 600 mg dose of Evusheld (the TACKLE study[51] [see clarification response, question B4]) are summarised in Table 5.

It should be noted that three additional RWE studies (Al Jurdi *et al*.,[52] Bertrand *et al*.,[53] and Kaminski *et al*.[35]) were identified by the company. The evidence from these studies was not considered by the company to be the most relevant for informing both the clinical effectiveness of Evusheld in the real-world setting and suitable for economic modelling (CS, Section B2.1.2.1, p34). The reasons for exclusion, as noted in the CS (Table 35, p35 and Evidence Submission Summary, Section A6, p17) include small study sample sizes, the lack of generalisability to the population in whom are likely to receive treatment in UK clinical practice, no useable data to inform the inputs of the economic evaluation and restricted populations (limited to solid organ transplant recipients). The EAG and their clinical advisors consider solid organ transplant recipients to be an important high-risk clinical subgroup within the overall immunocompromised population. The inclusion and analysis of this evidence in the CS would have been helpful.

Although the original CS failed to provide details of all completed and ongoing studies that should provide additional evidence in the next 12 months for the indication being appraised, this information was provided by the company following a clarification request. In summary, a number of studies are ongoing or planned but the most relevant is the sub-study within PROVENT[18] and the ENDURE study[19]. As noted in the company's clarification response to question A1, the PROVENT sub-study is designed to investigate the safety and pharmacokinetic profile of repeat doses of Evusheld in PROVENT study participants who may benefit from repeat dose of Evusheld, and whether repeat dosing can maintain serum levels associated with protection against COVID-19. The sub-study specifically examines the 300 mg dose (Evusheld redosing at 6 and 12 months) and the 600 mg dose (Evusheld redosing at 6 months). Data reported at 12-months for the 300 mg dose and 6-months for the 600 mg dose is anticipated to be available [redacted]. The ENDURE study, a phase II, randomised, open-label, repeat dose-ranging study is designed to assess the safety, immunogenicity, pharmacokinetics, and pharmacodynamics of Evusheld (600 mg followed by 300 mg every 3 months [5 doses totally, administered by intramuscular injections] compared with 1200mg by intravenous infusion followed by 600 mg every 6 months by intramuscular injections [3 doses totally]) for preexposure prophylaxis of COVID-19 in adults and paediatric individuals (≥ 12 years of age weighing at least 40 kg), who are moderately to severely immunocompromised.[19] [redacted]. For further details of all other ongoing and planned studies see the company's clarification responses to question A17.

Table 5: Summary of key studies (adapted from CS, Tables 6-10; Sections B2.3 to B2.5 and Evidence submission summary, Table 2)

Study name	Design	Recruitment period	Population	Sample size	Intervention	Comparator	Primary outcome(s)
Clinical studies							
Levin *et al.*[20] **(PROVENT, NCT04625725)**	• Phase 3, randomised, double-blind, placebo-controlled trial • 87 sites, 5 countries including UK	• Recruited between Nov. 2020 and March 2021 • Period when Alpha and Delta variants were dominant	• Pre-exposure prophylaxis of COVID-19 in adults (aged ≥18 years) at increased risk for inadequate response to active immunization (predicted poor responders to vaccines or intolerant of vaccine) or having an increased risk for SARS-CoV-2 infection. • Negative point-of-care SARS-CoV-2 serology test result at screening	5197 (All unvaccinated at screening, 3.8% immuno-compromised [defined as those receiving immunosuppressive therapy or immunosuppressive disease]) *	• Evusheld, 300mg (n=3460) Administered as single dose (one 150 mg intramuscular injection of each antibody administered sequentially)	• Placebo, (n=1737) Administered as saline placebo (two 150 mg intramuscular injections)	• Incidence of COVID-19 (SARS-CoV-2 infection confirmed by RT-PCR with qualifying symptoms) on or before day 183 • Incidence of adverse events through 457 days post dose
Real-world evidence							
Young-Xu *et al.*[23]	• Retrospective cohort study • Multi-sites across the USA (Veteran Affairs healthcare system)	• Recruited between Jan. 2022 and April 2022 • Period during high prevalence of Omicron BA.1 variant and the early BA.2 and BA.2.12.1 surge	• Veterans (aged ≥18 years), immunocompromised or otherwise at high risk for COVID-19	8087 (matched population) (Majority vaccinated [2 doses: 21%; 3 doses: 74%]), 92% immunocompromised** and 8% high risk for COVID-19)	• Evusheld, 300mg and 600 mg (n=1733 [after matching]) Initially administered as single dose (one 150 mg intramuscular injection of each antibody administered sequentially). Following the FDA's revision of emergency use authorisation, dose increased to 600 mg	Propensity matched controls, no Evusheld (n=6354)	• Composite of SARS-CoV-2 infection (confirmed by RT-PCR or antigen testing), COVID-19-related hospitalisation (within 30 days of positive tests), and all-cause mortality during follow-up

Study name	Design	Recruitment period	Population	Sample size	Intervention	Comparator	Primary outcome(s)
					(83% of patients received the higher dose)		
Kertes *et al.*[24]	• Retrospective cohort study • Multi-sites across Israel (Maccabi Healthcare services)	• Recruited between Feb. 2022 and May 2022 • Period during when Omicron BA.1 and BA.2 were predominant	• Immunocompromised individuals (aged ≥12 years and >40kg) considered at high risk for COVID-19 infection and complication	5124 (Majority vaccinated (1-2 doses: 11%; 3-4 doses: 79%), all immunocompromised)†	• Evusheld, 300mg (n=825) Administered as single dose (one 150 mg intramuscular injection of each antibody)	• Unmatched controls, no Evusheld (n=4299)	• Incidence of SARS-CoV-2 infection confirmed by positive PCR or positive antigen test during follow-up
Additional safety evidence (600 mg dose)							
Montgomery *et al*.[51] (TACKLE, NCT04723394)	• Phase III randomised, double-blind, placebo-controlled trial • 95 sites, 15 countries including UK‡	• Recruited between Jan. 2021 and July 2021 • Period when Alpha and Delta variants were dominant	• Non-hospitalised adults (≥18 years) with laboratory-confirmed (RT-PCR or antigen test) COVID-19 infection and who had not received a COVID-19 vaccination. WHO Clinical Progression Scale score ≥1 to <4.	903 (All unvaccinated; 5% immunocompromised, not defined)	• Evusheld, 600mg (n=452) Administered as single dose (one 300 mg intramuscular injection of each antibody)	• Placebo, (n=451) Administered as saline placebo (two 300 mg intramuscular injections)	• Composite of either severe COVID-19 or death from any cause (until and including day 29)

* In contrast, in the publication by Young-Xu *et al*.,[23] the authors discussion of the PROVENT study defined the immunocompromised population as those in receipt of immunosuppressive therapy, have immunosuppressive disease or cancer, 11%. The CS (p77) on the other hand defines the immunocompromised population more broadly as individuals at increased risk for inadequate response to active immunisation i.e., history of chronic kidney disease, immunosuppressed disease, immunosuppressive treatment, chronic liver disease, cancer, or solid organ transplant, [redacted]
** Young-Xu *et al*.,[23] defined the immunocompromised status on 1) whether the patient received an immunosuppressive medication during the 30 days before the index date or 2) the presence of at least one qualifying immunocompromising condition, based on ICD-10 codes (for full list of codes see Young-Xu *et al*.,[23] Appendix II), during the two years before index date. Severely immunocompromised defined as those who had a solid organ transplant or received anti-rejection medication for transplant or chemotherapy for cancer treatment in the prior month
† Kertes *et al*.,[24] defined severe immunosuppression as individuals diagnosed with and/or receiving treatment for hypogammaglobulinemia, chronic lymphocytic leukaemia, Anti-CD20 monoclonal antibody–mediated B-cell depletion therapy, bone marrow transplant, chimeric antigen receptor T-cell (CAR-T) therapy, solid-organ transplant, aggressive lymphoma, multiple myeloma
‡ Information sourced from https://clinicaltrials.gov/ct2/show/NCT04723394

3.2.1 PROVENT trial[20]

The PROVENT study is an ongoing phase 3, randomised, double-blind, placebo-controlled, multi-centre, pre-exposure prophylaxis trial designed to evaluate the efficacy and safety of Evusheld with placebo for the prevention of symptomatic, PCR-confirmed, COVID-19. The study recruited 5197 unvaccinated (46.1% female, 73.0% white) adults aged ≥18 years (mean 53.5 years; 43.4% aged ≥60 years; 4.2% aged ≥75 years) with an increased risk of an inadequate immune response to vaccination (73.3%) and/or having an increased risk of exposure to SARS-CoV-2 infection (defined as those whose locations or circumstances put them at appreciable risk of exposure to SARS-CoV-2 [52.5%]) at 87 sites in 5 countries (including the UK). The study excluded people with a history of SARS-CoV-2 infection, a positive SARS-CoV-2 result, or previous receipt of a vaccine or biologic agent indicated for the prevention of SARS-CoV-2 or COVID-19. Between 21 November 2020 and 22 March 2021, participants with a negative point of care SARS-CoV-2 serologic test result at screening were randomised to receive a single 300 mg dose of Evusheld (administered by two consecutive intramuscular injections, one containing 150 mg tixagevimab and the other containing 150 mg cilgavimab, n=3460) or saline placebo (n=1737).

The primary efficacy endpoint was the first episode of COVID-19 (with SARS-CoV-2 infection confirmed by means of RT-PCR with qualifying symptoms) occurring after administration of Evusheld or placebo on or before day 183. The safety follow-up duration was 15 months (AEs from injection to day 457 [CS, Table 10, p45]). Given the extreme vulnerability of this trial population, participants were allowed to unblind once they became eligible for vaccination against COVID-19 and the results of these patients were censored in the primary endpoint analysis. A protocol amendment modified the primary analysis to reduce the potential impact of unblinding and/or COVID-19 vaccination on the trial's ability to robustly quantify placebo-controlled efficacy. The primary analysis was originally scheduled to occur after 183 days but was amended to take place either after 24 events or when the trial reached an unblinding rate of 30% (at which point the ability to observe primary endpoint events is expected to have diminished), whichever occurred first. This resulted in a reduced follow-up time. The data cut-off for the primary analysis occurred on 5 May 2021, with a median follow up of 83 days. An additional extended follow-up data cut-off for the primary endpoint occurred on 29 August 2021, with a median follow-up of 196 days (this analysis was not pre-specified and was decided after study unblinding).[54] The study was financially supported by AstraZeneca and the U.S. government.

The company's assessment of the design, conduct and internal validity of the PROVENT trial is summarised in Table 6. The EAG broadly agrees with the company's risk of bias assessments based on the full trial population, although the EAG considers it important to highlight that the target population for the CS is aligned with a subgroup of participants at highest risk (e.g., immunocompromised groups

[as defined in Table 5]) that was not statistically powered to detect differences in efficacy for any of the measured outcomes.

Table 6: Quality assessment results for the PROVENT study,[20] as assessed by the company (adapted from CS, Section B2.7, p69)

Quality assessment criteria	PROVENT trial[20]	
	Company's assessment	EAG's assessment
Was randomisation carried out appropriately?	Yes	Yes
Was the concealment of treatment allocation adequate?	Yes	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes	Yes
Were there any unexpected imbalances in dropouts between groups? If so, were they explained or adjusted for?	No	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No
Did the analysis include an intent-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	Yes
Is there any evidence of bias in the selection of the reported results?	Not assessed*	Yes
* Domain not assessed by the company despite a clarification request to question A15		

In general, based on this quality assessment, the EAG considered the PROVENT trial[20] to be a well-reported and conducted study; however, some further discussion around specific points is required.

In the PROVENT trial, adequate methods of randomisation, allocation concealment, blinding and analysis methods were used in the conduct of the trial. However, there are some concerns across the outcomes assessed as the extended follow-up at a median of 193 days was not pre-specified in the study protocol.[20, 54] In addition, unblinding to assigned treatment was allowed in the trial if participants wanted to consider COVID-19 vaccination. It is not fully clear how large the extent of unblinding might have affected the results and as noted in Levin *et al*.,[20] unblinding for COVID-19 vaccination decreased the number of participants who were available for longer-term, double blind follow-up and the introduction of vaccines. Other measures and different variants across different countries throughout the course of

the study may have affected the incidence of SARS-CoV-2 infection during the study[20] and progression to severe outcomes such as hospitalisations/death is unknown.

Moreover, the generalisability of the results from the PROVENT trial to UK clinical practice is unclear. The PROVENT study was not conducted in vaccinated patients or at a time when the Omicron variant was dominant. During the PROVENT study, the Alpha, Beta, and Delta variants of concern were identified in the study population. Currently, the omicron sub-variant of COVID-19, BA.5, including all sub-lineages, remains the dominant lineage in the UK at greater than 75% of all sequenced samples in the UK.[55] In addition, there is emerging evidence to suggest that Evusheld has some activity against omicron; however, it appears to be notably less effective against the currently prevalent Omicron subvariants BA.4 and BA.5, when compared to other subvariants such as BA.2.[23, 38, 52, 56, 57] Concerns have also been noted that only cilgavimab but not tixagevimab may retain antiviral activity against Omicron variants (e.g. BA.2 and BA.5) and the use of combination therapy may give rise to escape variants, or viral resistance.[58-60] In response to a clarification request (question A6) the company comments that '*Despite the reduction in in-vitro neutralising activity, Evusheld has been shown to be effective in preventing symptomatic and severe COVID-19 throughout the BA.1 and BA.2 waves (Young-Xu et al. Al Jurdi et al., Kertes et al.)… In the case of BA.2, BA.4, and BA.5, where one of the antibodies appears to have lost neutralising activity, the other antibody remains able to potently neutralise the virus. This is because the activity of each antibody is not dependent on the other. Each individual antibody works together to increase overall activity of the product against certain variants. This also enables prevention against potential viral evolution in the case where one antibody is less active against a certain variant.*' This is discussed further by the EAG in Section 3.4.

In the PROVENT trial, all eligible participants were required to have a negative point of care SARS-CoV-2 serologic test result. However, as noted in clarification response B1 (p35-36) no testing is foreseen in clinical practice. As such it is unclear whether a similar magnitude of benefit will be observed in clinical practice or whether the treatment effect will be diluted by a proportion of patients receiving Evusheld after they have been infected but before they experience symptoms. The size of this will depend on the incidence of SARS-CoV-2 infections in the population being offered Evusheld at the time it is made available

Finally, the PROVENT trial does not currently inform on the appropriateness and timing of repeat dosing with an expected 600mg dose of Evusheld every 6 months (clarification response A1), which is the treatment course assumed in the economic model. However, this is being investigated in the PROVENT sub-study and the ENDURE Dose Ranging Study[19] (company's clarification response to question A1 and A17). In addition, the PROVENT trial does not provide any evidence on the use of Evusheld in those under 18 years of age or pregnant women and provides limited evidence in those

aged over 75 years (a group at significant mortality risk).[61, 62] The EAG further notes that it is not entirely clear how the immunocompromised population was defined in the trial (e.g. receipt of immunosuppressive therapy or have immunosuppressive disease, 3.8% [196/5197]) and how it aligns with the highest clinical risk groups defined in the McInnes report (CS, Table 4, p21). It is noteworthy that the CS (p77) defines the immunocompromised population in the PROVENT study more broadly as individuals at increased risk for inadequate response to active immunisation i.e., history of chronic kidney disease, immunosuppressed disease, immunosuppressive treatment, chronic liver disease, cancer, or solid organ transplant, [redacted]

3.2.2 Real-world evidence studies

3.2.2.1. Young-Xu et al.[23]

Following the publication of the PROVENT trial, Young-Xu *et al*.,[23] conducted a retrospective cohort study using real-world data to assess the effectiveness of Evusheld for prevention of SARS-CoV-2 infection and severe disease among immunocompromised and high-risk US veteran patients, who were aged ≥18 years and received healthcare through the US Department of Veteran Affairs (VA) healthcare system until 30 April 2022 or until death (whichever occurred earlier). Initially, the first patients received pre-exposure prophylaxis at VA centres on 13 January 2022. Patients received a single 300 mg dose of Evusheld (administered by intramuscular injections, one containing 150 mg tixagevimab and the other containing 150 mg cilgavimab). On 24 February 2022, in response to concerns regarding effectiveness of the Evusheld against certain Omicron subvariants, the US FDA revised the Emergency Use Authorisation and increased the dose of Evusheld to 600 mg (administered as 300 mg tixagevimab and 300 mg cilgavimab) in the US. Patients who previously received the lower dose were advised to receive an additional dose.[63] The analysis compared a cohort of patients who had received at least 1 dose of Evusheld (n=1,733; 83% received the higher dose of 600 mg; mean age 67.4 years [69% aged ≥65 years; 25% aged ≥75 years]; 22% had 2 vaccine doses and 73% had 3 vaccine doses; and 9% were female) to a propensity score (PS) matching control cohort of immunocompromised or high-risk patients who did not have Evusheld over the follow-up period (n=6,354; mean age 68.1 years [71% aged ≥65 years; 26% aged 75 years]; 21% had 2 vaccine doses and 74% had 3 vaccine doses; and 9% were female). Immunocompromised status was defined as having an immunosuppressive medication within 30 days before the index date or the presence of an immunocompromising condition within 2 years before the index date (92% in both groups after matching). The analysis excluded all patients who were diagnosed with SARS-CoV-2 infection via a positive RT-PCR result or antigen testing within 3 months prior to the date or pseudo-date of Evusheld administration. The primary outcome was a composite of SARS-COV-2 infection confirmed by RT-PCR or antigen testing, COVID- 19 hospitalisation (defined as having both an admission and discharge diagnosis for COVID-19 from a hospital or within 30 days of positive SARS-CoV-2 RT-PCR result or antigen test), and all-cause mortality during the follow-up period.

The company's assessment of the design, conduct and internal validity of the Young-Xu *et al*.,[23] study is summarised in Table 7. The EAG broadly agrees with the company's risk of bias assessments.

Table 7: Quality assessment results for the Young-Xu *et al*.,[23] study, as assessed by the company using the ArRoWS critical appraisal tool for RWE studies (adapted from company's clarification response, question A16, p46-47)

Item	Young-Xu *et al.*[23] 2022	
	Company's assessment	**EAG's assessment**
1. Is the research question or objective(s) clear?	Good	Good
2. Is the study sample representative of its target population?	Good	Moderate
3. Has a sample size, power calculation or measure of uncertainty (e.g., confidence intervals, standard errors) been provided?	Yes	Yes
4. Are the exposure measures clearly defined and appropriate?	Unclear	Unclear
5. Is/are the outcome(s) clearly defined and appropriate?	Good	Moderate
6. Are confounders clearly defined and appropriate?	Good	Good
7. Are the statistical analyses clearly defined and appropriate?	Good	Moderate
8. Are the limitations of the study defined and appropriate?	Good	Good
9. Have the authors drawn appropriate conclusions from their results?	Good	Good
Cohort studies		
A1. Are the methods of follow up defined and appropriate?	N/A	Good
A2. Is the length of follow up sufficient to ascertain outcomes?	N/A	Good
A3. If the authors are measuring treatment effects, is the analysis appropriate (e.g., matching, propensity scoring, instrumental variables)?	N/A	Good
Case-control and comparative effectiveness studies		
A4. Have the authors explained their choice of cases and controls?	Good	N/A*
A5. If a matched case-control study, have the authors described their matching criteria?	Good	N/A*
A6. If a matched case-control study, was matching taken into account in the analysis?	Good	N/A*
Electronic database studies		
A7. Have the authors listed/referenced (from previous literature) a code set for relevant tests, procedures, treatments and clinical events (e.g., ICD codes, Read codes)?	Good	Good

Abbreviations: ICD – International classification of diseases; N/A – Not applicable.
* The EAG do not consider the Young-Xu *et al*.,[23] study to be a case-control study as individuals were selected by their exposure status rather than outcome/disease status.

In general, based on this quality assessment, the EAG considered the Young-Xu *et al*.,[23] study to be a well-reported and conducted observational study; however, some further discussion around specific points is required.

In addition to the known limitations of retrospective observational analyses (e.g. recording/coding and interpretive errors, presence of bias or potential confounding influences),[64-69] Young-Xu *et al*.,[23] also noted other study limitations such as confounding by indication and immortal time bias (i.e. a span of time in the observation or follow-up period of a cohort during which the outcome under study could not have occurred[70]). In addition, the study only recorded all-cause mortality (and not COVID-related mortality) in people at high risk of serious illness and the definition for COVID-19 hospitalisation was not clear (i.e., requiring a COVID infection to be recorded at both admission and discharge from hospital; not all individuals will have been discharged). Further critique of the statistical methods is provided in Section 3.3.2.1.

Moreover, the generalisability of the population from Young-Xu *et al*.,[23] study to UK clinical practice is unclear. For example, as noted by Young-Xu *et al*.,[23] the VA has a unique population (mostly male and elderly), only includes data and healthcare encounters that occur in VA medical centres, the use of specific codes (ICD-10) from claims data may inadequately capture comorbidity and functional status and potentially result in selection bias and the study excluded patients who were diagnosed with SARS-CoV-2 in the 3 months before Evusheld administration (i.e. only focuses on new infections). In addition, the analysis coincided with the Omicron BA.1 surge across the US and may not be generalisable to the current UK context and may be less effective against the currently prevalent UK Omicron subvariants such as BA.5 (see Section 3.2.1). Given these concerns, the FDA's revision of Emergency Use Authorisation dose to 600 mg (tixagevimab 300 mg/ cilgavimab 300 mg)[60] and the FDA's recent advice on 3 October 2022 about the risk of COVID-19 due to certain variants not neutralised by Evusheld,[63] it is unclear if higher doses will be needed or considered for emerging and future variants. As noted in the company's clarification response to question A2 (p15) the company '*maintains its position that the 600 mg dose is the dose supported by the totality of currently available data*'. Although the Young-Xu *et al*.,[23] study does not provide any evidence on the timing of repeat dosing with an expected 600mg dose of Evusheld every 6 months, the company's clarification response to question A1 and A17 suggests that this is currently being investigated in the PROVENT sub-study and the ENDURE study[19] (for further study details see company's clarification response to question A1 and A17).

3.2.2.2. Kertes et al.[24]

Kertes *et al*.,[24] conducted a retrospective observational study to assess whether Evusheld reduces the risk of SARS-CoV-2 infection and severe disease among a selected group of immunocompromised

individuals using real-world data identified in the Maccabi HealthCare Services (MHS) (a large health maintenance organisation in Israel) database.

Between 23 February 2022 and 2 May 2022, all individuals aged ≥12, weighing at least 40 kg, who did not have a positive COVID-19 test result (PCR or antigen) in the last month, were not vaccinated against COVID-19 in the previous 2 weeks, and had evidence of severe immunosuppression were invited by Short Message Service (SMS) or email to receive a single 300 mg dose of Evusheld (administered by intramuscular injections, one containing 150 mg tixagevimab and the other containing 150 mg cilgavimab). Severe immunosuppression in the study was defined as those diagnosed with and/or receiving treatment for hypogammaglobulinemia, chronic lymphocytic leukaemia, anti-CD20 monoclonal antibody–mediated B-cell depletion therapy, bone marrow transplant, chimeric antigen receptor T-cell therapy, solid-organ transplant, aggressive lymphoma or having multiple myeloma undergoing active treatment)

The study population was divided into 2 groups: those who were administered Evusheld (n=825: 37.9% were female; 37.3% were ≥70 years; 91.3% had at least 3 vaccine doses) and those who were not administered Evusheld (n=4,299: 46.7% were female; 31.2% were ≥70 years; 76.3% had at least 3 vaccine doses). This unmatched non-administered group was defined as those who did not respond to the invitation, were not interested in receiving the study drug or did not take steps to make or attend an appointment for whatever reason. The study excluded people who died/left the Maccabi HealthCare Service or were found to have COVID-19 on the day of the first SMS/e-mail receipt or day of Evusheld administration. The Evusheld group was followed up between the date of administration and the end of the study period (26 May 2022: median 53 days). The non-administered group was followed up between the date of first SMS/ email and the end of the study period (median 73 days). The primary outcome was the rates of SARS-CoV-2 infection, defined as any person with a recorded positive PCR or antigen test result in the follow-up period. As noted in the CS (Section 2.6.3, p68), although no matching was undertaken between the administered Evusheld group and the non-administered group, potential confounding variables (age, sex, socioeconomic status, comorbidities, prior COVID-19 infection) were adjusted for in the analysis of primary and secondary outcomes (COVID-19 infection, COVID-19 hospitalisation or all-cause mortality).

The company's assessment of the design, conduct and internal validity of the Kertes *et al*.,[24] study is summarised in Table 8. The EAG broadly agrees with the company's risk of bias assessments.

Table 8: Quality assessment results for the Kertes *et al.*,[24] study, as assessed by the company using the ArRoWS critical appraisal tool for RWE (adapted from company's clarification response, question A16, p46-47)

Item	Kertes *et al.*[24] 2022	
	Company's assessment	**EAG's assessment**
1. Is the research question or objective(s) clear?	Good	Good
2. Is the study sample representative of its target population?	Good	Moderate
3. Has a sample size, power calculation or measure of uncertainty (e.g., confidence intervals, standard errors) been provided?	Yes	Yes
4. Are the exposure measures clearly defined and appropriate?	Unclear	Unclear
5. Is/are the outcome(s) clearly defined and appropriate?	Good	Moderate
6. Are confounders clearly defined and appropriate?	Poor	Poor
7. Are the statistical analyses clearly defined and appropriate?	Good	Moderate
8. Are the limitations of the study defined and appropriate?	Good	Good
9. Have the authors drawn appropriate conclusions from their results?	Good	Good
Cohort studies		
A1. Are the methods of follow up defined and appropriate?	N/A	Good
A2. Is the length of follow up sufficient to ascertain outcomes?	N/A	Good
A3. If the authors are measuring treatment effects, is the analysis appropriate (e.g., matching, propensity scoring, instrumental variables)?	N/A	Poor
Case-control and comparative effectiveness studies		
A4. Have the authors explained their choice of cases and controls?	Good	N/A*
A5. If a matched case-control study, have the authors described their matching criteria?	N/A	N/A
A6. If a matched case-control study, was matching taken into account in the analysis?	N/A	N/A
Electronic database studies		
A7. Have the authors listed/referenced (from previous literature) a code set for relevant tests, procedures, treatments and clinical events (e.g., ICD codes, Read codes)?	Good	Unclear

Abbreviations: ICD – International classification of diseases; N/A – Not applicable.
* The EAG do not consider the Kertes *et al.*,[24] study to be a case-control study as individuals were selected by their exposure status rather than outcome/disease status.

In general, based on this quality assessment, the EAG considered the Kertes *et al*.,[24] study to be well-reported; however, it does not provide reliable RWE due to a number of methodological limitations. In addition to the known limitations of retrospective observational analyses,[64-69] Kertes *et al*.,[24] highlighted a number of study limitations, particularly related to selection bias. For example, it was unknown what proportion of patients in the control group never opened the SMS/email invite or intended to have treatment but did not complete the process. In addition, healthcare practices between those who presented for treatment and those who refused or lacked the motivation for treatment may be different. While it was assumed that all patients who were positive for SARS-CoV-2 presented to MHS, it is likely that not all patients presented to the service as the majority of those infected with the Omicron variant may have experienced mild or no illness and the availability of antigen home testing kits may have precluded testing at appointed centres. The study provided limited details on potential types of confounders; it did not take into account the differences in the use of other antiviral treatments that may have been available, e.g., nirmatrelvir, which may have affected severe disease prevalence; only recorded all-cause mortality (and not COVID-related mortality) and the length of follow up was shorter in the Evusheld administered group than the non-administered group, therefore there was more time for events to occur in the non-administered group. Modelling the risk of SARS-CoV-2 infection included adjustment for a limited set of patient characteristics including age, number of doses of COVID-19 vaccine received, prior COVID-19 illness, socioeconomic status, and chronic kidney disease (which were identified as factors which were found to have significant associations with the outcome variable). However, modelling the risk of severe disease (COVID-19–related hospital infection or all-cause mortality) was based on adjustment for only two factors (age group and cardiovascular disease); Kertes *et al*., state that this was due to only small number of study participants (n=64) reporting severe disease outcomes.[24] The adjustment for only a limited number of baseline characteristics means there is the potential for residual confounding; for example, there were observed differences in regard to the incidence of prior infection and vaccination rates (which were lower in the non-Evusheld cohort). Therefore, this raises serious concerns with the statistical analysis undertaken, particularly regarding the interpretation and generalisability of results from the logistic regression modelling.

The generalisability of the population from Kertes *et al*.,[24] study to UK clinical practice is unclear. As noted earlier, a major limitation of the Kertes *et al*.,[24] study is the potential for selection bias (including the inclusion of people with selected severely compromised immunity [it was unclear how these individuals were identified and selected within the MHS database]). In addition, the analysis coincided with the Omicron surge (predominantly BA.1 between February and March 2022, with the BA.2 variant becoming the most prevalent from April 2022) across Israel, which may not be generalisable to the current UK context given that the dominant subvariant in the UK is BA.5 (see Section 3.2.1).

Finally, the Kertes *et al*.,[24] study does not provide any evidence on the appropriateness and timing of repeat dosing with an expected 600mg dose of Evusheld every 6 months (clarification response A1); however, this is being investigated in the PROVENT sub-study and the ENDURE Dose Ranging Study[19] (company's clarification response to question A1 and A17). In addition, this study does not provide any evidence on the use of Evusheld in pregnant women and children aged under 12 years and provides very limited evidence in those aged 12 to 39 years (4.1% of total population).

3.2.3 Additional safety evidence – the TACKLE trial[51]

Given that the company anticipates usage at a 600mg dose in clinical practice, additional safety evidence from the TACKLE trial was presented in the CS to inform the safety profile of the 600 mg dose of Evusheld. As noted in the company's clarification response to question A14, a systematic review of adverse effects was not undertaken to demonstrate the safety profile of the anticipated higher dose of Evusheld. However, the company's clarification response (question A14) notes that supplementary searches were conducted to supplement the SLR and all studies and publications reporting outcomes on Evusheld (for licensed and higher doses and outside the target population) were included in the CS (Appendix F).

The TACKLE study is a phase 3, randomised, double-blind, placebo-controlled, multi-centre, trial designed to evaluate the safety and efficacy of a single 600 mg intramuscular dose of Evusheld for the treatment of COVID-19 in non-hospitalised adults (aged ≥18 years) with mild to moderate COVID-19 to prevent progression to severe disease or death. The study recruited 910 non-hospitalised unvaccinated adults aged ≥18 years who had a confirmed SARS-CoV-2 infection test (determined by RT-PCR or an antigen test) 3 days or less prior to enrolment across 95 sites in the USA, Europe, Latin America and Japan. A WHO Clinical Progression Scale score of ≥1 to <4 was also required for inclusion. Between 28 January 2021 and 22 July 2021, participants were randomised to receive a single 600 mg dose of Evusheld (administered by two consecutive intramuscular injections, one containing 300 mg tixagevimab and the other containing 300 mg cilgavimab, n=456) or saline placebo (n=454). The primary endpoints were severe COVID-19 or death from any cause through to day 29, and AEs. The primary safety endpoints were AEs, serious AEs, and AEs of special interest throughout the study. AEs of special interest included anaphylaxis and other serious hypersensitivity reactions, including immune complex disease and injection site reactions. The safety analysis was done in the safety analysis set, which included all participants who received the study drug up to 456 days after receiving the study drug. Although the company did not provide an assessment of methodological quality of the TACKLE study,[51] the EAG was unable to undertake any additional quality assessments due to time constraints.

3.3. Clinical effectiveness results

Based on information reported in the CS (including Appendices), this Section presents the main results from the PROVENT trial[20] along with RWE (Young-Xu *et al*.[23] and Kertes *et al*.[24]) and safety evidence of the 600 mg dose of Evusheld (the TACKLE study)[51] for the prevention of COVID-19. Additional information, not reported in the CS, was provided by the company in the company's clarification response.

3.3.1 PROVENT trial[20]

- Incidence of COVID-19 (symptomatic SAR-CoV-2 infection)

A summary of the key results from the PROVENT trial are summarised in Table 9. In the full pre-exposure analysis set, which consisted of all participants who had undergone randomisation, received at least one injection and did not have RT-PCR-confirmed SAR-CoV-2 infection at baseline (n=5172), the use of Evusheld was associated with a statistically significant reduction in the incidence of COVID-19 (RT-PCR-positive symptomatic illness) compared to placebo with a relative risk reduction (RRR) of 76.7% (95% confidence interval (CI): 46.1 to 90.0, p <0.001), as of the primary analysis data cut-off of May 2021 (median 83 days; range 3 to 166 days).[17] With an extended median 6-month follow-up (post hoc analysis conducted to provide updated safety and efficacy analyses; data cut-off August 2021) the beneficial effects of Evusheld were sustained but a lower incidence of symptomatic illness was observed in the Evusheld group than in the placebo group, with a RRR of 82.8% (95% CI: 65.8 to 91.4% [11/3441 (0.3%) compared to 31/1731 (1.8%)], respectively). The median duration from dose of Evusheld to 6-month follow-up was 196 days. The time to first COVID-19 RT-PCR-positive symptomatic illness was significantly delayed in the Evusheld group compared with the placebo group and was consistent (until August 2021 data-cut-off) over time (hazard ratio [HR] 0.23; 95% CI: 0.10 to 0.53; p<0.001).[71]

Although the PROVENT study was not designed to detect treatment differences with high statistical power within subgroups, the PROVENT study reported selected subgroup analyses for pre-specified subgroups (across baseline demographics and comorbidities [see CS, Section B2.8.1.5 for further details) and these were generally consistent with those obtained for the overall population. Most notably, as noted in the CS, (Section B2.8.1.5, p77), in the subset population of those categorised as being immunocompromised (defined as at increased risk for inadequate response to active immunisation i.e., history of chronic kidney disease, immunosuppressed disease, immunosuppressive treatment, chronic liver disease, cancer, or solid organ transplant, [redacted] the incidence of COVID-19 (RT-PCR-positive symptomatic illness) compared to placebo (a data cut-off of May 2021)
were [redacted] The EAG note that these results are slightly different to that reported in Levin *et*

al.,[20] due to the differences in defining the immunocompromised population and the length of follow-up. For example, for those participants receiving immunosuppressive treatment (173/5172 [0.3%], the RRR was 71.7% (95% CI: -301.0 to 98.0) at a median 6-month follow-up; however, for those with immunosuppressive disease (25/5172 [0.5%]), the RRR could not be estimated as there were no instances of COVID-19 (RT-PCR-positive symptomatic illness).[20] The study authors of the PROVENT trial further note that '*The limitations of our trial include the low number of events in smaller but important subgroups, including immunocompromised persons, so that efficacy in these groups could not be estimated*'[20]

Table 9: Primary outcome of PROVENT* (reproduced from CS, Table 3 with minor amendments, page 73)

First case of COVID-19 (RT-PCR-positive symptomatic illness)	Primary analysis				Median 6-month Follow-up†		
	Evusheld (n = 3,441)	Placebo (n=1,731)	Relative risk reduction % (95% CI)	P-value	Evusheld (n = 3,441)	Placebo (n=1,731)	Relative risk reduction % (95% CI)
Primary endpoint: first case of illness, with data censored at unblinding or receipt of COVID-19 vaccine	8 (0.2%)	17 (1.0%)	76.7 (46.0, 90.0)	<0.001	11 (0.3%)	31 (1.8%)	82.8 (65.8, 91.4)
Key supportive analyses							
First case of illness, regardless of unblinding or receipt of COVID-19 vaccine	10 (0.3%)	22 (1.3%)	77.3 (52.0, 89.3)	<0.001	20 (0.6%)	44 (2.5%)	77.4 (61.7, 86.7)
First case of illness, including all deaths, with data censored at unblinding or receipt of COVID-19 vaccine	12 (0.3%)	19 (1.1%)	68.8 (35.6, 84.9)	0.002	18 (0.5%)	36 (2.1%)	75.8 (57.3, 86.2)

*The full pre-exposure analysis set consisted of all the participants who had undergone randomisation, received at least one injection of Evusheld or placebo, and did not have RT-PCR-confirmed SARS-CoV-2 infection at baseline. Estimates were based on a Poisson regression with robust variance. The model included trial group (Evusheld or placebo) and age at informed consent (≥60 years or <60 years), with the log of the follow-up time as an offset. Unadjusted RRRs (95% CI) for the primary end point were the same as the adjusted RRRs for both the primary analysis and the median 6-month follow-up. An estimated relative risk reduction greater than 0 favoured Evusheld, with a p-value of less than 0.05 indicating statistical significance. † This analysis was not pre-specified in the trial protocol, so P-values were not calculated. Abbreviations: CI – Confidence interval; COVID-19 – Coronavirus disease 2019; RRR – Relative risk reduction; SARS-CoV-2 – severe acute respiratory syndrome coronavirus 2

In response to clarification question A23, the company provided an assessment of whether the proportional hazards (PH) assumption was met for the incidence of COVID-19 (RT-PCR-positive symptomatic illness). This additional information was requested during clarification because when this assumption is not valid, HR estimates may not be considered a robust measure of the treatment effect. In addition, a constant HR is assumed within the company's economic analysis, and therefore an assessment of whether PH assumption holds is useful in validating the company's modelling assumption. Although data from the PROVENT study are not used in the company's base case analysis, the EAG were interested to know whether this assumption held in the PROVENT study over its 6-month follow-up period. As part of one of the company's clarification question responses (question A23), the company also provided an assessment of the PH assumption in the PROVENT trial; the company presented a log (-log) plot (based on the full pre-exposure analysis set [data cut-off date: 29AUG2021]) to assess proportionality of hazards (see Figure 1). Based on the log (-log) plot, the company considered that from visual inspection of the curves, the curves remain parallel "*which supports the PH assumption, meaning that the HR is representative over the presented time period*". However, the company did not present results from a quantitative test of the PH assumption, nor did they provide a plot based on an assessment of the Schoenfeld residuals to further explore the validity of the PH assumption.

Figure 1: Log of Negative Log of Survival Functions (Full Pre-exposure Analysis Set, DCO Date: 29AUG2021) (reproduced from Figure 12 of company's response to clarification question A23)

- **Post-dosing SARS-CoV-2 nucleocapsid antibody positive**

The incidence of a post-treatment response (negative at baseline to positive at any time post baseline) for SARS-CoV-2 nucleocapsid antibodies (produced in response to a natural infection and therefore a measure of symptomatic and asymptomatic infections), was statistically significantly lower for participants who had received Evusheld compared to placebo, with a RRR of 51.1% (95% CI: 10.6 to 73.2; p=0.020) in the primary efficacy analysis and 57.7% (95% CI: 34.7 to 72.7; p= not reported) at the median 6 month follow-up.[20]

- **Incidence of COVID-19 related outcomes**

At the data cut-off date for the primary analysis, the incidence of SARS-CoV-2 RT-PCR-positive severe or critical symptomatic illness was low, with no events occurring in the Evusheld group (0/3441) compared with 0.1% (1/1731) in the placebo group.[20] With extended follow-up, and additional four cases of severe or critical symptomatic illness were reported, for a total of 5 cases (0.3%), all of which occurred in the placebo group.[20]

Only a small proportion of patients reported visits to the emergency department. As stated in the CS (Section B.2.8.1.4.c, page 77) '*Emergency department visits are distinct from hospitalisations and were captured on the emergency room visit electronic case report form where the primary reason for emergency room visit was selected as COVID-19 symptoms. The participant was not required to have a positive PCR test and the COVID-19 symptoms were determined by the investigator and did not need to meet the qualifying symptoms or duration of symptoms that were applied to the primary endpoint*.' For the primary analysis, there were 6/3441 (0.2%) participants in the Evusheld group compared with 0/1731 in the placebo arm who had Emergency Department visits. The 6 participants in the Evusheld group were not hospitalised and 3 of them subsequently tested positive for COVID-19.[20]

At the time of the primary data cut-off, there were 0 hospitalisations due to Covid-19 (regardless of prior vaccination or unblinding) in the Evusheld group compared to 3/1731 (0.2%) hospitalisations in the placebo group. With extended follow-up (median 6-month follow-up) 0 and 7 (0.4%) participants in the Evusheld and placebo groups, respectively, had been hospitalized due to Covid-19, regardless of prior vaccination or unblinding.[20]

- **Safety outcomes**

A summary of the AEs from the PROVENT trial are summarised in Table 10 (data cut-off date for the primary analysis) and Table 11 (median 6 month data cut). In general, at the data cut-off date for the primary analysis, 35.3% (1221/3461) of participants in the Evusheld group (single 300mg dose) and 34.2% (593/1736) of participants in the placebo group had at least one AE in the trial. Most AEs were mild or moderate in intensity with no notable differences between groups. The most common AE of

special interest was an injection site reaction, which occurred in 2.4% (82/3461) of the participants in the Evusheld group and in 2.1% (36/1736) of those in the placebo group. In addition, as noted in the EMA assessment report,[71] other common AEs included headache and fatigue. The incidence of serious AEs was similar in the two groups (1.4% [50/3461] vs.1.3% [23/1736], respectively). With extended follow-up, results were consistent with those obtained at the data cut-off date for the primary analysis. Discontinuations due to AEs were low and the proportion of participants who discontinued were similar between the Evusheld (0.1% [2/3461]) and placebo group (0.1% [1/1736]) and no additional AEs of special interest or unexpected longer-term signals were identified. Overall, 16 deaths occurred in the trial (0.3% [9/3461] in the Evusheld group and 0.4% [7/1736] in the placebo group). There were no COVID-19 related deaths in those treated with Evusheld. In the placebo group 2 deaths were adjudicated to be COVID-19 related by an independent and external Morbidity Adjudication Committee. However, none of the AEs leading to death were considered by the investigator to be related to Evusheld or placebo.[20]

Table 10: Adverse Events in the safety analysis set* (reproduced from Levin *et al.*,[20] with minor amendments)

Adverse event	Evusheld (N=3461)	Placebo (N=1736)	Total (N=5197)
Adverse events			
Any adverse event	1221 (35.3%)	593 (34.2%)	1814 (34.9%)
Mild	761 (22.0%)	369 (21.3%)	1130 (21.7%)
Moderate	387 (11.2%)	191 (11.0%)	578 (11.1%)
Severe	64 (1.8%)	27 (1.6%)	91 (1.8%)
Serious adverse events			
Any serious adverse event	50 (1.4%)	23 (1.3%)	73 (1.4%)
Related to Evusheld or placebo ‡	1 (<0.1%)§	0	1 (<0.1%)
Adverse events leading to trial discontinuation	1 (<0.1%) ¶	0	1 (<0.1%)
Medically attended adverse events	360 (10.4%)	157 (9.0%)	517 (9.9%)
Adverse events of special interest			
Any adverse event of special interest	93 (2.7%)	37 (2.1%)	130 (2.5%)
Injection-site reaction	82 (2.4%)	36 (2.1%)	118 (2.3%)
Anaphylaxis ‖	1 (<0.1%)	0	1 (<0.1%)
Immune complex disease **	1 (<0.1%)	0	1 (<0.1%)
Other	9 (0.3%)	2 (0.1%)	11 (0.2%)
Related to Evusheld or placebo	87 (2.5%)	36 (2.1%)	123 (2.4%)
Adverse events leading to outcome of death ††			
All adverse events	4 (0.1%)	4 (0.2%)	8 (0.2%)
Illicit-drug overdose	2 (0.1%)	2 (0.1%)¶¶	4 (0.1%)
Myocardial infarction	1 (<0.1%)	0	1 (<0.1%)
Renal failure	1 (<0.1%)	0	1 (<0.1%)
COVID-19 ‡‡	0	1 (0.1%)	1 (<0.1%)
COVID-19–related acute respiratory distress syndrome ‡‡	0	1 (0.1%)	1 (<0.1%)

* The safety analysis set consisted of all the participants who had undergone randomization and received at least one injection of Evusheld or placebo. Listed are data from participants with at least one event. Participants may have had more than one event. Adverse events were coded with the use of the *Medical Dictionary for Regulatory Activities,* version 24.0. ARDS denotes acute respiratory distress syndrome.

† One participant was assigned to receive placebo and incorrectly received Evusheld; in accordance with the trial protocol, this participant was included in the Evusheld group for the safety analysis.

‡ Events were determined to be related to Evusheld or placebo according to the judgment of the investigators.

§ The participant was hospitalized for severe (grade 3) inferior mesenteric-artery thrombosis. The investigator considered the event to be related to receipt of the trial agent. The sponsor did not find evidence to suggest a causal relationship between the event and the trial agent because of insufficient information about the circumstances surrounding the event, including possible risk factors, the clinical course, the trial agent received, and a detailed etiologic and diagnostic workup. The participant remained in the trial.

¶ The participant, who had a medical history of type 2 diabetes mellitus and chronic kidney disease, died from kidney failure. The investigator did not consider the event to be related to the trial agent and determined that the most likely cause of death was renal failure.

‖ The participant had severe chest pain shortly after receiving an injection, and because of the participant's laboured breathing, the investigator determined that the participant had had an anaphylactic reaction. The participant was hospitalized on the same day for a severe (grade 3) elevated troponin level. The investigator considered the event (anaphylaxis) to be an adverse event of special interest because of the timing of administration and the onset of shortness of breath. The sponsor's medical team assessed the causality of the adverse event of special interest and did not agree that the event was anaphylaxis because the event did not meet the protocol definition of anaphylaxis. The participant remained in the trial.

** The participant had hypothyroidism that was initially categorized as immune complex disease, an adverse event of special interest, but this event was later removed as an adverse event of special interest because it did not meet the protocol definition of immune complex disease.

†† All deaths were determined by the investigator to be unrelated to Evusheld or placebo.

¶¶ Data discrepancy with Table 11

‡‡ The independent and external adjudication committee determined that this death was related to COVID-19.

Table 11: Safety data, median 6-month data cut (reproduced from Levin *et al.*,[20] with minor amendments)

Participants with at least one event, n (%)*	Evusheld (n=3461) †	Placebo (n=1736)†	Total (N=5197)
Adverse events	1579 (45.6%)	790 (45.5%)	2369 (45.6%)
Mild AEs	835 (24.1%)	419 (24.1%)	1254 (24.1%)
Moderate AEs	596 (17.2%)	295 (17.0%)	891 (17.1%)
Severe AEs	128 (3.7%)	65 (3.7%)	193 (3.7%)
SAEs	130 (3.8%)	58 (3.3%)	188 (3.6%)
Intervention-related‡ SAEs	1 (<0.1%)	0	1 (<0.1%)
AEs leading to study discontinuation	2 (0.1%)	1 (0.1%)	3 (0.1%)
Medically attended AEs	641 (18.5%)	280 (16.1%)	921 (17.7%)
AEs of special interest	92 (2.7%)	37 (2.1%)	129 (2.5%)
Injection site reaction	82 (2.4%)	36 (2.1%)	118 (2.3%)
Anaphylaxis	1 (<0.1%)	0	1 (<0.1%)
Immune complex disease§	0	0	0
Other	9 (0.3%)	2 (0.1%)	11 (0.2%)
Intervention-related‡ AEs of special interest	87 (2.5%)	36 (2.1%)	123 (2.4%)
All AEs with outcome of death‖	9 (0.3%)	7 (0.4%)	16 (0.3%)
Illicit drug overdose	2 (0.1%)	1 (0.1%)¶¶	3 (0.%1)
Narcotic toxicity¶	0	1 (0.1%)	1 (<0.1%)
Covid-19**	0	1 (0.1%)	1 (<0.1%)
Covid-19 ARDS**	0	1 (0.1%)	1 (<0.1%)
Septic shock	1 (<0.1%)	0	1 (<0.1%)
Arrhythmia	1 (<0.1%)	0	1 (<0.1%)
Cardio-respiratory arrest	1 (<0.1%)	0	1 (<0.1%)
Congestive cardiac failure	1 (<0.1%)	0	1 (<0.1%)
Myocardial infarction	1 (<0.1%)	0	1 (<0.1%)
End-stage renal disease	1 (<0.1%)	0	1 (<0.1%)
Renal failure	1 (<0.1%)	0	1 (<0.1%)
Hepatic cirrhosis	0	1 (0.1%)	1 (<0.1%)
Malignant neoplasm (unknown primary site)	0	1 (0.1%)	1 (<0.1%)
Dementia (Alzheimer's type)	0	1 (0.1%)	1 (<0.1%)

*Participants may have had more than one event.
†One participant was randomized to placebo and incorrectly received Evusheld; per study protocol this participant was assessed in the Evusheld group for the SAS.
‡Events were determined to be intervention-related by investigators based on their judgment.
§Immune complex disease was removed as an AE of special interest following adjudication
‖All deaths were determined by the investigator to not be related to the study drug received.
¶Participant died as a result of accidental exposure to two substances controlled under Schedule I of the 1961 United Nations Single Convention on Narcotic Drugs.
¶¶ Data discrepancy with Table 10
**Cases were adjudicated to be Covid-19 related by the independent and external Morbidity Adjudication Committee.
AEs were coded using the Medical Dictionary for Regulatory Activities, version 24.0.
Abbreviations: AE–adverse event; ARDS – acute respiratory distress syndrome; COVID-19 – coronavirus disease 2019; SAE – serious adverse event; SAS – safety analysis set.

3.3.2 Real-world evidence studies

3.3.2.1. Young-Xu et al.[23]

- **Summary of company's PS matching approach**

As discussed in Section 3.2.2.1 the company presented results from a PS analysis published by Young-Xu *et al.*[23] Due to the retrospective nature of the study, the study lacked a control arm, however, matched controls were selected from patients who were immunocompromised (or otherwise at high-risk of COVID-19) who were not treated with Evusheld.

The primary composite outcome included the incidence of SARS-CoV-2 infection (detected by RT-PCR or antigen testing), hospitalisation and all-cause mortality, and patients were followed up until 30th April 2022 or until death (whichever occurred first). The two groups evaluated in the study were:

1) Evusheld patients (who received at least one dose during the observation period; first dose administered 13 January 2022)
2) Matched controls who were identified using PS methods (and who were immunocompromised or otherwise high-risk patients who did not receive Evusheld).

The company provided details in the CS in regard to the methodology adopted for the PS matching, including nearest neighbour matching using a calliper of 0.2 and a ratio of 1:4 with replacement. Matching was considered successful when "at least 90% of the covariates included in the PS model had standardised mean difference (SMD) of 10 or less" (CS, page 68). The EAG notes that the absolute SMD is greater than 10 for three high-risk comorbidities (cancer, metastatic cancer and chronic kidney disease). This may infer that there is residual confounding present even after PS matching. Patient characteristics were reported for both Evusheld and the control group (including prior to- and after matching). A summary of the baseline characteristics is presented in.

Table 12: Selected baseline characteristics (Young-Xu *et al.*[23] [reproduced from CS, Table 16, page 56-59])

	Before matching			After matching		
	Controls (N= 251,756)	**Evusheld (N= 1,848)**	**SMD**	**Controls (N= 6,354)**	**Evusheld (N= 1,733)**	**SMD**
Sex						
Male	222,642 (88%)	1,688 (91%)	9.7	5,796 (91%)	1,579 (91%)	-0.4
Age at 31 Dec 2021						
Mean (SD)	64.6 (14.7)	67.5 (10.9)	22.6	68.1 (11.5)	67.4 (11.0)	-5.7
Age category						
18-49	41,873 (17%)	131 (7%)	-29.8	493 (8%)	126 (7%)	-1.9
50-64	63,835 (25%)	448 (24%)	-2.6	1,378 (22%)	420 (24%)	6.1
65-69	31,171 (12%)	291 (16%)	9.7	952 (15%)	268 (15%)	1.3
70-74	52,227 (21%)	531 (29%)	18.6	1,861 (29%)	491 (28%)	-2.1
75-79	34,498 (14%)	300 (16%)	7.1	1,125 (18%)	284 (16%)	-3.5
>79	28,152 (11%)	147 (8%)	-11	545 (9%)	144 (8%)	-1
Race / ethnicity						
Black: non-Hispanic Black	49,021 (19%)	285 (15%)	-10.7	804 (13%)	277 (16%)	9.5
Hispanic any race	15,899 (6%)	79 (4%)	-9.1	237 (4%)	76 (4%)	3.3
Other	18,802 (7%)	139 (8%)	0.2	452 (7%)	130 (8%)	1.5
White: non-Hispanic White	168,034 (67%)	1,345 (73%)	13.2	4,861 (77%)	1,250 (72%)	-10
Number of vaccinations						
0 dose vaccine	67,753 (27%)	98 (5%)	-61.5	286 (5%)	88 (5%)	2.7
1 dose mRNA vaccine	0	0	0	0	0	
Two dose vaccine (includes one dose of Janssen)	108,134 (43%)	386 (21%)	61.5	1,377 (21%)	385 (22%)	-2.7
3rd dose of vaccine	75,869 (30%)	1,364 (74%)	97.2	4,691 (74%)	1,260 (73%)	-2.5
BMI category						
Missing	11,478 (5%)	55 (3%)	-8.3	239 (4%)	52 (3%)	-4.2
Normal	56,600 (22%)	530 (29%)	14.2	1,703 (27%)	493 (28%)	3.7
Overweight / obese	183,678 (73%)	1,263 (68%)	-10.1	4,412 (69%)	1,188 (69%)	-1.9
Deyo-Charlson Comorbidity Index (DCCI)						
Mean St Dev	1.6 (2.1)	2.7 (2.3)	52.1	2.4 (2.3)	2.6 (2.3)	9.7
High-risk comorbidities						
Asthma	41,011 (16%)	313 (17%)	1.7	958 (15%)	289 (17%)	4.4
Cancer	30,842 (12%)	670 (36%)	58.3	1,844 (29%)	597 (34%)	11.7

	Before matching			After matching		
	Controls (N= 251,756)	**Evusheld (N= 1,848)**	**SMD**	**Controls (N= 6,354)**	**Evusheld (N= 1,733)**	**SMD**
Coronary Artery Disease	35,504 (14%)	312 (17%)	7.7	1,041 (16%)	286 (17%)	0.3
Cancer Metastatic	7,327 (3%)	49 (3%)	-1.6	325 (5%)	49 (3%)	-11.7
Congestive Heart Failure	17,451 (7%)	190 (10%)	12	485 (8%)	173 (10%)	8.3
Chronic Kidney Disease	26,551 (11%)	442 (24%)	36	1,125 (18%)	391 (23%)	12.1
Chronic Obstructive Pulmonary Disease	44,214 (18%)	347 (19%)	3.2	1,056 (17%)	321 (19%)	5
Cardiovascular disease	11,256 (4%)	86 (5%)	0.9	318 (5%)	74 (4%)	-3.5
Dementia	4,057 (2%)	NR	NR	89 (1%)	NR	S
Diabetes Mellitus w/complications	26,865 (11%)	293 (16%)	15.3	815 (13%)	268 (15%)	7.6
Diabetes Mellitus w/o complications	41,315 (16%)	291 (16%)	-1.8	1,021 (16%)	275 (16%)	-0.5
Hypertension	130,311 (52%)	1,111 (60%)	16.9	3,694 (58%)	1,029 (59%)	2.5
Liver disease, mild	12,834 (5%)	167 (9%)	15.4	455 (7%)	160 (9%)	7.6
Liver disease, severe	1,367 (1%)	32 (2%)	11.2	60 (1%)	27 (2%)	5.5
Renal disease	28,839 (11%)	488 (26%)	38.9	1,312 (21%)	429 (25%)	9.8
Immunocompromised						
Based on diagnoses	81,540 (32%)	1,336 (72%)	87.2	4,225 (66%)	1,226 (71%)	9.2
Based on diagnoses or use of immune suppressants	211,390 (84%)	1,707 (92%)	26.2	5,863 (92%)	1,595 (92%)	-0.9

Abbreviations: CS – company submission; DCCI – Deyo-Charlson Comorbidity Index; mRNA – Messenger ribonucleic acid; N – number of patients; NR – Not reported; SD – Standard deviation; SMD – Standardised mean difference; w/ – with; w/o – without.

The company stated that the covariates included in the PS matching were "*measured before treatment initiation to avoid adjustment for potential mediators*" (CS, page 68). As part of the clarification response (question A24), the company confirmed that the following factors were considered to be prognostic factors or treatment-effect modifiers and were therefore included in the PS matching: age, gender, race/ethnicity, body mass index (BMI), co-morbidities[1], immunocompromised status, Care Assessment Need (CAN) score and number of vaccinations. The company stated that the factors

[1] Comorbidities included asthma, cancer, coronary artery disease, metastatic cancer, congestive heart failure, chronic kidney disease, chronic obstructive pulmonary disease, cardiovascular disease, dementia, diabetes (with or without complications), dyslipidaemia, HIV, hypertension, liver disease (either mild or severe), myocardial infarction (history of), paraplegia, hemiplegia, peripheral vascular disease, rheumatoid arthritis, renal disease.

included in the matching were "*relevant and capture the key factors expected to influence the risk of severe COVID-19 outcomes*" (response to clarification question A24a). The company also noted that prior COVID-19 infection may also be a relevant treatment-effect modifier, however, the company also stated in the clarification response (question A24) that "*patients who were diagnosed with COVID-19 via positive RT-PCR test within 3 months of the date (or pseudo-date for controls) of Evusheld administration were excluded from the analysis"* to ensure the focus was on new infections.

The company stated that PS matched survival analyses using a Cox PH model was used to estimate HRs and corresponding 95% CI to compare patients who received Evusheld and their matched controls and to assess whether there was an association between receipt of Evusheld and the outcomes, i.e., to assess "*the effectiveness of Evusheld for prevention of COVID-19 infection and severe disease among immunocompromised and high-risk patients during the Omicron surge*." (CS, page 42).

The company also reported results from a "*difference-in-difference (DiD) analysis*" (CS, page 67), which was used to assess outcomes. Residual confounding following a PS matching analysis was adjusted for using the *"prior event rate ratio (PERR) approach"* (CS, page 67-8); this approach accounts for two distinct time periods (e.g., before and after the use of the intervention) and the results of each outcome were calculated for each cohort (i.e., either Evusheld or matched controls) and then compared before and after the intervention within the extended study period. The relative effectiveness of Evusheld versus control is estimated from the PERR, which is calculated as the rate ratio (RR) (defined as the rate of the outcome among Evusheld recipients divided by the rate of the outcome in the control arm) and was calculated in the observation period (RR_0) and the baseline period (RR_b). The PERR was then calculated using the formula:

$$PERR = (RR_O)/(RR_b)$$

The relative effectiveness of Evusheld versus control is then defined as:

$$(1 - PERR) * 100\%$$

The company presented a summary of the PS matched survival analysis for four cohorts: (1) all patients, (2) immunocompromised patients, (3) severely immunocompromised patients and (4) patients who were not immunocompromised but at high-risk. Results for the overall population were presented for both the composite outcome as well as each outcome individually.

- **Summary of company's PS matching results (composite of SARS-CoV-2 infection, COVID-19 hospitalisation, and all-cause mortality)**

A summary of the Cox regression results reported by the company (CS, page 81-2) (represented by the HR and associated 95% CI for the comparison of Evusheld versus matched controls) are presented in Table 13Table 13, along with the matched PERR-adjusted effectiveness RR from the DiD analysis. The results of the analysis showed that compared with propensity-matched controls, Evusheld recipients had a lower incidence of the composite outcome (defined as SARS-CoV-2 infection, COVID-19 hospitalisation, and all-cause mortality) overall (17/1733 [1.0%] vs 206/6354 [3.2%]; HR 0.31; 95% CI: 0.18 to 0.53). Similar results were observed within the study populations of electronic health record-confirmed immunocompromised (HR 0.32; 95% CI: 0.18 to 0.62), severely immunocompromised (HR 0.44; 95% CI: 0.21 to 0.93), and for Veterans aged ≥65 years (HR 0.33; 95% CI: 0.18 to 0.61). Further analysis of the overall cohort also showed a lower incidence of individual composite outcomes, including test confirmed SARS-CoV-2 infection (HR 0.34; 95% CI: 0.13 to 0.87), COVID-19 hospitalisation (HR 0.13; 95% CI: 0.02 to 0.99), and all-cause mortality (HR 0.36; 95% CI: 0.18 to 0.73). The EAG note that no data on COVID-related death were reported by Young-Xu *et al*.[23]

Table 13: Relative effectiveness of Evusheld versus untreated controls using propensity-score matched analysis and difference-in-difference (Young-Xu *et al.*[23] [reproduced from CS with minor amendments, Table 26, page 80-81])

	Matched controls N=6,354	Evusheld recipients N=1,733	Propensity-score survival analysis	Difference-in-difference analysis*
	Number of events (%)	Number of events (%)	Hazard ratio (95% CI)	Incidence rate ratio (95% CI)
Composite outcome (SARS-CoV-2 infection, COVID-19 hospitalisation, and all-cause mortality)				
Overall cohort	206 (3.2%)	17 (1.0%)	0.31 (0.18, 0.53)	
Immunocompromised	147 (3.5%)	12 (1.0%)	0.32 (0.18, 0.62)	
Severely immunocompromised	87 (3.7%)	11 (1.4%)	0.44 (0.21, 0.93)	
Not immunocompromised** but at high risk	59 (2.8%)	(<1%)†	0.27 (0.13, 0.56)	
Individual outcome (overall cohort)				
SARS-CoV-2 infection	69 (1%)	(<0.5%)†	0.34 (0.13, 0.87)	0.32 (0.24, 0.44)
COVID-19-related hospitalisation	38 (0.5%)	(<0.5%)†	0.13 (0.02, 0.99)	0.10 (0.05, 0.22)
All-cause mortality	99 (2%)	(<0.5%)†	0.36 (0.18, 0.73)	

*DiD analysis was not performed on outcomes involving mortality data because matched cohorts were all alive at index dates.

**Electronic data regarding immunocompromised conditions or immunosuppressant use were found.

†Numbers not shown to protect patient information.

Abbreviations: CI – confidence intervals; COVID-19 – Coronavirus disease 2019

The matched PERR-adjusted effectiveness (measured by the RR) was estimated to be 0.32 (95% CI: 0.24 to 0.44) against SARS-CoV-2 infection verified by a positive test, and 0.10 (95% CI: 0.05 to 0.22)

against COVID-19-related hospitalisations. These findings are consistent with those obtained from the PS matching analysis (also presented Table 13). The company concluded that this consistency of findings indicated that the PS matching analysis were considered to be "*robust and the benefit of Evusheld is unlikely to be due to any confounding*" (CS, page 81). The company did not perform a DiD analysis for mortality (including the composite outcome); the company state that this was because "*both actual and pseudo-Evusheld use required the subjects to be alive, PERR analysis was not able to be performed on mortality, including the composite outcome*" (CS, page 81).

The company stated that the use of electronic health records from the VA (an integrated healthcare system in US) in this study demonstrated that the clinical effectiveness of Evusheld in reducing the incidence of SARS-CoV-2 infections, COVID-19 related hospitalisations and all-cause mortality in immunocompromised patients as well as patients at high-risk from COVID-19. The company concludes that the analyses informed by RWE support the effectiveness of Evusheld in preventing SARS-CoV-2 infections caused by the Omicron variants, including predominantly BA.1 and the early BA.2 and BA.2.12.1 surge.

- **Critique of PS matching analyses**

The results presented by the company (CS, Section B.2.8.2) is based on the PS analyses reported by Young-Xu *et al.*[23] and is informed by one of the largest healthcare systems in the US. The EAG agrees with the use of PS analysis to estimate treatment effects in observational study as this technique aims to reduce bias when comparing interventions in an observational setting. The EAG notes that a key strength of this analysis is its large sample size – the overall cohort included 1,733 patients receiving Evusheld and 6,354 control patients (after matching). Additionally, use of PS matching methods have been adopted in an attempt to reduce the bias ensuing from the comparison of non-randomised data. Due to the large sample size evaluated in the PS analysis, this enabled the adjustment for a number of potential confounding variables. However, it was not explicitly specified in the CS which factors were adjusted for in the PS analysis; as part of the clarification response (question A24a), the company confirmed which factors were included in the PS matching analysis. As part of the clarification response (question A24b), the company clarified that the authors of the study did not provide details of the identification and selection of the baseline characteristics, however, the company stated that "*UK clinical experts consulted have validated their appropriateness for use in the propensity score analysis*." The EAG considers this to be reasonable despite further information not being provided by the study authors. The company also noted in the clarification response (question A24c) that that there was no *"reason to suspect any significant residual confounding that would impact the observed results."* Despite adopting a PS matching approach in an attempt to overcome observable differences between the two cohorts, it is anticipated that residual confounding might be present, which may, in turn, affect the reliability of inferences based on this evidence. The EAG notes that Yao *et al.*[72] who developed a

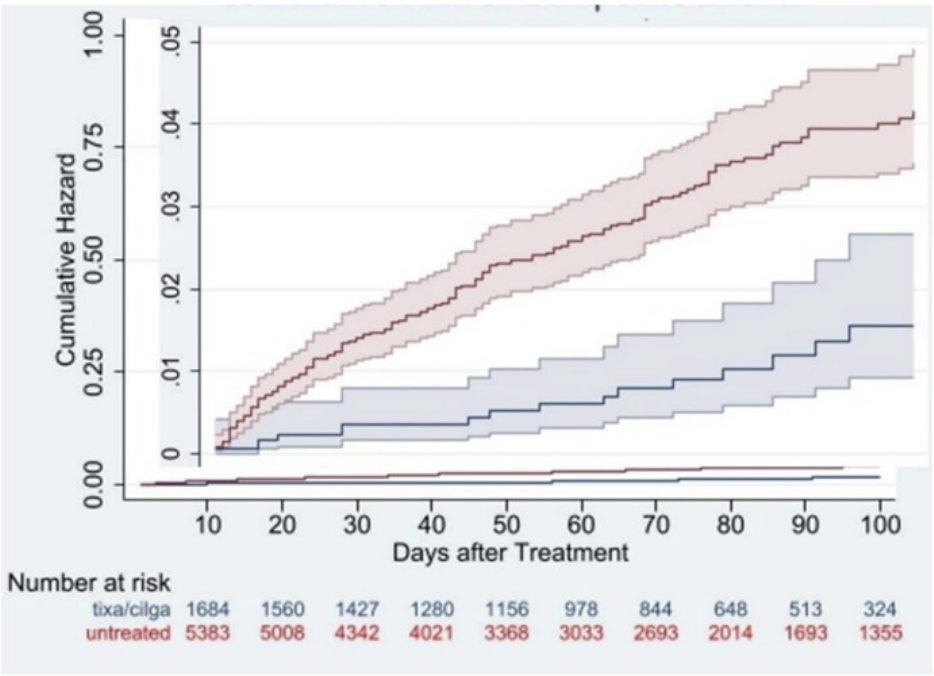
checklist to aid and assist with the standardised reporting of PS analyses recommended exploring the possibility of incomplete or insufficient matching and to consider the potential influence of this. The company did explore a *"difference-in-difference (DiD)"* analysis in an attempt to adjust for unmeasured residual confounders (time-varying factors). The EAG notes that this element of the checklist has been explored by the company. The EAG does note, however, that the matched sample size is notably smaller than the original sample size, particularly for the control cohort (prior to matching – Evusheld: N=1,848, controls: N=251,756; after matching – Evusheld: N=1,733, controls: N=6,354). Young-Xu *et al*. do not explicitly state why they excluded 115 patients from the Evusheld group and whether this relates to an inability to match these patients to controls. However, they do describe excluding patients with a positive RT-PCT test in the 3 months prior to Evusheld administration and the numbers excluded for this reason are not documented so this could be the reason. Furthermore, the recommendations published by Yao *et al.* (2017)[72] include presenting the unadjusted estimated alongside the PS analysis estimates and their precision (e.g., 95% confidence interval). The company did not present results from the unadjusted PS analysis; therefore, it is not possible to assess the magnitude of change that the PS matching has had on the relative efficacy results.

Whilst the results from the PS matching analysing using RWE favour Evusheld over control for reducing the incidence of SARS-CoV-2 infections, and COVID-19 related hospitalisations or death, the findings are based on non-randomised evidence which may lack the robustness that an RCT would have. There are also several limitations of the published RWE, primarily that the health care records were only captured in VA medical centres, meaning that infections and/or hospitalisations which occurred elsewhere may have been excluded from the VA dataset. It is unclear to the EAG whether deaths occurring outside the VA medical centres would have been recorded as this is not described or commented on by Young-Xu *et al*. however, the EAG would expect that these are captured within all-cause mortality endpoint. There are also concerns noted by the authors of the study that that some patients' immunocompromised status have been misclassified – a small proportion were not considered immunocompromised based on the definition used in this study.

Furthermore, the VA data are based on a largely older, male population (69% of Evusheld recipients were aged ≥65 years), meaning that results may not be generalisable to a wider population who were treated outside the VA centres. Another concern is that across both study arms, 95% of patients had received two doses of a COVID-19 mRNA vaccine, and most patients (75%) were fully vaccinated before receiving Evusheld, however, none of the patients in the PROVENT trial were vaccinated, and moreover, the company's positioning of Evusheld includes patients *"for whom COVID-19 vaccination is not recommended"* (CS, page 30). Therefore, the findings from the RWE published by Young-Xu *et al.*[23] may not be relevant when considering the company's anticipated use of Evusheld.

The results of the PS analysis presented by the company include a treatment effect represented by a HR estimate and associated 95% CI between Evusheld and the matched control across all populations (overall cohort, immunocompromised patients [including severely immunocompromised] as well as patients who were not immunocompromised but who were at high-risk). The company also incorporated HR estimates from the PS analysis into the economic model. However, HR estimates rely on the assumption of PH, which underpins the use of Cox PH regression, which, when violated, may not be considered a robust measure of the treatment effect. As part of the company's clarification response (questions A24e and A24f), the company provided a brief assessment of the PH assumption. The company stated that "*inferences with regards to the appropriateness of the PH assumption relating to the HR from Young-Xu et al. (2022) are difficult to make*" due to the absence of "*data over time for the test-confirmed SARS-CoV-2 infection rates*". However, the company stated that the study publication presented the cumulative risk of the composite outcome (i.e. SARS-CoV-2 infection rates, COVID-19 hospitalisations or all-cause mortality), as shown in Figure 2, the company stated that the cumulative hazard rates *"continue to separate over time"* – the company concluded that there is no expectation that the PH assumption does not hold. However, the company did not present results from statistical tests and graphical diagnostics based on the scaled Schoenfeld residuals in the absence of relevant data and information reported in the publication by Young-Xu *et al*.[23]

Figure 2: Cumulative risk of composite COVID-19 outcomes for Evusheld recipients compared to untreated controls (reproduced from company's clarification response to question A24e)



Composite COVID-19 outcomes were SARS-CoV-2 infection, COVID-19 hospitalization, or all-cause mortality

- **Safety outcomes**

No safety or AE data were reported in the Young-Xu *et al*.[23] study.

3.3.2.2. Kertes et al.,[24]

- **SARS-CoV-2 infection**

A summary of the key results from the Kertes *et al*.,[24] study are summarised in Table 14. In all the immunocompromised individuals who were administered Evusheld, 3.5% (29/825) of the participants subsequently became infected with SARS-CoV-2 compared with 7.2% (308/4299) of the immunocompromised population who were not administered Evusheld. As shown in, the odds of SARS-CoV-2 infection for the Evusheld administered group compared to the non-administered Evusheld group was significantly reduced by almost 50% (OR after adjustment: 0.51, 95% CI: 0.30 to 0.84).

Table 14: Factors associated with SARS-CoV-2 infection among selected immunocompromised individuals, logistic regression model, MHS, Feb-May 2022 (Kertes *et al*.,[24] [reproduced from CS with minor amendments, Table 27, page 83-84])

Characteristic	Category	N	OR	95% CI
Evusheld	Not administered	4299	-	
	Administered	825	0.51	0.30, 0.84
Prior COVID-19 episode	No	3840	-	
	Yes	1,284	0.17	0.11, 0.28
Age group	12-79	4,643	2.43	1.50, 3.93
	80+	481	-	
Socioeconomic status	Low	879	-	
	Middle	2,463	1.78	1.20, 2.64
	High	1,782	2.45	1.65, 3.66
CKD	No	2488	-	
	Yes	2,636	1.42	1.13, 1.79
Number coronavirus vaccine doses	None	526	0.60	0.37, 0.95
	One-two	564	0.79	0.49, 1.24
	Three-four	4034	-	
Number of follow-up days		5,124	1.02	1.0, 1.04

Abbreviations: CI – Confidence intervals; COVID-19 – Coronavirus disease 2019; CKD – Chronic kidney disease; OR – Odds ratio

- **Severe COVID-19 disease (defined as either COVID-19-related hospitalisation and/or all-cause mortality)**

Only 0.1% (1/825) of the participants in the Evusheld administered group were hospitalised for COVID-19 compared with 0.6% (27/4299) in the non-Evusheld administered group (p=0.05 as reported in main text of published paper[24]; however, this is also reported as p=0.07[24] in abstract and CS, Section B2.8.3.2). No deaths occurred in the Evusheld administered group during the follow-up period compared to 40/4299 deaths (0.9%) in the non-Evusheld administered group (p=0.005). In all, only 0.1% of the Evusheld administered group had evidence of severe disease compared to 1.5% of the non-administered group (p=0.001). Due to the small number of patients with severe disease (n=64), a logistic regression was conducted, including age group and cardiovascular disease. After adjustment, the Evusheld group odds of having severe disease were 0.08 (95% CI: 0.01 to 0.54) compared with those not administered Evusheld.

- **Safety outcomes**

No safety or AE data were reported in the Kertes *et al*.,[24] study

3.3.3 Additional safety evidence – TACKLE trial[51]

The TACKLE study,[51] a Phase III, double blind, placebo-controlled clinical trial for the treatment of adult patients (≥18 years of age) with mild to moderate COVID-19, was part of the evidence base submitted by the company to support the safety of the higher 600mg dose of Evusheld. A final analysis will be conducted once all participants have completed the study at day 457. Published results available as of September 2022 have a median safety follow-up of 84.0 days in both groups (interquartile range: Evusheld 31.0–86.0, placebo 30.0–86.0). In general, the safety profile of the higher dose is in line with that of the 300 mg dose of Evusheld (CS, Section B3.1.3, page 90-92). A summary of the AEs from the TACKLE trial[51] are presented in Table 15 and Table 16.

In general, 29% (132/452) of participants in the Evusheld group and 36% (163/451) in the placebo group had at least one AE in the trial. Most AEs were mild or moderate in severity. The most common AE of special interest was an injection site reaction, which occurred in 2% (8/452) of the participants in the Evusheld group and in 2% (10/451) of those in the placebo group. Serious AEs were reported by 33 (7%) participants in the Evusheld group and 54 (12%) in the placebo group. The most common AE was COVID-19 pneumonia in both groups, experienced by 6% (26/452) of Evusheld patients and 11% (49/451) of placebo patients. As shown in Table 15, while there were fewer COVID-19 reported deaths in the Evusheld group compared with the placebo group (3 vs 6 deaths, respectively), all-cause mortality rates were similar in both groups (6 vs 6 deaths, respectively).

Table 15: Adverse events in the safety analysis set (Montgomery *et al*.,[51] [reproduced from CS with minor amendments, Table 31, page 90-91])

Participants with an AE (average follow-up 84 days), n (%)	Evusheld (n=452)	Placebo (n=451)
Any adverse event*	**132 (29%)**	**163 (36%)**
Mild	67 (15%)	65 (14%)
Moderate	34 (8%)	50 (11%)
Severe	22 (5%)	30 (7%)
Total deaths	**6 (1%)**	**6 (1%)†**
Acute myocardial infarction or acute left ventricular failure	1 (<1%)	0
Sudden cardiac death	1 (<1%)	0
COVID-19 pneumonia with outcome of death	2 (<1%)	4 (<1%)
COVID-19 with outcome of death	1 (<1%)	1 (<1%)
COVID-19 pneumonia, superinfection bacterial, or septic shock	0	1 (<1%)
Malignant disease progression	1 (<1%)	0
Any serious adverse event including death	**33 (7%)**	**54 (12%)**
Any treatment-related adverse event‡	**23 (5%)**	**21 (5%)**
Any adverse event leading to study withdrawal§	**5 (1%)**	**7 (2%)**
Common adverse events		
COVID-19 pneumonia	26 (6%)	49 (11%)
Headache	5 (1%)	2 (<1%)
Any adverse event of special interest	**15 (3%)**	**15 (3%)**
Injection site pain	8 (2%)	10 (2%)
Injection site erythema	2 (<1%)	2 (<1%)
Injection site discomfort	2 (<1%)	1 (<1%)
Injection site bruising	1 (<1%)	1 (<1%)
Injection site haematoma	1 (<1%)	1 (<1%)
Injection site induration	1 (<1%)	0
Injection site inflammation	1 (<1%)	0
Injection site nodule	1 (<1%)	0
Injection site warmth	0	1 (<1%)

*Each participant is counted only once (based on their maximum reported intensity) within a treatment group.

†This differs from the initial number of deaths shown in figure 1 because one death occurred after the data cut-off, but the adverse event began before the data cut-off, thus the outcome was recorded.

‡Possibly related, as assessed by the investigator. Includes adverse events that occurred through to the end of the study.

§Two participants in the placebo group discontinued from the study due to adverse events. Percentages are based on the total numbers of participants in the treatment group.

Participants with multiple events of the same preferred term are counted only once in that preferred term. Participants with events in more than one preferred term within the same system organ class are counted only once in that system organ class row. Includes adverse events that occurred through to the end of the study. Adverse events of special interest include injection site reactions and anaphylaxis and other serious hypersensitivity reactions, including immune complex disease.

Abbreviations: AE – Adverse event; COVID-19 – Coronavirus disease 2019

Table 16: Serious adverse events by system organ class and preferred term, safety analysis set (Montgomery *et al*.,[51] [reproduced from CS with minor amendments, Table 32, page 91-92])

Participants with a SAE (average follow-up 84 days), n (%)	Evusheld (n=452)	Placebo (n=451)
Any SAE	**33 (7.3%)**	**54 (12.0%)**
Infections and infestations	25 (5.5%)	37 (8.2%)
COVID-19 pneumonia	23 (5.1%)	49 (10.9%)
COVID-19	1 (0.2%)	9 (2.0%)
Vascular disorders	3 (0.7%)	0
Cardiac disorders	2 (0.4%)	1 (0.2%)
Renal and urinary disorders	2 (0.4%)	1 (0.2%)
Blood and lymphatic system disorders	1 (0.2%)	0
General disorders and administration site conditions	1 (0.2%)	0
Musculoskeletal and connective tissue disorders	1 (0.2%)	0
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	1 (0.2%)	0
Nervous system disorders	1 (0.2%)	3 (0.7%)
Respiratory, thoracic, and mediastinal disorders	1 (0.2%)	1 (0.2%)
Gastrointestinal disorders	0	2 (0.4%)
Hepatobiliary disorders	0	2 (0.4%)
Injury, poisoning, and procedural complications	0	2 (0.4%)
Abbreviations: COVID-19 – Coronavirus disease 2019; SAE – Serious adverse event		

3.3 Summary of the neutralising activity of Evusheld

At the time of writing, the omicron sub-variant of COVID-19, BA.5, including all sub-lineages, remains the dominant lineage in the UK.[55] As noted in the SPC,[17] the recommended dosages of Evusheld is 300 mg and 600 mg. The SPC[17] states that '*A higher dose of 600 mg of Evusheld, as 300 mg of tixagevimab and 300 mg of cilgavimab, may be more appropriate for some SARS-CoV-2 variants (for example, Omicron BA.1, Omicron BA.1.1) based on in vitro neutralisation susceptibility data which show reduced susceptibility for Evusheld…*' The CS (Table 2, p16 and Evidence submission summary, Table 1, p8) further notes that '[redacted]'

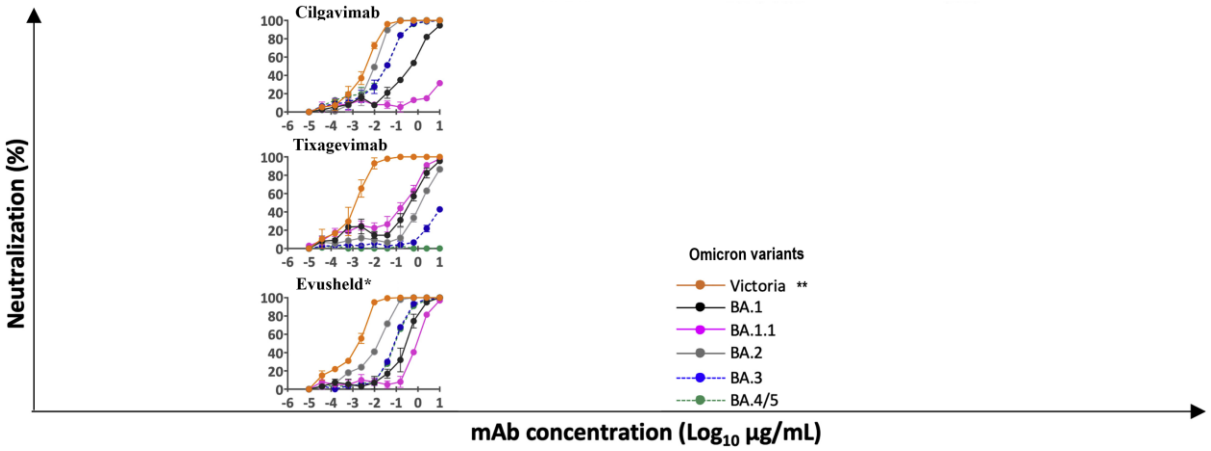
The CS (Appendix D.1.5, p20-22 and the company's clarification response to questions A5 and A7) provided supporting information on the neutralisation effect of Evusheld against all variants of concern, including Omicron. The company's systematic review included studies of authentic tixagevimab plus cilgavimab (Evusheld) only (company's clarification response to question A5). All studies of generic tixagevimab plus cilgavimab (i.e., antibodies generated in a research laboratory) were excluded. The company's clarification response to question A5 states that '*Multiple laboratories have published in-vitro neutralisation results using antibodies referred to as Evusheld or its components. These*

laboratories have generated the antibodies that make up Evusheld themselves using publicly available sequence information. It is not possible for the quality and potency of antibodies generated in individual laboratories to be verified for similarity to the genuine Evusheld product and therefore the IC50 values generated from the use of these generic antibodies cannot be assumed to be an accurate representation of what would be observed with Evusheld.' This is discussed further below.

Although the EAG requested further details of the SLR methodology (see company's clarification response to question A5) the company failed to clearly justify and provide details of the validity, robustness and reliability of the SLR approach taken (e.g., how relevant studies were selected, data extracted [including consistency of definitions], quality assessed, and data synthesised). In addition, limited details were provided on the number studies excluded as well as reasons for exclusion e.g., generic tixagevimab plus cilgavimab (see company's clarification response to question A10).

The company's SLR included 3 pivotal publications (see company's clarification response to question A7) on the neutralisation activity of authentic Evusheld. This included a study from the University of Oxford,[73] Washington University,[74] and the Francis Crick Institute in London.[75] An assessment of methodological quality was not reported in the CS and the results were described narratively for each study. In brief, as reported in the CS (see company's clarification response to question A7), the Oxford study[73] evaluated the neutralisation of BA.4 and BA.5 using a range of vaccine and naturally immune serum and panels of monoclonal antibodies. As noted in Figure 3 and the company's clarification response to question A7, the study authors found that '*for AZD1061 [cilgavimab], activity against BA.4/5 was similar to that against BA.2 (<2-fold reduction), while for AZD8895 [tixagevimab], residual activity against BA.2 was knocked out (the antibodies that combine as Evusheld [tixagevimab plus cilgavimab]). Irrespective of this, the activity of the combination of both antibodies for Evusheld continued to show activity against BA.4/5 at ~65 ng/mL, although this was reduced 8.1-fold compared with BA.2*.'[73] The EAG found this data difficult to interpret as it is unclear how the monoclonal antibody concentrations relate to the drug dose and the time since drug administration.

Figure 3: Neutralisation curves for tixagevimab cilgavimab or both, related to IC50 titres (adapted from Figure 6 and Table 5, company's clarification response to question A7)



IC50 (µg/mL)***						
Pseudoviruses						
Commercial monoclonal antibodies	**Victoria (wild type)**	**BA.1**	**BA.1.1**	**BA.2**	**BA.3**	**BA.4/5**
Tixagevimab	0.001	0.246	0.1	1.333	10	10
Cilgavimab	0.002	0.308	10	0.008	0.019	0.015
Evusheld* (Tixagevimab plus cilgavimab)	0.001	0.232	0.806	0.008	0.065	0.065

* Commercial Evusheld (tixagevimab plus cilgavimab) – dose and concentrations not reported.
** Victoria (wild type) indicates the original SARS-CoV-2 virus strain first detected in late 2019.
*** IC50, Half-maximal inhibitory concentration (defined as concentration of an inhibitory substance or antagonist that reduces a given biological process or biological component by 50% [CS, Appendix D.1.5] - the lower the IC50 value the more potent the drug)[76]

In the Washington University study,[74] the authors evaluated the protective efficacy against three SARS-CoV-2 Omicron lineage strains (BA.1, BA.1.1, and BA.2) of tixagevimab plus cilgavimab which correspond to what is used to treat or prevent SARS-CoV-2 infections in humans. Despite losses in neutralisation potency in cell culture, tixagevimab plus cilgavimab reduced BA.1, BA.1.1, and BA.2 lung infection in susceptible mice that express human ACE2 (K18-hACE2) in prophylactic and therapeutic settings. The authors concluded that despite the reduced neutralising activity in cell culture, tixagevimab plus cilgavimab therapy can limit inflammation and pathogenesis in the lung caused by Omicron variants.[76]

In a study from the Francis Crick Institute in London, reported as a correspondence letter,[75] the authors utilised an assay calibrated to WHO International Standard for anti-SARS-CoV-2 immunoglobulin and reported neutralisation titres in International Units to facilitate standardised comparisons of different monoclonal antibodies against various variants. Using this assay, the authors calculated IC50 values by fitting a four-parameter dose–response curve to 288 independent data points, generated from three independent repeats of 12 independent titrations, each consisting of two technical replicates of a four-point dilution series against live SARS-CoV-2 variants. The authors found that only cilgavimab retained strong neutralisation activity against omicron BA.2, BA.2.12.1, BA.4, and BA.5 (Figure 4 and Figure 5)[75] However, the CS (see company's clarification response to question A6 and A7) further concluded that the combination of both tixagevimab plus cilgavimab showed strong neutralisation activity with all omicron variants tested (BA.1, BA.2, BA.2.12.1, BA4/5).

Figure 4: IC50 values and confidence intervals for neutralisation of SARS-CoV-2 variants by monoclonal antibodies (reproduced from company's clarification response, question A7)

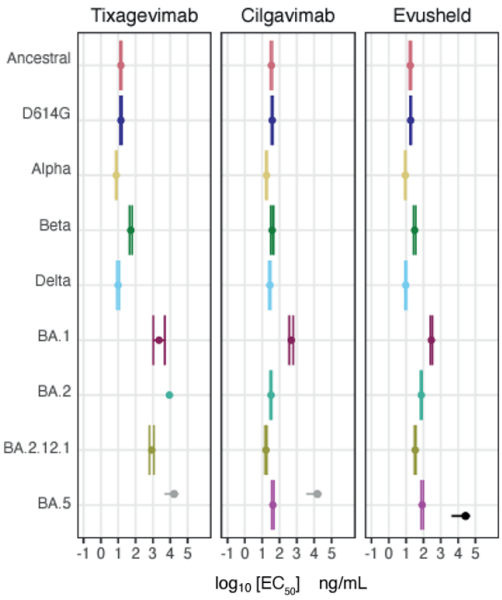
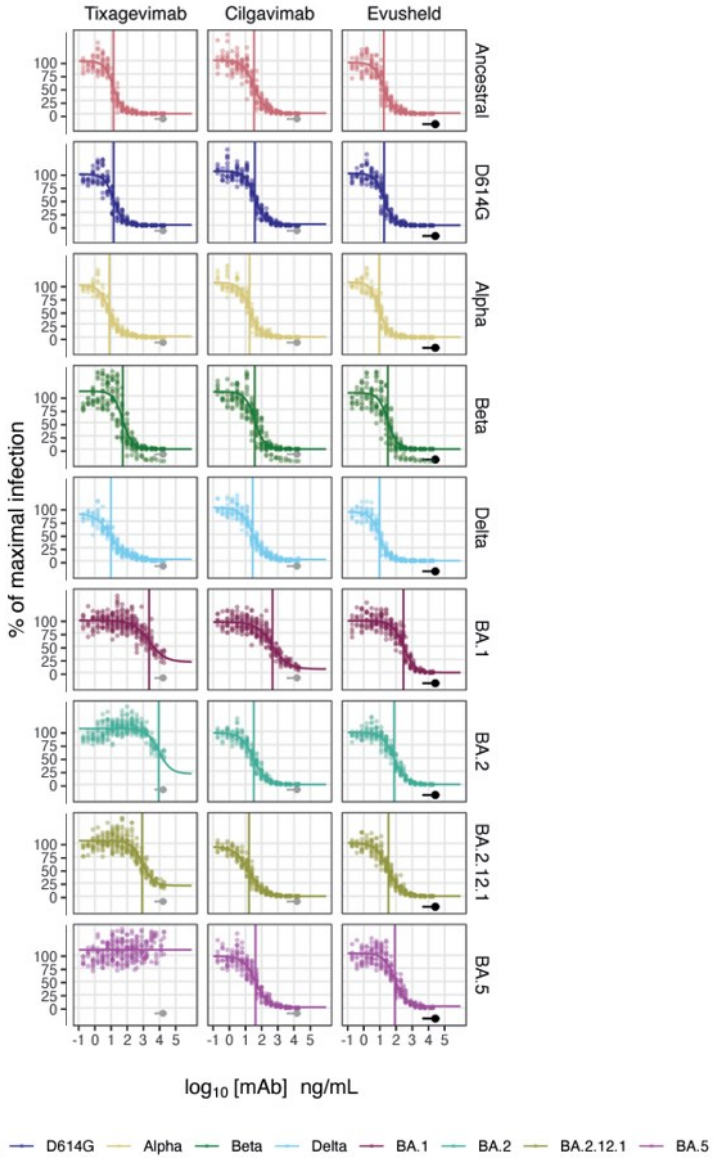


Figure 5: Neutralisation of SARS-CoV-2 variants by monoclonal antibodies (reproduced from company's clarification response to question A7)



The CS (Section B2.1.3, p35; Appendix D.1.5 and company's clarification response to questions A4 and A5) suggests that based on the evidence from the company's SLR, Evusheld retains in vitro neutralising activity against all variants of concern including Omicron BA.4/5 and is supported by the clinical evidence presented in the CS.[20, 23, 24] The EAG notes that although Evusheld may be effective against all variants of concern including Omicron BA.4 and BA.5, these neutralisation studies[73-75] (as well as other in-vitro neutralisation studies using generic Evusheld)[38, 57, 59, 77] also suggest that Evusheld may be notably less effective against the currently prevalent Omicron subvariants BA.4 and BA.5, when compared to other subvariants such as BA.2.[23, 38, 52, 56, 57, 59, 77] There are also emerging concerns, based on laboratory testing, that Evusheld may have reduced or no efficacy against newer variants including

BQ.1, BQ.1.1, XBB and others,[78, 79] some of which may become the dominant variant in the UK.[80] However, as noted in a systematic review of 51 studies (including 15 Evusheld studies) evaluating the neutralising activity of FDA-authorised monoclonal antibodies against Omicron variants the authors identified variable and inconsistent methods for assessing neutralising susceptibility which made the evidence base challenging to interpret and indicated the need for improved monoclonal antibody susceptibility test standardisation.[77] In addition, the CS did not provide any robust evidence of correlation between in vitro neutralisation and clinical outcomes. The SPC[17] states that '*It is not known how pseudotyped VLP or authentic SARS-CoV-2 neutralisation susceptibility data correlate with clinical outcome. Data collection is ongoing to better understand how reductions in activity seen in authentic SARS-CoV-2 or pseudotyped VLP assays may correlate with clinical outcomes*'. Moreover, concerns have also been noted that cilgavimab alone may retain antiviral activity against Omicron variants (e.g., BA.2 and BA.5) and the use of combination therapy may give rise to escape variants, or viral resistance.[58-60]

3.5 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

No indirect comparison was undertaken by the company to supplement the direct evidence as there is only one trial that has evaluated the use of Evusheld compared with no prophylaxis for preventing COVID-19. The EAG agreed with this position.

3.6 Critique of the indirect comparison and/or multiple treatment comparison

No indirect comparison was undertaken by the company (see Section 3.5).

3.7 Additional work on clinical effectiveness undertaken by the EAG

No additional work was undertaken by the EAG

3.8 Conclusions of the clinical effectiveness section

3.8.1 Completeness of the CS with regard to relevant clinical studies and relevant data within those studies

The clinical evidence in the CS is based on a systematic review of Evusheld for preventing COVID-19. Despite poor reporting of the SLR, the EAG is confident that all relevant controlled trials (published and unpublished) were included in the CS, including data from ongoing/planned studies. However, the EAG is not confident that all relevant non-controlled studies have been identified and included in the CS, as details of the systematic review process (e.g. the identification and selection of evidence

including providing valid reasons for excluding potentially relevant studies) were lacking in the CS (including in the company's clarification response to questions A9 and A5).

3.8.2 Interpretation of treatment effects reported in the CS in relation to relevant population, interventions, comparator and outcomes

The key evidence for the target population in the CS was informed by the PROVENT trial[20] along with RWE studies (Young-Xu *et al*.[23] and Kertes *et al*.[24]) and the TACKLE study,[51] which estimated safety of the 600 mg dose of Evusheld.

The CS (Section B3.3.2.3 and Evidence Submission Summary, Section A6) considered the Young-Xu *et al*.[23] study (n= 8087) to represent the most generalisable population to the target population in the CS (95% received COVID-19 vaccination and 83% of Evusheld recipients received a single 600mg dose of Evusheld). Due to the retrospective nature of the study design, the study lacked a control arm; however, matched controls were selected from patients who were immunocompromised (or otherwise at high-risk of COVID-19) who were not treated with Evusheld. The PS matching results suggested that Evusheld recipients had a lower incidence of composite COVID-19 outcomes (defined as infection, hospitalisation, and all-cause mortality) versus controls (HR 0.31; 95% CI: 0.18 to 0.53 [17/1733 [1.0%] vs 206/6354 [3.2%]). Results were similar within the immunocompromised (HR 0.32; 95% CI: 0.18 to 0.62) and severely immunocompromised (HR 0.44; 95% CI: 0.21 to 0.93) subgroups. When evaluating the outcomes individually, the results showed statistically significant benefits in favour of Evusheld over the matched control, including test-confirmed SARS-CoV-2 infection (HR 0.34; 95% CI: 0.13 to 0.87), COVID-19 hospitalisation (HR 0.13; 95% CI: 0.02 to 0.99), and all-cause mortality (HR 0.36; 95% CI: 0.18 to 0.73). COVID-19 related mortality and AEs were not reported in the Young-Xu *et al*.[23] study.

The EAG believes there are some limitations associated with this analysis used to estimate the treatment effect between Evusheld versus a matched control. For example, in Young-Xu *et al*.[23] the width of the 95% CIs (which reflect the uncertainty around the treatment effect) are wide, particularly for the individual outcomes of the composite outcome. There is also the potential for residual confounding to be present (despite matching on a number of baseline characteristics), and further, there are concerns regarding the generalisability of the results (particularly in relation to the UK population) and moreover, the analysis was conducted when the Omicron BA.1 variant was dominant. Therefore, the results of the PS matching analysis conducted should be interpreted with caution. However, the EAG considers that this PS analysis reported by Young-Xu *et al*.[23] is the most methodologically robust out of the RWE presented in the CS.

Although the results from the PROVENT trial (n=5197) are not considered by the company (CS, Section B3.3.2.3 and Evidence summary, Section A.6) and the EAG to be the most generalisable to the UK context (all unvaccinated and received a single 300mg dose of Evusheld; negative point of care SARS-CoV-2 serologic test result at screening; unclearly defined immunocompromised population but CS suggest [redacted]; analysis conducted when Alpha and Delta variants were dominant) the results showed that Evusheld was associated with a significant reduction in the risk of experiencing COVID-19 (RT-PCR positive symptomatic illness) compared with placebo. COVID-19 (RT-PCR positive symptomatic illness) occurred in 8/3441 participants (0.2%) in the Evusheld group compared with 17/1731 participants (1.0%) in the placebo group (RRR, 76.7%; 95% CI: 46.0 to 90.0; P<0.001) from administration to 83 days (median). With extended follow-up, at a median of 6 months, the results showed a RRR of 82.8% (95% CI: 65.8 to 91.4). Five cases of severe or critical COVID-19 and two COVID-19-related deaths occurred, all in the placebo group. Safety analyses generally indicate that Evusheld (300 mg, single dose) is well tolerated.

The Kertes *et al*.[24] study was a large retrospective study (n=5124) but was considered to have significant methodological limitations (unmatched control, no PS analysis, only some confounders adjusted for in the regression analysis; analysis conducted when the Omicron BA.1 and BA.2. were dominant; and unclear generalisability to the UK context due to potential for selection bias). Despite this, the results showed that fewer Evusheld recipients (29/825 [3.5%]) became infected with SARS-CoV-2 compared with the non-administered Evusheld (308/4299 [7.2%]) group (OR after adjustment, 0.51; 95% CI: 0.30 to 0.84). One person in the Evusheld administered group (0.1%) was hospitalised for COVID-19 compared with 27 (0.6%) in the non-administered group (P = 0.07). No deaths occurred in the Evusheld group compared with 40 deaths (0.9%) in the non-administered group (P = 0.005). Due to the small number of patients with severe disease (n=64), a logistic regression was conducted, including only age group and cardiovascular disease. After adjustment, the Evusheld administered group odds of having severe disease were 0.08 (95% CI: 0.01-0.54) compared with the non-administered group. AEs were not reported in the Kertes *et al*.[24] study. In general, the EAG advises caution when interpreting these results.

With regards to safety and AEs of the higher dose of Evusheld, the overall results from the TACKLE study (single 600 mg dose) were in line with that of the 300mg dose from the PROVENT study and was considered to be generally well-tolerated.

3.8.3. Uncertainties surrounding clinical effectiveness

The EAG identified several weaknesses and uncertainties relating to the evidence presented by the company to estimate the relative effectiveness of Evusheld. While the EAG considers the propensity

matching approach applied by the company to be reasonable, data quality issues and methodological limitations (e.g., inconsistencies in the matching of the controls, potential baseline differences between prognostic factors not included in the matching process and residual confounding and other statistical issues) may have impacted the estimates of effectiveness. As such, the magnitude of benefit in reducing the incidence of SARS-CoV-2 infection, COVID-19 hospitalisation and all-cause mortality in the target population remains uncertain. In addition, there are no data available to inform on the efficacy and safety of Evusheld (600 mg dose) beyond 6 months after initial administration or repeat dosing. However, this is currently being investigated in the PROVENT sub-study and the ENDURE Dose Ranging Study[19] (company's clarification response to question A1 and A17).

The current clinical evidence does not provide information on the efficacy of Evusheld against the newest variants of concern that are now prevalent (e.g. BA.5) or emerging in the UK (e.g. BQ.1, BQ.1.1, XBB and others).[55, 80] Despite the lack of evidence on the correlation between in vitro neutralisation and clinical outcomes, neutralisation studies using authentic 'live' assays suggest that Evusheld may be effective against all variants of concern including Omicron BA.4 and BA.5.[73-75] However, these studies[73-75] as well as other in-vitro neutralisation studies using generic Evusheld[38, 57, 59, 77] (i.e., antibodies generated in a research laboratory [company's clarification response to question A5]) also suggest that Evusheld may have lower potency against the currently prevalent Omicron subvariants BA.4. and BA.5 and newer emerging variants. Concerns have also been noted that only cilgavimab but not tixagevimab may retain antiviral activity against Omicron variants (e.g. BA.2 and BA.5) and the use of combination therapy may give rise to escape variants, or viral resistance.[58-60] The EAG notes that given the reduced effectiveness against new variants was the primary reason for the increased dose of 600mg Evusheld being licensed for pre-exposure prophylaxis, it is unclear if higher doses will be needed or considered for emerging and future variants.[60, 81] In addition, the supporting studies included in the CS do not provide any evidence on the use of Evusheld in pregnant women and children aged under 12 years and it is unclear how the immunocompromised populations from the PROVENT trial,[20] Young-Xu *et al*.,[23] and Kertes *et al*.[24] align with the highest clinical risk groups defined in the McInnes report (CS, Table 4, p21), and the target population in the CS (Budget Impact Analysis, p2-3).

4 COST EFFECTIVENESS

4.1 EAG's comment on company's review of cost-effectiveness evidence

4.1.1 Objective of cost effectiveness review

The company performed systematic literature searches for i) published economic models and cost-effectiveness studies (CS Appendix G) ii) health-related quality-of-life studies of economic evaluations (CS Appendix H) iii) cost and resource use studies (CS Appendix I) of preventative/prophylactic treatments of COVID-19.

4.1.2 The methods used to identify relevant studies

4.1.2.1 Searches

The EAG has identified several limitations in the electronic database searches:

- Field-restricted searching for the population (title only)
- Restricted use of economic evaluation search terms in the cost-effectiveness study searches
- Restricted use of geographical search terms in the cost and resource searches.

In the cost-effectiveness study search and models (Appendix G), the following sources were searched in May 2022: MEDLINE [via Ovid], Embase (via Ovid), and EconLit (via Ovid). The company searched several key conference abstracts from 2021 and 2022 via Embase (via Ovid): Academy of Managed Care Pharmacy, International Society for Pharmacoeconomics and Outcomes Research, Infectious Diseases Society of America, Society for Healthcare Epidemiology of America, Human Immunodeficiency Virus Medical Association, Paediatric Infectious Diseases Society, Society of Infectious Diseases Pharmacists, and European Respiratory Society International Congress. The EAG does not have access to the conference abstract databases via the Embase.com host platform. The search could be complemented by searching conference websites, especially for the most recent conference abstracts that are not immediately indexed in Embase (for example, the ISPOR Presentations database at https://www.ispor.org/heor-resources/presentations-database/search).

In the health-related quality-of-life studies search (CS Appendix H), fewer but key databases, including living databases, were searched in June 2022: MEDLINE (via PubMed), Embase (via Embase.com), COVID L-OVE and the WHO global research on coronavirus disease (COVID-19) database. Supplementary backward and forward citation searches of included studies at the full-text review stage and grey literature searching using Google Scholar were conducted.

In the cost and resource search (Appendix I) was conducted on 10th August 2022 in the following sources: MEDLINE (via Ovid), MEDLINE in Process (via Ovid), EMBASE (via Ovid), HTA database (EBM Reviews), NHS EED (EBM Reviews), Cochrane Central Register of Controlled Trials (EBM Reviews), and Database of Abstracts of Reviews of Effects (EBM Reviews), Cochrane Database of Systematic Reviews (EBM Reviews), EconLit (via Ovid). The company conducted reference tracking, including extensive grey literature searching in online health economic repositories and registries (Health Economics Research, Cost-effectiveness Analysis Registry, Research Papers in Health Economics). Two HTA libraries were searched (NIHR Library and the International Network of Agencies for Health Technology Assessment database) and three COVID living databases were searched (COVID-NMA, COVID L-OVE, and the WHO global research on coronavirus disease database).

Similar to the traditional database searches for clinical effectiveness and safety, all three searches used limited but relevant terms for population, including field-restricted searching to titles only. The NICE filters by Levay & Finnegan (2021)[22] have used multiple field searches (title, abstract, keyword heading, and keyword heading word), including MeSH heading searches (SARS-COV-2/ and COVID-19/). The company acknowledged that title field searching was not a form of high-sensitivity search but that this would be mitigated by citation searches (CS clarification response to A25).

The cost-effectiveness modelling (Tables 11-15), HRQoL (Tables 30-31), and cost and resource search statements (Tables 37-40) in the database searches are considered comprehensive. However, there are terms specific to economic evaluation search filters that are absent in (CS Appendix G, Tables 11-15) such as those found in the NHS EED filters for economic evaluations.[82] In addition, there are published UK-sensitive search filters published by NICE that could be applied to both MEDLINE and Embase searches and are listed in Appendix I, Tables 30-31 by Ayiku *et al*.[83, 84]

Despite the database search limitation described in the above sections, the EAG believes that this could be mitigated by the extensive supplementary searches across a wide range of sources conducted by the company.

4.1.2.2 Inclusions/ exclusion criteria

The inclusion and exclusion criteria used by the company are presented in CS Appendix G Table 17 for the cost-effectiveness studies, Appendix H Table 32 for HRQoL studies, and Appendix I Table 41 for cost and healthcare resource studies. The EAG considers the inclusion criteria to be appropriate to capture recent and relevant evidence.

4.1.3 Findings of the cost effectiveness review

The results of the SLR were provided in CS Appendix G2 Tables 18 to 27 for identified economic evaluation studies. 20 of the 21 publications identified were related to COVID-19 treatments whereas the remaining one was concerned with post-exposure prophylaxis. Therefore, none of the studies were related to the decision problem addressed here.

CS Table 47 and 48 summarise the results from 17 studies identified for utility values, whereas CS Appendix I Table 42 describes the 24 included studies for cost and utilisation data. For both categories, the SLRs were used alongside more targeted searches to inform the model parameters as detailed through this section.

4.1.4 Conclusions of the cost effectiveness review

None of the published cost-effectiveness analyses identified addressed the specific decision problem outlined in the NICE scope. The company therefore submitted a *de novo* economic analysis.

4.2 Summary of the company's submitted economic evaluation

As part of their submission to NICE, the company submitted an executable model programmed in Microsoft Excel.® The company submitted an updated model following clarification. In this section the EAG describes this later updated model but also notes where this differs from the original model described in the main CS. The scope of the economic analysis is summarised in Table 17.

Table 17: Scope of the company's economic analyses

Population	Adults who are not currently infected with SARS-CoV-2 and who have not had a known recent exposure to a person infected with SARS-CoV-2 and: • are at the highest risk of an adverse COVID-19 outcome, namely hospitalisation and death, or • for whom COVID-19 vaccination is not recommended.
Time horizon	Lifetime horizon
Intervention	One year of Evusheld treatment consisting of an initial 600mg dose, followed 6 months later by a second 600mg dose.
Comparator	Standard of care (SoC) in the absence of any pre-exposure prophylaxis for COVID-19 infection
Type of economic analysis	Cost-utility analysis
Outcome	Incremental cost per QALY gained
Perspective	NHS and PSS
Discount rate	3.5% per annum
Price year	Unclear*

*Different price years are used for different unit costs ranging from 2017/18 reference costs for adverse events to 2021 Personal Social Services Research Unit (PSSRU) unit costs for nurse time to administer Evusheld.
Abbreviations: QALY, quality-adjusted life year; NHS, National Health Service; PSS, Personal Social Services

4.2.1 Population

The population reflected in the company's economic evaluation is,

> "*adults who are not currently infected with SARS-CoV-2 and who have not had a known recent exposure to a person infected with SARS-CoV-2 and:*
>
> - *are at the highest risk of an adverse COVID-19 outcome, namely hospitalisation and death, or*
> - *for whom COVID-19 vaccination is not recommended."*

The CS acknowledges that this is a subgroup of the licensed indication but states that this aligns with their proposed positioning of Evusheld for use in the group with the highest unmet need as described in Section 2.3.1. The company states that for the purposes of modelling, the group of patients for whom COVID-19 vaccination is not recommended is assumed to comprise <1% of the target population with the vast majority being those who are at higher risk of adverse outcomes due to underlying health conditions compromising their immunity. Therefore, many of the evidence sources informing the model have been selected to reflect patients with compromised immunity.

4.2.2 Interventions and comparators

The model assumes that Evusheld is given at a 600mg dose once at the start of the model and again at 6 months to provide a 1-year treatment period. The company's rationale for not modelling ongoing use of Evusheld beyond 1 year is firstly that "*the environment for COVID-19 is constantly changing and it is unclear how long Evusheld will be prescribed as the risk of COVID-19 infection and associated adverse outcomes changes over time."* (CS Section B3.2.2, p108) The CS notes that there is uncertainty regarding both future changes in the virus itself and future changes in the treatment pathway that make it difficult to extrapolate the longer-term impact of any COVID-19 treatment. Secondly, the company notes that some patients will only be eligible for Evusheld for a time-limited period due to changes in their clinical status such as completing a course of treatment or recovering from an acute illness. As discussed previously in Section 2.3.2, the SPC for Evusheld states that there are no safety or efficacy data available for repeat dosing with Evusheld.[17] In response to clarification, the company provided a scenario analysis exploring the use of a single dose of 600mg over a 6-month treatment period, but maintained the assumption of two dose 1-year treatment course in their base case analysis. This is further discussed in Section 4.3.4.1.

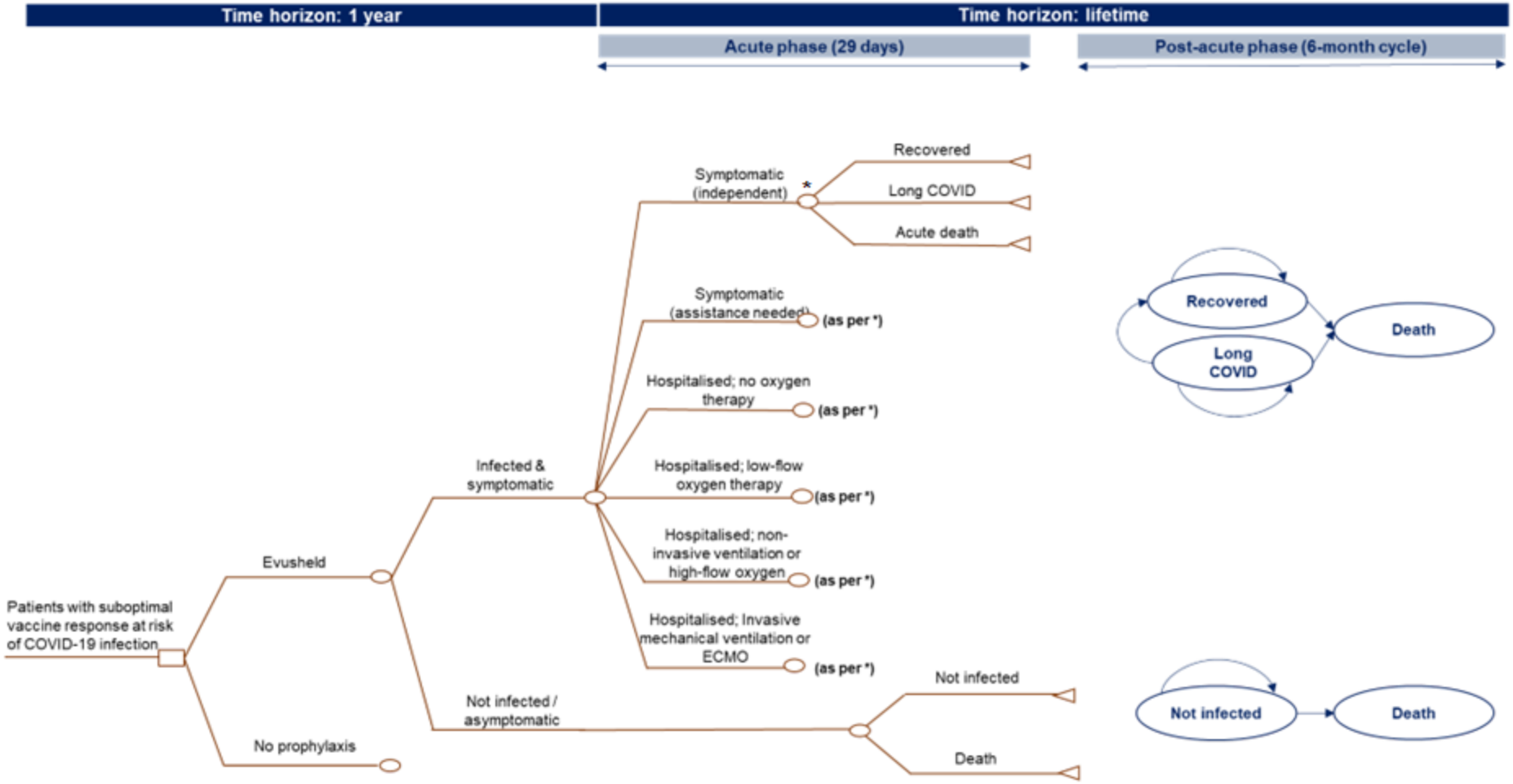
The comparator in the model is standard of care in the absence of pre-exposure prophylaxis (abbreviated as SoC) which is in-line with the decision problem as described in Section 2.3. It should also be noted that any COVID-19 treatments included within NICE's ongoing MTA are assumed to be absent from the treatment pathway as they are not covered by routine commissioning at the present time. These are therefore not considered either as comparators or as downstream treatment costs which could be avoided by preventing infections. This is problematic as many of these treatments have been available within

the NHS through NHS England's Interim Clinical Commissioning and their effect on COVID-19 outcomes may be captured within recent data on hospitalisation and mortality rates.[21] The impact of this is not explored in the company's analyses, although the EAG notes that the impact of this depends on whether the company has used data sources from a period when these treatments were widely available or from earlier periods.

4.2.3 Perspective, time horizon and discounting

The model is described in the CS as taking an NHS and PSS perspective, with discounting of costs and benefits at 3.5% per annum, in line with the NICE reference case. The company's economic model incorporates a lifetime horizon overall, however, there are three distinct periods within that time horizon. Firstly, there is the 1-year treatment period over which patients are at risk of an initial SAR-CoV-2 infection. Secondly, there is an acute 29-day period to account for the acute effects of COVID-19 including hospitalisation chosen to match the longest duration of hospital stay for infected patients.[85] Finally, there is a long-term state-transition (Markov) model covering the patient's remaining lifetime which is necessary both to estimate the life-time QALY losses due to fatal infections, and the impact on costs and QALYs of long-term morbidity from long COVID. The EAG is satisfied that a lifetime horizon was appropriate in this case but makes further comment in Section 4.2.4 on which clinical risks are captured within the long-term model.

Figure 6: Model structure [reproduced from CS, Figure 16]



4.2.4 Model structure

The company's model structure consists of a decision tree, to capture the impact of Evusheld on COVID-19, followed by a long-term state-transition (Markov) model to extrapolate survival and ongoing morbidity over the patient's lifetime. The EAG notes that the decision tree phase implicitly covers the year in which patients receive either Evusheld or SoC, during which time patients are at risk of infection, as well as the 29 days patients spend in an infected or non-infected state (see Figure 6).

Within the decision tree, symptomatic infected patients are separated according to disease severity, which is classified according to the need for hospitalisation and the level of ventilation support required using the WHO clinical progression scale. These are summarised in Table 18. The EAG notes that whilst the company's model structure distinguishes between non-hospitalised patients who do and do not need assistance, these health states are identical in the model implementation and could be combined into a single state with no impact on outcomes. For each of the health states defined in Table 18, there are three possible outcomes from COVID-19: death, recovery and long COVID.

The EAG also notes that the patients with asymptomatic SARS-CoV-2 infection fall outside of any of the states presented in Table 18, and are considered alongside individuals who are not infected within the decision tree structure. These patients only have two possible outcomes at the end of the decision tree phase: not infected and dead (see Figure 6). However, the EAG notes that none of these patients are in the dead state at the end of the decision tree, implying that all-cause mortality is not applied during the acute decision-tree phase of the model. This is consistent with the assumption applied to infected patients who are also only at risk of COVID-related mortality during the acute decision tree phase.

A long-term state-transition (Markov) model with a 6-month cycle length is then used to extrapolate costs and QALY gains. During this long-term model, patients with long COVID can die, move to the recovered state, or remain in the long COVID state. Patients in the recovered state can only transition to the death state. Patients who were not infected or who had asymptomatic infections during the acute phase of the model start in the 'not infected' state and can only transition to the death state. Half-cycle corrections are applied when estimating the life-time costs and QALYs gained in the long-term model. The long-term model structure itself (as shown in Figure 6) does not allow for infections occurring beyond year one, so instead the impact of infections occurring after the decision tree phase are handled using simple adjustments (see 4.2.6.20 Post year one cases of COVID-19).

Table 18: Description of acute modelled health states [adapted from CS, Table 34]

Model health states classifying infection severity	WHO clinical progression scale	
Not hospitalised – no assistance needed	2	Symptomatic; independent
Not hospitalised – assistance needed	3	Symptomatic; assistance needed
Hospitalised; no oxygen therapy	4	Hospitalised: no oxygen therapy
Hospitalised; low-flow oxygen therapy	5	Hospitalised: oxygen by mask or nasal prongs [a]
Hospitalised; non-invasive ventilation (NIV) or high-flow oxygen	6	Hospitalised; oxygen by NIV or high-flow
Hospitalised; Invasive mechanical ventilation (IMV) or extracorporeal membrane oxygenation (ECMO)	7 8 9	Intubation and MV, pO2/FiO2 ≥ 150 or SpO2/FiO2 ≥200 MV pO2/FiO2 <150 or SpO2/FiO2 <200 or vasopressors MV pO2/FiO2 <150 and vasopressors, dialysis or ECMO

Abbreviations: FiO2 – Fraction of inspired oxygen; MV – Mechanical ventilation; NA – not applicable for the WHO clinical progression scale NIV – Non-invasive ventilation; pO2 – Partial pressure of oxygen; SpO2 – Peripheral capillary oxygen saturation; WHO – World Health Organization

[a] In CS, Table 34, this descriptor was allocated to the 'Hospitalised; no oxygen therapy' health state but the EAG believes that this is a typographical error and has allocated this WHO clinical progression scale to the 'Hospitalised; low-flow oxygen therapy' state as this appears consistent with the description of this state how the model is presented in the CS as a whole.

4.2.5 Key assumptions employed in the company's model

The company's model employs the following key assumptions

- The treatment effect for Evusheld is applied to the whole of the first year (decision tree phase) assuming an average constant protective effect over the whole year
- Evusheld is assumed to have no treatment effect beyond the first year
- A direct utility improvement is applied for the first year in patients receiving Evusheld who are not infected or who have a non-fatal infection
- Patients with asymptomatic infections are aggregated together with those who are not infected and are assumed to have the same future risks as those not infected
- Patients cannot be infected twice in the first year
- The risk of infection in the second year and beyond is not affected by whether patients had an infection in the first year (i.e., infection confers no future protective effect)
- The annual infection risk at the start of the model is assumed to be constant in all future years
- There is no risk of long COVID in those infected after the first year

- The severity of COVID-19 within the group who are hospitalised is the same for those receiving Evusheld and SoC
- All patients hospitalised with COVID-19 are assumed to have long COVID at discharge
- Utility loss associated with hospital admission is applied in addition to utility loss of acute infection
- Utility values experienced during hospitalisation are determined based on the most intensive treatment required by the patient during the whole of their hospital stay (i.e., utility decrements for patients requiring ICU care are applied for the whole of the patient's hospitalisation regardless of the proportion of time in ICU)
- Patients discharged from hospital incur monitoring costs for one year post discharge, but non-hospitalised patients do not incur monitoring costs
- AEs associated with two doses of Evusheld are assumed to be twice those associated with a single dose
- Patients in the target population have lower base-line utility and lower life-expectancy than the general population due to the presence of comorbidities that are used to define the target population
- Patients discharged from hospital after receiving care in ICU have an increased risk of mortality for 5-years (applied to those requiring high-flow oxygen, NIV or IMV)
- Utility decrements for long COVID in patients who did not require hospitalisation are assumed to be equivalent to the values applied in those requiring hospitalisation without oxygen therapy
- No carer disutility is applied and no indirect costs (e.g., productivity costs) are included
- No implementation costs are included for logistics related to the identification of patients eligible to receive Evusheld and the organisation of clinics to administer Evusheld in an efficient manner
- All other factors that influence infection risk are assumed to be equivalent between those receiving Evusheld and those not receiving Evusheld including vaccination uptake and infection avoidance behaviours such as mask wearing and avoiding crowded indoor settings.

4.2.6 Evidence used to inform the company's model parameters

The key evidence used to inform the company's base case analysis is summarised in Table 19. The sources used to derive these model parameters are discussed in detail in the subsequent sections.

Table 19: Summary of evidence used to inform the company's base case analysis

Parameter / group	SoC (no pre-exposure prophylaxis for SARS-CoV-2 infection)	Evusheld
Patient characteristics (age, proportion male)	Based on characteristics of participants in the PROVENT study.[20]	
Utility in the target population	Disutility for patients with cardiovascular comorbidities compared to those without is assumed to apply to all patients in the target population (Rafia 2022).[86] This disutility is applied to age and sex adjusted estimates of general population utility values (Ara and Brazier 2010)[87] to estimate utility values in non-infected and recovered individuals	
All-cause mortality in the target population	Standardised mortality ratio for common variable immunodeficiency disorders compared to general population is assumed to apply to all patients in the target population (Odnoletkova 2018).[88] This is applied to all-cause mortality in the general population (ONS lifetables)[89] to estimate all-cause mortality in the target population	
Direct treatment utility gain	None	Impact of lockdown on HRQoL in general population based on CANDOUR study (Violato *et al*. 2022)[90]
Risk of infection	1-year risk of infection derived from the 7-day attack rate in the general population averaged over the period Aug 2021 to Aug 2022.[91]	RRR from Young-Xu *et al*.[23] RWE study applied to risk without Evusheld
Risk of hospitalisation for infected patients	Risk of hospitalisation in patients with primary and secondary immune deficiency infected with SARS-CoV-2 in UK cohort study (Shields 2022)[10]	RRR from Young-Xu *et al*.[23] RWE study applied to risk without Evusheld
Distribution of hospitalised patients across severity states	Proportions receiving different levels of care among patients admitted to a single UK hospital (Cusinato 2022)[92]	
Mortality of acute infection in hospitalised patients	US cohort study for patients requiring no or low-flow oxygen (Ohsfeldt 2021)[93] ICNARC report on mortality rates for COVID-19 in critical care for those requiring more than low-flow oxygen[9]	
Proportion of infected patients having long COVID	Proportion of non-hospitalised patients having long COVID taken from non-UK cohort study (Augustin 2021)[94] All hospitalised patients assumed to have long COVID	
Time to recovery from long COVID	Log-normal time-to-event curve fitted to ONS data by Metry *et al*.[95] and adjusted to account for lower recovery observed at 1-year in the PHOSP-COVID UK cohort (Evans 2022)[96]	
Disutility of long COVID	Disutility for hospitalised patients is stratified by severity of COVID-19 and estimated from the PHOSP-COVID UK cohort (Evans 2021, Evans 2022)[96, 97] Disutility for non-hospitalised patients is assumed to be equivalent to disutility in those hospitalised but not requiring oxygen.	
Mortality risk post discharge from critical care	Increased risk of mortality for patients receiving critical care in the 5-years after discharge (Lone 2016)[98]	
AE incidence	Incidence in the placebo arm of TACKLE study[51] ¶	Incidence in the Evusheld arm of TACKLE study (600mg dose used in outpatient treatment of symptomatic COVD-19)[51] ¶

Parameter / group	SoC (no pre-exposure prophylaxis for SARS-CoV-2 infection)	Evusheld
QALY loss of AEs	Duration based on duration of admission for relevant Healthcare Resource Group (HRG) codes[99] Utility loss based on various published sources for proxy conditions [100-107]	
QALY loss of acute infection	Utility loss from influenza modelling study (Smith 2002)[108] Duration of symptoms taken from a published analysis plan for a COVID-19 economic model (ICER 2021)[109]	
QALY loss of hospital admission	Utility loss based on French study of patients hospitalised with clostridium difficile (Barbut 2019)[110]	
Drug acquisition costs	Not applicable	Company provided list and PAS prices *
Drug administration costs	Not applicable	PSSRU unit costs for nurse administration in a primary care setting [111]
Post discharge monitoring for hospitalised patients	Frequency of monitoring based on assumptions used in the ScHARR COVID-19 MTA model (Metry 2022)[95]. PSSRU and NHS reference costs applied[111, 112]	
Long COVID costs	Cost used in scenario analysis within ScHARR MTA model[± 95]	
Resource use and costs for hospitalisation	Cost per day based on NHS reference costs used by Rafia *et al*.[86] Duration of stay in different inpatient settings estimated from ACTT-1 study (Beigel 2020)[85]	
AE costs	NHS reference costs for relevant HRG codes[99]	

¶ incidence from PROVENT used in pre-clarification model

* PAS not accepted by PASLU at time or writing so only list price analyses presented in the EAG report

± pre-clarification model used cost for chronic fatigues from ScHARR COVID-19 MTA model base case

4.2.6.1 Population characteristics

The baseline characteristics for the modelled population are based on the population recruited to the PROVENT trial (53.5 years, 53.9% male, 85.7kg).[20] The age and proportion of patients who are male are relevant as these are used to estimate all-cause mortality for the long-term model. An average probability of death from all causes is estimated for each age assuming the proportion of males is fixed over time at the baseline proportion. The dose is not dependent on weight so this is not relevant in the model.

The target population for the company's economic analysis is people who are at increased risk of the consequences of SARS-CoV-2 infection, many of whom will have an underlying condition which results in immune suppression, or which requires a treatment which suppresses their immune system. The company has therefore applied an increased risk of mortality compared to members of the general population to reflect the comorbidities present in this group (see Section 4.2.6.8). For the same reason, the company has also allowed for a reduced HRQoL compared to the general population (see Section 4.2.6.10).

4.2.6.2 Costs for Evusheld acquisition and administration

Drug acquisition costs for Evusheld are £1,600 per 600mg dose at the list price. Therefore, the two doses of 600mg of Evusheld that form the 1-year treatment plan modelled by the company has a total cost of £3,200 at the company's proposed list price. The company has proposed a simple discount (PAS) price of [redacted] per 600mg, giving a 1-year cost for 2 doses of [redacted], but at the time the EAG report was prepared, this proposed PAS had not been accepted by the PASLU. Therefore, the company's model results are presented in the EAG reporting using the list price.

In the original CS, the company stated that Evusheld would be administered in primary care, requiring 1.5 hours of nursing time including 30 minutes for administration and 1 hour for observation. In response to clarification question B2, the company stated that this approach did not allow for any efficiencies to be gained by multiple patients being monitored simultaneously. They therefore reduced their estimate of nursing time for administration in their base case down to 30 minutes per dose administered. The company applied the unit cost for nursing time in primary care from PPSRU of £42 per hour to estimate an administration cost of £42 over 2 doses in their updated base case analysis.[111] The EAG notes that the company's updated approach assumes no resources are allocated for the 1 hour post-administration observation period. The EAG discusses the appropriateness of these treatment administration assumptions in Section 4.3.4.2.

4.2.6.3 Risk of COVID-19 without Evusheld

The risk of COVID-19 (i.e. symptomatic SARS-CoV-2) applied in the model is 22.58% per annum and this is based on the average 7-day attack rate for England over the period August 2021 to August 2022.[91] The EAG notes that this has been estimated from the average risk across the general population of recording a specimen positive for SARS-CoV-2, and this is then applied in the model as the risk of COVID-19. The EAG has concerns regarding the applicability of this estimate of infection risk which are further discussed in Section 4.3.4.5.

4.2.6.4 Hospitalisation risk in those with COVID-19

The probability of hospitalisation for patients infected with COVID-19 was based on data from a paper by Shields *et al*. (2022),[10] which assessed the impact of vaccination on hospitalisation and mortality from COVID-19 in patients with primary and secondary immunodeficiency in the UK. This provided data on the hospitalisation rate for patients with primary and secondary immunodeficiency infected with SARS-Cov-2 between January 2021 and April 2022. The average hospitalisation rate across this cohort, incorporated in the company's updated post-clarification model, was 18.06% (NB: this was previously stated as being 17.13% in the company's original submission, based on a pre-print version of this paper; see clarification response B7).[10] Shields *et al*. reported a high rate (>90%) of completion of the primary vaccination course (2 doses) in this cohort and noted that 76.5% of infections in this cohort occurred

after November 2021 when the more transmissible Omicron variant became dominant.[10] The appropriateness of the estimate applied in the company's base case is discussed further in Section 4.3.4.6.

4.2.6.5 Severity of COVID-19

In the company's base case, the proportion of patients requiring different levels of hospital care is estimated from a paper by Cusinato *et al*. which reports data on all patients admitted in a South London hospital to COVID-19 specific wards from January 2020 to March 2021.[92] These estimates therefore reflect the severity of COVID-19 and the hospital care required to treat patients from the general population who are admitted with COVID-19 and are not specific to the target population for Evusheld. The EAG also noted that Cusinato *et al*. provide the same data estimated separately for the first and second waves of COVID-19 in the UK (defined as before / after 31st June 2020 respectively) and that whilst the requirement for oxygen was similar between waves (75.6% versus 73.1%, p=0.148), the use of invasive high flow nasal oxygen and NIV were more prevalent in the second wave (22.2% vs 9.2%, p<0.001) and the use of IMV was less prevalent in the second wave (13.0% vs 20.1% p<0.001).[92] In response to clarification, the company provided a scenario analysis in which data specific to the second wave were incorporated but did not update its base case analysis which used the data averaged across both waves. The company also provided a scenario analysis in which the proportion requiring IMV was reduced to reflect the proportion of hospitalised patients in ventilation beds from routine data for the NHS in England averaged across the year to 5th October 2022. In this scenario the additional cases were distributed across the other hospitalised states using the proportions from Cusinato *et al*. These data are summarised in Table 20. The appropriateness of the data applied in the company's base case is discussed further in Section 4.3.4.8.

Table 20: Distribution of hospitalised [a] patients across different care settings [reproduced from Table 42 of the company's response to clarification]

	Original (Total, Cusinato *et al*)[92]	Sensitivity 1: Second Wave (Cusinato *et al*)[92]	Sensitivity 2: gov.uk accessed October 2022[113] for IMV and second wave (Cusinato *et al*)[92]
No oxygen therapy	26.10%	26.90%	29.40%
Low-flow oxygen therapy	40.70%	37.90%	41.42%
NIV or high-flow oxygen	17.80%	22.20%	24.26%
IMV or ECMO	15.40%	13.00%	4.92%

[a] Non-hospitalised patients with COVID-19 are split equally between the 'no assistance needed' and 'assistance needed' health states but as these states are equivalent the distribution is unimportant.

4.2.6.6 Efficacy – reductions in risk of infection and hospitalisation

The effectiveness of Evusheld is captured by the relative risk reduction (RRR) for symptomatic infection and the RRR for hospitalisation (risk of hospitalisation in infected patients). In the base case analysis these estimates are taken from the RWE study in US Veterans (Young-Xu 2022).[23] Data from the PROVENT study, the pivotal phase III RCT for Evusheld in this indication[20], and data from an alternative RWE study conducted in Israel (Kertes 2022),[24] are used in scenario analyses. The efficacy inputs are summarised in Table 21. The EAG notes that none of the studies report the RRR of hospitalisation given COVID-19 and it was therefore necessary for the company to calculate this from the measures reported in the various studies.

The CS reports in the footnotes to Table 39 that no additional benefit was assumed for the RRR for hospitalisation given COVID-19 due to the low number of events reported, with a RRR of 100% being used to indicate this in the table. However, the EAG notes that the RRR of hospitalisation given infection should be 0% not 100% if the company wishes to assume that Evusheld only reduces hospitalisations through its impact on infections. Also, as part of its model verification process, the EAG estimated this figure directly from the intermediate model outcomes and found that the RRR for hospitalisation given COVID-19 applied in the model is 82.8% not 100%. Therefore, the company is assuming a RRR of 82% for COVID-19 attributable to Evusheld treatment, and then a further 82.8%

RRR for hospitalisation within the population experiencing COVID-19 attributable to Evusheld treatment. This issue is further discussed in Section 4.3.4.9.

Table 21 Efficacy parameters included in the economic analysis base case and scenario analyses [adapted from CS, Table 39]

Source	RRR of COVID-19 for Evusheld vs no prophylaxis	RRR of hospitalisation given COVID-19 for Evusheld vs no prophylaxis, as reported in CS	RRR of hospitalisation given COVID-19 for Evusheld vs no prophylaxis as estimated by the EAG from intermediate model outcomes
Base case: Young-Xu *et al*. 2022[23]	66%	61.8%	61.8%
Scenario: PROVENT study[20]	82.8%	100%*	82.8%
Scenario: Kertes *et al*. 2022[24]	49%	62.3%**	62.3%**

*No additional benefit assumed due to low hospitalisation numbers as only three patients (0 with Evusheld and three with placebo) were hospitalised at the time of primary data cut (regardless of prior vaccination status or unblinding).

**RRR of hospitalisation in Kertes *et al*. was estimated as *1 – the risk of being hospitalised given infection*. The risk of being hospitalised given infection was calculated as the HR of hospitalisation (0.19) divided by the HR of infection (0.51).

Abbreviations: HR – Hazard ratio; RRR – Relative risk reduction

4.2.6.7 Efficacy – direct utility gain associated with receiving Evusheld

The company's model assumes that patients who receive Evusheld have an improvement in HRQoL due to a reduction in their anxiety regarding SARS-CoV-2 infection and its potentially life-threatening consequences and due to a reduction in infection avoidance behaviours (i.e., shielding or other less restrictive measures to avoid infection). This direct utility gain associated with Evusheld treatment is estimated from the CANDOUR study which conducted a longitudinal web-based survey of adult members of the general public across 13 countries and asked them to report the impact of the COVID-19 pandemic on their HRQoL using the EQ-5D-5L.[90] This was estimated as the difference between utility pre-pandemic (measured by retrospective recall) compared to utility at the time of the survey (between 24th November and 17th December 2020) using UK valuations set for the EQ-5D-5L. This

gave an average utility loss of [redacted] across all participants from any country.

The modelling assumes that the target population for Evusheld will currently be experiencing a utility decrement equivalent to that experienced by the general population during lockdown, and this will be reversed when they receive Evusheld. Therefore, a utility gain of [redacted] is applied to all patients receiving Evusheld in the model. The company describes this utility gain as being applied to all patients receiving Evusheld for the duration of treatment (i.e., 1 year). However, there is a mismatch between how this is described and how this is implemented in the model, and this is further discussed in Section 4.3.4.4.

4.2.6.8 All-cause mortality

The company applies a HR of 1.7 to the all-cause mortality estimates from the general population life-tables[89] to reflect the higher risk of mortality in the target population who are immunosuppressed compared to the general public. This estimate is from a registry study and is specific to patients with common variable immunodeficiency disorders. (Odnoletkova 2018).[88] This is applied to all patients in the long-term phase of the model regardless of whether they have been infected in year 1. The appropriateness of applying this estimate to reflect all-cause mortality across the whole target population is discussed further in Section 4.3.4.3.

4.2.6.9 Covid-related mortality

The decision-tree phase of the model includes a risk of covid-related mortality associated with the acute infection period. For hospitalised patients in the two highest severity states (NIV/high-flow oxygen and IMV/ECMO), the model uses data from the ICNARC report on COVID-19 in critical care in England, Wales and Northern Ireland.[9] For hospitalised patients in the two lowest severity states (no oxygen and low-flow oxygen) data on 28-day mortality from the COV-BARRIER RCT (medical care without oxygen and medical care with oxygen respectively) are applied.[93] There is no risk of COVID-19 related mortality in patients whose COVID-19 is not sufficiently severe to require hospital treatment. The risk of death during COVID-19 is summarised in Table 22. The EAG had difficulty verifying the figures given by the company from the sources cited and this is discussed further in Section 4.3.4.11.

Table 22: COVID-19 related mortality applied to patients hospitalised for COVID-19 [adapted from CS, Table 44]

	Infection not requiring hospital care	No oxygen therapy	Low-flow oxygen therapy	NIV or high-flow oxygen therapy	IMV or ECMO
COVID-19 related mortality	0%	4.6%	7.6%	13.9%	47.0%

Abbreviations: COVID-19 – Coronavirus disease 2019; ECMO – Extracorporeal membrane oxygenation; IMV – Invasive mechanical ventilation; NIV – Non-invasive ventilation

In addition, patients who have been discharged from hospital having required critical care (those requiring high-flow oxygen or any form of ventilation) have a HR of 1.33 for all-cause mortality applied for the 5 years after hospital discharge. This estimate is based on a HR of 1.33 reported by Lone *et al*. for death in the 5 years following discharge from ICU compared to matched hospital patients not requiring ICU.[98] In response to clarification, the company stated that only 60.5% of the ICU cohort defined by Lone *et al*. had IMV and therefore it was reasonable to apply this HR to both those requiring IMV and those requiring only NIV or high-flow oxygen.

Patients having long COVID are not at any increased risk of mortality compared to those recovering without long COVID.

4.2.6.10 Utility values in patients who are not infected and those who have recovered

The utility values for patients who were not infected and those who have recovered (i.e. not currently experiencing long COVID) are based on age specific estimates for the UK general population which have then been adjusted to reflect the comorbidities that are likely to be present in the target population.[87] This adjustment is supposed to reflect the fact that the target population are likely to have health conditions that either cause immunosuppression or require immune suppressant treatments.

The utility decrement applied (0.1160) to reflect the health conditions present in the target population was taken from an estimate applied by Rafia *et al*. (2022) in a cost-effectiveness model examining the use of Remdesivir.[86] Rafia *et al*. used the decrement to reflect the fact that patients hospitalised with COVID-19 are more likely to have comorbidities. Rafia *et al*. in their earlier 2021 Decision Support Unit report on Remdesivir (Rafia 2021)[114] describe this as being based on the median decrement in utility values, when comparing those who reported a specific health condition with respondents of a similar age irrespective of health status, in the general population utility study described by Ara and Brazier (2011).[115] Based on a comparison of the selected data with the cited source study, the EAG believes that the data point selected by Rafia *et al*. from the study by Ara and Brazier (2011) is for

people with heart conditions (other than hypertension).[115] It is therefore not specific to the comorbidities likely to present in the target population. The appropriateness of using this estimate to reflect the utility decrement from the various comorbidities prevalent across the whole target population is discussed further in Section 4.3.4.3.

The absolute utility in those who were not infected is also assumed to apply to those who have recovered from COVID-19 without developing long COVID and those who have recovered from long COVID. For all other groups in the model, absolute utility decrements related to their current health states (i.e., acute infection, hospitalisation, and long COVID) are applied to the absolute utility value for uninfected / recovered patients.

4.2.6.11Utility decrement from acute COVID-19

The company's model applies a disutility of 0.19 during the period of acute COVID-19. This is described as being sourced from an influenza modelling study by Smith *et al*. (2002) [108] which the company identified through their targeted systematic review of HRQoL data. The EAG had concerns regarding the relevance of this estimate which are discussed in more detail in Section 4.3.4.12. The utility decrement for acute COVID-19 is applied for the duration of symptoms, which the company estimated from the ICER modelling analysis plan identified in their targeted literature review of published models. It should be noted that this is applied to all patients experiencing acute COVID-19, regardless of whether they result in hospital admission, with further utility decrements applied to reflect severe COVID-19 in hospitalised patients.

4.2.6.12 Utility decrement from hospitalisation

The utility decrements applied for hospitalised patients are described as being based on disutility estimates from a French study in patients with clostridium difficile by Barbut *et al*. (2019).[110] These were identified because they had been used in a published model identified in the company's targeted systematic review of published models (Whittington 2022).[116] The estimate from Barbut *et al*. was obtained by comparing EQ-5D-3L data from patients during hospital admission for clostridium difficile to retrospectively obtained score for the period prior to the clostridium difficile episode.[110] This provided a utility decrement of 0.492 for being hospitalised with clostridium difficile.[110] No estimates are provided by Barbut *et al*. for the variation in utility for patients requiring different levels of care e.g. ward care versus critical care.[110] It is unclear to the EAG how this relates to the estimates of 0.30, 0.50 and 0.60 applied in the company's analysis, although the EAG accepts that these have been lifted from other published models which also cite the paper by Barbut *et al*. (Whittington 2022, ICER 2021).[109, 116] Further discussion of this issue is provided in Section 4.3.4.12, although the EAG notes these utility values are not significant drivers of the ICER due to the short period over which they are applied.

The company also presents a scenario analysis which they describe as using the utility decrements applied in the ScHARR COVID-19 MTA model. The values applied in the ScHARR COVID-19 MTA model for those not requiring oxygen therapy were based on estimates from patients with clostridium difficile (Wilcox 2017),[117] and for patients requiring low or high oxygen therapy or NIV they were based on estimates for patients with influenza (Hollmann 2013).[118] The values used in the company's scenario analysis are provided in Table 23 for comparison. The EAG notes that there were various discrepancies between the company's implementation of this scenario and the implementation of the utility values within the ScHARR COVID-19 MTA model. These are described further in Section 4.3.4.17 (also briefly noted in the footnotes of Table 23 for reference). However, the EAG notes that these utility values do not have a significant impact on the ICER due to the short duration over which they are applied.

Table 23: Disutilities associated with acute COVID-19 and hospitalisation for COVID-19 [adapted from company submission table 51]

	Company base case				Company scenario using ScHARR COVID-19 MTA disutilties[a]			ScHARR COVID-19 MTA disutilities	
	Hospital-isation disutility	Total disutility	Duration (days)	QALYs lost	Hospital-isation disutility	Total disutility	QALYs lost	Total disutility	QALYs lost
Not hospitalised	0.00	0.19	11.0	0.0057	0	0.19[b]	0.0057	0	0.0000
No oxygen therapy	0.30	0.49	17.0	0.0228	0.36	0.55[b]	0.0256	0.36	0.0168
Low-flow oxygen therapy	0.30	0.49	19.0	0.0255	0.58	0.77[b]	0.0401	0.58	0.0302
NIV or high-flow oxygen	0.50	0.69	21.0	0.0397	0.58	0.77[b]	0.0443	0.58	0.0333
IMV or ECMO	0.60	0.79	28.0	0.0627	0.58[b]	0.77[c]	0.0611	0.74	0.0585

[a] The EAG believes that these were the values used by the company in their scenario, but as the scenario has been implemented manually, the EAG cannot be sure. However, results that agree with those presented by the company have been obtained by using the values presented here.

[b] ScHARR did not apply the additional 0.19 and therefore applied the values in the column to the left.

[c] ScHARR did not apply a utility decrement but instead assumed zero utility during this period, which would be equivalent to a utility decrement of 0.74 in the company's model.

4.2.6.13 Adverse events

The company acknowledged, in their response to clarification question B4, that the TACKLE study may provide a more robust estimation of the safety profile of the 600mg dose which is the dose assumed in the economic analysis. The company has therefore applied AEs from the TACKLE RCT in their updated post-clarification base case analysis.[51] This is despite the fact that the TACKLE study was conducted in patients who had tested positive to COVID-19 and was therefore less generalisable to the modelled population than the PROVENT study. However, the EAG notes that AEs were not a significant driver of cost-effectiveness when using either source as SAEs were low in both studies and Evusheld was generally well tolerated.

The AEs rates included in the model are summarised in Table 24. The EAG notes that these have been calculated as twice the incidence observed after a single dose of either Evusheld (or placebo) in TACKLE to account for the fact that the company's 1-year treatment schedule includes two doses of Evusheld, whereas TACKLE involved only a single dose. The AEs included in the model have been restricted to treatment-emergent serious AEs occurring in >=5 patients in either arm of PROVENT (but using incidence from TACKLE).

The utilities applied to patients experiencing the various types of serious AEs were identified from a targeted literature review of published models or utility studies. These are summarised in Table 24. The duration over which the disutility was applied for patients experiencing AEs was based on the duration of hospital stay for relevant HRG codes. For this purpose, the 2017/18 Reference Costs were used as later version of the NHS reference costs do not include data on the average length of stay. Overall, the QALY losses due to AEs is estimated to be 0.000154 QALYs for Evusheld and 0.000225 QALYs for SoC (equivalent to 1.3 and 2.0 hours of full health lost respectively). Therefore, Evusheld is expected to marginally reduce the QALYs lost due to AEs. This is due to having Evusheld having a lower incidence of some AEs when using data from TACKLE. When using AE incidence data from PROVENT(see CS Table 49), the QALY losses for Evusheld were greater than for SoC but were very small as the AEs reported were less frequent (equivalent to 0.4 vs 0.3 hours of full health lost).

The unit costs applied were based on the 2017/18 NHS reference costs for relevant HRG codes.[99] These are also summarised in Table 24. Overall, the costs due to AEs are £120.32 for Evusheld and £182.61 for SoC. Therefore, Evusheld is expected to marginally reduce the costs of AEs, due to having a lower incidence of some AEs. When using the incidence data from PROVENT (see CS Table 49), the costs due to AEs were marginally higher for Evusheld than SoC (£35.13 versus £26.32) respectively.

Overall, the EAG believes that Evusheld is well tolerated with AEs having a small impact on both costs and QALYs. Therefore, an in-depth critique of the methods used to incorporate AE in the model was not considered necessary given the limited impact this is likely to have on the estimation of the ICER.

Table 24: Incidence, utility decrements and unit costs for adverse events during acute COVID-19

	Incidence (double that observed in TACKLE)[51]		Utility decrement		QALY loss per patient experiencing AE	Unit cost	
Adverse event	**No prophylaxis**	**Evusheld**	**Size**	**Duration (months)**		**Value**	**Relevant HRG codes**
Infections and Infestations	8.20%	5.53%	0.171[102, 105]	0.17	0.002	£1,872.20	Weighted average of WH07A-G HRG codes[99]
Injury, Poisoning or Procedural Complications	0.44%	0.00%	0.110[102]	0.13	0.001	£1,138.31	Weighted average of WH04A-E and WH07A-G HRG codes[99]
Nervous System Disorders	0.67%	0.22%	0.070[104, 107]	0.20	0.001	£1,649.98	Weighted average of AA25C-G and AA29C-F HRG codes[99]
Cardiac Disorders	0.22%	0.44%	0.108[101, 102]	0.20	0.002	£1,556.36	Weighted average of AA35A-F, EB02A-7E and EB10A-15C HRG codes[99]
Gastrointestinal Disorders	0.44%	0.00%	0.135[100]	0.16	0.002	£1,446.16	Weighted average of FD10A-M HRG codes[99]
Renal and Urinary Disorders	0.22%	0.44%	0.250[103, 106]	0.14	0.003	£1,408.75	Weighted average of LA09J-Q and LB19C-G HRG codes[99]

4.2.6.14 Resource use for acute admission

The company sourced the total duration of hospital stay by care setting from the ACTT-1 trial.[85] This was estimated to be 5, 7, 15, and 29 days for patients requiring no oxygen, low-flow oxygen, high-flow oxygen, and IMV respectively (CS Table 60). The EAG notes that these figures reflect the early waves of infection and that ScHARR calibrated them to align with the current figures from the UK coronavirus dashboard in the ScHARR COVID-19 MTA model. For example, length of stay recorded for patients admitted in need of IMV in the ICU setting was 17 days as per Beigel *et al*. 2020 in contrast to 6.6 days as estimated by ScHARR's model for the COVID-19 MTA.[95] The EAG has explored using the costs for admission from the ScHARR COVID-19 MTA, which incorporate these length of stays, in a scenario analysis (see Section 4.4.2.10).

Daily bed costs by care setting were derived from Rafia *et al*. 2022.[86] The EAG notes that COVID-19 specific HRG costs were not available at the time that Rafia *et al.* prepared their report, and therefore relevant costs had to be estimated from the reference costs available. This was complicated by the fact that reference costs provide the cost of a complete episode of care, with daily rates only provided for specific 'unbundled' services such as critical care. Therefore, the cost of hospitalisation for patients not requiring critical care had to be estimated by Rafia *et al.* from the available data, none of which were specific to COVID-19.[112] There are now specific COVID-19 NHS reference costs for COVID-19 and these have been incorporated by EAG in their exploratory analyses for non-critical care patients alongside the most recent reference costs for critical care (see Section 4.4.2.10).

4.2.6.15 Resource use for monitoring

Patients hospitalised with COVID-19 are assumed to require monitoring in the year after discharge. This is assumed to consist of two chest x-rays and six GP consultations. In summary, this results in a cost of £263 for each patient discharged from hospital. These costs are included in the acute decision tree phase of the model. No monitoring costs are applied to those recovering from COVID-19 without requiring hospital care. Resource use associated with monitoring for patients discharged from hospital was not a significant driver of cost-effectiveness and therefore the EAG has not critiqued these assumptions in detail. However, the EAG notes that the cost assumed in the ScHARR COVID-19 MTA model based on the same resource use was higher at £384 due to the application of different unit costs (per e-consultation versus per GP contact lasting 9.22 minutes in same version of PSSRU[111]; latest direct access plain film HRG cost[112] vs unit cost from published analysis uplifted[95]).

The EAG also notes that at the time of writing, no guidance was provided on follow-up, discharge or rehabilitation within the COVID-19 rapid guideline NG191 (except for those with ongoing symptomatic COVID-19 or post-COVID-19 syndrome, who are covered by NG188). The EAG therefore believes

that it is likely that there will be variation in post-discharge care across the NHS for those not experiencing long COVID (accessed 4th Nov 2022).[119]

4.2.6.16 Long COVID risk

Long COVID was one of the four health states included in the post-acute Markov model described in Section 4.2.4. The long COVID health state is used to capture costs and QALY losses in patients who develop long-term sequelae that occur or persist beyond the 28 days defined as acute COVID-19. Emerging evidence suggest that some patients continue to experience symptoms, are at elevated risk of death and require long-term management and monitoring.[96, 97]

It was assumed that a proportion of patients who are not hospitalised transition to the long COVID health state, which was estimated at 34.8% as per Augustin *et al.* 2021.[94] This study included 958 non-hospitalised patients, of which 353 had follow-up at 7 months post infection and 34.8% (=123/353) of these patients had at least one COVID-19 symptom at 7 months.[94] For comparison, the ScHARR COVID-19 MTA model assumed that 10% of patients experiencing COVID-19 who did not require hospitalisation would experience long COVID.[95] The appropriateness of the company's estimate for the proportion of non-hospitalised patients with COVID-19 who experience long COVID is further discussed in Section 4.3.4.13

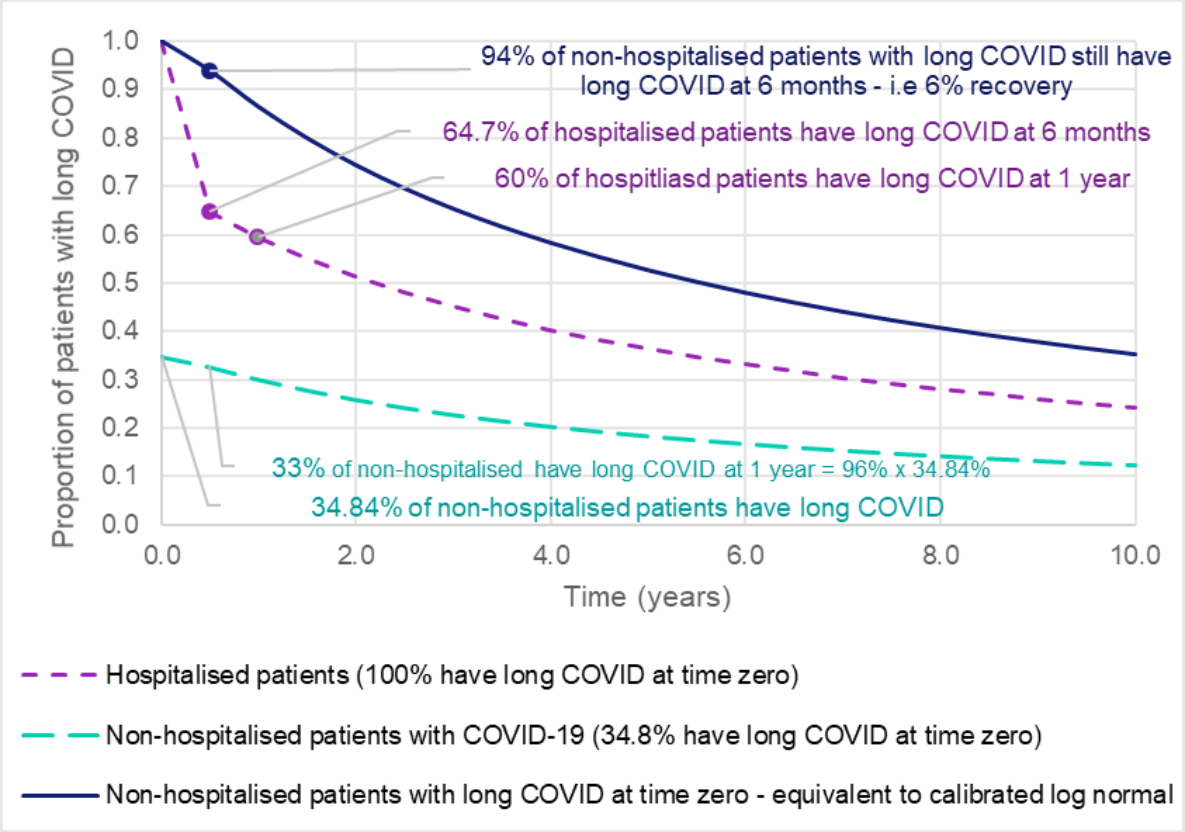
In addition, all hospitalised patients who survive their acute infection are assumed to start the long-term model in the long COVID state (i.e., 100% incidence of long COVID at discharge). This matches the assumption in the ScHARR COVID-19 MTA model, however, in that model the hospitalisation rate was lower and therefore, the assumption affected a smaller proportion of the cohort. The distribution of patients at the end of the model decision tree and transitioning to the long COVID health state at the start of the Markov model were presented in Table 42 of the CS.

4.2.6.17 Long COVID recovery

The mean duration of long COVID was estimated using the extrapolation approach used by ScHARR for the COVID-19 MTA.[95] However, the company noted the ONS data used were from the general population rather than a high-risk population and that updated data from PHOS-COVID cohort, reported by Evans *et al.* (2022) showed higher estimates of patients not recovered from long COVID than those predicted by ScHARR's extrapolation at year 1 (50% vs 37%).[96] The company still used the ONS data to draw the lognormal curve for the extrapolation as it had more data points (12 weeks, 1 year and 2 years rather than 5 months and 1 year with Evans 2022), and then adjusted the curve using the 1-year data point from Evans 2022 where the company assumed that half of those 'unsure' of recovery did not recover.[96] This meant that 64.7% and 60% have not recovered by 5 months and 1 year respectively. The curve was then adjusted to ensure that 92.65% (60%/64.7%) of the population with long COVID after

5 months from hospital discharge do not recover by 1 year. These assumptions resulted in the uplifting of the ScHARR's lognormal fit where the selected lognormal distribution had an intercept of -3.63 and a slope of 0.64 (on the log scale). However, for hospitalised patients, this curve was used to estimate the rate of recovery only from 6 months, with the proportion unrecovered at 6 months manually set to 64.7% to match the figure from Evans 2022.[96] For non-hospitalised patients, the proportion at 6 months is not manually set to 64.7%, but instead the adjusted lognormal curve is applied from time zero to 6 months. This results in a lower rate of recovery in the first 6 months of 6% compared with the 35.3% recovery rate at 5 months in Evans 2022.

Figure 7: Proportion of patients experiencing long COVID in the company's base case



4.2.6.18 Long COVID utilities

The company's model linked the disutility applied with long COVID to the severity of the COVID infection. Evans 2021 reported the change from baseline in EQ-5D stratified by the oxygen requirement in hospital from the PHOS-COVID cohort (Table 53 of the CS).[97] The company reported that the 'average' disutility reported in Evans 2022 of 0.22 was greater than that reported in Evans 2021 (0.13) and increased the severity stratified disutility values by a factor of 1.71 (=0.22/0.13) (this reduces the utility for patients experiencing long COVID). The EAG had concerns regarding the method used to calculate the uplift of 1.71 which are further discussed in Section 4.3.4.15. This resulting disutility values are reported in Table 54 of the CS and are summarised alongside the unadjusted values in Table

25 below. The company assumed non-hospitalised patients would get the same disutility due to long COVID as the cohort who needed no oxygen. The adjusted disutility values shown in Table 25 are applied for the duration of long COVID, which is 8.5 years on average for hospitalised patients with long COVID and 12.2 years on average for non-hospitalised patients with long COVID (duration estimates extracted 'Calculations sheet' of company model by EAG).

Table 25: EQ-5D-5L values [adapted from Tables 53 and 54 of the CS]

Severity	WHO class 3-4*	WHO class 5	WHO class 6	WHO class 7-9	Total
Model states applied to	No oxygen therapy**	Low-flow oxygen	NIV or high-flow oxygen	IMV	N/A
PHOS-COVID cohort 5 month follow-up: Evans 2021[97]					
Pre-COVID-19	0.82	0.84	0.82	0.87	0.84
Post-COVID-19	0.72	0.76	0.69	0.67	0.71
Disutility (change from baseline)	0.09	0.09	0.11	0.21	0.13
Disutility applied after adjustment (x 1.71)	0.154	0.154	0.188	0.360	NR

* although WHO class 3 indicates where COVID-19 severity does not require hospitalisation, the Evans 2021 cohort were all patients who had been discharged after being admitted to either a medical assessment unit or ward for COVID-19

** also applied to non-hospitalised patients experiencing long COVID

Abbreviations: N/A, not applicable; IMV, invasive mechanical ventilation; NIV, non-invasive ventilation; NR, not reported

The EAG questioned that post-acute disutility values are applied for the whole duration of long COVID. In response to clarification question B13, the company performed a scenario where the disutility values linearly reduce by annual decrements to 50% of its original value by year 5.

4.2.6.19 Resource use for long COVID

Initially, the company estimated the annual costs associated with management of long COVID to be similar to chronic fatigue syndrome (£1,128) as detailed in the ScHARR COVID-19 MTA and sourced from Vos-Vromans *et al*. (2017).[120] However in their updated base case post-clarification, the company decided to apply instead a cost of £2,500. This corresponded to a figure used by the EAG for the COVID-19 MTA in a sensitivity analysis, to explore the impact of attempting to account for additional

costs resulting from possible organ damage. The appropriateness of incorporating this estimate in the company's base case is discussed in Section 4.3.4.16.

4.2.6.20 Post year one cases of COVID-19

The total costs and QALYs for the Evusheld and SoC arms were adjusted to account for new instances of COVID-19 occurring after the first year. As no treatment effect is applied for Evusheld beyond the first year, the COVID-19 incidence is assumed to the same for both treatment arms. It is set equal to the COVID-19 incidence in the SoC arm in year one (12% per 6 months) and is the same regardless of whether the patient experienced an infection in year one or not. The impact of these infections is captured by an acute cost (£366.09 post clarification) and an acute QALY loss (0.0024 post clarification) which the EAG believes is intended to reflect the costs and QALY losses in the acute-phase model for patients experiencing an infection whilst receiving SoC. These include resource use associated with hospital admission, post discharge monitoring in the year after COVID-19 requiring hospitalisation, QALY losses for the acute phase of infection and QALY losses associated with hospitalisation. However, the EAG noted an error in the calculation of these acute costs and QALY losses, in that they are estimated as the average across the whole SoC arm including both patients with and without COVID-19 (see Section 4.3.4.18). Therefore, they do not capture the average cost or QALY loss per patient experiencing COVID-19.

In addition to the acute phase costs and QALY losses resulting from cases of COVID-19 occurring in the second year and beyond, the company has attempted to estimate the QALY losses due to deaths following these cases of COVID-19 occurring after year one. The mortality rate is the average mortality rate for patients experiencing COVID-19 in the SoC arm during year one (2.5% in the post-clarification model). The company states that "a *post-hoc adjustment was made to total QALYs in each cycle such that 0.29% (2.4% x 12%) of patients were set to have a utility of 0*", where 12% is the risk of COVID-19 in each 6 month cycle and 2.4% was the risk of death in those experiencing COVID-19 in the pre-clarification model. However, the EAG notes that there is an error in the company's implementation of their intended approach (see Section 4.3.4.18). The EAG also notes that the approach used does not allow deaths for fatal COVID-19 occurring after year 1 to accrue over time (see Section 4.3.4.18) because only a fixed proportion of surviving patients are assumed to have a utility of zero. The EAG also notes that under the company's approach, cases of COVID-19 occurring in the second year and beyond do not result in long COVID as the only long-term impact captured is QALY losses due to deaths. This impact of this omission is discussed further in Section 4.3.4.18.

4.2.7 Model validation and face validity check

The company describes their validation approach as including a discussion of the anticipated positioning of Evusheld and key clinical assumptions with UK clinical experts and a discussion of key

modelling assumptions with UK health economics experts. The CS does not report any process for model verification or any attempt to assess the model's external validity. It does provide a comparison of the model inputs and assumptions against those used in the ScHARR COVID-19 MTA model (CS, Table 35), but the EAG notes that the decision problem specified in the scope of the MTA is different from that specified for this appraisal because the MTA is examining COVID-19 treatments for patients who have COVID-19 rather than the use of any intervention as a pre-exposure prophylaxis.

4.2.8 Cost effectiveness results

All results presented in this section include the company's list price for Evusheld as the PAS submitted by the company was not approved. Therefore, on the 15th of November, the company submitted updated results without the PAS, which were used by the EAG to report the company's cost effectiveness results in this and upcoming sections.

4.2.8.1 Central estimates of cost-effectiveness

The company's base case cost-effectiveness results are presented in Table 26. The probabilistic version of the model suggests that Evusheld is expected to generate an additional [redacted] QALYs at an additional cost of [redacted] per patient compared to no prophylaxis resulting in an ICER of [redacted] per QALY gained. The deterministic version of the model produces a slightly lower ICER, however the model appears relatively linear based on the similarity of the deterministic and probabilistic estimates.

Table 26: The company's base case results

Technology	Total life years accrued	QALYs accrued	Total costs incurred	Incremental			ICER
				Life years	QALYs	Costs	
Probabilistic model (1000 runs by the EAG)							
No prophylaxis	15.82	[redacted]	[redacted]	-	-	-	
Evusheld	15.90	[redacted]	[redacted]	0.08	[redacted]	[redacted]	[redacted]
Deterministic model							
No prophylaxis	15.76	[redacted]	[redacted]	-	-	-	
Evusheld	15.84	[redacted]	[redacted]	0.08	[redacted]	[redacted]	[redacted]

The company presents disaggregated outcomes in terms of costs and QALYs accrued by different elements or health states in the deterministic model, these results are presented in Table 27. The differences in costs are primarily associated with the acquisition cost of Evusheld and costs associated with long COVID whilst more than two thirds of the additional QALY gain is a consequence of the direct utility gain associated with the behavioural changes from receiving Evusheld as detailed in Section 4.2.6.7. The QALY loss related specifically to long COVID is not presented separately in Table

27. However, the EAG notes that when QALY loss due to long COVID was excluded, the incremental QALYs decreased to [redacted] and the ICER increased to [redacted]. Removing the cost savings from preventing long COVID, shown in Table 27, would increase the ICER to [redacted]. Finally, removing both costs and QALYs related to long COVID increased the ICER to [redacted].

Table 27: Base case disaggregated outcomes for company's base case

Description	Evusheld	No prophylaxis	Increment
Disaggregated costs (discounted)			
Acquisition costs	[redacted]	[redacted]	[redacted]
Administration costs	[redacted]	[redacted]	[redacted]
AE costs	[redacted]	[redacted]	[redacted]
Routine monitoring costs in hospital	[redacted]	[redacted]	[redacted]
Medical hospital resource use costs	[redacted]	[redacted]	[redacted]
Long-term costs due to long COVID	[redacted]	[redacted]	[redacted]
Costs for post year one cases of COVID-19	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]
Disaggregated QALYs (discounted)			
Acute phase (29-day decision tree)	[redacted]	[redacted]	[redacted]
Long-term QALY gained by infected	[redacted]	[redacted]	[redacted]
Long-term QALY gained by non-infected	[redacted]	[redacted]	[redacted]
QALY loss due to post year one cases of COVID-19	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]

4.2.8.2 Uncertainty around the central estimate of cost-effectiveness from the probabilistic sensitivity analysis (PSA)

Table 26 shows the EAG's probabilistic estimates of the company's base case estimated using the average costs and QALYs across 1000 PSA samples when the model was rerun by the EAG. The company also presented the results of the PSA using cost-effectiveness planes and CEACs for Evusheld compared with no prophylaxis. The company's PSA suggests the probability that Evusheld generates more net monetary benefit than other comparators at a willingness-to-pay (WTP) threshold of £20,000 and £30,000 per QALY gained is 98.3% and 99.8% respectively. Figure 8 presents the company's base case PSA scatterplot at a willingness-to-pay threshold of £20,000 per QALY gained, whereas Figure 9 shows the CEAC.

Figure 8: Company's base case PSA scatterplot (run by the EAG)

Figure 9: Company's base case CEAC (run by the EAG)

4.2.9 Company's deterministic sensitivity analyses

The company's deterministic sensitivity analyses are presented using a tornado plot (see Table 5 and Figure 3 of the company's additional results at list price). Most of these analyses are performed by using the lower and upper bounds of 95% confidence intervals assuming that the standard error was set as 20% of the mean. The exceptions were the efficacy data where sample size information was available to derive the standard error around the mean RRRs.

The company's results show that the parameter which had the biggest impact on the ICER were: the baseline risk of COVID-19 in the target population; proportion of non-hospitalised patients who get long COVID; the percentage of symptomatic cases requiring hospitalisation, and the direct utility gain associated with Evusheld.

4.2.10 Company's scenario analyses

The company carried out several scenario analyses that were updated post-clarification in addition to other scenario analyses requested by the EAG. These are presented in Sections 2.4, Table 6 and Section 2.5, Table, 7 of the additional results submitted by the company at list price. The scenarios with the biggest impacts were those exploring alterative methods to estimate the duration of long COVID. Using the updated ONS data to model long COVID duration without calibration increased the ICER to [redacted], whereas using the same data with calibration increased the ICER to [redacted]. Increasing and reducing the risk of COVID-19 did not have a large impact over the range explored by the company (±20%) with the ICER ranging from [redacted] to [redacted] (latter figure extracted by EAG from the model as this figure was missing from the company's results Table 7).

Using Kertes *et al.* as the efficacy source instead of Young-Xu *et al.* and adjusting proportion of non-hospitalised patients getting long COVID down from 34.8% to 20.7% to account for the findings of Ballering *et al.* increased the ICER to [redacted] and [redacted] respectively. Using PROVENT as the efficacy source decreased the ICER to [redacted].

The following scenarios had less impact on the ICER compared to the above mentioned scenarios; not considering cases of COVID-19 past the first year, sourcing disutilities due to hospitalisation from the ScHARR COVID-19 MTA report, assuming one dose of Evusheld, increasing or decreasing the risk of COVID-19 after the first year by 20%, applying the distribution of hospitalised patients as per the second wave only from Cusinato *et al.*, assuming no excess mortality risk for patients hospitalised in need of NIV, and assuming lower annual disutility value associated with long COVID for non-hospitalised patients.

4.3 Critique of company's submitted economic evaluation by the EAG

4.3.2 Methods for reviewing the company's economic evaluation and health economic model

The EAG examined the company's implementation of the model within Microsoft Excel® and compared the parameters in the model with the sources described in the CS and the company's response to the clarification. The EAG also compared the parameters used in the company's model with those implemented in the ScHARR COVID-19 MTA model to identify any areas of inconsistency and considered if these were justified given the differences in the decision problems for these two appraisals. During the verification process the EAG identified programming errors after the clarification stage which related to the modelling of post year one cases of COVID-19; these are described further in Section 4.3.4.18. The EAG were not able within the time available to conduct any duplicate programming of the model. However, the EAG believes the company's post clarification version of the model to be generally well programmed despite the errors in modelling post year one COVID-19 cases, and no other significant programming errors were identified.

4.3.3 Adherence of the company's model to the NICE reference case

The EAG considers that the company's economic model largely complied with the NICE reference case. The most important exception was the source used for the long COVID cost. There were also concerns regarding the source of utility values for COVID-19 and hospital admission, but these had a low impact on the ICER and therefore were considered less significant deviations.

In addition, the EAG notes that the model results can only be considered to apply to the target population specified in the company submission which is narrower than the population identified in the scope. The EAG's specific comments regarding compliance with the reference case are provided in Table 28.

Table 28: Adherence of the company's economic analysis to the NICE reference case

Element	Reference case	EAG comments
Defining the decision problem	The scope developed by NICE	The company's economic analysis focuses on a narrower population than defined by the license or the NICE scope as it focuses on those groups at highest risk of serious adverse consequences from a SARS-CoV-2 infection. Specifically, this is defined as: *"Adults who are not currently infected with SARS-CoV-2 and who have not had a known recent exposure to a person infected with SARS-CoV-2 and:* • *are at the highest risk of an adverse COVID-19 outcome, namely hospitalisation and death, or* • *for whom COVID-19 vaccination is not recommended."* This differs from the group defined in the scope which was: *"Adults who are not currently infected with SARS-CoV-2 and who have not had a known recent exposure to a person infected with SARS-CoV-2 and* *• who are unlikely to mount an adequate immune response to COVID-19 vaccination or* *• for whom COVID-19 vaccination is not recommended"* The EAG believes that this focus on the highest risk patients is reasonable but notes that the cost-effectiveness estimates from the model should be interpreted as applying only to this specific group and not to the whole population covered by the licensed indication.
Intervention	As listed in the scope developed by NICE	The intervention is Evusheld (tixagevimab and cilgavimab administered by two consecutive intramuscular injections) as listed in the NICE scope. However, the EAG notes that the economic analysis assumes one year of Evusheld treatment consisting of an initial 600mg dose, followed 6 months later by a second 600mg dose. As discussed previously in Section 2.3.2, the SPC for Evusheld states that there are no safety or efficacy data available for repeat dosing with Evusheld.
Comparator(s)	As listed in the scope developed by NICE	The comparator is SoC in the absence of any pre-exposure prophylaxis. This is in line with the NICE scope and is therefore consistent with the NICE reference case
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Health gains accrued by patients are valued in terms of QALYs gained. Health impacts on caregivers were not included in the analysis. The EAG considered this appropriate and consistent with the NICE reference case

Element	Reference case	EAG comments
Perspective on costs	NHS and PSS	The analysis adopts an NHS and PSS perspective. This is therefore consistent with the NICE reference case
Type of economic evaluation	Cost-utility analysis with fully incremental analysis	The CS is consistent with the NICE reference case.
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	A life-time horizon is adopted which is considered by the EAG to be consistent with the NICE reference case.
Synthesis of evidence on health effects	Based on systematic review	No synthesis has been conducted. Three studies were identified which provided information on clinical effectiveness. One was an RCT, and the two others were RWE studies. The company has chosen to use estimates from a single RWE study in the base case economic analysis (Young-Xu *et al*.)[23] and has explored alternative estimates from the other two studies (one RCT and one RWE study) in sensitivity analyses. The EAG considers that it was reasonable not to combine the estimates from the identified studies due to differences in their populations, doses of Evusheld and methods for controlling for confounding (randomisation in the RCT vs statistical methods in the RWE studies)
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of HRQoL in adults.	Health gains are valued in terms of QALYs. No utility values were directly measured in the identified studies of Evusheld. Utility values in patients not having COVID-19 or having recovered from COVID-19 were based on EQ-5D values for the general population and are consistent with the reference case.
Source of data for measurement of HRQoL	Reported directly by patients and/or carers	

Element	Reference case	EAG comments
Source of preference data for valuation of changes in HRQoL	Representative sample of the UK population	The study used to estimate utility decrements for long COVID measured EQ-5D-5L in patients discharged from hospital after admission for COVID-19. These are therefore consistent with the reference case. The utility decrements for acute COVID-19 were based on estimates from the literature for a proxy condition (influenza) and are not considered by the EAG to be consistent with the NICE reference case. (see Section 4.3.4.12). The EAG was unable to verify all of the sources for the utility decrements for admission with COVID-19 but the only cited source it could verify was for a proxy condition (admission for clostridium difficile). Therefore, the EAG does not consider these to be consistent with the NICE reference case (see Section 4.3.4.12).
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	No additional equity weighting is applied to estimated QALY gains. The EAG considers this to be consistent with the NICE reference case.
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	The economic model generally used appropriate estimates of resource use and unit costs that were consistent with the NICE reference case. An exception was the estimate for long COVID cost which was taken from a scenario analysis conducted in the ScHARR COVID-19 MTA, which was exploratory and not based on any specific evidence. The EAG also noted that the costs for hospital admission for COVID-19 did not reflect the fact that specific reference costs for COVID-19 are now available (see Section 4.2.6.14) but instead used estimates implemented in published analysis (Rafia *et al.* 2021),[114] which were based on earlier versions of the NHS reference costs (2017/19 and 2018/19).
Discount rate	The same annual rate for both costs and health effects (currently 3.5%)	Costs and health effects are discounted at a rate of 3.5% per annum. This is consistent with the NICE reference case.

4.3.4 EAG critique of the modelling performed by the company

4.3.4.1 Assumption of a two-dose treatment course

The EAG is concerned that the company has assumed that Evusheld will be implemented in clinical practice as two doses, six months apart, with a constant treatment effect over a 1-year period. As previously noted in Section 2.3.2, there is currently no published safety or clinical effectiveness evidence for repeat dosing with Evusheld. Furthermore, the company has simply assumed that the RRR measured in the RWE study by Young-Xu *et al*.[23] will apply for 6 months after each dose (i.e. a 1-year period). The EAG notes that Young-Xu *et al*. only followed patients up for a maximum of four months (1st Jan 2022 to 30th April 2022) with the average duration of follow-up likely to be less than this as the first dose was not administered until 13th Jan 2022.[23] The company states, in its response to clarification question A24, that there is no reason to suspect that the PH assumption does not hold for the RR of symptomatic infection reported by Young-Xu *et al*. However, the EAG would argue that it is not possible to assess whether the RR is constant over 6 months from the 4-month follow-up data provided by Young-Xu *et al*. and if the PH assumption does not hold across the full 6 months, then applying the RR estimated over 4 months to a 6 month period in the model may overestimate the treatment effect. Furthermore, there is no information about the efficacy of a second dose at 6 months.[23] The RRR measured in the PROVENT study was estimated over a median 6-month up,[20] and the company did attempt to assess whether the PH assumption held over 6-months during the PROVENT study but did not fully explore the validity of the PH assumption. Therefore, the EAG believes that there is significant uncertainty associated with assuming that the treatment effect estimated over the Young-Xu *et al*. study will be maintained over 1-year by providing two doses of Evusheld. Therefore, the treatment effect applied in the model may by over-optimistic.

The company has provided a scenario analysis exploring the impact of a single 600mg dose with a 6-month duration of treatment effect (see clarification response, B3). This analysis assumes that the risk of infection during the 6-month period of treatment effect will be half that expected over one year. However, this approach assumes a constant risk of infection over time, which is not consistent with the experience so far that COVID-19 infections often arrive in waves. Therefore, this analysis does not capture the uncertainty related to whether the 6-month period of treatment effect will coincide with a high or low period of infection risk.

The EAG also notes that whilst the company has explored the impact of assuming a single 600mg dose in a scenario analysis, they have not provided any exploration of the cost-effectiveness of treatment with Evusheld if treatment were to be extended beyond one year.

4.3.4.2 Administration costs

The SPC states that "*administration should be under conditions where management of severe hypersensitivity reactions, such as anaphylaxis, is possible*".[17] This implies the availability of other members of the GP team to deal with the immediate management and transfer to secondary care of any patient experiencing anaphylaxis. The period of monitoring required (1 hour) is also significantly greater than that required for routine vaccinations given in primary care (e.g. 15 minutes close observation for the Pfizer/BioNTech COVID-19 Vaccine, Comirnaty, which is currently only required in those with a previous allergic reaction to vaccines). [121, 122]The EAG does not believe that accounting for only the 30 minutes of administration time is reasonable given the long observation period required. Whilst it is possible that there may be efficiencies achieved by setting up clinics in which multiple patients are observed simultaneously, the logistical resources required to organise these clinics, and the feasibility of providing them within a primary care setting, are not accounted for in the company's model. The EAG would argue that the logistical resource required to administer Evusheld to the estimated 1.8 million eligible patients identified by the company as being within the target population (CS, B1.3.5, page 20) would be substantial and may be better estimated by considering the cost for administering COVID-19 therapeutics in the community through COVID Medicine Delivery Units (CMDUs). The EAG acknowledges that the provisions required to deliver COVID-19 therapeutics through CMDUs may differ in some ways to the provisions required to deliver Evusheld as pre-exposure prophylaxis, especially if an administration programme provided in primary care rather than secondary care is implemented. However, the CMDU unit cost was considered to better reflect the likely resource use than the company's base case, which simply assumes that GP practice nurse time can be allocated for Evusheld administration within primary care. In reality, the EAG expects that some form of coordinated provision would need to be set up for the administration of Evusheld, to the 1.8 million patients that the company estimate would be eligible, and this would fall outside of any existing agreements for routine care by primary care providers, or routine vaccinations within primary care. Therefore, the incorporation of administration costs from CMDUs is explored in the EAG's exploratory analysis (see Section 4.4.2.5) as a proxy for the provision likely to be required to administer Evusheld.

4.3.4.3 Heterogeneity within the modelled cohort

The EAG notes that the target group of patients identified within the CS as being those at the highest risk of an adverse COVID-19 outcome are a heterogeneous cohort (see Section 2.3.1) This is important in several ways. Firstly, it is unclear if there will be heterogeneity in the efficacy estimates across the different groups that make up the target population. Young-Xu *et al*. reported consistent results between their overall cohort who they describe as being immunocompromised and the severely immunocompromised subgroup (HR of 0.44; 95%CI, 0.21-0.93 for severely immunocompromised vs 0.31; 95%CI, 0.18-0.53 for overall cohort for the composite outcome of SARS-CoV-2 infection, COVID-19 hospitalisation or death).[23] However, the company excluded several studies in particular

subgroups which would have been useful in determining the effectiveness of Evusheld in those particular groups, such as solid organ transplant recipients (see Section 3.2, p36). Secondly, many of the model parameters have been selected to reflect particular groups and may not reflect the average characteristics in the target population as a whole or the heterogeneity with the target population. For example, the standardised mortality ratio for all-cause mortality was based on patients with common variable immunodeficiency disorders and may be less reflective of groups of patients receiving immune suppressant treatments for cancer or individuals with renal of liver disease. Similarly, the utility loss incorporated for all patients to reflect the prevalence of comorbidities within the target population, which appears to be based people with heart conditions (see Section 4.2.6.1), may under- or overestimate HRQoL in the various subgroups of patients that make up the target population. For this reason, the EAG has conducted additional exploratory analyses in which they have tested the model's sensitivity to the various parameters to determine which of these are likely to be most important drivers of heterogeneity in the ICER within the target population.

4.3.4.4 Direct utility gain

The direct utility gain is applied to all surviving patients in the Evusheld arm of the model (uninfected / asymptomatic SARS-CoV-2 and those surviving COVID-19), for the first two 6-month cycles of the long-term model and is undiscounted and based on health state occupation prior to half-cycle correction. Presumably this is because it is assumed to apply from the instant the first dose is administered and for the whole of the subsequent year, rather than being a health state, patients gradually transition into over the first 6 months and then out of during months 12 to 18. The fact that it is applied only to surviving patients seems at odds with the idea that it is a benefit accrued during the 1-year period in which patients are at risk of infection (first phase of Figure 6) as the company's model seems to assume that infection occurs at the end of that year. The EAG would suggest that it would have been more correct to have applied a full year of utility gain to patients not infected in year 1, and half a year of utility gain to infected patients. This would reflect two assumptions: that the timing of infection is on average half-way through the year of treatment; and that patients would no longer feel the reduced anxiety of being protected by Evusheld if they were to experience COVID-19 after receiving it. Ideally, the calculation of QALYs gained due to the direct utility gain would also account for all-cause mortality in the treatment year. However, this is difficult to implement within the company's analysis, because the treatment year is implicitly rather than explicitly modelled within the untimed decision tree phase of the model and all-cause mortality is not applied in this phase of the model. However, as it is currently modelled, uninfected patients, those with asymptomatic SARS-CoV-2 and those surviving COVID-19 do have their direct QALY gain adjusted for all-cause mortality because this QALY gain is estimated during the first year of the long-term model rather than during the decision tree phase. The EAG has estimated the direct QALY gain using its preferred assumptions in exploratory analysis (see Sections 4.4.2.3 and 4.4.2.4).

The EAG also has some concerns regarding the appropriateness of using the estimate from the CANDOUR study to estimate the direct utility gain attributed to Evusheld. The EAG notes that although the CANDOUR study provides an estimate of the impact of the broad impact of the COVID-19 pandemic on the general population, it does not specifically estimate the utility loss associated with the shielding behaviours and anxiety regarding COVID-19 that the company claim will be diminished in those receiving Evusheld. Also, the company describes the estimate from CANDOUR as being an estimate of the impact of lockdown. However, a full national lockdown in UK only overlapped with the first 9 days of the survey period, with varying degrees of restrictions in place across the UK for the remaining period of the survey due to the introduction of the tiered system on the 2nd December 2020. In addition, the EAG also notes that the size of utility difference for the subset of CANDOUR patients located in the UK was [redacted] which is [redacted] than the estimate based on the average obtained across all countries. The EAG also notes the potential for recall bias for participants completing the EQ-5D-5L for their pre-pandemic health state.[90]

The EAG also notes that the company is assuming that the HRQoL changes that result directly from patients knowing that there are protected by Evusheld will switch on at the time that they receive their first dose and off a year later, six months after their second dose. This does not necessarily take into account the fact that the benefits of feeling protected may be realised gradually as individuals adopt new behaviours. In addition, people may not wish to commit to large changes in their circumstances, such as returning to their previous place of work, if they know that the protection being offered is time limited.

The EAG also notes that the company has reported that 82% of clinically extremely vulnerable patients take extra precautions to protect themselves from contracting COVID-19 and 13% continue to shield entirely (CS, page 24). Although the company has assumed that the direct utility gain applies to all patients, a scenario analysis was provided in which the direct utility gain was applied only to the 82% of patients currently taking extra precautions. The EAG believes that this still overestimates the likely impact of Evusheld for several reasons. Firstly, because the disutility estimated is intended to reflect shielding, it is unclear how much it would apply to the 69% who are not shielding but who are taking extra precautions. Secondly, the EAG believes that whilst some patients receiving Evusheld may return to their pre-pandemic levels of engagement with society, it is difficult to predict how much shielding behaviours will be reduced and how much the average patient's HRQoL will be improved as this will be somewhat dependent on the amount of confidence patients have in the efficacy of Evusheld to protect them. The EAG's clinical experts noted that this may depend on how the effectiveness of Evusheld was described to patients by their healthcare provider. The EAG notes that both the US's FDA and the Government of Canada have issued warnings to clinicians that they should inform patients receiving

Evusheld about the potential for a lack of effectiveness against certain SARS-CoV-2 variants.[63, 123] Finally, the EAG notes that the company has not provided any direct measures of HRQoL in patients who have received Evusheld to support their claim that HRQoL will be improved. The EAG has therefore explored alternative assumptions regarding the proportion who will benefit from the direct utility gain (see Sections 4.4.2.14).

4.3.4.5 Risk of COVID-19 during the year of Evusheld/SoC treatment

The EAG believes that there is large uncertainty regarding the risk of COVID-19 in the target population in the year after Evusheld would be introduced if the outcome of this appraisal were to be positive guidance on the use of Evusheld by NICE in 2023 (expected date of first committee meeting is 24th January 2023 with draft guidance expected on 14th February 2023). The risk of COVID-19 (i.e., symptomatic SARS-CoV-2 infection) in the model is based on the historical risk of a positive specimen being recorded in the general population of England in the period August 2021 to August 2022. This metric may overestimate the risk of COVID-19, particularly during periods where routine asymptomatic testing was widespread within schools, workplaces and healthcare settings, as it will include cases of asymptomatic SARS-CoV-2 infection. However, this metric may also underestimate the risk of COVID-19 during periods where free access to testing for the general public was restricted (post 1st April 2022). Furthermore, it represents the average risk over a historic period in the general population as a whole and this may not reflect future risks in the group likely to receive Evusheld which will be dependent on the dominant variant, the effectiveness and uptake of vaccinations available prior to that date, the prevalence of non-pharmacological measures to reduce transmission in the general public and the infection avoidance behaviours in the group offered Evusheld. The EAG's clinical advisors felt that infection rates may be lower in the target population due to the prevalence of infection avoiding behaviours in this group, although this may depend on whether these behaviours reduce in response to receiving Evusheld. Whilst the company explored a range of infection risks in their scenario analysis in response to clarification question B5, they only adjusted the risks by +/- 20% of their baseline value. The EAG believes that the uncertainty intrinsic in the estimation of future infection risks is much greater than this. The EAG has therefore explored a wider range of infection risk estimates in its exploratory scenario analyses.

4.3.4.6 Hospitalisation risk

The EAG believes that it is possible that hospitalisation risk may now be much lower than observed in the cohort reported by Shields *et al*.[10] Shields *et al*. report that within their immunocompromised cohort, hospitalisation rates were significantly lower during the Omicron wave 9.9% vs 41.5% for prior variants.[10] It is unclear how much of this is attributable to increased access to a third dose of vaccination, with Shields *et al*. reporting higher vaccination for those infected during the omicron wave (3.0 vs 1.9 doses, $p<0.0001$) than those infected in previous waves, and a consequent greater percentage having

antibodies (62.3% vs 19.4%, p=0.0001).[10] However, it does suggest that the risk of hospitalisation is variant dependent and therefore may be higher or lower than the 18.06% assumed in the company's analysis, depending on the dominant variant circulating in the year after Evusheld is recommended, should the appraisal result in positive guidance. During the factual accuracy check, the company highlighted that Shields *et al*.[10] also reports that in the period after COVID-19 therapeutics became available (after December 16th 2021), there was a higher hospitalisation risk for those not receiving COVID-19 therapeutics (15.9% versus 4.3%, p=0.03). As COVID-19 therapeutics are not currently covered by routine commissioning, the EAG has applied the risk of hospitalisation estimated in the cohort not receiving COVID-19 therapeutics in its base case analysis (see Section 4.4.2.9).

4.3.4.7 Mortality risk post receiving critical care for COVID-19

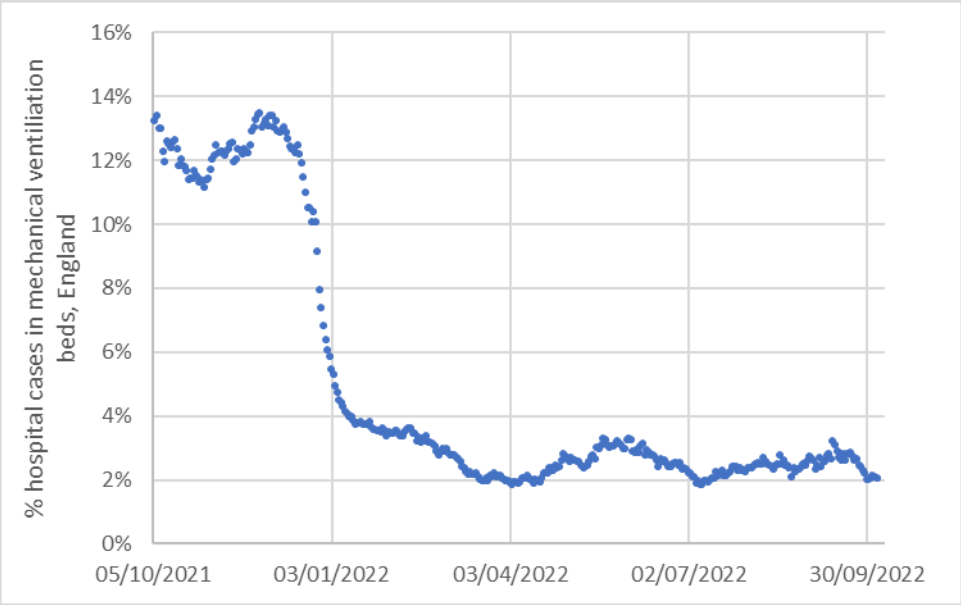
The EAG prefers the scenario analysis provided by the company in which an increased risk of mortality for the 5 years post discharge is applied only to those patients discharged having received IMV. Whilst the EAG accepts that the HR for mortality was estimated from a study in which not all patients received IMV, it was none the less from a study in which all patients were discharged from ICU. It may not therefore reflect the expected excess mortality in patients receiving high-flow oxygen or NIV. The EAG's clinical experts advised that whilst it is accepted that there is a post-discharge mortality risk for those requiring IMV, the post-discharge mortality risk for patients needing NIV was less well understood and recognised. Therefore, the EAG believe that applying the mortality risk estimated from a population discharged from ICU to all patients in the high-flow / NIV state may have overestimated the long-term mortality associated with severe COVID-19 requiring either high-flow oxygen or NIV. The company provided an additional scenario analysis, in response to clarification question B19, which demonstrated that assuming no excess mortality for patients discharged from the high-flow / NIV state did not have a large impact on the ICER. Therefore, the EAG has not explored this issue further in their exploratory analyses.

4.3.4.8 Proportion of hospitalised patients requiring different levels of hospital care

The EAG believes that the data from the Cusinato *et al*.[92] demonstrate a significant shift in the proportions receiving IMV and NIV between the first and second waves of COVID-19 in the UK and therefore it is not appropriate for the company to use the data averaged across both waves in their base case analysis. The EAG also notes that the period covered by Cusinato *et al*. ended in March 2021 and therefore does not reflect the Delta or Omicron waves.[92] It can be seen from the data used by the company to estimate the average proportion of hospitalised patients in mechanical ventilation beds (see Figure 10), that there as a substantial fall in the proportion requiring mechanical ventilation beds around the time that Omicron became the dominant variant (end of 2021). Therefore, the EAG believes that the proportion used in the scenario analysis which is intended to reflect rates of IMV in the general population admitted with COVID-19 should be estimated as an average across a more recent period,

such as over the past 3 months. This would give a proportion of 2.51% as opposed to the estimate of 4.92% obtained by the company's approach. The EAG's clinical experts advised that the target population for Evusheld may have a higher likelihood of requiring IMV than the general population and therefore the EAG decided that the proportion of 2.51% should be used to represent the lower plausible range for this value. The EAG has included this as a scenario analysis in Section 4.4.2.11. The EAG also notes that any future change in the dominant variant could result in changes in the proportion requiring IMV which may move in either direction.

Figure 10: Proportion of hospitalised COVID-19 patients in England in mechanical ventilation beds [EAG has plotted the data included in the company's model]



4.3.4.9 Efficacy estimates from PROVENT[20] and Kertes et al. [24] applied in the scenario analyses

For the scenario analysis using efficacy data from the PROVENT RCT, the company states that they have assumed no additional benefit on hospitalisation risk due to low hospitalisation numbers (CS,Table 39 footnote) and the CS describes the RRR of hospitalisation given infection as being 100% (CS, Table 39). However, the EAG considers that if there was no additional benefit of Evusheld, then this figure for the RRR would be 0% not 100% as reported in CS, Table 39. However, during its model verification process, the EAG estimated a RRR of 82.8% from the intermediate model outcomes. Therefore, in the scenario analysis using efficacy data from PROVENT, the company is assuming an 82.8% reduction in COVID-19 and an 82.8% reduction in the hospitalisation within the population who have COVID-19. This is equivalent to a 97% RRR for hospitalisation within the cohort at risk of infection. Taking the numbers experiencing COVID-19-related hospitalisation from the post hoc analysis of PROVENT and adding a continuity correction of 0.5 patients per arm to deal with the zero incidence in the Evusheld arm would have given a RRR of 97%. This suggests that whilst the company's explanation of what they

have done is not accurate, the RRR for hospitalisations is not grossly inconsistent with estimates based on the very sparse data hospitalisation data available for PROVENT. However, the scenario analysis using efficacy data from PROVENT should be considered with caution given that the 82.8% figure for the RRR of hospitalisation given COVID-19 has not been calculated from the study data and has instead been set equal to the RRR for COVID-19. Also, the EAG notes that the hospitalisation outcome was a *post hoc* outcome within the PROVENT RCT, further contributing to uncertainty regarding its use in the model.

For the scenario using data from Kertes *et al*.[24] the intermediate model outcomes appear to correspond to the study outcomes provided that the OR of 0.51 for SARS-CoV-2 infection and the OR of 0.19 for hospitalisation can be interpreted to be approximately equivalent to the HRs for COVID-19 and hospitalisation respectively. As HRs and ORs are only similar when the absolute risks are small, the EAG does not believe that it is correct to apply the ORs estimated by Kertes *et al*. as HRs within the model with a baseline risk in the SoC arm of ~22%. The EAG accepts estimates of the RRs that have been adjusted for confounding variables using regression were not provided by Kertes *et al*. However, it argues that the regression adjusted ORs for symptomatic infection could have been applied to the odds within the model rather than assuming that they are equivalent to RRs. The EAG also notes that the RR for hospitalisation given COVID-19 has been estimated by the company from the raw data presented by Kertes *et al*.[24] and therefore does not benefit from the regression analysis adjustment to reduce confounding. The EAG also notes their conclusion in Section 3.8.2 that caution should be exercised when interpreting the results from Kertes *et al*. As such the scenario analysis using the data from Kertes *et al*. should also be interpreted with caution.

4.3.4.10 Mortality during the first year at risk of infection

The model does not apply all-cause mortality during the first year of the model when people are at risk of COVID-19 as this period is implicitly captured within the decision tree model. The EAG believes that this error is likely to have a small impact on the ICERs because the risk of all-cause mortality is low at 0.6% per annum (this includes adjustment for HR for death compared to general population described in Section 4.2.6.8). The EAG notes that the direct QALY gains related to Evusheld treatment are estimated using the patients surviving the first year after COVID-19, with all-cause mortality applied during this year. Therefore, the direct QALY gains are not overestimated for this reason. The EAG is therefore content not to attempt to correct the model to apply all-cause mortality during the year included within the decision tree phase of the model.

4.3.4.11 Mortality during acute admission – verification issue

The EAG were unable to verify the exact mortality rates cited by the company in CS Table 44 in either the July 2022 ICNARC report provided alongside the original submission[9] or the October 2022 report

provided later alongside the clarification response. However, the EAG notes that mortality rates are reported separately for patients admitted between 1st May 2021 and December 2021 and those admitted after 1st January 2021, and it is unclear if the company has used one of these rates or the average across both. The mortality rates from January 2021 onwards are complicated by the fact that a significant proportion of patients remain alive and still in critical care and therefore still at risk of death but not included within the mortality figures. The EAG notes that in the October 2022 ICNARC report the mortality rate for patients invasively ventilated (advanced life support) was 43.1% when using data from the 1st May 2021 to December 2021, but lower at 32.2% when using patients admitted since January 2022. However, 16.6% of patients in the later cohort are still in critical care (ICNARC 7th October 2022 report, Table 18). This suggests a mortality rate between 32.3% and 48.8% for invasively ventilated patients using the latest data depending on the outcomes for those still in critical care. For patients receiving basic respiratory support, which includes those receiving high-flow oxygen and NIV, the mortality rates are 13.5% when using data from 1st May to December 2021 and 17.7% when using data post January 2022 in which 7.6% of patients are still in critical care. This would suggest a mortality rate with a range of 13.5% to 25.3% if it is pessimistically assumed that none of the currently admitted patients survive.

The EAG was unable to verify the mortality rates for patients on low-flow oxygen or no oxygen therapy from the cited sources. The CS cites a modelling study by Ohsfeldt *et al*. as the source but this modelling paper appears to used data from the COV-BARRIER study.[93, 124] Data from Figure 3 of the COV-BARRIER paper would give a 28-day mortality rate of 3.2% when averaged across both trial arms for NIAID-OS score 4 (hospitalised but not requiring oxygen).[124] Similarly for a NIAID-OS score of 5 (hospitalised and requiring low-flow oxygen) the mortality rate would be 7.3% when averaged across both arms. However, these don't align with the figures of 4.6% and 7.6% reported respectively in the CS. The figures reported also did not align with the proportions assumed to be recovered for the corresponding health states in the cited modelling paper by Ohsfeldt *et al*. (2021).[93]

Overall, the company estimates an average mortality risk of 2.5% for patients with COVID-19 in the SoC arm of their model. This compares to an infection fatality rate (IFR) of 3.42% for patients with primary immunodeficiency and 7.89% for patients with secondary immunodeficiency estimated by Shields *et al*. in their January 2021 to March 2022 cohort.[10] However, they also report the IFR in the cohort as a whole falling from 9.8% to 2.7% (p=0.07) when comparing those infected with SARS-CoV-2 before and during the Omicron wave. These figures are not directly comparable to the 2.5% mortality rate for COVID-19 in the SoC arm of the model, as not all patients included in the IFR estimated by Shields *et al.* were symptomatic (85% of primary immune deficiency and 82% of secondary immune deficiency patients were symptomatic). However, this gives some external validity to the acute

mortality risks attributed to COVID-19 within the company's model, despite some uncertainty regarding how the individual mortality risk for each hospital health states has been obtained.

4.3.4.12Utility decrement for acute COVID-19

The EAG is concerned that the estimate of utility decrement for acute COVID-19 not requiring hospitalisation (0.19) has not been estimated directly from patients experiencing COVID-19. In particular the estimate appears to be based on values sourced from an influenza modelling study (Smith 2002) which was estimated by comparing estimates from two separate studies (Gold 1998 and Sackett 1978).[125, 126] with one providing estimates for a well population and other for a population with 'untreated influenza'. However, the value for 'untreated influenza' is based on a 1978 study using a time-trade off method in a Canadian general population sample.[126] From comparing the value quoted with the source study, it appears that the state valued was described as "*home confinement for an unnamed contagious disease"* with a duration of 3 months. The EAG would argue that this health state is not a good proxy for a COVID-19 not requiring hospitalisation, and the methods used to obtain this estimate do not comply with NICE's reference case requirement given that a Canadian population was used to value the health states rather than a UK general population sample. In addition, the estimate for the well state taken from Smith *et al*.[108] appears to correspond to the median utility in 55 to 64 year old females from Gold *et al*.[125] The EAG was not certain how Gold *et al*. valued the health states, but does not believe that this study would meet the NICE reference case given that it used a US rather than a UK general population sample. Furthermore, a comparison of two values from two sources that used wholly different methods to estimate utility is unlikely to provide a good estimate of the disutility for a health state. However, the EAG also notes that the utility loss during acute COVID-19 is not a particularly important driver of the ICER.

As indicated previously in Section 4.2.6.12, the EAG were unclear how the company had estimated the utility decrements applied for hospitalisation with COVID-19 from the cited sources. The EAG speculates that the utility decrement of 0.19 for COVID-19 has been compared with the utility decrement of 0.49 for hospital admission with clostridium difficile and this has been used to estimate the additional utility loss for severe COVID-19 requiring hospitalisation without oxygen therapy. The EAG requested copies of the cited ICER report to try to determine the source of these utility values but could not trace what data or assumptions they were based upon from the documents provided. Therefore, the EAG is unable to verify the applicability of the cited data or whether they are compliant with the NICE reference case, other than to confirm that they have been applied in other modelling studies. However, the EAG notes that these utility values do not have a significant impact on the ICER due to the short duration over which they are applied.

4.3.4.13 Proportion of non-hospitalised patients experiencing long COVID

The figure of 34.8% taken from Augustin *et al*. as the proportion of non-hospitalised patients experiencing long COVID is based on those patients with data at 7 months (34.8%=123/353).[94] However, the group experiencing long COVID correspond to only 12.8% (=123/958) of the original cohort as there was a high drop-out rate (N=958 at baseline, N=442 at 4 months and N=353 at 7 months). The prevalence of long COVID was 27.8% (=123/442) in those attending the 4-month follow-up. In the later peer reviewed version of the same paper, the authors reported attempts to reach those lost to follow-up at 4 months. The authors reported that they managed to reach 60% (=310/516) of patients lost to follow-up by phone and 24.2% (=22/310) of this group reported long COVID at 7 months.[127] , the authors conclude that *"12.8-27.8% of patients suffer from long-lasting symptoms",*[94, 127] which is lower than the 34.8% applied in the company's' base case. The EAG also notes that the presence of any one of four symptoms (anosmia, ageusia, fatigue or shortness of breath) was sufficient to categorise patients as experiencing long COVID in this study and no attempt was made to quantify severity. However, Augustin *et al*. also report that 11% of patients could still not fully participate in everyday and work life at 7 months, suggesting that the prevalence of severe symptoms which significantly impact HRQoL of life was lower.[94]

The EAG notes that the figures from Augustin *et al*. seem considerably high compared to those based on the ONS survey, where of triple-vaccinated adults, 4.2% only reported having long COVID 12 to 16 weeks after a confirmed positive SARS-CoV-2 test compatible with the Omicron BA.2. (defined as those with the S gene from 24th January 2022 to 27th May 2022).[128] Additionally, the company response to clarification questions B14 and B16 showed a considerable increase in the ICER (14% and 29%) when the company's estimate dropped to 27.8% and 20.7% respectively, suggesting that the ICER is sensitive to this parameter.

The EAG notes that the odds of patients reporting symptoms beyond 28 days has been reported as being approximately halved in patients having 2 vaccine doses compared to unvaccinated patients using data from the ZOE app (OR =0.51, 95%CI 0.32 to 0.82; Antonelli 2022a) and a reduction in the odds of 41% has been reported for self-reported long COVID symptoms at 12 weeks in the UK general population (OR=0.59 ONS statistical bulletin Jan 2022).[129, 130] In addition, the risk of long COVID appears to be reduced for patients infected with the Omicron variant compared to those infected with the Delta variant using data from the ZOE app (OR 0.24 to 0.50 depending on age and time since vaccination; Antonelli 2022b)[131] and data from the ONS surveys (OR=0.52) respectively.[128] The EAG acknowledges that this increases the uncertainty around the likelihood of patients with COVID-19 experiencing long COVID as it is likely to depend on the circulating variant at the time and the protection provided by vaccination in the target population. Given that the target population have been selected on the basis that they may not be adequately protected by vaccination, it seemed reasonable to

assume a higher proportion than observed in double vaccinated patients during the Omicron wave (4%) and use a figure closer to the risk observed in unvaccinated patients, which was 14.6% based on data prior to the emergence of Omicron in the UK.[130]

An alternative source is provided by an observational study from the Netherlands which compared symptoms in patients reporting COVID-19 and matched controls (Ballering 2022).[132] This study estimated a prevalence of long COVID symptoms of 21.4% (381/1782) in patients reporting COVID-19 and 8.7% (361/4130) of matched controls. In this analysis they required people to have had at least one symptom substantial increase to at least moderate severity 3 months after COVID-19 to be included in the definition of long COVID. The authors state that this implies that 12.7% of patients with COVID-19 have chronic symptoms attributable to COVID-19. This dominant variant at the time this study finished was the Alpha variant, and only 9.8% were fully vaccinated at the time of the last included case, therefore it may not reflect long COVID risk in more highly vaccinated populations or for later variants.

The EAG has used the estimate of 12.7% from Ballering *et al*.[132] in its base case analysis because this estimate adjusted for the incidence of long COVID symptoms in those not reporting an infection and required symptoms to be of at least moderate severity. But given the previously described uncertainty related to the impact of vaccination and dominant variants, the EAG has explored a range of values from 4.2% to 34.8% (see Section 4.4.2.4).

4.3.4.14 Long COVID duration

The company states that the average duration of long COVID under their base case assumption is 5.0 years and that the proportion of patients in the long COVID state reaches 22% at approximately 4.5 years (clarification response to B11). However, the EAG does not believe that these figures have been calculated appropriately. The EAG estimates that the mean duration of long COVID is 8.5 years in hospitalised patients who survive their admission [extracted from the 'Calculations' sheet in the model by the EAG directly from the extrapolation curve which doesn't account for post discharge mortality]. When accounting for post-discharge mortality, the mean number of years with long COVID is 6.16 to 6.22 years for patients surviving their acute admission (which varies due to higher mortality for those discharged from critical care). For non-hospitalised patients who have long COVID at the start of the long-term model, the average duration of long COVID is 8.9 years when accounting for mortality and 12.2 years when not accounting for mortality. The company's figure of 5.0 years is the average duration of long COVID across all patients with COVID-19. Whereas the EAG estimate the average duration of long COVID across patients starting the long-term model with long COVID as 10.8 years when not accounting for mortality. When accounting for mortality this estimate is lower at 7.9 years.

The EAG therefore conclude that the approach used in the company's model results in substantially longer durations of long COVID than those estimated directly for the ONS data which were assumed to apply in the ScHARR COVID-19 MTA model (108.6 weeks).[95] This is true for both hospitalised and non-hospitalised patients, but counterintuitively, the duration of long COVID is longer for non-hospitalised patients with long COVID, despite the company stating that hospitalised patients are less likely to recover. This is because the proportion recovered at 6 months in the non-hospitalised group is not manually adjusted to match the data from Evans 2022 as it is in the hospitalised group (see Section 4.2.6.17). Although the EAG also notes that the estimate of 108.6 weeks for the duration of long COVID applied in the ScHARR COVID-19 MTA model may be an underestimate as patients were administratively censored (i.e., some were yet to recover at the time that the observation period ended) and therefore the estimate is based on an extrapolation of the time-to-recovery data from the ONS.

In response to clarification question B11, the company claimed that their estimates align with the ONS data where 22% of people with self-reported long COVID first had COVID-19 at least two years previously.[133] It states that the proportion of patients in the non-hospitalised state having long COVID reaches 22% at approximately 3 years, but again this is estimated for all non-hospitalised patients. The proportion of non-hospitalised patients with long COVID who still have long COVID at 3 years is 65.3% (22.8% out of 34.8% who had long COVID), not 22% as stated by the company. This is the appropriate number to compare with the ONS statistics in which it is stated that 22% of patients with long COVID have had it for more than 2 years. The company also states that the proportion of patients in the long COVID state reaches 22% at approximately 4.5 years (clarification response to B11), but again, this figure is not suitable for comparison with the ONS data as it is not estimated for only those patients starting in the long COVID state. The EAG has incorporated alternative assumptions regarding the long COVID duration in their exploratory analyses (see Section 4.4.2.6).

The EAG's preference is to use to the log normal curve fitted to the latest ONS data (scenario 3 in company's response to clarification question B11) without adjustment for the proportion recovering between month 5 and 1 year from the PHOS-COVID data reported by Evans et *al.* (2022). However, the EAG also believes that it is inconsistent to have a higher proportion of hospitalised patients recovering in the first 6 months. Therefore, the EAG has set the proportion not recovered to 64.7% to match the 5-month data from Evans 2022 in both hospitalised and non-hospitalised.[96] This results in a mean duration of long COVID of 1.4 years for both hospitalised and non-hospitalised patients who have long COVID at the start of the long-term model when accounting for mortality. If the restriction of setting the 6 months value to match the hospitalised cohort is removed for the non-hospitalised cohort, then the mean duration of long COVID is 1.7 years in this group, when accounting for mortality. The EAG has also explored using the latest ONS data for both hospitalised and non-hospitalised without manually setting the proportion at 6 months to 64.7%, giving a mean duration of long COVID of 1.7

years in both hospitalised and non-hospitalised patients. The aim of this scenario is to remove the impact of the data from the PHOS-COVID cohort entirely, as this study did not assess the proportion with long COVID at 4 weeks or 3 months and therefore, the proportion recovered might be reflecting a mix of recovery from long COVID and recovery from the impact of severe COVID-19 requiring hospitalisation. In particular, the EAG's clinical experts were of the opinion that although there was a high likelihood of patients reporting ongoing symptoms after discharge from hospital, this may differ slightly from the long COVID you would see in non-hospitalised patients, in particular for those admitted to ICU who may have ongoing symptoms similar to post-ICU syndrome. Therefore, it is possible that if long COVID symptoms had been assessed at 3 months in the PHOS-COVID cohort, then some additional patients would have recovered from their acute illness and the trajectory for the remaining unrecovered patients would be more similar to that reported in the ONS data. In addition, the incidence of long COVID at 5 months included half of those who responded 'not sure' when asked if they had recovered. The EAG's clinical experts were of the opinion that although some patients may be uncertain whether they have recovered due to fluctuating symptoms, the inclusion of patients who are 'not sure' if they had recovered had the potential to underestimate the likelihood of recovery from long COVID.

4.3.4.15 Long COVID disutility

The EAG is concerned about the method used to calculate the uplift factor of 1.71, which was used to adjust the 5-month utility decrements reported from the PHOS-COVID cohort by Evans *et al.* (2021), to reflect what they described as an increase in disutility between 5 months and 1 year reported in the later paper by Evans *et al.* (2022).[96] The EAG notes that the figures compared to estimate this uplift (0.13 and 0.22) are not reporting the same thing. The first reports the average drop in utility from baseline (pre-COVID retrospectively assessed) to 5 months regardless of whether the patient reported having recovered. Whilst the second reports the average difference in utility between baseline utility and utility at 1 year in patients who report that they are not recovered (0.89-0.67) which the company have estimated by digitising the plots in Evans 2022 (see clarification response B13).[96] The EAG notes the data supplement for Evans 2022, provides the average utility at both 5 months and 1 year allowing a direct comparison, and this shows no increase in utility decrement across the cohort as a whole (0.88 pre covid, 0.75 at 5 months and 0.74 at 1 year; Evans 2022 Table S11)[96] suggesting minimal uplift is necessary (ratio of disutility of 1.08). However, the EAG does agree that the estimate of the disutility for 'not recovered' patients increased from 0.19 at 5 months to 0.22 at 1 year (calculated from Evans 2022, Table S3a and S11).[96]

Furthermore, the company is including patients who are 'not sure' if they have recovered in the estimates of the proportion with long COVID from Evans 2022. But the company is then taking the utility decrement for long COVID from the group who are sure they have not recovered. These patients

have a lower utility value at both 5 months and 1 year than the 'not sure' group. If the average utility decrement is estimated across both groups (not recovered and unsure) then the utility decrement at 1 year is 0.19 compared to 0.22 when estimated just in the not recovered group (calculated from Evans 2022, Table S3a and S11).[96]

The EAG prefers to take the average utility across recovered and unsure at one year (0.19) and to adjust this for the various WHO severity groups provided by Evans 2021. The adjustment factor is the ratio between the disutility for that class and the average across all severity classes (e.g., for class 5 the disutility is 0.9 compared to 0.13 for the average of the whole groups at 5 months so for unrecovered patients in class 5 at 1 year it is estimated =0.19*0.9/0.13=0.133). This gives utility decrements of 0.133, 0.133, 0.162 and 0.310 for WHO severity classes 3 to 4, 5, 6 and 7 to 9. For comparison, if the same approach was used but using the utility value just from the unrecovered patients (0.22) these figures would be 0.152, 0.152, 0.186, and 0.355 respectively. These latter figures are within 2% of the values used by the company, and therefore the main difference in the EAG's approach is the use of average utility decrements across not recovered patients and not sure patients. The EAG believes this is appropriate given that the proportions experiencing long COVID have been estimated using a combination of these two groups. The EAG has explored the impact of using their alternative long COVID utility decrements in Section 4.4.2.8.

The EAG previously noted that the disutilities for long COVID are applied for the duration of long COVID which amounts to an average period of 6.2 years for hospitalised patients and 8.9 years for non-hospitalised patients. The EAG is concerned that this assumption lacks clinical plausibility as it assumes that patients can experience long COVID for a very long period without any improvement based on data from a study that reports only 1 year follow-up. However, the EAG acknowledges the long-term health trajectory of patients with long COVID is unknown. In addition, there may be heterogeneity in the trajectory of recovery depending on the exact pathophysiology causing the symptoms with some patients having a permanent reduction in HRQoL and others having symptoms that gradually improve with either time or treatment. As shown in response to clarification question B13, a gradual reduction in the decrement over 5 years to 50% of its starting value had a significant increase in the ICER (~13%). This suggests that the ICER is sensitive to the duration of time over which this disutility is applied, and this has been further explored by the EAG in its exploratory analyses (see Section 4.4.2.8).

Furthermore, the EAG highlights that the high disutility values applied in the company's base case apply to 34.8% of the non-hospitalised patients with COVID-19, a proportion of which may have reported only one symptom, such as anosmia, according to the definition of long COVID applied by Augustin *et al*.[94] (see Section 4.3.4.13). Given that Evans *et al*. report heterogeneity in the disutility according to the cluster of symptoms reported and the level of respiratory support required in

hospitalised patients,[96] the average utility decrement for hospitalised patients reporting that they are not recovered may not apply equally to all patients meeting the long COVID criteria applied by Augustin *et al*.

4.3.4.16 Long COVID resource use

The EAG notes that the figure of £2,500 which the company applied in their post-clarification base case which the company describe in their clarification response as being *"aligned with the ongoing NICE MTA of therapeutics for people with COVID-19"*, was a figure that was arbitrarily selected by the MTA's EAG to measure the sensitivity of the results to the change in the costs of long COVID. It was not informed by any specific evidence and was not included in the EAG's base case analysis for the COVID-19 MTA.[95] Therefore, the EAG's preference is to use the estimate for chronic fatigue (£1128) employed in the ScHARR COVID-19 MTA base case analysis.

4.3.4.17 Scenario analysis implementing ScHARR utility values for acute COVID-19.

The company presents a scenario analysis which they describe as using the utility decrements applied in the ScHARR COVID-19 MTA model. However, the EAG notes several discrepancies between the approach used by the company in their scenario analysis and the actual implementation of the utility values within the ScHARR COVID-19 MTA model. Firstly, the EAG notes that the company maintained the utility decrement for non-hospitalised patients at their base case value (0.19), and for hospitalised patients they applied the utility decrements from the ScHARR COVID-19 MTA model in addition to the utility decrement for COVID-19 for the other states. This differs from the ScHARR COVID-19 MTA model, in which Metry *et al*. applied no utility decrement for non-hospitalised patients.[95] In addition, in the ScHARR COVID-19 MTA model, a zero utility value was assumed for those receiving IMV rather than a utility decrement relative to non-infected patients.[95] The EAG estimates that this would be equivalent to a utility decrement of 0.74 in the company's model, whereas the company appears to have applied the same utility decrement as for NIV (0.77). This suggests a state worse than death for patients receiving IMV for COVID-19. The EAG has decided not to correct the implementation of this scenario analysis due to the limited impact of these utility values on the ICER.

4.3.4.18 Approach used to capture post year one cases of COVID-19

Although, the company's model captures costs and QALY losses in the second year and beyond separately for those experiencing a first episode of COVID-19 and those a second episode of COVID-19, the costs and QALY losses from acute COVID-19 are the same for both outcomes and the risk of experiencing COVID-19 after the first year is not reduced in those who have survived COVID-19 during the first year. Therefore, the outcome that differs between the Evusheld and SoC arms is the QALY losses from deaths associated with cases of COVID-19 in the second year and beyond. These differ between the Evusheld and the SoC arms because there are fewer patients alive and at risk of COVID-

19 in the SoC arm, and the ones who are alive are more likely to have long COVID reducing their HRQoL and therefore the QALYs lost from an early death are lower if they subsequently experience death from COVID-19. Therefore, the treatment effectiveness of Evusheld in preventing COVID-19, hospitalisations and long COVID in year one, results in a healthier population with slightly greater QALY losses and slightly greater costs from cases of COVID-19 occurring in the second year and beyond, but this is a small difference. A greater difference would be seen if it were assumed that experiencing COVID-19 in year one reduced the risk of experiencing COVID-19 in later years, as the SoC arm would have fewer post year one cases of COVID-19.

There is an error in the company's estimation of QALY losses due to mortality following reinfections. For patients experiencing a second episode of COVID-19, the future risk of COVID-19 is (correctly) only applied to those surviving their first episode of COVID-19. But the QALY loss is calculated by multiplying the risk by the average QALYs gained across all patients with COVID-19 irrespective of whether they survived. This error results in the QALY losses due to deaths recurrent COVID-19 being 1.19 to 2.29 times smaller than what they should be depending on whether their first episode of COVID-19 had a low or high mortality risk. However, in addition to this error, the QALYs lost due to deaths are not adjusted to account for the cycle length being 6 months, resulting in them being overestimated 2-fold.

In the company's model, the QALY losses due to deaths from post year one cases of COVID-19 are correct for those dying in the year 2 but do not accumulate as more patients die each year. The calculations are therefore equivalent to death only being possible in the second year of the model. This is because the QALY loss is based on a fixed proportion of the patients currently alive losing all their QALYs due to fatal COVID-19, whereas in reality, as the deaths accumulate due to cases of COVID-19 occurring every year, an increasing proportion should lose QALYs due to deaths following COVID-19. The EAG estimates that the company's approach results in a loss of 0.074 life-years (LYs) (undiscounted) due to deaths following post year one case of COVID-19 whereas a correct approach allowing deaths from these post year one case of COVID-19 to accumulate would result in a loss of 0.917 LYs (undiscounted).

In the company's model, post year one cases of COVID-19 do not result in any new instances of long COVID in the population. This overestimates the benefit of preventing infections in year one because it means that patients who survive the first year without experiencing long COVID are protected life-long from experiencing long COVID which artificially inflates the difference in years spent in the long COVID state between the Evusheld and SoC arms. Whilst the EAG was not able to fully build the state-transition model required to estimate the impact of this on incremental costs and QALYs, it is noted that introducing long COVID as a competing risk for post year cases of COVID-19 would reduce the

benefits gained from using Evusheld to COVID-19 in year one and would therefore likely increase the ICER. The EAG believes that it would be better if the company attempted to model post year one cases of COVID-19 using a model structure that tracks the number of patients who remain at risk of long COVID over time. This impact of this further explored in Section 4.4.2.12.

The main issues identified by the critical appraisal

Box 1: Summary of the main issues identified within the company's health economic model

- The company's base case assumes that the RRR from the RWE study with 4 months follow-up can be applied as a constant treatment effect across 6 months following each dose.
- The company's economic analysis uses historical risks for COVID-19 that may not reflect the risk of COVID-19 in the year after guidance on Evusheld is published.
- There were errors identified in the company's adjustments to incorporate the impact of post year one cases of COVID-19 and the company's approach does not include a risk of long COVID for these cases.
- The company has applied a direct utility gain to reflect reduced shielding to all patients receiving Evusheld and not only to those patients continuing to follow shielding advice.
- There is uncertainty in the risk of long COVID for patients with COVID-19 who do not require hospitalisation and the EAG prefers to use an alternative estimate.
- The EAG believes that the costs of administering Evusheld to the large eligible cohort have not been properly estimated.
- The company's estimate of the duration of long COVID does not reflect the most recent ONS data and it results in a longer duration of long COVID for non-hospitalised patients.
- The company's estimate of the cost of long COVID is not evidence-based.
- The EAG does not agree with the method used by the company to estimate the utility decrements for long COVID and it prefers to assume a linear reduction over 5 years
- The risk of hospitalisation and risk of requiring IMV for COVID-19 has reduced over time and this is not captured in the company's base case.
- The company has not incorporated the newly available COVID-19 specific reference costs in its estimates of hospitalisation cost.
- The target population for Evusheld is likely to be heterogeneous but the impact of this heterogeneity on cost-effectiveness has not been explored in the company's analysis.

4.4 Exploratory analyses undertaken by the EAG

4.4.1 Overview of EAG's exploratory analyses

The exploratory analyses performed by the EAG are explained in Section 4.4.2. These included correcting implementation errors in the model (Section 4.4.2.1), implementing the EAG's preferred assumptions (Sections 4.4.2.2 to 4.4.2.12), and exploring alternative plausible assumptions (Sections 4.4.2.13 to 4.4.2.14). Section 4.4.3 reports on the results of these analyses, whereas Section 4.4.4 indicates the EAG's preferred analysis.

4.4.2 EAG's exploratory analyses – methods

4.4.2.1 Correcting implementation errors in the company's economic model

The EAG corrected the identified errors listed under Section 4.3.4.18 as follows:

(a) Acute phase outcomes for post year one cases of COVID-19

The EAG recalculated the costs and QALYs gained during the acute phase for a post year one case of COVID-19 by calculating the weighted average across all groups with COVID-19 (either hospitalised or not). This is a correction to the company's approach where the weighted average was estimated across all patients including those without COVID-19.

(b) Correcting the adjustments for cycle length in the calculations to account for post year one cases of COVID-19

The EAG removed the cycle length adjustment for the acute costs associated with post year one cases of COVID-19 as these costs reflect an acute cost applied once for every patient having COVID-19 and not a cost per annum that needs adjusting for cycle length. On the other hand, the cycle length adjustment was applied when estimating the QALY loss due to fatal post year one cases of COVID-19 as in this case the time spent in the health state was relevant.

(c) Subtracting deaths due to re-infections from the cohort alive

The EAG subtracted the cohort expected to die from post year one cases of COVID-19 from columns U, V, and BB in the long-term Markov sheet and added them to columns W and BC.

4.4.2.2 Varying size of direct utility gain or size of group it is applied for to 13%

The EAG has assumed in its base case that the direct utility gain attributed to patients being able to stop shielding will only apply to the 13% of patients currently reported as still following shielding advice.

4.4.2.3 Halving the duration of direct utility gain for those infected on Evusheld

The EAG has assumed that the direct utility gain will apply for a full year to those who do not experience COVID-19 but only for half a year for those who experience COVID-19. The basis for this is that it is assumed that SARS-CoV-2 infections will occur on average half-way through the one-year prophylaxis period and any patients who experience COVID-19 despite receiving Evusheld will no longer benefit from feeling protected by Evusheld and are likely to resume shielding behaviours to avoid recurrent SARS-CoV-2 infection with a consequent impact on HRQoL.

4.4.2.4 Assuming 12.7% of the non-hospitalised cohort would develop long COVID

The EAG has used the estimate of 12.7% from Ballering *et al.*[132] in its base case and have explored alternative values ranging from 4.2% to 34.8% in sensitivity analysis (see discussion of these sources in Section 4.3.4.13).

4.4.2.5 Assuming cost of administration for Evusheld of £410 based on CMDU costing exercise

The EAG has applied the unit costs for administering COVID-19 therapeutics in the community through CMDU's in their base case analysis. The costs were those provided to ScHARR by NICE for the purposes of the COVID-19 therapeutics MTA and consist of a unit cost of £410 for delivery of an oral antiviral and £820 for delivery of an intravenous nMAB.[134] As no cost was provided for administration of a subcutaneous injection, it was assumed in the MTA that the cost of administering oral antivirals would apply for Evusheld when given as a treatment. Therefore, the EAG applied a cost of £410 per dose administered in their base case analysis.

4.4.2.6 Using the October update of the ONS data to estimate the duration for long COVID without the Evans adjustment

The EAG base case uses the company's scenario where ONS data reported in October 2022 for long COVID were used for extrapolation without adjustment. This was done by selecting Option 'Sensitivity 3' at cell D72 in the 'EAG_Qu' sheet. In addition, the EAG removed the 6-month adjustment applied by the company from Evans *et al.* for the hospitalised cohort (described in Section 4.2.6.17) by changing cells U45 and V45 in the long-term Markov sheet. This results in a higher proportion of non-recovered patients in the hospitalised group at 5 months but ensures that the rates of recovery are not higher in the hospitalised group than the non-hospitalised group.

A scenario was explored where the calibrated October 2022 log normal extrapolation was used with such an adjustment to match the 5-month data from Evans *et al.* for both cohorts. A scenario is also presented using the company's preferred estimate of long COVID duration.

4.4.2.7 Using the long COVID annual costs of £1128 assuming chronic fatigue as proxy

The EAG base case uses the annual cost estimate for long COVID from the original CS which was £1128.

4.4.2.8 Recalculating disutility values due to long COVID and assuming linear QoL improvement by time

The EAG recalculated the disutility values due to long COVID from the two papers reporting outcomes from the PHOS-COVID cohort (Evans 2021 and Evans 2022) as described in Section 4.2.6.18. The EAG's estimates were as follows: 0.133 for the non-hospitalised patients and those in need of no oxygen or low-flow oxygen; 0.162 for those in need of high-flow oxygen; and 0.310 for patients admitted requiring IMV. In addition, the EAG base case adopts the linear reduction scenario created by the company, as described in Section 4.2.6.18.

4.4.2.9 Using 15.9% as the risk estimate of hospitalisation for infected patients

The EAG has used the data from Shields *et al*.[10] which reflects the hospitalisation risk for immunocompromised patients infected during the Omicron wave who did not receive COVID-19 therapeutics (15.9%) as these are not currently covered by routine commissioning.

4.4.2.10 Updating hospitalisation reference costs associated with acute admissions

For patients receiving low flow oxygen or no oxygen, the EAG applied the new reference costs for the COVID-19 specific HRG codes as a single cost for the whole episode of care.[135] The HRG code of "COVID-19 infection [DX21A]" (£2,764) was assumed to apply to patients not on oxygen and the HRG code for "COVID-19 infection, with pneumonia [DX11A]", was assumed to apply to patients requiring low-flow oxygen (£3,160). Both were estimated as the average across non-elective short and long stay spells. The reference cost for "COVID-19 infection, with major manifestations [DX01A]" (£4,493) was applied to patients requiring critical care to cover the period prior to critical care admission.

The EAG updated the critical care unit costs for patients receiving IMV (weighted average for adult critical care one or more organs supported [XC01Z-XC06Z]) and those receiving high-flow oxygen or NIV (Adult Critical Care, 0 Organs Supported [XC07Z]) implemented by Rafia *et al*. to use equivalent data from 2020-21 reference costs. This increased the costs per day in critical care from £1518 to £2,417 and £933 to £1,977 for IMV/ECMO and NIV/high-flow oxygen respectively. When combined with the estimates for time spent in critical care from the ScHARR-TAG MTA model, and the reference cost for non-critical care in patients with major manifestations (£4,493) these gave total costs for these health states of £28,552 and £24,289 respectively.

The costs updated to include the latest COVID-19 specific reference costs were used in the EAG's preferred base case analysis, but an exploratory analysis using the costs applied in the COVID MTA has also been provided. For reference the different values used are provided in Table 29

Table 29: Costs of admission applied according to the level of care required for different scenarios

Level of care required	Company's analysis	Updated with COVID-19 specific reference costs (EAG base case)	ScHARR-MTA (EAG scenario)
No oxygen	£1,734	£2,763	£7,327
Low-flow oxygen	£2,966	£3,160	£12,988
NIV/high-flow oxygen	£9,932	£24,289	£21,579
IMV/ ECMO	£34,301	£28,551	£25,130

4.4.2.11 Reducing proportion of hospitalised patients requiring invasive ventilation

The EAG base case adopted the company's second scenario analysis regarding hospitalisation distribution as detailed in the clarification response to question B8. This reduces patients admitted who required IMV from 15.4% of the total hospitalised cohort as per the original CS to 4.92%.

The EAG has explored a lower range for the estimate of the proportion of hospitalised patients requiring IMV of 2.51% in a scenario analysis.

4.4.2.12 Applying long COVID to new infections after 1 year

The EAG applied long COVID to the new infections every cycle after year one. First, the EAG simulated the cohort who remain at risk of experiencing a first episode of COVID-19 throughout the model time horizon. This was done in columns CO and CP of the long-term Markov sheet. Second, one-off average total costs and QALY losses for long COVID were applied to the new cases of COVID-19 occurring every cycle, taking discounting into account by taking the midpoint discount rate for the average duration (e.g., for COVID-19 cases occurring in year 3 where the average duration of long COVID is expected to last until year 7, the discount rate of year 5 was assumed). These cost and QALY calculations are in columns CR to CU of the Long-term Markov sheet. These were then summated in CR45 to CU45 and added to the data table in rows 14 to 23.

4.4.2.13 Assuming reduction in relative efficacy by one third

The EAG explored a scenario, applied to the EAG's corrected company base case, where the RRRs for COVID-19 and hospitalisation for COVID-19 were reduced to one third of their reported values from Young *et al.* The intention of this scenario was to explore the impact of reduced efficacy in months 4 to 6 after treatment with Evusheld, because the efficacy data were taken from a study with 4 month follow-up. This means that for this scenario the risk reductions used were 44% and 41% for infections and hospitalisations respectively.

4.4.2.14 Additional scenario analyses

In addition to its base case amendments and scenarios listed above, the EAG performed the following scenarios:

(a) The EAG ran a two-way sensitivity analysis varying both the baseline risk of COVID-19 and the RRR for COVID-19 due to Evusheld to examine how sensitive the results are when both these parameters are varied simultaneously.
(b) The company's scenario analysis which incorporates the efficacy data from PROVENT has been amended to assume no further impact on hospitalisation over and above the impact on reduced cases of COVID-19. This is to bring the analysis in line with the company's stated assumption and to reflect the fact that the hospitalisation events within PROVENT were a *post hoc* analysis and insufficient events were recorded to estimate the RRR of hospitalisation given COVID-19. This change only affects the scenario analysis and is therefore not incorporated in the EAG's base case which uses the efficacy data from Young-Xu *et al.*[23]
(c) The EAG ran a scenario analysis using the baseline characteristics from the PROVENT subpopulation of immunocompromised as detailed in Table 83 of the clarification response. This meant increasing the mean age of the starting cohort from 53.5 to 60.3 years, and a slight change in sex distribution from 53.9% male to 53.4%.
(d) The EAG ran a scenario analysis using the hospitalisation costs associated with the per the ScHARR MTA report where daily costs of £563, £828, £1977, £2393 were assumed for patients hospitalised in need of no oxygen, low-flow oxygen, high-flow oxygen, and IMV respectively.

4.4.3 Results of the EAG's exploratory analyses

4.4.3.1 Impact of individual changes on the ICER

Table 30 presents the results of the EAG's deterministic exploratory analyses when making individual changes to the model, and when combining several changes. The ICER for Evusheld versus no prophylaxis is estimated to be [redacted] per QALY gained in the company's base case. The corrections implemented by the EAG brought the ICER up to [redacted] (this is referred to as the EAG's corrected company base case). These EAG corrections to the company's base case were included in all analyses presented in subsequent rows of Table 30.

First the EAG explored applying individual changes in isolation to the EAG's corrected company base case (EAG exploratory analyses 1 to 12 in Table 30). The largest change in the ICER was seen when the EAG used the updated ONS data to model long COVID without calibration and without using the 5-month data from the PHOS-COVID cohort (Evans 2021) to adjust the proportion with long COVID at 6 months for the hospitalised cohort. This increases the ICER to [redacted] per QALY gained. Applying the direct utility gain for Evusheld only to the 13% who are currently following shielding advice increased the ICER to [redacted]. Assuming a higher cost for administering Evusheld, based on the costs of delivering COVID-19 therapeutics in a CMDU, increased the ICER to [redacted]. Assuming only 12.7% of the non-hospitalised cohort would develop long COVID increased the ICER to [redacted]. The ICER was fairly insensitive to a reduction in the proportion of hospitalised patients requiring IMV, updating the costs for COVID-19 admission to include COVID-19 specific reference costs and halving the duration of direct utility gain for those experiencing COVID-19 in the year after receiving Evusheld.

The scenario exploring a one-third reduction in the RRR for COVID-19 and the RRR for hospitalisation increased the ICER to [redacted]. The intention of this scenario was to explore the potential for any waning of treatment effect from 4 to 6 months to increase the ICER. Therefore, this result suggests that this factor alone is unlikely to increase the ICER to above £20,000 per QALY.

The EAG's preferred base case included all the analyses denoted 1 to 11 in Table 30. The probabilistic ICER for the EAG's preferred base case was estimated at [redacted] per QALY; this was similar to the deterministic ICER for the EAG's preferred base case at [redacted] per QALY.

The EAG then conducted scenario analyses using their preferred base case as the starting point (EAG scenarios 1 to 8 in Table 30). The following four scenario analyses showed a further increase of approximately £2000 to £9000 per QALY: assuming 4.2% of the non-hospitalised cohort would develop long COVID; PROVENT efficacy data was used with no impact on hospitalisation risk; baseline characteristics from the immunocompromised subpopulation of PROVENT were assumed; and reducing proportion of hospitalised patients requiring IMV to 2.51%. Assuming that 34.8% of the non-hospitalised cohort with COVID-19 would develop long COVID as assumed in the company's base case decreased the ICER for the EAG's preferred base case to [redacted] per QALY gained. Using the calibrated ONS data and applying the adjustment at 6 months when estimating the duration of long COVID decreased the EAG's preferred base case ICER to [redacted] per QALY. Using the daily hospitalisation costs from the ScHARR COVID-19 MTA model reduced the ICER to [redacted]. When the EAG used the company's preferred estimate of the duration of long COVID but will all other EAG preferences, the ICER was [redacted].

Table 30: Results of the EAG's exploratory analyses

Option	Life years	QALYs	Costs	Incremental			ICER
				Life years	QALYs	Costs	
Company base case (Deterministic)							
No prophylaxis	15.76	[redacted]	[redacted]	-	-	-	
Evusheld	15.84	[redacted]	[redacted]	0.08	[redacted]	[redacted]	[redacted]
EAG's corrected company base case: correcting implementation errors in the company's economic model							
No prophylaxis	14.76	[redacted]	[redacted]	-	-	-	
Evusheld	14.83	[redacted]	[redacted]	0.07	[redacted]	[redacted]	[redacted]
EAG exploratory analysis 1: Varying size of direct utility gain or size of group it is applied for to 13%							
No prophylaxis	14.76	[redacted]	[redacted]	-	-	-	
Evusheld	14.83	[redacted]	[redacted]	0.07	[redacted]	[redacted]	[redacted]
EAG exploratory analysis 2: Halving the duration of direct utility gain for those infected while on Evusheld							
No prophylaxis	14.76	[redacted]	[redacted]	-	-	-	
Evusheld	14.83	[redacted]	[redacted]	0.07	[redacted]	[redacted]	[redacted]
EAG exploratory analysis 3: Assuming 12.7% of the non-hospitalised cohort would develop long COVID							
No prophylaxis	14.76	[redacted]	[redacted]	-	-	-	
Evusheld	14.83	[redacted]	[redacted]	0.07	[redacted]	[redacted]	[redacted]
EAG exploratory analysis 4: Assuming cost of administration for Evusheld of £410 based on CMDU costing exercise							
No prophylaxis	14.76	[redacted]	[redacted]	-	-	-	
Evusheld	14.83	[redacted]	[redacted]	0.07	[redacted]	[redacted]	[redacted]
EAG exploratory analysis 5: Using the October 2022 update of the ONS data to estimate the duration for long COVID without the Evans 2022 adjustment							
No prophylaxis	14.76	[redacted]	[redacted]	-	-	-	
Evusheld	14.83	[redacted]	[redacted]	0.07	[redacted]	[redacted]	[redacted]
EAG exploratory analysis 6: Using the long COVID annual costs of £1128 assuming chronic fatigue as proxy							
No prophylaxis	14.76	[redacted]	[redacted]	-	-	-	
Evusheld	14.83	[redacted]	[redacted]	0.07	[redacted]	[redacted]	[redacted]

Option	Life years	QALYs	Costs	Incremental			ICER
				Life years	QALYs	Costs	
EAG exploratory analysis 7: Recalculating disutility values due to long COVID and assuming linear HRQoL improvement by time for 5 years							
No prophylaxis	14.76	[redacted]	[redacted]	-	-	-	
Evusheld	14.83	[redacted]	[redacted]	0.07	[redacted]	[redacted]	[redacted]
EAG exploratory analysis 8: Using 15.9% as the risk estimate of hospitalisation for infected patients							
No prophylaxis	14.88	[redacted]	[redacted]	-	-	-	
Evusheld	14.95	[redacted]	[redacted]	0.07	[redacted]	[redacted]	[redacted]
EAG exploratory analysis 9: Updating hospitalisation reference costs associated with acute admissions							
No prophylaxis	14.76	[redacted]	[redacted]	-	-	-	
Evusheld	14.83	[redacted]	[redacted]	0.07	[redacted]	[redacted]	[redacted]
EAG exploratory analysis 10: Reducing proportion of hospitalised patients requiring IMV							
No prophylaxis	15.04	[redacted]	[redacted]	-	-	-	
Evusheld	15.10	[redacted]	[redacted]	0.06	[redacted]	[redacted]	[redacted]
EAG exploratory analysis 11: Applying long COVID to new infections after 1 year							
No prophylaxis	14.76	[redacted]	[redacted]	-	-	-	
Evusheld	14.83	[redacted]	[redacted]	0.07	[redacted]	[redacted]	[redacted]
EAG exploratory analysis 12: Assuming reduction in relative efficacy by one-third							
No prophylaxis	14.76	[redacted]	[redacted]	-	-	-	
Evusheld	14.81	[redacted]	[redacted]	0.06	[redacted]	[redacted]	[redacted]
EAG base case applying analyses 1-11 (Deterministic)							
No prophylaxis	15.14	[redacted]	[redacted]	-	-	-	
Evusheld	15.19	[redacted]	[redacted]	0.05	[redacted]	[redacted]	[redacted]
EAG base case applying analyses 1-11 (Probabilistic)							
No prophylaxis	15.19	[redacted]	[redacted]	-	-	-	
Evusheld	15.24	[redacted]	[redacted]	0.05	[redacted]	[redacted]	[redacted]
EAG scenario 1 (PROVENT efficacy data with no impact on hospitalisation risk)							
No prophylaxis	15.14	[redacted]	[redacted]	-	-	-	
Evusheld	15.18	[redacted]	[redacted]	0.05	[redacted]	[redacted]	[redacted]
EAG scenario 2 (baseline characteristics from the immunocompromised subpopulation of PROVENT)							

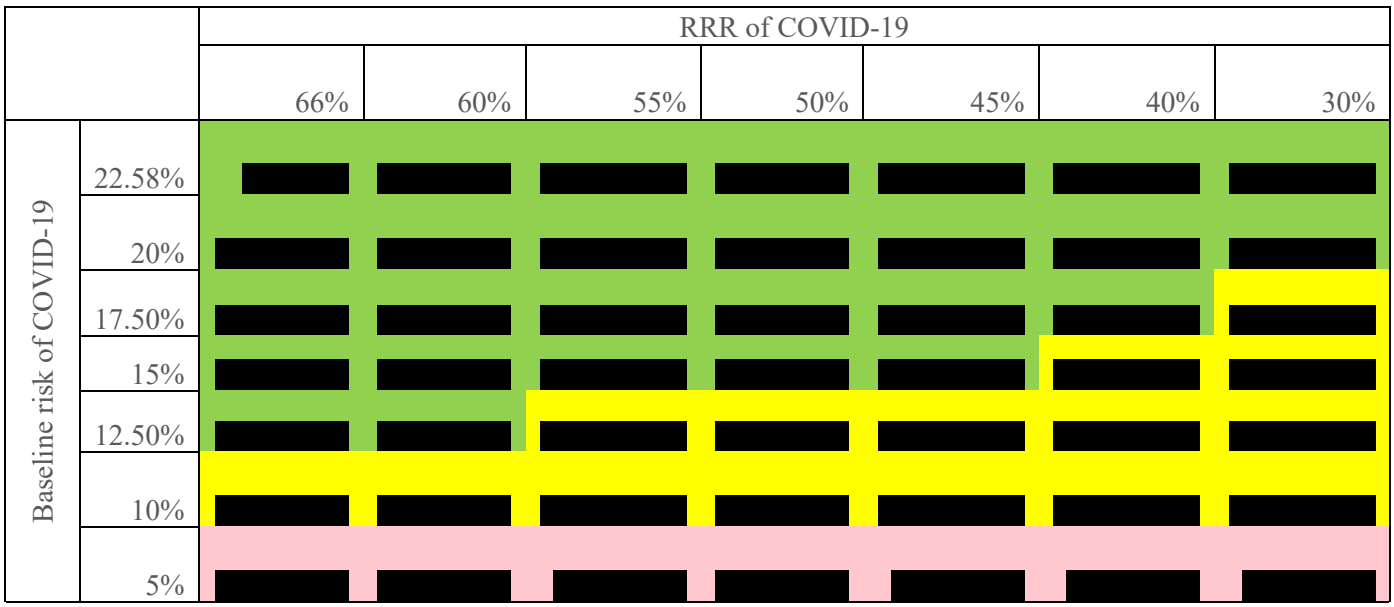
Option	Life years	QALYs	Costs	Incremental			ICER
				Life years	QALYs	Costs	
No prophylaxis	12.94	[redacted]	[redacted]	-	-	-	
Evusheld	12.99	[redacted]	[redacted]	0.04	[redacted]	[redacted]	[redacted]
EAG scenario 3 (assuming 4.2% of the non-hospitalised cohort would develop long COVID)							
No prophylaxis	15.14	[redacted]	[redacted]	-	-	-	
Evusheld	15.19	[redacted]	[redacted]	0.05	[redacted]	[redacted]	[redacted]
EAG scenario 4 (assuming 34.8% of the non-hospitalised cohort would develop long COVID)							
No prophylaxis	15.14	[redacted]	[redacted]	-	-	-	
Evusheld	15.19	[redacted]	[redacted]	0.05	[redacted]	[redacted]	[redacted]
EAG scenario 5 (Using the calibrated October 2022 update of the ONS data to estimate the duration for long COVID with the Evans 2022 adjustment applied to both cohorts)							
No prophylaxis	15.14	[redacted]	[redacted]	-	-	-	
Evusheld	15.19	[redacted]	[redacted]	0.05	[redacted]	[redacted]	[redacted]
EAG scenario 6 (Reducing proportion of hospitalised patients requiring IMV to 2.51%)							
No prophylaxis	15.20	[redacted]	[redacted]	-	-	-	
Evusheld	15.25	[redacted]	[redacted]	0.05	[redacted]	[redacted]	[redacted]
EAG scenario 7 (Using the daily hospitalisation costs reported in the ScHARR COVID MTA report)							
No prophylaxis	15.14	[redacted]	[redacted]	-	-	-	
Evusheld	15.19	[redacted]	[redacted]	0.05	[redacted]	[redacted]	[redacted]
EAG scenario 8 (Using the company's preferred estimate of the duration of long COVID)							
No prophylaxis	15.14	[redacted]	[redacted]	-	-	-	
Evusheld	15.19	[redacted]	[redacted]	0.05	[redacted]	[redacted]	[redacted]

4.4.3.2 The two-way sensitivity analysis on the EAG's corrected company base case

The EAG has presented a two-way sensitivity analysis exploring the impact of reduced COVID-19 risk and a reduced RRR (i.e., lower efficacy) for Evusheld in Table 31 (described in Section 4.4.2.14). The intention of this analysis was to explore how sensitive the ICER is to these factors which the EAG consider to be inherently uncertain due to the risk of new variants emerging. As both of these factors increase the ICER, this two-way scenario has not been conducted for the EAG preferred base case where the ICER is already above £30,000 per QALY.

Table 31 presents the results of the two-way sensitivity analysis for the EAG's corrected company base case. It can be seen that the ICER is above £20,000 per QALY when a baseline COVID-19 risk of 10% is assumed and the RRR is left at its base case value of 66%. However, the ICER also increases to above £20,000 per QALY when a baseline COVID-19 risk of 17.5% is combined with a RRR of 30%. A baseline COVID-19 risk of 5% provides ICERs above £30,000 even when the RRR of 66% is maintained.

Table 31: The EAG's 2-way sensitivity analysis on the corrected company's base case



*The EAG's corrected company base case including the corrections described in section 4.4.2.1

4.4.4 The EAG's estimate of the ICER

The exploratory analyses conducted by the EAG, which are provided in Table 30, indicate that there are plausible changes to parameter values which would considerably increase the company's estimate of the ICER but where the most appropriate value remains uncertain. Such parameters include: the appropriate extrapolation for long COVID duration; the direct utility gain assumptions associated with Evusheld; and proportion expected to develop long COVID from the non-hospitalised patients.

The exploratory analysis which has the largest impact on the ICER is the use of the October 2022 update for the ONS data to model and parameterise the duration of long COVID without calibration and without the 6-month adjustment to match the proportion recovered in the PHOS-COVID cohort (Evans 2022). The EAG believes this approach is more appropriate than the company's base case approach because it predicts more plausible durations of long COVID in line with the 2 years predicted in the ScHARR COVID-19 MTA model. Although the EAG acknowledges that the target population in this appraisal differs from that specified in the COVID-19 therapeutics MTA and evidence on the duration

of long COVID in different populations is still emerging. The EAG's most plausible estimate of the ICER is approximately [redacted] per QALY gained, although the EAG accepts that there is some uncertainty associated with this estimate given that the scenario analyses produced ICERs ranging from [redacted] to [redacted]

Several factors were also found to increase the ICER considerably as shown in Section 4.4.3 such as the direct utility gain attributable to change in shielding behaviour because of Evusheld, and the proportion expected to develop long COVID from the group of patients having COVID-19 that did not require hospitalisation. The EAG notes that most of the QALY differential between the two arms of the model is driven by the direct utility gain and the impact of long COVID on HRQoL. The lack of any direct measurement of the utility gain from reduced shielding in patients receiving Evusheld and the immaturity of evidence available to characterise long COVID means that these aspects of the analysis are subject to considerable uncertainty.

There is also considerable uncertainty related to the future risks of COVID-19 and the efficacy of Evusheld in the context of new emerging variants. The EAG also notes that although the two-way sensitivity analyses exploring the impact of lower COVID-19 risks and reduced efficacy was not conducted for the EAG's preferred base case, both factors would have the potential to increase the ICER.

5 OTHER FACTORS

The company has not submitted any evidence to support the implementation of a severity modifier in this appraisal (CS, Section B3.6). Although the company has not done the necessary calculations to estimate the absolute and proportional QALY losses required to evaluate whether a severity modifier should be applied in this case, the EAG does not believe that it is likely that the requirements would be met in this appraisal. A managed access scheme has not been proposed.

6 OVERALL CONCLUSIONS

In general, the efficacy (e.g., incidence of COVID-19, SARS-CoV-2 infections, COVID-19 hospitalisation, and all-cause mortality) and safety (300 mg or 600 mg single dose) of Evusheld for preventing COVID-19 was positively demonstrated (compared with controls) in the key studies included in the CS. However, there are several limitations and uncertainties in the evidence base which warrant caution in its interpretation. The RWE study by Young-Xu *et al*.[23] (n= 8087) was considered by the company to represent the most generalisable population to the target population specified in the CS (95% received COVID-19 vaccination and 83% of Evusheld recipients received a single 600mg dose of Evusheld). Due to the retrospective nature of the study design, the study lacked a control arm; as such, propensity matched controls were selected from patients who were immunocompromised (or otherwise at high-risk of COVID-19) who were not treated with Evusheld. While the EAG considers the propensity matching approach to be reasonable, data quality issues and methodological limitations (e.g., inconsistencies in the matching of the controls, potential baseline differences between prognostic factors not included in the matching process and residual confounding and other statistical issues) may have impacted the estimates of effectiveness. As such, the magnitude of benefit in reducing the incidence of SARS-CoV-2 infection, COVID-19 hospitalisation and all-cause mortality in the target population remains uncertain. In addition, there are no data available to inform on the efficacy and safety of Evusheld (600 mg dose) beyond 6 months after initial administration or repeat dosing. However, this is currently being investigated in the PROVENT sub-study and the ENDURE Dose Ranging Study.[19] Furthermore, the current clinical evidence in the CS does not provide information on the efficacy of Evusheld against the newest variants of concern that are now prevalent (e.g. BA.5) or emerging in the UK (e.g. BQ.1, BQ.1.1, XBB and others), and the supporting studies included in the CS do not provide any evidence on the use of Evusheld in pregnant women, children aged under 12 years and specific subpopulation within the overall target population.

The economic analysis submitted by the company largely complied with the NICE reference case with the most important exception being that the cost of long COVID was not evidence-based. The EAG considered the model structure to be appropriate with the exception of the company's handling of cases of COVID-19 occurring after the first year. The EAG identified a number of errors in the company's economic analysis which related to the modelling of post year one cases of COVID-19; the most significant of which was that the company's approach did not allow for deaths from post year one cases of COVID-19 to accrue over time. The EAG also identified that the company's model did not allow for patients having a post year one case of COVID-19 to develop long COVID. This led to a potential overestimation of the benefits of offering Evusheld to prevent COVID-19 in the first year of the model. The EAG attempted to correct this omission within their exploratory analyses. However, the EAG

believes that it would be better if the company attempted to model post year one cases of COVID-19 using a model structure that tracks the number of patients who remain at risk of long COVID over time.

The CS states that many immunocompromised people are taking extra precautions to protect themselves and some have continued to follow shielding advice leading to a significant reduction in HRQoL. The company's base case analysis applies a direct utility gain to patients receiving Evusheld to account for the fact that it believes that Evusheld will result in a reduction in such behaviours and a consequent increase in HRQoL. This direct utility gain has a large impact on the ICER, however, no direct measure of utility in patients receiving Evusheld has been provided by the company to support this estimate. Furthermore, the company has applied the direct utility gain to all patients receiving Evusheld, whilst the EAG prefers to assume that it applies only to the proportion of patients who are continuing to follow shielding advice.

Many of the parameters that inform the company's analysis are uncertain because they depend on factors which are difficult to predict such as the risk of COVID-19 in the year after Evusheld would be made available if NICE published positive guidance and the efficacy of Evusheld against variants circulating at that time. The EAG has demonstrated that the ICER is sensitive to changes in these parameters even when using the EAG's corrected company's base case. Many of the other parameters, such as the risk of hospitalisation from COVID-19, the risk of needing IMV if hospitalised and the risk of death from COVID-19 have changed over subsequent waves of COVID-19. However, it is sometimes unclear whether this is due to the impact of vaccination, changing variants or better care such as the availability of COVID-19 therapeutics. This makes it difficult to determine the most appropriate estimates for these parameters in the immunocompromised population, especially in the context of emerging variants. Other factors such as the risk of long COVID, the duration of long COVID symptoms, the impact of long COVID on HRQoL and the costs of care for people with long COVID are uncertain as evidence on this new condition is still emerging. The EAG also believes that the costs of administering Evusheld to the large eligible cohort have not been properly estimated by the company.

The ICER for the EAG's preferred base case analysis, in which the EAG has included the assumptions and parameters that it believes are most plausible, is substantially higher than the estimate provided by the company at [redacted] per QALY (deterministic) compared with [redacted] for the company's base case. However, the EAG's scenario analyses indicates a range for the ICER of [redacted] to [redacted] per QALY.

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8 APPENDICES

Appendix 1:

Table 32. EAG additional searches for safety: Embase 1974 to 2022 October 31

1st November 2022

#	Searches	Results
1	evusheld.mp.	74
2	tixagevimab.mp.	248
3	cilgavimab.mp.	252
4	(AZD7442 or AZD8895 or AZD1061 or AZD-7442 or AZD-8895 or AZD-1061).mp.	58
5	or/1-4	266
6	(adrs or adverse drug effect* or adverse drug reaction* or adverse effect* or adverse event* or adverse outcome* or adverse reaction* or complication* or harm or harmful or harms or risk or safe or safely or safety or side effect* or tolerability or toxicity or treatment emergent or undesirable effect* or undesirable event* or unexpected effect* or unexpected event*).mp.	10162016
7	5 and 6	109
8	adverse drug reaction/ or drug safety/ or drug monitoring/ or drug hypersensitivity/ or drug surveillance program/ or intoxication/ or side effect/ or postmarketing surveillance/ or drug recall/ or product recall/	1193645
9	5 and 8	34
10	(am or ae or co or to or si).fs.	3474643
11	5 and 10	21
12	7 or 9 or 11	109

Table 33: EAG additional searches to compare COVID-19 population terms:

Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions 1946 to November 02, 2022
3rd November 2022

#	Searches	Results
1	SARS-CoV-2/ or COVID-19/	196135
2	(corona* adj1 (virus* or viral*)).ti,ab,kw,kf.	5616
3	(CoV not (Coefficien* or "co-efficien*" or covalent* or Covington* or covariant* or covarianc* or "cut-off value*" or "cutoff value*" or "cut-off volume*" or "cutoff volume*" or "combined optimi?ation value*" or "central vessel trunk*" or CoVR or CoVS)).ti,ab,kw,kf.	104187
4	(coronavirus* or 2019nCoV* or 19nCoV* or "2019 novel*" or Ncov* or "n-cov" or "SARS-CoV-2*" or "SARSCoV-2*" or SARSCoV2* or "SARS-CoV2*" or "severe acute respiratory syndrome*" or COVID*2).ti,ab,kw,kf.	315328
5	or/1-4	322659
6	(corona* adj1 (virus* or viral*)).ti.	744
7	(CoV not (Coefficien* or "co-efficien*" or covalent* or Covington* or covariant* or covarianc* or "cut-off value*" or "cutoff value*" or "cut-off volume*" or "cutoff volume*" or "combined optimi?ation value*" or "central vessel trunk*" or CoVR or CoVS)).ti.	48363
8	(coronavirus* or 2019nCoV* or 19nCoV* or "2019 novel*" or Ncov* or "n-cov" or "SARS-CoV-2*" or "SARSCoV-2*" or SARSCoV2* or "SARS-CoV2*" or "severe acute respiratory syndrome*" or COVID*2).ti.	268814
9	6 or 7 or 8	270297
10	(covid-19 or covid19 or corona-virus or sars-cov-2 or sars-cov2 or coronavirus disease or ncov or n-cov).ti.	249261
11	9 not 10	21036
12	5 not 10	73398

Tixagevimab–cilgavimab for preventing COVID-19: A Single Technology Appraisal

ADDENDUM

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1 Introduction

In November 2022, NICE communicated to stakeholders that it would omit the Technical Engagement step from the appraisal process for this topic in order to facilitate an earlier date for the first committee meeting. In the absence of a Technical Engagement step, NICE agreed to accept additional evidence submitted by the company to address key areas of uncertainty raised in the External Assessment Group (EAG) report in advance of the first committee meeting. This addendum to the EAG report provides the EAG's critique of the additional evidence submitted by the company in December 2022 and should be read in conjunction with the main EAG report.

This EAG addendum is structured around the three key issues discussed in the company's additional evidence. Sections 2.1 to 2.3 summarise the additional evidence submitted in support of the company's preferred approach and also includes the EAG's critique of the new data and/or assumptions. In addition to the additional evidence, the company also presented two sets of updated results. The first is described as an 'updated revised EAG base case' in which the company has made several amendments to the EAG base case to incorporate the additional evidence and to adjust for data sources and assumptions which they disagreed with within their factual accuracy check (FAC) response. The second set of results is the revised company base case including all the company's preferred data sources and assumptions, including those informed by their additional evidence. The EAG has summarised these scenarios in Sections 3.1 and 3.2. The EAG has also conducted additional exploratory analyses, including an EAG revised base case, which are described in Section 3.3. Results for the company's and the EAG's additional economic analyses are provided in Section 4, followed by overall conclusions in Section 5.

2 Summary of the company's response to the ACD and EAG critique

2.1 Estimation of the direct utility gain attributable to Evusheld

The economic analysis in the original company submission applied a direct utility gain to all patients receiving Evusheld. This direct utility gain was intended to capture the potential impact of Evusheld on shielding and other infection avoidance behaviours. This direct utility gain ([redacted]) was estimated from an international web-based survey of the general public (CANDOUR study),[1] as the difference between utility measured by EQ-5D for their health-state at the time of the survey (between 24th November and 17th December 2020) and their health-state pre-pandemic (from retrospective recall). The EAG raised concerns regarding the appropriateness of this estimate because it reflects the broad impact of the COVID-19 pandemic on the general public (EAG report, Section 4.3.4.4). It is therefore not a direct measure of the utility loss associated with the shielding behaviours and anxiety regarding COVID-19, that the company claim will be diminished in those receiving Evusheld. In addition, the company applied this direct utility gain to all patients, despite reporting that only 13% of patients in the target population continue to follow shielding advice. Based on the information available at the time of the EAG report,

the EAG preferred to apply the direct utility gain only to the proportion of patients who are shielding (13%).

In response to the concerns raised in the EAG report, the company has provided additional evidence in the form of a utility study by Gallop et al., which was commissioned by the company.[2, 3] The EAG has summarised the utility study based on the details provided in the study protocol and research report provided.[2, 3]

2.1.1 Research objectives of the utility study

The research objectives of the utility study as stated in the research report were:[2]

- *To develop and validate vignettes describing the health-related quality of life (HRQoL) of immunocompromised patients included in the highest-risk clinical subgroups before and after a prophylactic treatment for COVID-19.*
- *To estimate utilities for each health state using two different approaches:*
    - *Immunocompromised patient-completed EQ-5D-5L for current HRQoL and 'treated' HRQoL based on a vignette describing prophylactic treatment for COVID-19*
    - *General population utility estimates from TTO interviews and EQ-5D-5L valuation of vignettes*

The protocol stated that the inclusion of caregiver health state vignettes will be considered if patients report in the interviews that their being at high risk of COVID-19 infection has an impact on their informal caregiver. The EAG notes that no mention of this research objective or any results relating to caregivers is discussed in the study report. The EAG also notes that the research objective to estimate health utility for immunocompromised patients' current health stated and a vignette based 'treated' health-state was not included in the research objectives in the protocol.[3] Instead the protocol describes this as an alternative method of utility estimation which would be piloted in the initial 10 patients interviewed and extended to a sample size of 50 immunocompromised patients if successful.

The methods and results for the general population sample, and the sample of immunocompromised patients are described in sections 2.1.2 and 2.2.2 respectively.

2.1.2 Utilities derived from the general population valuation of vignette

The three vignettes for valuation by the general public were described as follows:

- *Health state 1: Patient is immunocompromised and 'highest-risk' and not treated with a prophylactic (shielding)*
- *Health state 2: Patient is immunocompromised and 'highest-risk' and not treated with a prophylactic but does engage in some social activities (semi-shielding)*
- *Health state 3: Patient is immunocompromised and 'highest-risk' but has received prophylactic treatment (post-treatment)*

The vignettes were informed by a targeted literature review and interviews with four health-care professionals and ten immunocompromised patients (seven were interviewed initially and a further three were interviewed after initial revisions to the vignettes were made).

The post-treatment vignette includes the statement, *"You have received a treatment that protects you from COVID-19. This is an additional treatment to any vaccines you may have received. You now have a level of protection from COVID-19 which is similar to that given by vaccination in individuals who have a healthy immune system.*[2] In contrast the shielding and semi-shielding states, "*You may have been vaccinated but are still at risk of COVID-19".*[2] In addition, the health state vignettes describe each state in terms of how the person is able or not able to socialise, work, exercise, go shopping and use public transport. It also describes their behaviour in terms of whether they feel able to attend crowded events and whether they wear a mask indoors or outdoors in public spaces. The vignette also explicitly describe how the patients feel in each health-state in terms of anxiety, depression and loneliness. The final vignettes are provided in Appendix B of the utility report by Gallop et al.[2]

The study protocol states that 100 members of the general public would be recruited but the sample size in the report is [redacted], with no reason given for this discrepancy. The EAG had no concerns with the representativeness of the general population sample. The general public valuations of the three health states using the EQ-5D-5L score are provided in Table 1. The EQ-5D-5L rating for each state was scored for UK preference weights, using a mapping function to map from EQ-5D-5L to EQ-5D-3L, as recommended for the NICE reference case. Utility values for the three health-states for a TTO valuation exercise and from a 0 to 100 Visual Analogue Scale (VAS) are also reported (but are not reproduced here).

The EQ-5D valuation of the three health states by the general public are not incorporated within the company's updated economic evaluation, which used instead the utility values estimated from the immunocompromised patient sample. However, the company's additional evidence submission reports the differences between the shielding/ semi-shielding health states and the post-treatment health state

from the general population ([redacted] and [redacted] respectively) and uses these to claim that their chosen approach is conservative.

Table 1: General public valuations of health states: EQ-5D-5L scores (N = 83) [reproduced from Gallop et al. 2022,[2] Table 5]

Health state	Mean (SD)	Range	SE	95% CI
Utility values				
1 Shielding	[redacted]	[redacted]	[redacted]	[redacted]
2 Semi-shielding	[redacted]	[redacted]	[redacted]	[redacted]
3 Post-treatment	[redacted]	[redacted]	[redacted]	[redacted]
Differences between health states				
Shielding → post-treatment	[redacted]			[redacted]
Semi-shielding → post-treatment	[redacted]			[redacted]
Shielding → Semi-shielding	[redacted]			[redacted]

CI, Confidence Interval; SD, Standard Deviation; SE, Standard Error

2.1.2 Utility values derived from immunocompromised patients

To be eligible for inclusion in the patient sample, in addition to having a condition that means their immune system is compromised, patients had to be interested in receiving a preventative treatment for COVID-19 and to have experience of shielding from COVID-19, either currently or in the past. The sample of immunocompromised patients included the 10 patients involved in the pilot interview phase and a further 40 patients recruited thereafter ([redacted]), but health-state valuation responses from two participants were excluded, *"based on interviewer feedback relating to understanding and effort".*[2] The characteristics for the 48 patients with responses are provided in

Table ***2***. It can be seen that the majority of patients were either still shielding partially or taking some preventative behaviours (41.7% and 43.8% respectively), with a minority shielding completely (6.3%) or no longer shielding or modifying their behaviour at all (8.3%).

Table 2: Socio-demographic characteristics of the immunocompromised patient sample ([redacted]) [reproduced from Gallop et al. 2022,[2] Table 8]

Characteristic		**Sample ([redacted])**
Age	Mean (SD)	[redacted]
	Range	[redacted]
Sex	Male	[redacted]
	Female	[redacted]
Condition	Rare neurological conditions	[redacted]
	Solid organ cancer	[redacted]
	Haematological disease or SCT	[redacted]
	Renal conditions	[redacted]
	Liver conditions	[redacted]
	Solid organ transplant recipients	[redacted]
	Receiving immunosuppressant therapy	[redacted]
	Immune deficiency	[redacted]
Current behaviour	Yes, shielding completely (not leaving home)	[redacted]
	Yes, shielding partially (e.g. leave home but don't go to busy places)	[redacted]
	Yes, some preventative behaviours (e.g. wear a mask in public places)	[redacted]
	No, I was shielding or modifying my behaviour but no longer do	[redacted]
Current behaviour modifications	Stay at home completely	[redacted]
	Only go out to open/outdoor places	[redacted]
	Avoid busy places or events	[redacted]
	Avoid public transport	[redacted]
	Wear a face mask outdoors	[redacted]
	Wear a face mask indoors (except at home)	[redacted]
Had COVID-19	Yes, I've had a positive test	[redacted]
	Yes, most likely but I've not had a test to confirm	[redacted]
	No	[redacted]
	Don't know	[redacted]
Contact the NHS when they thought they had COVID-19	Yes	[redacted]
	No	[redacted]
	Not applicable	[redacted]
	Yes	[redacted]

Characteristic		Sample ( )
Admitted to hospital due to COVID-19	No	
	Not applicable	

Abbreviations: CI, Confidence Interval; SD, Standard Deviation; SE, Standard Error

The report provides the EQ-5D scores for the immunocompromised patients' current health state and for a vignette that describes a treated patient. It should be noted that this is different from the post-treatment vignette used in the general population sample. The final vignette for the treated health-state, which was used for the majority of health-state valuations ( ) in the immunocompromised patient sample, was as follows:[2]

- *You have received a treatment that protects you from COVID-19. This is an additional treatment to any vaccines you may have received. You now have a level of protection from COVID-19 which is similar to that given by vaccination in individuals who have a healthy immune system*
- *As your risk of COVID-19 infection is reduced, you no longer need to modify your behaviour to protect yourself from COVID-19*
- *Your underlying health condition is not affected*

The original vignette used in the 10 pilot interviews was slightly different in that it did not explicitly state that the treatment was in addition to any vaccines received and it said *"you can return to your pre-pandemic behaviour",* rather than *"you no longer need to modify your behaviour to protect yourself from COVID-19."*[2] However, the core statement about the level of protection from COVID-19 being *"similar to that given by vaccination in individuals who have a healthy immune system"* is identical.[2]

The report provides EQ-5D scores for the whole cohort ( ), and also for the subgroup who are partially shielding ( ) and the subgroup who are fully shielding (No subgroup results are provided for the subgroup who are no longer shielding or modifying their behaviour (The EQ-5D utility results are summarised in Table 3.

In the company's updated base case economic analysis, the direct utility gain attributable to Evusheld is estimated from the difference in utility between the patient's own health-state and the vignette-based treated state. However, rather than using the estimate from the whole patient cohort ( ), the company has estimated a weighted average ( ) across the group who are fully shielding ( ) and the group who are partially shielding ( ), using the proportions reported from the Office for National Statistics (ONS) survey (13% and 69% respectively).[4] This weighted average is then applied to all patients receiving Evusheld, rather than to the 82% who are either fully or partially shielding according to the ONS survey.[4] The justification for this given by the company is that as, *"Evusheld*

would only be administered for people who desire prophylaxis, it is reasonable to suggest that patients would have some form of modified behaviour".

The utility study also asked patients enrolled after the pilot stage ([redacted]) about whether they would change their behaviour after receiving the treatment described in the vignette. The majority of patients [redacted] reported that they would modify their behaviour, but [redacted] said they would not and [redacted] were unsure. Participants were also asked, *"if the change in their behaviour would depend on the variant of COVID-19 that was most common at the time (i.e. if there was a new variant that the treatment was not effective against."* [redacted] of the participants responded that their behaviour would depend on the variant and they would return to their pre-treatment behaviour if there was a new variant that the treatment was not effective against.

Table 3: Patient valuations of health states: EQ-5D-5L scores (N = 48) [adapted from Tables 10, and data provided in Appendix C of the utility report by Gallop et al.[2]]

Health state	Mean (SD)	Range	SE	95% CI
Whole patient cohort ([redacted])				
Participant's current HRQoL (current)	[redacted]	[redacted]	[redacted]	[redacted]
Rating of treatment vignette (treated)	[redacted]	[redacted]	[redacted]	[redacted]
Difference between treated and current	[redacted]			[redacted]
Partially shielding only ([redacted])				
Participant's current HRQoL (current)	[redacted]	[redacted]	[redacted]	[redacted]
Rating of treatment vignette (treated)	[redacted]	[redacted]	[redacted]	[redacted]
Difference between treated and current [a]	[redacted]			[redacted]
Shielding ([redacted])				
Participant's current HRQoL (current)	[redacted]	[redacted]	[redacted]	[redacted]
Rating of treatment vignette (treated)	[redacted]	[redacted]	[redacted]	[redacted]
Difference between treated and current [b]	[redacted]			[redacted]

CI, Confidence Interval; SD, Standard Deviation; SE, Standard Error

[a] p-value t-test difference between full sample and semi-shielding only = 0.96
[b] p-value t-test difference between full sample and shielding only = 0.591

EAG critique

The EAG considers that an estimate of EQ-5D utility in the group of patients eligible to receive Evusheld would be preferrable to using the data from the CANDOUR study,[1] which reflects only the broad impact of the COVID-19 pandemic on the general population. However, the utility study by Gallop et al.[2] does not provide a direct measure of utility in patients before and after receiving Evusheld. Instead, a vignette has been used to describe the health-state for treated patients and this has been compared against patient's current health utility. Despite this limitation, the EAG considers that this estimate is preferrable to using the estimate from the CANDOUR study,[1] although it notes that it should still be treated with caution.

The EAG also agrees with the company that the estimates from the patient cohort are preferrable to those from the general population sample, as these are less reliant on the accuracy of the vignettes and the ability of the general population sample to understand what it is like to experience these health states and complete the EQ-5D accordingly. Although, the EAG notes that the estimates from the patient cohort are still reliant on the accuracy of the vignette for the treated health-state.

The EAG also agrees that using the EQ-5D valuations of the health-states is preferrable to the direct TTO valuation approach based on the hierarchy presented in Figure 4.1 of the NICE methods guide, which only advises using an alternative to the EQ-5D if there is evidence to show that the EQ-5D is not appropriate.[5]

The EAG does not however agree that it is right to apply the utility gain estimated as a weighted average across the groups who are shielding or otherwise modifying their behaviour to the whole cohort receiving Evusheld. A proportion of the patient cohort ([redacted]) recruited to the utility study described themselves as no longer shielding or modifying their behaviour despite saying that they were interested in receiving a preventative treatment for COVID-19.[2] This evidence and the data from the ONS study which reported that not all clinically extremely vulnerable patients were continuing to take extra precautions,[4] suggests that there may be a subgroup who are eligible for Evusheld and who would wish to receive it but who are not currently modifying their behaviour and would therefore not benefit from the direct utility gain. The EAG therefore prefers to apply the utility gain estimated by the company ([redacted]) only to the 82% of patients who are currently shielding or taking other precautions according to the ONS study.[4] This approach implicitly assumes no direct utility gain in those not currently modifying their behaviour to avoid COVID-19. The EAG also notes that the company's model assumes that the standard error for the direct utility gain is 20% of its mean value, whereas the utility study suggests a standard error of [redacted] of the mean value is more reasonable based on the data from the whole

cohort. Therefore, the parameter uncertainty associated with the direct utility gain is underestimated in the company's probabilistic analysis.

The EAG considers that this aspect of the economic analysis is subject to considerable uncertainty because the extent to which patients change their behaviour following Evusheld administration is likely to depend on many factors including the perceived effectiveness of Evusheld against currently circulating variants. As previously discussed in the EAG report (Section 4.3.4.4), the confidence patients have in the efficacy of Evusheld to protect them may depend on how the effectiveness of Evusheld is described to patients by their healthcare provider. This in turn is likely to depend on advice from regulatory bodies, such as the recent advice by the EMA that states that monoclonal antibodies targeting the spike protein are poorly effective at neutralising some Omicron strains (BA.4.6, BA.2.75.2 and XBB) and they do not significantly neutralise the BQ.1 and BQ.1.1 strains.[6] To explore the potential impact of this, the EAG has also conducted a scenario analysis in which only [redacted] of patients experience a direct utility gain to reflect the data from the utility study showing that [redacted] of patients would return to their pre-treatment behaviour if there was a new variant that the treatment was not effective against.[2]

2.2 Administration cost for Evusheld

In the original company submission, the company stated that Evusheld administration would require 1.5 hours of General Practice (GP) nursing time including, 30 minutes for administration and 1 hour for observation. In response to clarification question B2, the company stated that this approach did not allow for any efficiencies to be gained by multiple patients being observed simultaneously. They therefore reduced their estimate of primary care nursing time for administration in their base case down to 30 minutes per dose administered. In their additional evidence submitted in response to the EAG report, the company have argued that, "*Evusheld should be prescribed upon specialist advice, and is therefore expected to be administered as part of routine specialist care in a hospital, or via secondary care led community services."* The rationale for this is that, *"specialists would be best placed to make prescribing decisions for Evusheld and would be able to make informed decisions on the basis of the evolving COVID-19 landscape and changing variants."* In addition, the company notes that administration in a hospital setting, or a specialist-led community setting is important to reduce the risk of healthcare associated infections in immunocompromised individuals. The company has therefore updated its approach to replace primary care administration costs with secondary care administration costs. In their updated approach they have applied a cost for 1 hour of a band 5 hospital nurse, equivalent to £41 per dose administered.[7] The company state that this is likely to overestimate the cost because firstly patients will already be visiting specialists as part of routine care, and secondly there are likely to be efficiencies meaning that a 1:1 nurse-to-patient ratio is unlikely.

The company argues that the proxy cost used by the EAG, which was based on an oral medicine administered in a COVID-19 Medicines Delivery Unit (CMDU), is inappropriate because Evusheld does not need to be given urgently when used as a pre-exposure prophylaxis, and therefore the logistical resources required to offer a time-sensitive treatment service to a large number of people would not apply in this case. The company states that Evusheld can be offered as part of patients' routine outpatient appointments, or via secondary care led community services.

EAG critique

The EAG understands the company's rationale for stating that Evusheld should be prescribed upon specialist advice and delivered in a hospital or specialist-led community setting. However, the EAG is not convinced that the allocation of one hour of nursing time per dose administered is sufficient to cover the logistics required to identify and administer Evusheld as a pre-exposure prophylaxis to the 1.8 million patients that the company estimates would be within the target population. The company's approach assumes that Evusheld will be given during the patient's existing schedule of routine appointments. However, given the variety of different treatments and health conditions which would result in a patient being eligible to receive Evusheld, it is not clear that all patients would be receiving routine appointments sufficiently regularly to provide timely administration of Evusheld as part of routine care. Furthermore, it is unclear whether it is practical to have patients receiving a treatment during their outpatient appointment which requires them to be observed for an hour. The average unit cost of an outpatient attendance in a clinical immunology service is £308,[8] therefore the cost of any additional outpatient attendances required to administer Evusheld may be substantially higher than the cost assumed by the company. The EAG is also uncertain whether the administration of Evusheld in secondary care would be categorised as an outpatient procedure rather than being subsumed within routine outpatient appointments. Given these uncertainties, the EAG believes that the full cost of delivering Evusheld is unlikely to be properly accounted for in the company's updated base case. The EAG has therefore maintained its preference for using the CMDU cost (£410) for administering COVID-19 therapeutics,[9] as a proxy for the likely cost of using Evusheld as a pre-exposure prophylaxis. However, the impact of a lower administration cost, using the company's preferred estimate (£41), has been presented by the EAG as a scenario analysis.

2.3 Cost of long COVID

The company has stated that it prefers to apply a cost of £2,500 per annum for long COVID. As discussed in the EAG report (Sections 4.2.6.19 and 4.3.4.16), this was a value used in a scenario analysis in the NICE COVID-19 therapeutics MTA and was a figure that was arbitrarily selected by the EAG to measure the sensitivity of the results to an increase in the costs of long COVID for those patients experiencing organ damage.[10] This figure was not informed by any specific evidence and was not included in the EAG's base case analysis for the COVID-19 MTA. The evidence provided by the

company in support of using this estimate is a quote from a commentator on the MTA (on behalf of the Faculty of Pharmaceutical Medicine) who stated "*We consider this to be huge underestimate – the authors have not considered thrombosis and other conditions more serious than chronic fatigue".*[11] The company also states that the cost of long COVID was considered to be underestimated at the MTA meeting and cites the public slides from the first committee meeting for the COVID-19 therapeutics MTA.

EAG critique

The ACD for the COVID-19 therapeutics MTA states that the clinical experts described how patients with long COVID which developed after being hospitalised with acute COVID-19 may have more severe complications that incur greater costs than those with long COVID who were not hospitalised for their acute COVID-19.[12] The only committee conclusion given in the ACD on the appropriateness of the scenario analyses assuming a higher cost for long COVID was as follows: *"The committee agreed these scenarios had minimal effect on the cost-effectiveness estimates but considered that any new UK-specific evidence on long COVID costs should be included if available."*[12] Therefore, the EAG does not believe that the committee considerations from the COVID-19 MTA support the use of the higher figure in preference to the cost used in the EAG's base case which was based on chronic fatigue. However, the EAG accepts that there will be variation in the costs of managing long COVID, due to the heterogeneity of symptoms that may be experienced.

Since preparing its EAG report, the EAG has been made aware of an alternative UK-based estimate of the cost of chronic fatigue by Hunter et al.[13] This report estimates the annual healthcare costs of long COVID using a weighted average of resource use estimates from four published studies. Hunter et al. report an average total health care cost of £2095 per annum.[13] Inflating this from 2014/15 to 2020/21 prices,[7] gives a cost of £2267 per annum. As the previous estimates of the cost of chronic fatigue (£1,128) was based on a study in the Netherlands,[14] the EAG prefers this UK-based estimate, and has updated its base case to include a long COVID cost of £2267 per annum.

3 Additional economic analyses provided by the company and EAG

This section summarises the economic analyses presented by the company in their additional evidence document and the results of the additional analyses conducted by the EAG in response to the additional evidence. The two scenarios presented by the company and the EAG's preferred updated scenario are summarised in Table 4 in terms of how they differ from the EAG's base case analysis (post FAC version of the EAG report).

3.1 Company 'updated revised EAG base case' analysis

The company has provided what it describes as an 'updated revised EAG base case' in which they have amended the EAG base case, *"to remove the scenarios or amendments implemented by the EAG that are factually inaccurate/implausible,"* and have also incorporated further revisions to reflect the new evidence described above. The key changes included to incorporate the new evidence were as follows:

- Direct utility gain of [redacted] for 100% of patients receiving Evusheld
- Administration cost of £41 to reflect 1 hour of nursing time in secondary care
- Long COVID cost of £2500

The only change from the EAG's post-FAC base case which does not relate to the new evidence is the company's preference to maintain the disutility values applied to patients experiencing long COVID as a constant value for the duration of long COVID. The company raised this during the FAC process, but the EAG did not consider this to be a factual inaccuracy. The EAG preferred to maintain the linear reduction of long COVID related disunities to 50% of their initial value over 5 years, and noted that the linear reduction did not have a large impact on the ICER in the EAG's preferred base case.

3.2 Company's revised base case

The company also presents a revised base case which includes all its preferred data sources and assumptions. It can be seen from Table 4 that these include a mixture of the company's original preferred data sources and assumptions, those included in the EAG's preferred base case (post FAC), and those amended to reflect the additional evidence as described in section 3.1. The main differences from the 'updated revised EAG base case' scenario described in section 3.1 are;

- a higher incidence of long COVID in patients not requiring hospitalisation for COVID-19 (34.8% instead of 12.7%)
- a higher incidence of mechanical ventilation in hospitalised patients (15.4% instead of 4.92%)
- the company's original disutility values for long COVID.

3.3 Additional analyses conducted by the EAG

Whilst conducting analyses in response to the additional evidence submitted by the company, the EAG noted an error in the implementation of their preferred utility values for long COVID, whereby the company's original utility decrements are applied erroneously when selecting the linear reduction option. This error was corrected by the EAG within their updated base case which includes the linear reduction over 5 years for the disutilities associated with long COVID. It does not affect any of the ICERs presented by the company which exclude this linear reduction

The EAG has updated its preferred base case analysis to including the following;

- The estimate of the direct utility gain ([redacted]) from new utility study (Gallop et al.)[2]

- Assumption that the direct utility gain is applied this only to the proportion (82%) who are currently shielding or taking other precautions according to the ONS survey[4]
- Cost of long COVID based on a UK-based estimate of the cost of chronic fatigue[13]
- Correction of the error in the long COVID utilities for non-hospitalised cases of COVID-19 when selecting the linear reduction option

These changes are also summarised in Table 4 **Table *6*** where they can be compared against the company's updated base case.

The individual impact of each of these changes are presented in isolation using the EAG's previous base case as the starting point. These changes have then been combined to provide a revised EAG base case.

The EAG has provided the scenario analyses presented in the original report using the EAG revised base case as its starting point. The EAG has also provided supplementary scenario analyses (scenarios 9 and 10) exploring the impact of the following changes:

- reducing the proportion to which the direct utility gain is applied to [redacted]
- applying the company's preferred administration costs

Table 4: Summary of areas of agreement or disagreement with EAG's post FAC base case analysis (Yes indicates agreement) for the two scenarios presented by the company in their additional evidence and the EAG's updated base case

Aspect of model/ issue identified in the EAG report Section 4.3.4	Company's 'updated revised EAG base case' [a]	Company's updated base case [b]	Revised EAG's base case
EAG corrections to the company's base case - partially amended in response to the FAC	Yes	Yes	Yes
EA1: Varying size of direct utility gain or size of group it is applied for to 13%	New evidence included to update utility gain to [redacted] for 100% of target population	New evidence included to update utility gain to [redacted] for 100% of target population	New evidence included to update utility gain to [redacted] but applied to only for 82% of target population
EA2 Halving the duration of direct utility gain for those infected while on Evusheld	Yes	Yes	Yes
EA3: Assuming 12.7% of the non-hospitalised cohort would develop long COVID	Yes	No – 34.8% as per company's original base case	Yes
EA4: Assuming cost of administration for Evusheld of £410 based on CMDU costing exercise	Amended to £41.00 per administration	Amended to £41.00 per administration	Yes, maintained CMDU costs
EA5: Using the October 2022 update of the ONS data to estimate the duration for long COVID without the Evans 2022 adjustment	Yes	No, maintained company's original preferred approach using original calibrated lognormal from ScHARR MTA	Yes
EA6: Using the long COVID annual costs of £1128 assuming chronic fatigue as proxy	Amended to £2,500 per administration	Amended to £2,500 per administration	Amended to £2267 using an updated estimate of chronic fatigue cost
EA7: Recalculating disutility values due to long COVID and	Removed linear improvement over 5 years but retained EAG's preferred disutility values	No – applied company's original disutility values which are assumed constant for the duration of long COVID	Applied EAG's preferred disutility values and assumed linear improvement over 5 years but also corrected an error in which company

Aspect of model/ issue identified in the EAG report Section 4.3.4	Company's 'updated revised EAG base case' [a]	Company's updated base case [b]	Revised EAG's base case
assuming linear HRQoL improvement by time for 5 years			preferred utilities were applied to non-hospitalised patients
EA8: Using 15.9% as the risk estimate of hospitalisation for infected patients - amended from 9.9% in response to FAC	Yes	Yes	Yes
EA9: Updating hospitalisation reference costs associated with acute admissions	Yes	Yes	Yes
EA10: Reducing proportion of hospitalised patients requiring invasive mechanical ventilation (IMV)	Yes	No – original company base case value retained	Yes
EA11: Applying long COVID to new infections after 1 year - partially amended in response to the FAC	Yes	Yes	Yes

[a] Tables 1 (PAS price) and Table 4 (list price) of the company's additional evidence document
[b] Tables 2 (PAS price) and Table 5 (list price) of the company's additional evidence document
Abbreviations: CMDU, COVID-19 Medicines Delivery Unit; FAC, factual accuracy check; HRQol, health-related quality of life; IMV, invasive mechanical ventilation; ONS, Office for National Statistics

4 Cost-effectiveness results

The results for the two scenarios presented in the company's additional evidence are provided in Table 5 (using the list price for Evusheld). It can be seen that the ICER is close to £20,000 per QALY for the company's 'updated revised EAG base case' which includes some but not all of the EAG's preferences from the original EAG report. The ICER is lower at [redacted] per QALY for the company's updated base case. The largest single factor accounting for this difference is the method used to estimate the duration of long COVID.

Table 5: Cost-effectiveness results for the two scenarios presented in the company's additional evidence document (deterministic)

Option	Life years	QALYs	Costs	Incremental			ICER
				Life years	QALYs	Costs	
Company's 'updated revised EAG base case' [a]							
No prophylaxis	15.14	[redacted]	[redacted]	-	-	-	
Evusheld	14.19	[redacted]	[redacted]	0.05	[redacted]	[redacted]	[redacted]
Company's updated base case [b]							
No prophylaxis	14.88	[redacted]	[redacted]	-	-	-	
Evusheld	14.95	[redacted]	[redacted]	0.07	[redacted]	[redacted]	[redacted]

[a] Tables 1 (PAS price) and Table 4 (list price) of the company's additional evidence document
[b] Tables 2 (PAS price) and Table 5 (list price) of the company's additional evidence document

The results for the EAG's additional analyses are provided in Table 6. It can be seen that changing the size of the direct utility estimate has a smaller impact than increasing the proportion of patients that it is applied to, with the latter reducing the ICER to [redacted] when applied in isolation. The higher long COVID cost has a minimal impact in the EAG's preferred base case because a shorter duration of long COVID is assumed in the EAG's preferred base case than in the company's preferred base case. The correction to the long COVID utility values when applying the linear reduction also has minimal impact. The combined impact of all four changes results in an ICER of [redacted] per QALY for the EAG revised base case when using the deterministic model and [redacted] when using the outputs of the probabilistic sensitivity analysis.

The EAG's exploratory analyses provide ICERs ranging from [redacted] to [redacted], with the ICER being most sensitive to the administration cost for Evusheld and the proportion of patients assumed to experience a direct utility gain.

Table 6: Cost-effectiveness results for the EAG's additional analyses

Option	Life years	QALYs	Costs	Incremental			ICER
				Life years	QALYs	Costs	
EAG's previous base case [a]							
No prophylaxis	15.14	[redacted]	[redacted]	-	-	-	
Evusheld	15.19	[redacted]	[redacted]	0.05	[redacted]	[redacted]	[redacted]
EAG exploratory analysis 1: Varying size of direct utility gain to use company's estimate from the new utility study							
No prophylaxis	15.14	[redacted]	[redacted]	-	-	-	
Evusheld	15.19	[redacted]	[redacted]	0.05	[redacted]	[redacted]	[redacted]
EAG exploratory analysis 2: Vary size of the group the direct utility gain is applied to 82% (13% in previous EAG base case)							
No prophylaxis	15.14	[redacted]	[redacted]	-	-	-	
Evusheld	15.19	[redacted]	[redacted]	0.05	[redacted]	[redacted]	[redacted]
EAG exploratory analysis 3: Applying the updated direct utility gain to 82% (EA1 +EA2)							
No prophylaxis	15.14	[redacted]	[redacted]	-	-	-	
Evusheld	15.19	[redacted]	[redacted]	0.05	[redacted]	[redacted]	[redacted]
EAG exploratory analysis 4: Using long COVID annual costs of £2267 from Hunter et al. assuming chronic fatigue as proxy							
No prophylaxis	15.14	[redacted]	[redacted]	-	-	-	
Evusheld	15.19	[redacted]	[redacted]	0.05	[redacted]	[redacted]	[redacted]
EAG exploratory analysis 5: Correct implementation of long COVID utilities for non-hospitalised cases of COVID-19							
No prophylaxis	15.14	[redacted]	[redacted]				
Evusheld	15.19	[redacted]	[redacted]	0.05	[redacted]	[redacted]	[redacted]
Revised EAG base case applying analyses 1-4 (Deterministic)							
No prophylaxis	15.14	[redacted]	[redacted]				
Evusheld	15.19	[redacted]	[redacted]	0.05	[redacted]	[redacted]	[redacted]
Revised EAG base case applying analyses 1-11 (Probabilistic)							
No prophylaxis	15.20	[redacted]	[redacted]				
Evusheld	15.24	[redacted]	[redacted]	0.05	[redacted]	[redacted]	[redacted]
EAG scenario 1 (PROVENT efficacy data with no impact on hospitalisation risk)							
No prophylaxis	15.14	[redacted]	[redacted]				
Evusheld	15.18	[redacted]	[redacted]	0.05	[redacted]	[redacted]	[redacted]
EAG scenario 2 (baseline characteristics from the immunocompromised subpopulation of PROVENT)							
No prophylaxis	12.94	[redacted]	[redacted]				
Evusheld	12.99	[redacted]	[redacted]	0.04	[redacted]	[redacted]	[redacted]
EAG scenario 3 (assuming 4.2% of the non-hospitalised cohort would develop long COVID)							
No prophylaxis	15.14	[redacted]	[redacted]				
Evusheld	15.19	[redacted]	[redacted]	0.05	[redacted]	[redacted]	[redacted]
EAG scenario 4 (assuming 34.8% of the non-hospitalised cohort would develop long COVID)							
No prophylaxis	15.14	[redacted]	[redacted]				
Evusheld	15.19	[redacted]	[redacted]	0.05	[redacted]	[redacted]	[redacted]
EAG scenario 5 (Using the calibrated October 2022 update of the ONS data to estimate the duration for long COVID with the Evans 2022 adjustment applied to both cohorts)							
No prophylaxis	15.14	[redacted]	[redacted]				
Evusheld	15.19	[redacted]	[redacted]	0.05	[redacted]	[redacted]	[redacted]
EAG scenario 6 (Reducing proportion of hospitalised patients requiring IMV to 2.51%)							
No prophylaxis	15.20	[redacted]	[redacted]				
Evusheld	15.25	[redacted]	[redacted]	0.05	[redacted]	[redacted]	[redacted]

Option	Life years	QALYs	Costs	Incremental			ICER
				Life years	QALYs	Costs	
EAG scenario 7 (Using the daily hospitalisation costs reported in the ScHARR COVID MTA report)							
No prophylaxis	15.14	[redacted]	[redacted]				
Evusheld	15.19	[redacted]	[redacted]	0.05	[redacted]	[redacted]	[redacted]
EAG scenario 8 (Using the company's preferred estimate of the duration of long COVID)							
No prophylaxis	15.14	[redacted]	[redacted]				
Evusheld	15.19	[redacted]	[redacted]	0.05	[redacted]	[redacted]	[redacted]
EAG scenario 9 (Using the company's preferred estimate of the administration costs)							
No prophylaxis	15.14	[redacted]	[redacted]				
Evusheld	15.19	[redacted]	[redacted]	0.05	[redacted]	[redacted]	[redacted]
EAG scenario 10 (Applying the direct utility gain to a smaller proportion [ ])							
No prophylaxis	15.14	[redacted]	[redacted]				
Evusheld	15.19	[redacted]	[redacted]	0.05	[redacted]	[redacted]	[redacted]

[a] as reported in the post FAC EAG report dated 13th December 2022

5 Conclusions

Whilst the company has provided additional evidence on the direct utility gain attributable to reducing shielding behaviours, the EAG still believes that this aspect of the model is subject to considerable uncertainty. The size of the direct utility gain is uncertain because it is dependent on the accuracy of the health state vignette for treated patients which states that patients will, "*no longer need to modify your behaviour to protect yourself from COVID-19*." It is possible that not all patients will stop taking protective measures after receiving Evusheld, meaning that the size of the utility gain estimated in the utility study will be overestimated. The extent to which patients continue to modify their behaviour to protect themselves from COVID-19 will depend on the perceived effectiveness of Evusheld against the variants circulating in the year after it is administered. This is supported by the company's utility study which found that [redacted] of patients would anticipate returning to their pre-treatment behaviour if there was a new variant that the treatment was not effective against.[2] In addition, the cost-effectiveness estimates are very sensitive to the proportion of patients experiencing the direct utility gain and this is dependent on the prevalence and extent of infection avoidance behaviours in the cohort likely to receive Evusheld in clinical practice. The uncertainty related to the estimate of direct utility gain is important because the direct utility gain accounts for 64% of the QALYs gained in the EAG's revised base case analysis. This is demonstrated by the fact that the EAG's revised base case ICER increases from [redacted] to [redacted] when reducing the proportion of patients experiencing a direct utility gain from 82% to [redacted] The EAG believes that a real-world evidence study measuring EQ-5D-5L prospectively in patients receiving Evusheld would be beneficial to reduce the uncertainty associated with this direct utility gain. The EAG also believes that the cost of administering Evusheld is an area of unresolved uncertainty.

The EAG notes that several areas of uncertainty raised in the EAG report have not been addressed by the additional evidence submission and are not explored with the scenario analyses presented by the EAG. These include the lack of evidence on the safety and efficacy of repeat doses of Evusheld, the assumption of a constant treatment effect for 6 months after each dose, uncertainty regarding the efficacy of Evusheld against current and future variants, uncertainty regarding the future risk of COVID-19 in the population eligible to receive Evusheld, and heterogeneity in the characteristics of patients falling within the target population. The EAG refers the reader to section 1 of main EAG report for a more detailed summary of these key issues.

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Tixagevimab–cilgavimab for preventing COVID-19: A Single Technology Appraisal

2nd ADDENDUM

Produced by School of Health and Related Research (ScHARR), The University of Sheffield

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Declared competing interests of the authors

None of the authors have any conflicts of interest to declare.

Additional analyses requested by NICE

As requested by NICE on the 9th Jan 2023, the EAG has performed some additional scenario analyses exploring the following:

1. Reducing the proportion of patients experiencing a direct utility gain to [redacted] of those receiving Evusheld (as per EAG scenario 10 presented in Table 7 of the first addendum to the EAG report)
2. Reducing the efficacy of Evusheld for preventing COVID-19 from a relative risk reduction (RRR) of 66% to a RRR of 33%
3. Combining the changes in (1) and (2) in a single scenario.

The revised EAG base case in the first addendum to the EAG report was used as the starting point for each of these analyses. The reduction in efficacy in additional scenario 2 only applies to the RRR of experiencing COVID-19 for Evusheld versus no prophylaxis. The RRR for hospitalisation given COVID-19 for Evusheld versus no prophylaxis is unchanged from its base case value at 61.8%. However, the absolute risk of hospitalisation for patients receiving Evusheld is affected because a greater proportion of patients experience COVID-19 in this scenario, placing them at risk of hospitalisation. These scenarios are presented as additional exploratory analyses and do not represent a change to the EAG's preferred base case.

The results for each of these additional scenarios are provided in Table 1. They demonstrate that the ICER is sensitive to both the efficacy of Evusheld in preventing cases of COVID-19 and the proportion of patients who experience a direct utility gain. When both these changes are combined in the third additional scenario analysis, the ICER is increased to [redacted].

Table 1: Deterministic cost-effectiveness results for additional scenarios requested by NICE

Option	Life years	QALYs	Costs	Incremental			ICER
				Life years	QALYs	Costs	
Revised EAG base case applying analyses 1-4							
No prophylaxis	15.14	[redacted]	[redacted]				
Evusheld	15.19	[redacted]	[redacted]	0.05	[redacted]	[redacted]	[redacted]
EAG additional scenario 1 (Applying the direct utility gain to a smaller proportion [redacted]) [same as EAG scenario 10 in Table 7 of first addendum]							
No prophylaxis	15.14	[redacted]	[redacted]				
Evusheld	15.19	[redacted]	[redacted]	0.05	[redacted]	[redacted]	[redacted]
EAG additional scenario 2 (reducing the RRR of COVID-19 from 66% to 33%)							
No prophylaxis	15.14	[redacted]	[redacted]				
Evusheld	15.18	[redacted]	[redacted]	0.04	[redacted]	[redacted]	[redacted]
EAG additional scenario 3 (combining EAG additional scenarios 1 and 2)							
No prophylaxis	15.14	[redacted]	[redacted]				
Evusheld	15.18	[redacted]	[redacted]	0.04	[redacted]	[redacted]	[redacted]

National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

EAG report – factual accuracy check

Tixagevimab–cilgavimab for preventing COVID-19 [ID6136]

You are asked to check the EAG report to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies, you must inform NICE by the midday **5th December,** using the below comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

The factual accuracy check form should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Updated company response to draft EAG report

AstraZeneca would like to thank NICE and the EAG for the opportunity to review the draft EAG report.

On 29th November 2022, NICE communicated to stakeholders that the Committee meeting for this appraisal has been brought forward from 14th March 2022 to 24th January 2022, but as a result of this, NICE removed the Technical Engagement step from the appraisal process. AstraZeneca recognises the need to accelerate the appraisal timings to facilitate timely decision making for Evusheld to people in the UK. However, following receipt of the EAG report, AstraZeneca firmly believes that it is necessarily to provide additional evidence to NICE ahead of the rescheduled Committee meeting to directly address a number of key issues identified by the EAG. Therefore, as agreed with NICE:

- As part of this response, we will provide comments that pertain to factual inaccuracy as a consequence of error or misinterpretation.
- Following this response, we will separately:
    - Meet with NICE to agree on the approach and timelines for the provision of further evidence that pertains to directly addressing some of the key issues identified by the EAG; some of these data will have a material impact on the ICER and it is therefore critical that these data are considered in advance of the rescheduled Committee meeting.
- [redacted]
- Following receipt of the new evidence, NICE has agreed that this will be shared with the EAG and an updated EAG report will be issued prior to the NICE Committee Meeting on 24 January 2022

Factual inaccuracies are presented in this document. In particular there are some scenarios presented by the EAG in which factual errors have been highlighted, and the proposed changes and scenarios are not credible or plausible. Below we have listed the scenarios which should not be included or explored in the economic modelling as a consequence:

- **Implementation errors for Issues 5 and 13.** Whilst we agree with some of the proposed correction of errors put forward by the EAG for Issues 5 and 13. A perceived "error" is incorrect in the patient distribution is incorrect and has been misinterpreted by the EAG. See Company Issue 1.

- **EA1: Reducing the proportion of Evusheld patients experiencing a direct utility gain with Evusheld from 100% to 13% of the target population (reflecting shielding patients only):** The target population considers patients who desire a prophylaxis because they are at the highest risk of poor COVID-19 outcomes. To suggest that 87% of this population, who experience fear/anxiety and make lifestyle modifications (other than shielding), would receive zero quality of life benefit with Evusheld is clinically implausible and contrary to evidence observed in similar therapy areas assessed by NICE [TA246(2) and TA769(3)]. The EAG's assumption that benefit can only be conferred to a shielding population has no basis and is factually inaccurate. See Company Issue 2. Note that AstraZeneca will be providing additional evidence to further address this issue following this response.

- **EA7: Assuming linear HRQoL improvement by time for 5 years.** There is no evidence to support the waning of a utility benefit for people treated with Evusheld; the assumptions made by the EAG in their base case are hypothesis generating and therefore it is factually inaccurate to consider such assumptions as a reasonable base case. See Company Issue 3.

- **EA8: Using 9.9% as the risk estimate for infected patients**. The risk of hospitalisation used by the EAG (9.9%) includes patients treated in a CMDU with nMABs and antivirals. As agreed with NICE and the EAG during the decision problem meeting on the 17th of August 2022, treatments under evaluation in TA10936 are not included as comparators nor as subsequent treatments in the model, since these treatments are not in routine commissioning, and therefore the risk of hospitalisation should only be based on patients not treated in a CMDU.(1). See Company Issue 4.

In light of the comments above, we have recreated and amended the ICER table of the EAG report in Section 1.7, page 23 (Table 1) to remove the scenarios or amendments implemented by the EAG that are factually inaccurate/implausible to arrive at a revised EAG base case.

Table 2 presents the company's preferred base case, where errors and more appropriate sources/assumptions have been acknowledged and updated by AstraZeneca accordingly. For reference, the updated revised EAG base case ICER is [redacted], whilst the revised Company's base case ICER is [redacted]. Following the submission of additional evidence and a PAS on 9th December 2022, these ICERs will be updated to address the remaining uncertainties.

Table 1. Company's revised "EAG report Table 2" (EAG base case)

Scenario	Implemented	Incremental cost	Incremental QALYs	ICER
Company base case (Deterministic)	-	[redacted]	[redacted]	[redacted]
EAG's corrected company base case: correcting implementation errors in the company's economic model [included in all subsequent rows]	Partly – the EAG implementation was factually inaccurate	[redacted]	[redacted]	[redacted]
EA1: Varying size of direct utility gain or size of group it is applied for to 13%	No – factually inaccurate	[redacted]	[redacted]	[redacted]
EA2 Halving the duration of direct utility gain for those infected while on Evusheld	Included	[redacted]	[redacted]	[redacted]
EA3: Assuming 12.7% of the non-hospitalised cohort would develop long COVID	Included	[redacted]	[redacted]	[redacted]
EA4: Assuming cost of administration for Evusheld of £410 based on CMDU costing exercise	Included	[redacted]	[redacted]	[redacted]
EA5: Using the October 2022 update of the ONS data to estimate the duration for long COVID without the Evans 2022 adjustment	Included	[redacted]	[redacted]	[redacted]
EA6: Using the long COVID annual costs of £1128 assuming chronic fatigue as proxy	Included	[redacted]	[redacted]	[redacted]
EA7: Recalculating disutility values due to long COVID and assuming linear HRQoL improvement by time for 5 years	Partly – waning over 5 years factually inaccurate	[redacted]	[redacted]	[redacted]
EA8: Using 9.9% as the risk estimate of hospitalisation for infected patients.	Partly – risk during Omicron wave in target population is 15.9%	[redacted]	[redacted]	[redacted]

EA9: Updating hospitalisation reference costs associated with acute admissions	Included	[redacted]	[redacted]	[redacted]
EA10: Reducing proportion of hospitalised patients requiring invasive mechanical ventialiation (IMV)	Included	[redacted]	[redacted]	[redacted]
EA11: Applying long COVID to new infections after 1 year	Partly – the EAG implementation was factually inaccurate	[redacted]	[redacted]	[redacted]
EA12: Assuming reduction in relative efficacy by one-third	Included	[redacted]	[redacted]	[redacted]
EAG's preferred base case applying analyses EA1 to EA11 (minus factual inaccuracies noted in the corrected company base case, EA1, EA7, EA8, and EA11) - deterministic	-	[redacted]	[redacted]	[redacted]

Table 2. Revised company base case

Scenario	Implemented	Incremental cost	Incremental QALYs	ICER (change from company base case)
Company base case (Deterministic)	-	[redacted]	[redacted]	[redacted]
EAG's corrected company base case: correcting implementation errors in the company's economic model [included in all subsequent rows]	Partly – the EAG implementation was factually inaccurate	[redacted]	[redacted]	[redacted]
EA1: Varying size of direct utility gain or size of group it is applied for to 13%	No – factually inaccurate	-	-	-
EA2 Halving the duration of direct utility gain for those infected while on Evusheld	Included	[redacted]	[redacted]	[redacted]
EA3: Assuming 12.7% of the non-hospitalised cohort would develop long COVID	Not included – as per Company base case	-	-	-
EA4: Assuming cost of administration for Evusheld of £410 based on CMDU costing exercise	Not included – as per Company base case	-	-	-
EA5: Using the October 2022 update of the ONS data to estimate the duration for long COVID without the Evans 2022 adjustment	Not included – as per Company base case	-	-	-
EA6: Using the long COVID annual costs of £1128 assuming chronic fatigue as proxy	Not included – as per Company base case	-	-	-
EA7: Recalculating disutility values due to long COVID and assuming linear HRQoL improvement by time for 5 years	Not included – as per Company base case	-	-	-
EA8: Using 9.9% as the risk estimate of hospitalisation for infected patients.	Partly – risk during Omicron wave in target population is 15.9%	[redacted]	[redacted]	[redacted]
EA9: Updating hospitalisation reference costs associated with acute admissions	Included	[redacted]	[redacted]	[redacted]
EA10: Reducing proportion of hospitalised patients requiring invasive mechanical ventialiation (IMV)	Not included – as per Company base case	-	-	-

EA11: Applying long COVID to new infections after 1 year	Partly – the EAG implementation was factually inaccurate	[redacted]	[redacted]	[redacted]
EA12: Assuming reduction in relative efficacy by one-third	Not included – as per Company base case	-	-	-
Company's preferred base case applying appropriate corrections from EA2, EA8, EA9 and EA11 - deterministic	**-**	[redacted]	[redacted]	[redacted]

EAG response

The provision of additional analyses is outside of the remit of the factual accuracy check (FAC) process. Therefore, the EAG has limited its FAC response to the five issues highlighted below by the company.

Table 3. Abbreviations

AIC	Academic in confidence
CIC	Commercial in confidence
CMDU	COVID medicines delivery unit
COVID	Coronavirus disease
COVID-19	Coronavirus disease 2019
EA	Exploratory analyses
EAG	Evidence Assessment Group
ECMO	Extracorporeal membrane oxygenation
EQ-5D	European Quality of Life Five Dimension
HRQoL	Health-related quality of life
ICER	Incremental cost-effectiveness ratio
IMID	Immune-mediated inflammatory disorders
IMV	Intermittent mandatory ventilation
NICE	National Institute for Health and Care Excellence
ONS	Office for National Statistics
QALY	Quality adjusted life year
SARS-Cov 2	Severe acute respiratory syndrome coronavirus 2
SoC	Standard of Care

Company Issue 1 Implementation errors for Issues 5 and 13.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 1.1, Page 4: *"The EAG has corrected several errors in the company's modelling of post year one cases of COVID-19 <u>including ensuring that the level of hospital care required for post year one cases of COVID-19 was the same across those receiving either Evusheld or SoC in year one</u>"* **Section 1.5, Page 20:**	Certain text should be removed and the 'corrected company base case' and EA11 should be updated appropriately throughout the document. Leaving these errors in the EAG's results means that the patient distribution will not sum to one in the Evusheld arm, and will further result in counter-intuitive results for EA11.	Whilst we acknowledge and agree with some of the errors identified by the EAG, the underlined text in the description of problem column is not an error and its implementation in the model has been misunderstood by the EAG. Importantly, the distribution of COVID-19 severity for post year one cases is not based on the treatment received in year one. For re-infection, after year one, an equal cycle risk of re-infection (assumed ~12% in the base case) is applied in each cycle of the long-term Markov to people alive in the Evusheld and no prophylaxis treatment arms. A cost and QALY decrement associated with re-infection is informed by the estimates observed for SoC in the acute phase (from the no prophylaxis decision tree) and applied within the long-term Markov for both Evusheld and no prophylaxis treatment arms. Therefore, the outcomes from re-infection are assumed to be the same across treatment arms and are based	The EAG has reconsidered the issue of how patients who experience a post year one case of COVID-19 are distributed across the hospitalisation health states and it agrees that the company is correct. In response to the company raising this issue the EAG has taken the following actions. 1) The EAG has amended their formulae in cells F33:G33 of the 'Long-term CE Outcomes' sheet to match those in the model provided by the company dated 7th December 2022. 2) The EAG has also excluded the change to the distribution that the company has identified as being an error by setting the flag called "EAG_SameCDAfter1Yr"=0. This has been done in the EAG's corrected company base case and all subsequent analyses which use this as its starting point.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
"The EAG has attempted to estimate the impact of including a risk of long COVID for cases of COVID-19 occurring after the first year" **Section 4.3.4, Page 138:** *"During model verification, the EAG also identified that the distribution of COVID-19 severity (i.e., which patients require hospitalisation and the level of care provided) for the post year one cases of COVID-19 is*		on the severity observed in the no prophylaxis treatment arm. However, the cost-effectiveness model is programmed to generate results across the initial health states i.e., not hospitalised (no assistance needed), not hospitalised (assistance needed), no oxygen therapy, low-flow oxygen therapy, non-invasive ventilation or high-flow oxygen and IMV or ECMO. The model then weights the outcomes from each of the health states based on the initial proportion in each health state (the sum of which equals 100%). This weighting process is based on the initial health state and not on the outcome from re-infection. *Therefore, it is imperative that the weightings based on the initial distribution are maintained based on the original treatment arm. This does not influence the outcomes for people who are re-infected.* In the EAG's amended base case, the EAG weight the costs and QALYs calculated for re-infection by the initial distribution for no	3) All EAG analyses which use the EAG's corrected company base case as its starting point have also been updated in the report (Tables 2, 30 and 31). 4) All text in the EAG report referring to these results have been updated. The impact of these actions in isolation would be to decrease the EAG's corrected company base case from [redacted] to [redacted] and the EAG's preferred base case from [redacted] to [redacted]. However, when combined with the change to the hospitalisation risk described in Issue 4, the EAG's preferred deterministic base case ICER is now [redacted]. The EAG does not believe that the text quoted from page 139 is relevant to the issue raised by the company. However, these

<table>
<tr><th>Description of problem</th><th>Description of proposed amendment</th><th>Justification for amendment</th><th>EAG response</th></tr>
<tr>
<td>based on the treatment received in year one (SoC or Evusheld). The EAG believe that this is an implementation error as it is not consistent with the company's other assumptions regarding post year one cases of COVID-19, in which the risks and outcomes are the same for patients receiving either SoC or Evusheld in the first year..."

Section 4.3.4.18, Page 139:

The EAG estimates that patients who do not experience</td>
<td></td>
<td>prophylaxis in both treatment arms. This is factually incorrect and causes the proportion of patients in the Evusheld arm to not equal one, as shown below.

Evusheld arm distribution for post year one infections
<table>
<tr><th></th><th>EAG method</th><th>Company method</th></tr>
<tr><td>Not infected</td><td>92.32%</td><td></td></tr>
<tr><td>Not hospitalised – no assistance needed</td><td>9.25%</td><td>92.32%</td></tr>
<tr><td>Not hospitalised – assistance needed</td><td>9.25%</td><td>3.57%</td></tr>
<tr><td>Hospitalised - no oxygen</td><td>1.06%</td><td>3.57%</td></tr>
<tr><td>Hospitalised - LF Oxygen</td><td>1.66%</td><td>0.14%</td></tr>
</table>
</td>
<td>estimates were taken from an earlier attempt by the EAG to explore the impact of long COVID being excluded from post year one COVID-19 cases, which was not incorporated in the EAG's final model. As the EAG has not provided the company with the calculations used to generate the LY estimates quoted, this text has been removed from the EAG report.</td>
</tr>
</table>

<table>
<tr><th>Description of problem</th><th>Description of proposed amendment</th><th>Justification for amendment</th><th>EAG response</th></tr>
<tr><td>COVID-19 in year one would be expected to spend [redacted] LYs (undiscounted) in the well state if there is no risk of long COVID for post year cases of COVID-19 (after correcting the modelling of fatal infections). However, when allowing patients to experience long COVID following a post year case of COVID-19, the EAG estimates that patients will spend [redacted] LYs (undiscounted) in the well state and [redacted] LYs (undiscounted) in</td><td></td><td>
<table>
<tr><td>Hospitalised - Non-invasive</td><td>0.73%</td><td>0.22%</td><td></td></tr>
<tr><td>Hospitalised - Invasive/ ECMO</td><td>0.63%</td><td>0.09%</td><td></td></tr>
<tr><td>Total</td><td>115%</td><td>100%</td><td></td></tr>
</table>

This implementation issue is then repeated in the implementation of long COVID for patients who may be infected post year 1 (i.e. scenario EA11).

Whilst AstraZeneca agree patients that are infected post year one should carry the risk of long COVID, the implementation must be based on the initial health states by treatment arm to ensure the proportion of patients in the Evusheld arm sum to one.
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Description of problem	Description of proposed amendment	Justification for amendment	EAG response
the long COVID health state.			

Company Issue 2 EA1: The direct utility gain associated with Evusheld should be applied to 100% of patients in the target population.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 1.3, Page 13: *"The EAG suggests that the direct utility gain should only apply to the 13% of patients in the target population who are currently continuing to follow shielding advice."* **Section 4.4.2.2, Page 142:** *"The EAG has assumed in its base case that the direct utility gain attributed to patients being able to stop shielding will only apply to the 13% of patients currently reported as still*	Update the proportion of patients the utility gain is applied to 100%.	As ratified with several UK clinical experts, the direct utility gain for Evusheld should be applied to 100% of patients in the target population. The target population for Evusheld is the population at the highest risk of poor COVID-19 outcomes with the highest unmet need (see B1.1 and B1.3 of company Submission, Document B). These people would benefit most from the improved protection offered by Evusheld with benefits far broader than changes in shielding, such fewer lifestyle modifications and reduced fear and anxiety. *Importantly, only patients who desire Evusheld as a prophylaxis, and can benefit from treatment, will be offered Evusheld.* To suggest that 87% of patients who desire a prophylaxis and could benefit from Evusheld would have zero utility gain is clinically	This is not a matter of factual inaccuracy. However, the EAG would make the following points in response to the points the company has raised. The company implies that the CANDOUR study measured the quality of life gain achieved by the general public in response to vaccination. This is not the case. The CANDOUR study measured quality of life during the pandemic (using EQ-5D-5L) by surveying participants between 24th November and 17th December 2020 and compared this to pre-pandemic quality of life which was assessed by asking patients to recall their pre-pandemic health state. The company then assumes that the difference between these two values is the utility gain that would be achieved in patients offered Evusheld. Please see Sections 4.2.6.7 and 4.3.4.4 of the EAG report for further details.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
following shielding advice."		implausible and contrary to all evidence observed in relation to this: Evidence 1: For the general population who desired vaccination and were advised they would benefit, improvements in social functioning and mental wellbeing following vaccination rollout were stark and dramatic; estimated as [redacted] from the CANDOUR study.(4) This is despite the fact that individuals would not know their personal level of protection with vaccination, only that it had been shown to be effective at a cohort level. Evidence 2: The application of a direct utility gain to all patients follows a similar approach accepted by NICE in TA246 (2) and TA769 (3) in the use of a treatment which could improve outcomes from allergies to bee/wasp venom and peanuts, respectively. Therefore, the direct utility gain for Evusheld should be applied to 100% of the target population, which desire and could benefit from treatment. Assuming 13% of shielding patients would only receive such a benefit is	The EAG believes that the size of any direct quality of life improvement, the group it applies to and the duration it applies for will be dependent on many factors (see EAG report Section 4.3.4.4). These factors are specific to this treatment, its indication and the characteristics of the population it is offered to. Therefore, assumptions that are applied in other appraisals may not be relevant.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
		implausible and therefore factually inaccurate.	

Company Issue 3 EA7: There are no data to support a utility waning effect, and any such assumptions are hypothesis generating scenarios

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 1.3, Page 18: *"The EAG has also assumed that the utility decrements for long COVID linearly decline over 5 years to 50% of their starting value based on the approach used in a company scenario analysis."*	Without evidence of a timepoint for waning, or the magnitude of any such waning, this assumption cannot form a plausible base case, and should be retained as an exploratory scenario.	The linear reduction scenario created by the company was presented at the request of the EAG, as part of the EAG clarification questions. As noted in the response to B.13 at the Clarification Questions stage of the process, there is no evidence which suggests that waning is appropriate and waning of utilities for people with long COVID has not been documented in any of the identified literature. Further to this, the data available from Evans 2022(5), which is also presented in detail as	The EAG does not believe that this is a matter of factual inaccuracy. As stated in the EAG report (page 16), *"the long-term trajectory of recovery (i.e., > 2 years) is inherently uncertain because long COVID is a condition which has only been diagnosed since 2020."* It is therefore necessary to make some assumptions regarding the future trajectory of utility in patients with long COVID. The EAG accepts that the utility values for patients in the PHOS-COVID cohort (Evans 2022) who report that they are not fully

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 4.4.2.8, Page 143: *"In addition, the EAG base case adopts the linear reduction scenario created by the company, as described in Section 4.2.6.18."*		part of the response to clarification question B.13 indicates that of the evidence that is available, the indication is that there is a prolonged and sustained impact on HRQoL. Given that this scenario is exploratory – like the scenario included by the EAG in response to consultation comments for long-COVID-19 in the MTA, but not included in the base case – not evidence based, and the linear decrease in utility is arbitrary both in terms of timing and magnitude, it is factually inaccurate for the EAG to consider this as a reasonable base case.	recovered from COVID-19 are similar at 5 and 12 months. However, the EAG also notes that the mean duration of long COVID in the company's analysis is 6.2 years for hospitalised patients and 8.9 years for non-hospitalised patients. These durations are much longer than the 1-year follow-up provided in the PHOS-COVID study. Therefore, assuming a constant utility decrement for the duration of long COVID is itself a strong assumption. The EAG prefers to assume some improvement over time and has therefore included in their preferred base case scenario a linear reduction in the utility decrement over 5 years to 50% of its 1-year value. Taking the EAG's preferred base scenario (after the amendments made in response to Issue 1 and Issue 4), and excluding the linear reduction (but including all other EAG preferences) reduces the ICER from [redacted] to [redacted]. Therefore, the EAG accepts that this is an area of uncertainty for discussion by the committee, but notes that the importance of this assumption is minimal

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
			if the EAG's preferences regarding the duration of long COVID are accepted.

Company Issue 4 EA8: Using 9.9% as the risk estimate of hospitalisation for infected patients includes patients outside the target population for prophylaxis treatment with Evusheld

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 1.5, Page 19: *"Shields et al. also reported that the risk of hospitalisation was lower for patients infected during the period when Omicron was dominant compared to those infected in earlier waves (9.9% vs 41.5% for prior variants)."*	The company request that the EAG amend the risk of hospitalisation in patients to 15.9%.	Firstly, we acknowledge that the EAG has used the Shields et al. publication(1) and amended the proportion of patients hospitalised to reflect the period when Omicron was dominant. We agree with the principle behind this. However, the figure proposed (9.9%) includes patients during the Omicron wave who were treated in a CDMU, which includes patients treated in a CMDU with nMABs and antivirals. As agreed with NICE and the EAG during the decision problem meeting on the 17th of	The EAG agrees that the estimate excluding patients who received COVID-19 therapeutics in CMDUs is more applicable given that COVID-19 therapeutics are not currently covered by routine commissioning. The EAG has updated their preferred base case to use the 15.9% risk of hospitalisation suggested by the company. This change has been implemented in the model by changing the value in cell M31 of the 'EAG_Qu' sheet from 9.9% to 15.9%.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 4.3.4.6, Page 126: *The EAG believes that it is possible that hospitalisation risk may now be much lower than observed in the cohort reported by Shields et al. Shields et al. report that within their immunocompromised cohort, hospitalisation rates were significantly lower during the Omicron wave 9.9% vs 41.5% for prior variants.*		August 2022, treatments under evaluation in TA10936 are not included as comparators nor as subsequent treatments in the model, since these treatments are not in routine commissioning.(6) Therefore, only patients during the Omicron wave who were not treated in the CDMU (15.9%) should be considered for use in the economic model.	This change was made after correcting the error described in Issue 1. The EAG notes that making this change in the hospitalization rate (9.9% to 15.9%) reduces the ICER for the EAG's preferred base case from [redacted] to [redacted]. All scenario analyses that use the EAG preferred base case as their starting point (EAG scenarios 1 to 8) have also been updated accordingly in the post FAC version of the EAG report.

Company Issue 5 Typographic error of HRG codes

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 4.4.2 Page 143: *"The HRG code of "COVID-19 infection [DX01A]" (£2,764) was assumed to apply to patients not on oxygen and the HRG code for "COVID-19 infection, with pneumonia [DX11A]", was assumed to apply to patients requiring low-flow oxygen (£3,160). Both were estimated as the average across non-elective short and long stay spells. The reference cost for "COVID-19 infection, with major manifestations [DX21A]" (£4,493)*	*"The HRG code of "COVID-19 infection [**DX21A**]" (£2,764) was assumed to apply to patients not on oxygen and the HRG code for "COVID-19 infection, with pneumonia [DX11A]", was assumed to apply to patients requiring low-flow oxygen (£3,160). Both were estimated as the average across non-elective short and long stay spells. The reference cost for "COVID-19 infection, with major manifestations [**DX01A**]" (£4,493) was applied to patients requiring critical care to*	The HRG codes listed refer to the wrong currency description. The correct code and description are listed below: • DX21A- COVID-19 Infection, 19 years and over • DX01A- COVID-19 Infection, with Major Manifestations, 19 years and over	Thank you for identifying these typographical errors which have been corrected as suggested.

was applied to patients requiring critical care to cover the period prior to critical care admission."	*cover the period prior to critical care admission."*		

References

1. Shields AM, Tadros S, Al-Hakim A, Nell JM, Lin MMN, Chan M, et al. Impact of vaccination on hospitalization and mortality from COVID-19 in patients with primary and secondary immunodeficiency: The United Kingdom experience. Frontiers in Immunology [Internet]. 2022 [cited 2022 Oct 13];13. Available from: https://www.frontiersin.org/articles/10.3389/fimmu.2022.984376

2. National Institute for Health and Care Excellence. Evidence | Pharmalgen for the treatment of bee and wasp venom allergy | Guidance | NICE [Internet]. NICE; 2022 [cited 2022 Aug 9]. Available from: https://www.nice.org.uk/guidance/ta246/evidence

3. National Institute for Health and Care Excellence. NICE TA769: Palforzia for treating peanut allergy in children and young people [Internet]. 2022. Available from: https://www.nice.org.uk/guidance/ta769

4. Violato et al. The impact of the COVID-19 pandemic on health-related quality of life: a cross-sectional survey of 13 high and low-middle income countries (In press). In press. 2022;

5. Evans R, Leavy O, Richardson M, Elneima O. Clinical characteristics with inflammation profiling of Long-COVID and association with one-year recovery following hospitalisation in the UK: a prospective observational study. medRxiv. 2022;

6. UK Government. Defining the highest-risk clinical subgroups upon community infection with SARS-CoV-2 when considering the use of neutralising monoclonal antibodies (nMABs) and antiviral drugs: independent advisory group report [Internet]. [cited 2022 Jul 14]. Available from: https://www.gov.uk/government/publications/higher-risk-patients-eligible-for-covid-19-treatments-independent-advisory-group-report/defining-the-highest-risk-clinical-subgroups-upon-community-infection-with-sars-cov-2-when-considering-the-use-of-neutralising-monoclonal-antibodies

7. NHS England. COVID-19 Medicine Delivery Units (CMDUs) Clinical Triage & Assessment: Neutralising monoclonal antibodies (nMABs) or antivirals for non-hospitalised patients with COVID-19.

Single Technology Appraisal

Tixagevimab–cilgavimab for preventing COVID-19 [ID6136]

EAG report post FAC and EAG addendum – factual accuracy check and confidential information check

"Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release." (Section 5.4.9, NICE health technology evaluations: the manual).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **12pm on Wednesday 11 January 2023** using the below comments table.

All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and separately highlight information that is submitted as 'commercial in confidence' in turquoise, all information submitted as 'academic in confidence' in yellow, and all information submitted as 'depersonalised data' in pink.

Issue 1 EA4: The administration cost of Evusheld is not aligned to its deployment in clinical practice

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
The updated EAG report and the EAG critique of the additional evidence both reference the application of an administration cost of £410 for Evusheld based on CMDU. Examples are as follows EAG report post-FAC **Section 4.3.4.2, Page 124** *"The SPC states that "administration should be under conditions where management of severe hypersensitivity reactions, such as anaphylaxis, is possible".[17] This implies the availability of other members of the GP team to deal with the immediate management and transfer to*	Whilst the EAG has not accepted our updated position on the estimated costs of administration, AstraZeneca has since received a revised BIT from NICE/NHSE in which NHSE has reduced the administration cost from £410 to £216. On this basis, whilst we believe this is still likely to overestimate the costs, NICE and the EAG should update the costs to align with those used by NHSE.	NHS England has reduced the cost of administration assumed in the BIT calculations from £410 to £216. Therefore, NICE and the EAG should align with the administration costs provided by NHSE to inform model inputs.	NICE has informed the EAG that the budget impact assessment and cost-effectiveness assessments are separate processes and the technology appraisal team has not received any further information from NHS England about administration costs. Therefore, no changes are needed in the EAG's addendum

secondary care of any patient experiencing anaphylaxis" *"The EAG would argue that the logistical resource required to administer Evusheld to the estimated 1.8 million eligible patients identified by the company as being within the target population (CS, B1.3.5, page 20) would be substantial and may be better estimated by considering the cost for administering COVID-19 therapeutics in the community through COVID Medicine Delivery Units (CMDUs)."* *"In reality, the EAG expects that some form of coordinated provision would need to be set up for the administration of Evusheld, to the 1.8 million patients that the company estimate would be eligible, and this would fall outside of any existing agreements for routine care by primary care providers, or routine vaccinations within*			

primary care. Therefore, the incorporation of administration costs from CMDUs is explored in the EAG's exploratory analysis (see Section 4.4.2.5) as a proxy for the provision likely to be required to administer Evusheld." **Section 4.4.2.5, Page 143** *"Therefore, the EAG applied a cost of £410 per dose administered in their base case analysis."* <u>EAG critique of additional evidence</u> **Section 2.2, Page 11** *"The EAG has therefore maintained its preference for using the CMDU cost (£410) for administering COVID-19 therapeutics,[9]"*			

Issue 2 EA7: There are no data to support a utility waning effect, and any such assumptions are hypothesis generating scenarios

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
The updated EAG report and the EAG critique of the additional evidence both reference applying a linear decline in utility decrements for long COVID-19 over 5-years in the EAG base case. Examples are as follows EAG report post-FAC **Section 1.5, Page 18:** *"The EAG has also assumed that the utility decrements for long COVID linearly decline over 5 years to 50% of their starting value based on the approach used in a company scenario analysis."*	Without evidence of a timepoint for waning, or the magnitude of any such waning, this assumption cannot form a plausible base case, and should be retained as an exploratory scenario.	The Company FAC of the initial EAG report presented robust and comprehensive argumentation as to why it is not appropriate to include waning in the base case. Please see FAC submitted on the 7th December 2022 for full details (updated on 3rd January 2023)	This issue has been raised by the company previously and was responded to by the EAG at that time. Please refer to the previous response by the EAG.

Section 4.4.2.8, Page 144: *"In addition, the EAG base case adopts the linear reduction scenario created by the company, as described in Section 4.2.6.18."* <u>EAG critique of additional company evidence</u> **Section 3.1, Page 13:** *"The EAG preferred to maintain the linear reduction of long COVID related disutilities to 50% of their initial value over 5 years"*			

Issue 3 Typographical error

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 2.1.2, Page 9, Section 3.3, Page 13	The utility value of [redacted] should be change to [redacted].	The company used a utility value of [redacted] and not [redacted] in the model. This change will also ensure	The NICE team have agreed to update these values

The EAG critique of additional company evidence report has made a typographical error on the utility gain value applied by the company. These sections note a utility value of [redacted], this should be [redacted].		consistency throughout the document.	

From: [redacted]
Sent: 12 January 2023 14:48
To: Ross Dent <Ross.Dent@nice.org.uk>; [redacted]
Cc: [redacted]
Subject: RE: Clarification on Evusheld repeat dosing

Dear Ross

With thanks to MHRA colleagues:

With regard to Evusheld, efficacy data have been provided to the MHRA from single dose studies only. This is stated in the SmPC section 4.2. Adequate safety or efficacy data to support a repeat dose have not been presented to the MHRA to date.

Kind regards
[redacted]

[redacted]
Innovative Medicines Group - Healthcare, Quality and Access Divsision
Medicines and Healthcare products Regulatory Agency (MHRA)
10 South Colonnade, Canary Wharf, London E14 4PU
Direct line: [redacted]
[redacted]

From: Ross Dent <Ross.Dent@nice.org.uk>
Sent: 11 January 2023 13:40
To: [redacted]
Cc: [redacted]
Subject: Clarification on Evusheld repeat dosing

Dear all,

For the technology appraisal of Evusheld for preventing COVID-19, the company have modelled the intervention as Evusheld (600 mg) administered as an initial dose and again at 6 months. We are aware that that the Summary of Product Characteristics states “Evusheld has only been studied in single-dose studies. There are no safety and efficacy data available with repeat dosing”.

In previous verbal discussions with MHRA colleauges, you have indicated that you consider what the company has modelled for the technology appraisal to be outside of the current marketing authorisation for Evusheld. AstraZeneca believe that a repeat dose of Evusheld after 6 months is not precluded by the licence wording. The company are aware that NICE can only make recommendations that are within the marketing authorisation.

Please could you confirm that my understanding is correct. If it is, it would be very helpful to have a written clarification from the MHRA that we can include in the papers for the committee meeting.

Best wishes,
Ross

Ross Dent

Associate Director – Technology Appraisals
National Institute for Health and Care Excellence
Level 1A | City Tower | Piccadilly Plaza | M1 4BT | United Kingdom
Tel: [redacted]
Web: https://www.nice.org.uk/

INDEPENDENT ADVISORY GROUP (IAG) REPORT

Concerning the use of COVID-19 directed antibodies in the prophylaxis setting in the highest risk clinical subgroups.

Draft submitted 21 July 2022 by Iain B McInnes, Chair, on behalf of the IAG

1. Description of approach taken by the Independent Advisory Group (IAG).

This group was previously constituted to identify a set of patient conditions (or cohorts) that are deemed to be at the very highest risk of an adverse COVID outcome. The advisory group was asked to generate:

(i) a list of conditions/cohorts in order of greatest risk

(ii) identify a clinically useful list of people with such conditions that might by way of clinical advantage, render them recipients of neutralising monoclonal antibodies (nMABs) prophylaxis.

The advisory group was formed under Terms of Reference contained in our prior report to the CMO and constituted a range of clinical academics with requisite expertise, and some of whom had participated in the COVID-19 nMABs Access and Policy National Expert Group. Particular attention was paid to develop a diverse and inclusive group to represent the clinical subgroups necessitous of consideration based on the prior recommendations of the COVID-19 nMABs Access and Policy National Expert Group. Similarly, our methodology has been previously described in that report.

All meetings were conducted online, and additional interactions took place electronically to derive consensus statements. All were chaired by Prof Iain McInnes, University of Glasgow. These meetings took place by means of Zoom in December 2021 through 14th April 2022.

2. Overarching principles agreed by the independent advisory group

For this exercise we adopted the same approach as that adopted previously. This is summarised briefly as follows:

- As reported before, the IAG agreed to work towards ensuring consistency with the policies formed by the COVID-19 Neutralising Monoclonal Antibodies (nMABs) Access and Policy National Expert Group. That group had identified ten clinical groups at risk, but at a general level. We re-examined the QCOVID risk stratification tool as had been previously applied by that nMABs group. The QCOVID3 risk stratification tool is derived from a population-based cohort record linkage study that used primary care data to derive and validate risk prediction algorithms to estimate risk of COVID-19 mortality and hospitalisation in UK adults following one or two doses of COVID-19 vaccination. In this respect it interrogated the population most relevant to our commissioned task. Critically, as this dataset had not altered in the interim it meant that our focus remained upon the prioritized groups set out below. This also ensured continuity with the prior advice received for policy setting. In addition, the advisory group evaluated additional data from ISARIC Coronavirus Clinical Characterisation Consortium (https://ISARIC4C.net). The IAG accepted the principle previously established that once risk magnitude was established for a given (set of) condition(s), consideration was given to clinical capacity to benefit from introduction of a nMAB, or of an anti-viral. We did not conduct a conventional systematic literature review due to limitations of time and resource, but nevertheless performed a thorough literature review of clinical and immunologic functional studies that informed the likelihood of vaccine

efficacy in the distinct clinical subgroups. The advisory group also sought data from cohort datasets in preparation e.g. renal datasets, haematologic datasets to optimise the contemporaneous nature of our advices. This literature is contained in Appendix 2. It is notable that much risk evaluation is based on data emerging prior to the emergence of the Omicron variant of SARS-CoV-2. Moreover, several data sources were also derived prior to widespread booster or 3rd vaccination.

- The advisory group discussed in detail the potential for serology to support decision making. Precise serological correlates of protection against SARS-CoV-2 remain undefined, but data from SIREN and elsewhere shows that authentic live virus neutralising antibody titre is strongly associated with protection from infection. Most commercially available assays deployable at scale measure titres of binding antibody to the original Spike glycoprotein, and this is variably correlated with neutralisation of the current Omicron variant. Nationally funded studies such as SIREN (healthcare workers), VIVALDI (care home residents) and OCTAVE (immunosuppressed patients) have compared Roche and/or MSD anti-S with live virus neutralisation performed at the Francis Crick Institute (SIREN, VIVALDI) and the University of Oxford (OCTAVE). There are considerable uncertainties and extrapolation between platforms and variants is required to make an estimate of a protective titre. ***Across all these studies Spike binding titres corresponding to Roche anti-S titre above 4000 BAU/ml are predicted to be strongly associated with measurable neutralising antibodies against Omicron BA.1***.

- An interim recommendation for the application of serology testing therefore could be that if anti-S titres are to be used to identify patients who would most benefit from prophylactic neutralising antibodies then an appropriately timed measurement of 4000 BAU/ml on the Roche assay (or equivalent on an alternative platform) could be used as a threshold. This is above the usual dynamic range of these assays (250 BAU/ml for Roche), so this will necessitate sample dilution. The IAG also considers that serology testing would be most useful if applied across all groups in Group B as defined in the Table below.

- Further work defining the correlation between neutralising antibody titre, Spike binding and infection in different immunocompromised populations is required, as are investigations of the kinetics of waning in these groups. Monoclonal antibodies vary substantially in neutralising capacity between BA.1 and BA.2 and it is unclear what dosing regimes will be required for protection, or indeed against future emerging VoC. To inform ongoing recommendations as new variants emerge, tightly defined correlates of protection for neutralising monoclonals in animal models (such as the Syrian hamster model available at NIBSC) would be helpful.

- The advisory group recognised that most current evidence and approval of existing agents applies to individuals aged 18 and over. Nevertheless, we have offered advisory notes in the event that appropriate approvals for use emerge for individuals aged < 18 yrs. Given the substantially lower risk of severe disease in this age group, clinician discretion is advised for Groups A1, A2 and Group B, and the presence of multiple co-morbidities in addition to primary risk diagnoses may be required to reach the threshold for use of prophylactic treatment

3. Summary of our recommendations concerning pre-exposure prophylaxis

The following recommendations should be read as a prioritised list[1]. Thus, group A contains

[1] Update January 2023: This list is being reconsidered further. An update will be available in due course.

those conditions for which we consider there is high priority for prophylaxis. Group B defines a group of conditions in which consideration of prophylaxis might be given and which may be influenced by other co-morbidities for example, or definition of their serology status when this becomes widely available. Group C defines conditions in which prophylaxis is unlikely to be of added value given current state of knowledge.

Group	Description
Group A1 – Known failure of vaccination	• Person in any risk group unable to complete vaccination schedule according to contemporaneous recommendations[2] • Person in any risk group with one or more admissions due to moderate or severe COVID-19 despite completing recommended vaccinations
Group A2 – Anticipated failure of vaccination	• Any person with primary immunodeficiencies with impairment of antibody production[3] • Any person with secondary immunodeficiency receiving, or eligible for, immunoglobulin replacement therapy • Any person receiving anti-CD20 monoclonal antibodies or other B cell depleting therapy (including ATG and alemtuzumab) within the last 12 months • Allogeneic haematopoietic stem cell transplant (HSCT) recipients in the last 12 months or with active graft versus host disease (GVHD) regardless of time from transplant (including HSCT for non-malignant diseases) • Autologous HSCT recipients in the last 12 months (including HSCT for non-malignant diseases) • Any person receiving CAR-T cell therapy in the last 24 months • Any person with myeloma (excluding MGUS) or chronic B-cell lymphoproliferative disorders (e.g. chronic lymphocytic leukaemia, follicular lymphoma) or AL amyloidosis or myelodysplastic syndrome (MDS), or chronic myelomonocytic leukaemia (CMML) or myelofibrosis, who do not fit the criteria above • Solid organ transplant recipients
Group B – Anticipated sub-	• Any person with haematological malignancies

[2] People who have not yet completed their vaccination schedule should, wherever possible and appropriate, receive the necessary vaccinations in preference to commencing pre-exposure prophylaxis

[3] Primary immunodeficiencies include: common variable immunodeficiency (CVID), Undefined primary antibody deficiency on immunoglobulin (or eligible for Ig), Hyper-IgM syndromes, Good's syndrome (thymoma plus B-cell deficiency), Severe Combined Immunodeficiency (SCID), X-linked agammaglobulinaemia (and other primary agammaglobulinaemias)

optimal vaccination response: physician discretion advised	receiving systemic anti-cancer treatment (SACT) within the last 12 months, not already covered in A2. • Metastatic or locally advanced inoperable cancer • Lung cancer (at any stage) • People receiving any chemotherapy (including antibody-drug conjugates), PI3K inhibitors or radiotherapy[4] within 12 months • People who have had cancer resected [5]within 3 months and who received no adjuvant chemotherapy or radiotherapy • People with immune mediated inflammatory diseases (IMIDs) on biologics[6] or small molecule JAK-inhibitors (except anti-CD20 depleting monoclonal antibodies) or who have received these therapies within the last 6 months • People with IMIDs who have been treated with cyclophosphamide (IV or oral) in the 6 months prior to positive PCR • People with IMIDs who are on current treatment with mycophenolate mofetil, oral tacrolimus, azathioprine/mercaptopurine (for major organ involvement such as kidney, liver, *intestinal* and/or interstitial lung disease), methotrexate (for interstitial lung disease or inflammatory bowel diseases) and/or ciclosporin • People with IMIDs who exhibit at least one of: (a) uncontrolled/clinically active disease (i.e. required recent increase in dose or initiation of new immunosuppressive drug or IM steroid injection or course of oral steroids within the 3 months prior to positive PCR); and/or (b) major organ involvement such as significant kidney, liver or lung inflammation or significantly impaired renal, liver and/or lung function. • People who are on corticosteroids (equivalent to $\geq$ 10 mg/day of prednisolone) for at least the 28 days prior to positive PCR • People with CKD 4 or 5 • People with Liver cirrhosis (Childs Pugh A, B and C cirrhosis)

[4] Patients with thyroid cancer who have undergone radio-iodine ablation will be eligible for treatment

[5] Patients with basal cell carcinomas who have undergone local excision or topical treatment are not considered to be at sufficiently high risk to be eligible for treatment

[6] People on monotherapy with biologics as maintenance therapy in IMIDs (including anti-IL17A, anti-IL-6R, anti-BLyS, anti-TNF, anti-IL12/23, vedolizumab and abatacept) appear not be at significantly increased risk of severe COVID-19 on available evidence but may have variable responses to currently available vaccines; physician discretion is advised in the context of patients in receipt of combination immune modification.

	• Allogeneic or autologous stem cell transplant recipients beyond 12 months and without active GVHD • People with HIV infection with CD4 < 350 cells/mm3 OR not on treatment OR evidence of failure of treatment • People with Down's syndrome or other chromosomal disorders known to affect immune competence
Group C – Anticipated good vaccination response: unlikely to require prophylaxis	• People with sickle cell disease, thalassaemia or other inherited anaemia • People with rare neurological conditions (e.g. motor neuron disease, multiple sclerosis, myasthenia gravis or Huntington's chorea), unless on immunosuppression as defined in other groups • People who have had cancer resected within 3-12 months and receiving no adjuvant chemotherapy or radiotherapy. • People living with HIV stable on treatment (suppressed viral load) with CD4 >350 cells/mm3

4. Explanatory Notes and Research requirements

(i) The IAG has offered a provisional recommendation for serology testing in section 2 above. Clinicians should be aware that the recent administration of immunoglobulin products and anti-SARS-CoV-2 monoclonal antibodies are likely to result in false-positive results on serological assays.

(ii) Current data on pre-exposure prophylaxis is derived exclusively from studies on unvaccinated individuals prior to the advent of the Omicron variant. Coupled with this, pre-exposure prophylaxis has not been systematically evaluated in the majority of high-priority groups. The decision to administer pre-exposure prophylaxis to an individual should be regularly reviewed taking into account changes in treatment, disease status, vaccination recommendations and COVID-19 epidemiology

(iii) Consideration should be given to waning immunity which may differ among groups.

(iv) Although severe COVID-19 is uncommon in children and young people, children under 1 year of age are more likely to be admitted to hospital than other age groups. Predisposing factors for severe disease in this age group include age 0-3 months, prematurity and co-morbidities including immunocompromise and pulmonary disease (in particular, a baseline oxygen requirement. On the basis of the currently available evidence, and in the absence of an available SARS-CoV-2 vaccine for children under 5 years of age, if licensed, pre-exposure prophylaxis with a long-acting monoclonal antibody could be recommended as follows:

a. children under 9 months of age with chronic lung disease (defined as requiring oxygen for at least 28 days from birth) and who were born preterm;

b. children under 6 months of age with haemodynamically significant, acyanotic

congenital heart disease who were born preterm.

c. It may also be considered for:

- children under 1 year of age who require long-term ventilation
- children 1–2 years of age who require long-term ventilation and have an additional co-morbidity (including cardiac disease or pulmonary hypertension).

Where there is a licensed product for use in the prophylactic setting in children and young people aged 18 years and under, decisions to administer prophylaxis in this cohort should be discussed on a case-by-case basis with a paediatric multidisciplinary team.

(v) Prophylaxis should be offered to pregnant women if they are in any of the risk groups listed in this document, especially if they have additional risk factors as identified in the RCOG COVID-19 Guidance. Pregnancy in itself should not be a barrier to administering prophylaxis, particularly as outcomes are worse for the patients and the baby with severe COVID-19 infection. Although the majority of pregnant women are likely to have mild illness with COVID-19, it would be reasonable for clinicians to consider the following risk factors for severe COVID-19 in pregnant patients when making decisions regarding the administration of prophylaxis:

a. Unvaccinated pregnant women
b. Pregnant women from Black, Asian or other minority ethnic backgrounds
c. Pregnant women with a BMI >25
d. Pregnant women with a significant pre-pregnancy co-morbidity
e. Pregnant women aged 35 years or older

Appendix 1. Membership of the Advisory Group

Professor Iain McInnes (Chair)	Vice Principal and Head of College. College of Medical, Veterinary & Life Sciences, University of Glasgow
Professor Carl Goodyear	Professor of Translational Immunology, University of Glasgow
Dr Rupert Beale	Immunologist and clinical nephrologist, Clinical Researcher at Crick Institute
Professor Julia Hippisley-Cox	Professor of Clinical Epidemiology and General Practice, Chair COVID Risk Stratification Subgroup, NERVTAG
Professor Eleanor Barnes	Professor of Hepatology and Experimental Medicine Nuffield Department of Medicine, University of Oxford OUH Hospital NHS Trust
Dr David Lowe	Consultant Clinical Immunologist, Royal Free Hospital
Dr Siraj Misbah	Consultant Immunologist and Chair, Blood and Infection Programme of Care, NHS England
Dr Matthias Schmid	Consultant Physician & Head of Department Infection & Tropical Medicine, The Newcastle Upon Tyne Hospitals NHS Foundation Trust, Chair of Clinical Reference Group Infectious Diseases, NHS England
Professor Gavin Screaton	Head of Medical Sciences Division, University of Oxford
Professor Calum Semple	Professor of Child Health and Outbreak Medicine at University of Liverpool, Consultant Respiratory Paediatrician at Alder Hey Children's Hospital. Chair CO-CIN (a SAGE Subgroup), and NERVTAG member.
Professor Martin Underwood	Professor of Primary Care Research Warwick Clinical Trials Unit, Warwick Medical School
Professor Lucy Wedderburn	Professor in Paediatric Rheumatology, University College London
Dr Elizabeth Whittaker	Honorary Clinical Senior Lecturer Faculty of Medicine, Department of Infectious Disease, Imperial College London
Professor Matthew Snape	Professor in Paediatrics and Vaccinology, Oxford Vaccine Group
Dr Thushan de Silva	Senior Clinical Lecturer and Honorary consultant Physician in Infectious Diseases, University of Sheffield
Professor Paul Moss	Professor of Haematology, University of Birmingham
Dr Sean Lim	Associate Professor and Honorary Consultant in Haematological Oncology, University of Southampton

Professor Gary Middleton	Professor of Medical Oncology, University of Birmingham
Professor Emma Thomson	Professor in Infectious Diseases, University of Glasgow
Professor Jack Satsangi	Professor of Gastroenterology, University of Oxford
Professor Anthony Kessel (supporting)	Clinical Director National Clinical Policy, Specialised Commissioning NHS England & Improvement
Dr Dhivya Subramaniam (supporting)	National Clinical Policy Fellow, NHS England and NHS Improvement

Co-opted Members of the Advisory Group

Professor Stefan Siebert	University of Glasgow, Professor of Inflammation Medicine and Rheumatology
Professor Tariq Ahmed	University of Exeter, Consultant Gastroenterologist
Dr Nick Kennedy	University of Exeter, Consultant Gastroenterologist
Dr Nick Powell	Imperial College London, Consultant Gastroenterologist
Dr Paul Cockwell	University Hospital Birmingham, Consultant Physician
Dr Charlie Tomson	North Bristol NHS Trust, Consultant Nephrologist
Dr Katie Vinen	Kings College Hospital NHS Foundation Trust
Dr Michelle Willicombe	Imperial College Healthcare NHS Trust, Consultant Nephrologist
Dr Stephen McAdoo	Imperial College London, Consultant Nephrologist
Dr Laurie Tomlinson	London School of Hygiene & Tropical Medicine, Consultant Nephrologist
Dr Edward Carr	The Francis Crick Institute, Post-doctoral Clinical Fellow
Dr Tom Marjot	Oxford University NHS Trust, Clinical Fellow in Hepatology
Dr Jane Collier	Oxford University NHS Trust, Consultant Hepatology
Professor Kwee Yong	University College London Hospitals, Professor of Clinical Haematology
Professor Claire Harrison	Guy's and St Thomas' Hospital, Professor of Myeloproliferative Neoplasms
Professor Baba Inusa	Chair, National Haemoglobinopathy Panel, England; Professor of Paediatric Haematology and Sickle cell

	disease, Guy's and St Thomas NHS Foundation Trust
Dr Josh Wright	Consultant Haematologist, Sheffield Teaching Hospitals NHS Foundation Trust; Lead Clinician North East and Yorkshire Haemoglobinopathy Coordinating Centre
Prof Carlo Palmieri	Professor of Translational Oncology & Medical Oncologist, Molecular & Clinical Cancer Medicine, University of Liverpool

Appendix 2. Bibliography that informed the current panel deliberations and reported in detail in prior IAG report, March 2022.

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NICE National Institute for Health and Care Excellence

In vitro data on neutralising monoclonal antibodies for COVID-19: interim methods framework

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Background

NICE has published a suite of guidelines on COVID-19. We are also developing a multiple technology appraisal (MTA) on therapeutics for people with COVID-19, and a single technology appraisal (STA) on tixagevimab plus cilgavimab for preventing COVID-19. The MTA includes the neutralising monoclonal antibodies (nMAbs) casirivimab plus imdevimab, sotrovimab and tixagevimab plus cilgavimab for treating COVID-19 in people with severe COVID-19 or mild COVID-19 at high risk of progressing to severe disease. The STA covers tixagevimab plus cilgavimab for pre-exposure prophylaxis of COVID-19 in people who are unlikely to mount an adequate immune response to COVID-19 vaccination or in people for whom COVID-19 vaccination is not recommended.

The SARS-CoV-2 virus that causes COVID-19 evolves over time resulting in new variants and subvariants. Current clinical-effectiveness evidence for nMAbs is from clinical trials conducted before the Omicron variant became the predominant variant. Because the SARS-COV-2 virus is evolving rapidly, it is difficult to do clinical trials in real time. This means clinical trials on new variants will not be completed in time to help us understand how effective nMAbs are against those variants before the virus evolves again. It is also unlikely that findings from observational studies will be reported in the timeframe required to inform decision-making. We therefore need to develop methodology to help understand whether nMAbs developed for a previous variant can be used for people infected with, or at risk of infection with, a newer variant.

With little clinical trial and observational data on the efficacy of nMAbs against newer variants, policy makers are using in vitro data. In vitro data is generated from laboratory studies outside of a living body and usually involves cell culture. For these reasons, in vitro studies are not thought to fully replicate the conditions seen in humans, and the evidence type and quality differs from

clinical trial evidence. In vitro data on nMAbs is from laboratory studies investigating their neutralisation effect on cells infected with the COVID-19 variant of interest.

In general, some in vitro data suggests that some nMAbs may have reduced neutralisation against some of the more recent variants in circulation, such as the Omicron variant and subvariants. We are in a position where we need timely decisions on whether these nMAbs should be recommended for pre-exposure prophylaxis and treatment of COVID-19. However, the clinical-effectiveness and in vitro data cover different situations because clinical-effectiveness data was obtained when previous COVID-19 variants were dominant and in vitro data has been generated from newer circulating variants. The fundamental challenge for decision-making is around how in vitro data translates into clinical and health economic outcomes in the absence of clinical studies in people infected with, or at risk of infection with, new COVID-19 variants.

This document outlines a framework to assist technology appraisal and guideline committees in making these decisions.

Scope of this framework

This framework applies to in vitro data on neutralising monoclonal antibodies for pre-exposure prophylaxis or treatment of COVID-19 only. Although there has been some suggestion that antivirals (for example, paxlovid) could work differently against different variants, this hasn't transpired to date and therefore, the principles outlined here do not cover those treatments.

How this framework was developed

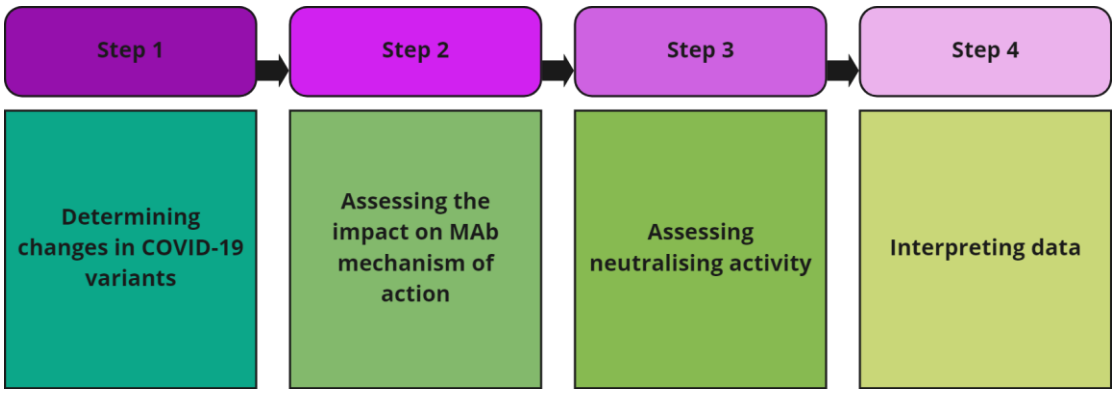
In December 2022, NICE established an in vitro data expert advisory group (IVAG, see Appendix 1) including people with expertise in using and understanding COVID-19 in vitro data or making clinical and health economic

decisions in the setting of uncertainty. The main aims of this group were to advise on translating in vitro evidence on neutralising activity of nMAbs into clinical and health economic outcomes to aid decision-making for NICE guidance. This is to determine when nMAbs are likely to be less effective or ineffective in the event of a new variant emerging, and to describe the uncertainty around those decisions. The group also advised on the type of data required to inform decision rules and how to use the data. The group met 4 times during December 2022 and the discussions were used to generate this interim framework and decision rules.

This is a living framework and will be updated as new information emerges.

Framework overview

Figure 1: summary of key considerations for using in vitro data on the effectiveness of nMAbs against new variants



Step 1: Determining changes in COVID-19 variants

Anticipated future trajectory of circulating variants

The IVAG acknowledged the uncertainty around predicting the incidence of future variants, with reduced COVID-19 testing in the UK adding to this uncertainty. However, reflecting on the patterns and emergence of previous variants, the IVAG anticipated that the following principles will apply:

- It is certain that new SARS-CoV-2 variants will emerge with significantly different antigenic properties. It is also possible but less likely that new variants will have different properties in terms of transmissibility, cell tropism and disease severity. It is expected that there will continue to be 2 types of evolution of the virus: 1) frequent incremental changes leading to small changes in antigenicity and 2) infrequent antigenic shifts leading to selective sweep of a new fit variant.
- There is a certain level of standing genetic diversity which can fluctuate over time and 'changes' to viral genotype are a continuous process. Historically there has been a major sweep approximately every 6 months. What constitutes a major sweep of a new lineage is somewhat subjective. Less dramatic changes are a continuous process; at any given time, some lineages will be growing and slowly replacing other lineages. Antigenically similar previous variants are unlikely to re-emerge because of population immunity but cannot be ruled out. It is possible that a new lineage could emerge which is partially or completely ancestral to a previous lineage like Delta, but this would likely be antigenically distinct.
- A future variant could be neutralised by a given nMAb where this hasn't been observed for previous variants.

Based on the above assumptions, the IVAG supports steps for regular monitoring of the emergence of variants and determining whether further action is needed.

Surveillance and identification of new emergent variants

The UK Health Security Agency (UKHSA) has a surveillance system in place for monitoring the emergence of changes to COVID-19 variants. This intelligence will be shared with NICE.

Additionally, the World Health Organization (WHO) defines variants of concern as those meeting the following criteria:

- increase in transmissibility or detrimental change in COVID-19 epidemiology, or
- increase in virulence or change in clinical disease presentation, or
- decrease in effectiveness of public health and social measures or available diagnostics, vaccines and therapeutics.

The WHO also has a list of variants which it monitors. NICE will also use this information as a source of intelligence. However, it's recognised that the WHO's information isn't always relevant to the UK because there have been previous variants of concern recognised by WHO (for example, Beta) that have been important globally but have never become dominant in the UK.

Monitoring increasing prevalence of a variant (or subvariant)

Variants of interest are typically antigenically different from previous variants and generally exhibit 'immune escape', that is, the person's immune system is no longer able to recognise and eliminate the virus. For this reason, the variants tend to quickly increase in prevalence across a population over a period of weeks to months.

Threshold for determining a new 'dominant' variant (or subvariant)

Predicting when a variant will become dominant is a complex task and depends on expert interpretation of evidence regarding the relative growth rates of cocirculating variants and interpretation of functional mutations in novel variants. There is also a distinction between genetic difference (such as a genetic shift away from a predominant variant) and immune escape, which links to the ability of a subvariant to increase in prevalence and replace other variants. The IVAG indicated that it is usually clear if a variant will replace others once it has reached about 10% sample frequency and has a logistic growth rate of over 25% per week. Intelligence from the UKHSA and the WHO

should indicate which variants are emerging and increasing in prevalence and should be used as a trigger to move to the next step in this framework.

Actions in this step of the framework:

- UKHSA shares surveillance intelligence on emerging variants that it anticipates will increase in prevalence or become dominant in the UK.
- NICE considers the UKHSA data in addition to the WHO's information on variants of concern.
- NICE, with input from the UKHSA, will decide whether there has been a step-change in variants from those which informed the decisions when the guideline recommendations were developed.

Decision point: If a new variant is becoming dominant, NICE will move to the next step on assessing impact on nMAb mechanism of action.

Step 2: Assessing impact on monoclonal antibody mechanism of action

Monoclonal antibodies and mechanism of action

Monoclonal antibodies have different mechanisms of action in terms of which proteins they bind to, meaning they can neutralise the SARS-CoV-2 virus in different ways. This is important when considering the monoclonal antibody of interest. Some treatments include a combination of 2 antibodies and it is possible that one but not the other may retain activity against a variant. NICE is evaluating the clinical and cost effectiveness of 3 nMAbs; these have the following reported mechanism of action against the SARS-CoV-2 virus:

- **Casirivimab plus imdevimab (Ronapreve)** is a combination of 2 non-competing recombinant human IgG1 monoclonal antibodies. This combination targets 2 distinct epitopes (the part of the virus to which the nMAbs attach) binding simultaneously to the S protein receptor binding

domain. Casirivimab plus imdevimab block the virus's interaction with the angiotensin-converting enzyme 2 (ACE2) receptor that is used by the virus to enter host cells.

- **Sotrovimab (VIR-7831)** is a dual-action, engineered human IgG1 monoclonal antibody that binds to a conserved epitope on the spike protein receptor binding domain of SARS-CoV-2. Amino acid substitutions in the Fc region result in a median half-life of 49 days while retaining the ability of the antibody to recruit effector functions.
- **Tixagevimab and cilgavimab (Evusheld)** is a combination of 2 recombinant human IgG1 monoclonal antibodies, with amino acid substitutions in the Fc regions that extend antibody half-life. Tixagevimab plus cilgavimab have longer half-lives of 87.9 and 82.9 days respectively. Tixagevimab and cilgavimab can simultaneously bind to non-overlapping regions of the spike protein receptor binding domain of SARS-CoV-2.

The IVAG noted that the nMAbs exhibit dose-linear and proportional pharmacokinetics across the range of doses at which they've been studied. What this generally means in practice is that if the dose is doubled, the concentrations in serum are doubled, and if the dose is halved then the concentration in serum is halved.

The majority of currently available nMAbs were developed in the context of early SARS-CoV-2 variants. Some in vitro data has shown that many of them may be less effective at neutralising newer variants resulting in a perception that they may work less well in people infected with or exposed to new variants.

Considering the mechanism of action of nMAbs with relation to new variants, NICE sought advice from the IVAG to determine whether it is likely that nMAbs could retain neutralising activity. For example, if a specific nMAb target epitope is lost in a new variant, this could be a potential trigger for considering whether neutralisation activity is reduced or lost.

Based on their experience, the IVAG indicated that:

- Neutralisation activity of combination treatments may be more resilient to changes in variants because they tend to have a broader mechanism of action.
- Drug-selected resistance has been observed during use against susceptible variants (up to Omicron BA.1).
- Marked reductions in neutralisation have been reported since Omicron BA.2 and subsequent sub-lineages emerged.
- Neutralisation can also be compromised when mutations occur outside of the specific epitope because of the overall impact on protein structure.

Actions in this step of the framework:

- Determine whether the nMAbs' mechanism of action is still effective against the new variant.
  - The main impact is expected when a variant has a mutation eliminating the target epitope of the nMAb or a mutation outside of the specific epitope that compromises neutralisation.
  - Assessment of impact will require a combination of evidence on mechanism of action and expert input.

Decision point: If there is a potential impact on the effectiveness of the nMAbs' mechanism of action move to next step of assessing neutralising activity.

Step 3: Assessing neutralising activity

Determining the evidence base

NICE requires in vitro data to inform discussions on whether the nMAbs included in NICE guidance still have neutralising activity against the new dominant variants. NICE's search strategy for identifying published evidence

is outlined in Appendix 2. NICE may obtain additional data from the UKHSA, regulators and manufacturers of nMAbs.

Relationship between in vitro neutralisation data and clinical effectiveness

Neutralisation assays are considered the gold standard for determining antibody efficacy against viruses. The results of these in vitro ELISA assays, usually reported as the 50% and 90% effective concentrations (EC50 and EC90), tell us the concentration of drug needed to neutralise 50% or 90% of the virus. The goal of neutralisation is not necessarily to neutralise the virus completely, but to reduce the growth rate of the virus to below a self-sustainable level. The IVAG indicated that different nMAbs may remain effective despite having reduced neutralising activity against a different variant than that prevalent when the clinical trial which led to marketing authorisation was done. This may occur if the concentration of the treatment used in clinical practice is, for example, 100-fold higher than that needed to reduce the viral level. In this example, the nMAbs may have a similar effect on viral growth rate even if there is a 100-fold reduction in neutralising activity against a new viral variant compared with original studies against older variants. In an attempt to maximise a positive outcome in clinical trials some companies have used the highest dose possible initially followed thereafter by lower doses. For example, a clinical trial on casirivimab plus imdevimab used doses of 8.0 g, 2.4 g and 1.2 g (O'Brien et al. 2021).

This is important to note when considering the neutralising activity of the nMAbs.

The gold standard for assessing clinical effectiveness of medicines is through blinded randomised clinical trials (RCTs). In the absence of RCTs on the effectiveness of nMAbs against new SARS-CoV-2 variants, we need to establish whether there could be a plausible link between in vitro neutralisation data and clinical and health economic outcomes. While there is

no consensus on the exact relationship between in vitro neutralisation data and clinical outcomes for COVID-19 (such as reducing hospitalisation rates or mortality), the IVAG concluded that it's plausible that an association exists. The main reason for this conclusion is because scientists have consistently used in vitro neutralisation data to select antibodies and doses for further testing in RCTs for several decades of antiviral pharmacological research. The IVAG noted, however, that a link between in vitro data showing a fold change in neutralisation activity against newer variants and clinical outcomes is difficult to establish because of how a new variant may impact disease severity.

One of the key methodological steps in the usual process of reviewing evidence of clinical effectiveness is to appraise the clinical trials to critically to assess quality and robustness, risk of bias and generalisability. There is no validated tool for appraising in vitro neutralisation data. Therefore, the IVAG discussed key components of quality for studies on in vitro neutralisation and identified important characteristics to consider when assessing studies. The IVAG was also aware of the ongoing work of the Department of Health and Social Care Antivirals and Therapeutics Taskforce which aims to standardise aspects of in vitro neutralisation studies.

Key components of in vitro neutralisation studies

Virus and cell lines

In vitro neutralisation studies typically use either pseudovirus or live virus. Pseudoviruses do not replicate and have their surface envelope proteins replaced with those of SARS-CoV-2. The IVAG agreed that it preferred studies using live SARS-CoV-2 virus but acknowledged that both types of virus were associated with uncertainty. The IVAG agreed that in vitro data from pseudovirus generally agrees with in vitro data from live virus, and the advantage is that results from pseudovirus are generated quicker.

The IVAG noted it is also important that the cell line used for viral culture has been clonally selected and that the batch of virus has been sequenced, characterised and reported in the studies. This would enable NICE to assess the consistency across studies.

Reproducibility of assays

The IVAG agreed that in vitro neutralisation assays should be reproducible, so studies should clearly detail the methods used.

Different manufacturers of nMAbs assume different degrees of tissue penetration, and some, but not all, companies also include a margin of error (up to 10-fold) in their assays. According to the IVAG, few companies use EC50 because inhibiting only 50% of replication is not a recognised basis for efficacy of medicines to prevent or treat viral illnesses, and EC90 is at least 9-fold higher than EC50.

The IVAG concluded that EC50 values would be acceptable to initially assess whether an nMAb has lost efficacy against new variants relative to older variants. But, when detailed pharmacokinetic and pharmacodynamic (PK/PD) assessments are needed, EC90 should be used.

Repeatability of results

When new SARS-CoV-2 variants emerge, it is likely that numerous groups of scientists will generate and publish in vitro data. The IVAG considered it important that results are broadly consistent across studies. The IVAG noted, however, that fold-differences in neutralisation between different variants have generally been more reproducible than the absolute concentrations of nMAb required for neutralisation.

Comparator

The IVAG discussed that in vitro neutralisation studies should report fold change in EC50 against the new variants relative to the ancestral or reference variants.

Measuring uncertainty in the results

The IVAG discussed that using 95% confidence intervals (95% CIs) when reporting EC50 and EC90 point estimates would be helpful for measuring uncertainty in the results. For example, comparing 2 absolute EC50 values without a 95% CI could be misleading. However, the IVAG acknowledged that 95% CIs are not always reported in the literature.

Actions in this step of the framework:

- Search for in vitro data to determine if there are any studies that report neutralisation data for nMAbs against new variants of interest.
- Determine the quality and reproducibility of the data using the appraisal approach outlined in Appendix 3.

Decision point: If there is in vitro data available that is of sufficient quality and reproducible, move to next step of interpreting the data.

Step 4: Interpreting changes to in vitro neutralisation by monoclonal antibodies

In vitro data presentation

There are generally 2 presentation types for in vitro data used in the published literature: heat maps (for example, as shown in Wang et al. 2022) and concentration dose–response curves (for example, as shown in Planas et al. 2022). These present the concentration of nMAbs needed to neutralise the variant in vitro to a stated degree (for example, EC50). Heat maps show the nMAbs drugs in columns, and the variants in rows. A red colour represents a loss of neutralising activity while no colour reflects maintained neutralising activity. A dose–response curve plots drug concentration on the x axis as a function of percent viral inhibition on the y axis. With separate plots per treatment, each neutralisation curve reflects neutralisation activity of therapeutic monoclonal antibodies against variants of interest. Although the

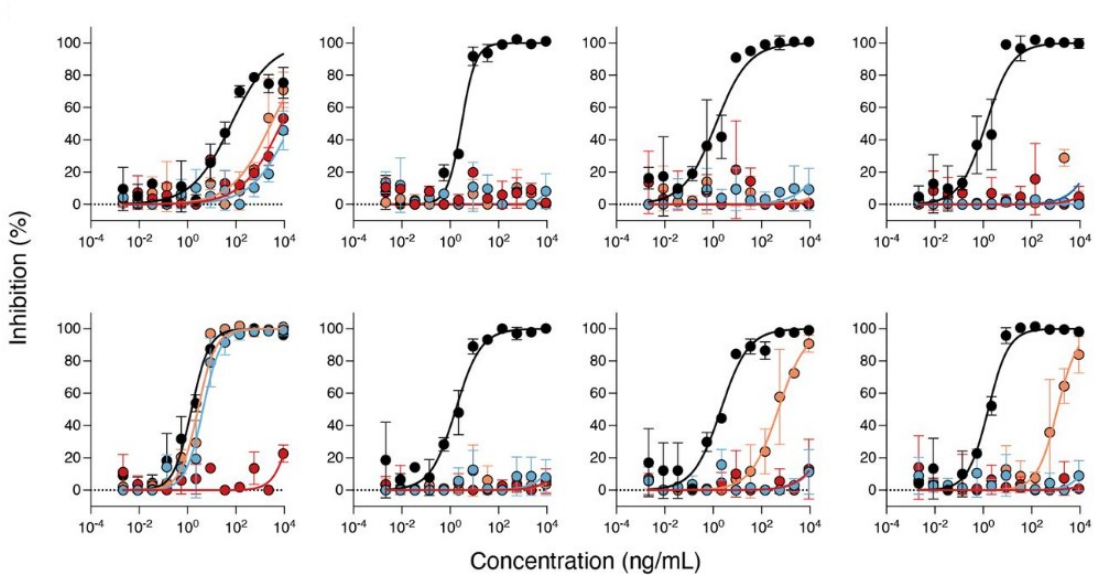
IVAG acknowledged that heat maps provide a good summary of a lot of data, the IVAG concluded that it preferred dose–response curves because they provide more information. Specifically, they enable assessment of whether the slope of the concentration response curve changes between variants. If the slope changes (showing that higher concentrations of nMAbs are needed to retain neutralisation), the EC90 moves even further away from the EC50 and, in some cases, the nMAb cannot achieve EC90.

Figure 2. Example heatmap from [Wang et al. 2022.]

IC$_{50}$ (μg/ml)	NTD	NTD-SD2	SD1	RBD Class 1				RBD Class 2				RBD Class 3											RBD Class 4	Evusheld
	C1520	C1717	S3H3	S2K146	Omi-3	Omi-18	BD-515	XGv051	XGv347	ZCB11	COV2-2196	LY-CoV1404	XGv289	XGv264	S309	P2G3	SP1-77	BD55-5840	XGv282	BD-804	35B5	COV2-2130	10-40	
D614G	0.002	0.125	0.022	0.004	0.004	0.012	0.010	0.001	0.002	0.002	0.002	0.002	0.002	0.001	0.023	0.001	0.003	0.002	0.001	0.011	0.014	0.007	0.049	0.003
BA.4/5	0.001	0.209	0.014	0.090	0.023	0.013	0.010	0.050	3.450	4.868	>10	0.001	0.038	0.002	0.514	0.002	0.005	0.009	0.001	0.019	>10	0.021	2.414	0.035
BQ.1	0.001	0.666	0.019	0.585	0.860	0.131	0.343	0.159	2.830	>10	>10	>10	0.425	0.494	0.600	1.608	>10	0.034	0.020	>10	>10	>10	>10	>10
BQ.1.1	0.003	1.117	0.025	0.527	0.804	0.170	0.377	0.191	3.311	>10	>10	>10	1.013	>10	2.140	>10	>10	>10	0.093	>10	>10	>10	>10	>10
BA.4/5-R346T	0.002	0.141	0.009	0.081	0.019	0.009	0.006	0.042	2.166	2.560	>10	0.001	0.045	0.003	1.726	0.041	>10	1.447	0.001	>10	>10	>10	5.069	>10
BA.4/5-K444T	0.002	0.116	0.009	0.104	0.016	0.010	0.006	0.040	4.766	3.731	>10	>10	0.161	0.273	0.552	1.245	4.007	0.038	0.006	>10	>10	>10	6.976	>10
BA.4/5-N460K	0.002	1.166	0.016	0.542	1.279	0.186	0.431	0.152	3.046	>10	>10	0.002	0.353	0.003	0.934	0.003	0.009	0.012	0.002	0.122	>10	0.030	>10	0.063
BA.2	0.002	0.561	0.016	0.028	0.015	0.005	0.012	0.001	0.003	0.012	1.924	0.001	0.067	0.003	0.833	0.002	0.006	0.014	0.001	0.036	0.827	0.009	8.770	0.019
XBB	>10	0.836	0.016	0.223	1.181	0.468	0.555	>10	>10	>10	>10	>10	>10	>10	0.343	>10	>10	>10	>10	>10	>10	>10	>10	>10	>10
XBB.1	>10	0.693	0.019	0.190	1.705	0.605	0.803	>10	>10	>10	>10	>10	>10	>10	0.405	>10	>10	>10	>10	>10	>10	>10	>10	>10	>10
BA.2-V83A	0.001	0.354	0.015	0.036	0.019	0.007	0.015	0.002	0.003	0.013	3.039	0.001	0.070	0.002	0.641	0.002	0.007	0.019	0.001	0.045	1.274	0.011	>10	0.025
BA.2-Del144	0.002	0.501	0.011	0.026	0.016	0.004	0.011	0.002	0.002	0.008	4.134	0.001	0.063	0.002	0.455	0.002	0.005	0.014	0.001	0.031	0.341	0.010	8.766	0.021
BA.2-H146Q	0.001	0.356	0.011	0.032	0.011	0.004	0.009	0.002	0.002	0.010	2.924	0.002	0.055	0.002	0.641	0.003	0.007	0.019	0.001	0.044	1.107	0.009	9.106	0.019
BA.2-Q183E	0.002	0.307	0.019	0.034	0.018	0.006	0.014	0.002	0.003	0.013	3.098	0.001	0.067	0.003	0.649	0.002	0.008	0.020	0.002	0.028	1.019	0.011	9.251	0.022
BA.2-V213E	0.002	0.406	0.013	0.030	0.014	0.004	0.010	0.002	0.002	0.006	2.177	0.001	0.047	0.003	0.720	0.002	0.006	0.014	0.001	0.026	1.247	0.009	8.198	0.018
BA.2-G252V	0.001	0.577	0.013	0.030	0.012	0.004	0.008	0.002	0.003	0.008	2.258	0.001	0.048	0.002	0.564	0.002	0.005	0.012	0.001	0.032	0.939	0.011	>10	0.026
BA.2-G339H	0.001	0.485	0.017	0.034	0.020	0.006	0.012	0.002	0.002	0.010	3.876	0.002	0.114	0.002	0.302	0.002	0.007	0.040	0.002	0.050	0.661	0.012	8.575	0.023
BA.2-R346T	0.003	0.372	0.012	0.017	0.010	0.003	0.007	0.001	0.002	0.007	2.109	0.002	0.048	0.004	1.433	0.007	>10	1.442	0.001	0.112	>10	>10	7.767	1.486
BA.2-L368I	0.003	0.453	0.019	0.027	0.010	0.004	0.010	0.002	0.001	0.006	2.603	0.001	0.030	0.002	0.605	0.002	0.005	0.021	0.001	0.026	0.324	0.008	3.202	0.018
BA.2-V445P	0.001	0.433	0.019	0.026	0.009	0.004	0.009	0.002	0.002	0.008	2.313	>10	>10	1.141	0.428	>10	0.007	0.144	>10	1.582	0.486	>10	6.311	3.135
BA.2-G446S	0.002	0.367	0.012	0.021	0.009	0.004	0.009	0.001	0.003	0.008	2.614	0.002	0.026	0.004	0.686	0.002	0.004	0.014	0.022	0.026	0.965	0.017	5.774	0.029
BA.2-N460K	0.002	1.323	0.012	0.132	0.784	0.013	0.358	0.007	0.004	0.073	1.756	0.001	0.355	0.003	0.878	0.002	0.011	0.017	0.001	0.058	1.957	0.013	>10	0.025
BA.2-F486S	0.002	0.677	0.008	>10	0.583	0.011	0.017	>10	>10	>10	>10	0.001	0.049	0.003	0.581	0.002	0.006	0.009	0.002	0.060	2.264	0.011	>10	0.023
BA.2-F490S	0.001	0.428	0.014	0.022	0.033	0.004	0.008	0.001	0.004	0.012	1.105	0.001	0.030	0.002	0.564	0.002	0.006	0.011	>10	0.048	>10	0.013	5.337	0.016
BA.2-R493Q	0.003	0.338	0.024	0.005	0.006	0.006	0.006	0.001	0.001	0.002	0.034	0.001	0.045	0.002	1.109	0.002	0.007	0.022	0.000	0.010	1.175	0.010	3.419	0.008

>10	1-10	0.1-1	0.01-0.1	<0.01

Figure 2. Example concentration dose–response curves from Planas et al. 2022



In vitro neutralisation activity interpretation

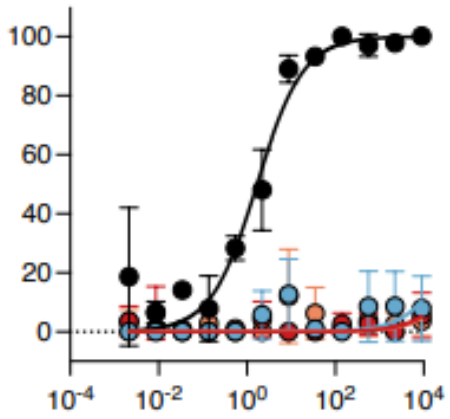
The IVAG discussed different scenarios (see table 1) of changes in neutralising activity against variants compared to the reference strains. It concluded that some scenarios had a clear interpretation that could inform recommendations made by technology appraisal or guidelines committees. These scenarios are when there can be no plausible argument for continuing efficacy for the antibodies against a new variant (see table 1). However, there will also be scenarios where the fold change in neutralising activity, particularly at higher concentrations of drugs, will be harder to interpret without further information. The IVAG indicated that if the in vitro data shows a fold change, but in vitro neutralisation is still achieved at concentrations that could be achieved in serum, then the nMAb may still be effective at a higher dose. However, the IVAG considered that this may require higher dosages than licensed and acknowledged that NICE must make recommendations based on the licensed dose only.

Table 1: Scenarios for changes in the in vitro neutralising activity relative to the reference variant (either ancestral variant or predominant variant in pivotal RCT) - applicable to prophylaxis and treatment

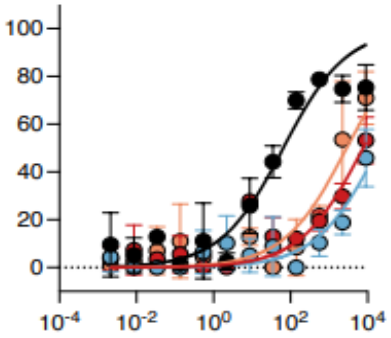
Scenario	Agreed action	Rationale
No or minimal fold change in neutralising activity relative to the reference variant	Use existing RCT evidence for decision-making	We are confident that the neutralising activity has been minimally impacted therefore the conclusions from the RCT hold
No or minimal neutralising activity at very high concentrations	Move to decision to not recommend a nMAb	These concentrations could not be achieved in the body Clear in vitro evidence that nMAbs will not be clinically effective (or by extension cost effective)
Some neutralisation at higher concentration, but substantial fold change compared with the reference variant	Insufficient information to make a decision	If there is a substantial fold change, PK/PD data is needed to attempt linking of the data to clinical outcomes

Visualising the scenarios

The following example from Planas et al. 2022 shows no or minimal neutralising activity at very high concentrations for the variants in blue and red compared with the black reference variant:



The following example from Planas et al. 2022 shows some neutralisation at higher concentrations:



Pharmacokinetic and pharmacodynamic (PK/PD) data

The IVAG stated that simply interpretating the fold-difference in an nMAb's ability to neutralise a variant without considering the compartmental pharmacokinetics, including how the drug interacts in different bodily compartments, does not give a complete picture.

In general terms, the plausibility of continued efficacy of a nMAb against new viral variants requires consideration of the plausibility of the antibody still achieving sufficient neutralisation activity in patients, and this requires an understanding of the pharmacokinetics. The nMAbs exhibit dose-linear and

proportional pharmacokinetics. What this means in practice is that if the dose is doubled, the concentrations in serum are doubled, and if the dose is halved then the concentration in serum is halved. The IVAG indicated that there is an important step in understanding the compartmental pharmacokinetics that correspond to the clinical-effectiveness measures achieved in RCTs. This includes the doses of nMAbs needed to neutralise and how a double dose that doubles the concentration in serum, for example, might overcome an expected fold reduction of neutralisation in vitro.

The IVAG concluded PK/PD data is required to try to link in vitro neutralisation data to clinical outcomes where there is a substantial fold change but some neutralisation is retained in vitro. Without this data, it is not possible to determine how this fold change may be associated with clinical outcomes.

The IVAG considered it essential to know the minimum concentration required to neutralise the ancestral (or reference) viral strain and if this differs from the licensed dose of a nMAb treatment. If this dose was substantially above the minimum concentration, then there is potentially still a tolerance to accommodate a large fold reduction in neutralisation in vitro. If the neutralisation activity achieved by the dose was close to the minimum needed for effectiveness in the ancestral (or reference) viral strain, then there is a high possibility that even a small fold change in neutralisation would render the nMAb clinically ineffective.

The IVAG agreed that clinical trials reporting failed doses provide important information. Although they did note that the more data points presented, the more confidence this adds to the dose-clinical response relationship. From this data we know what concentration of drug or level of neutralisation of virus the investigators found to be clinically ineffective. Unfortunately, for most nMAbs, IVAG acknowledged that this PK/PD data is not available, and suggested that the regulators and NICE should encourage companies to

collect this data in registrational trials to allow rapid assessment based on in vitro data.

Differences between the monoclonal antibodies

The IVAG noted that there is some in vitro data showing that tixagevimab and cilgavimab for pre-exposure prophylaxis of COVID-19 does not neutralise newer dominant variants of the virus. According to the IVAG, sotrovimab shows some neutralisation if the concentration used in vitro is increased. However, the higher concentrations of sotrovimab needed to inhibit some variants in vitro were much larger than the drug dosages used in published RCTs. Additionally, the IVAG indicated that the mechanism of sotrovimab differs from other nMAbs and that it may have additional beneficial effects beyond neutralisation through 'effector functions'. The IVAG acknowledged that this may be an additional benefit, but is hard to quantify. Overall, the IVAG concluded that evidence of in vitro neutralisation is a necessary requirement, and evidence of an effector function effect alone is insufficient to conclude clinical benefit.

Actions in this step of the framework:

- Use the appraised in vitro data to determine which scenarios from table 1 apply.
- Use the scenarios outlined in table 1 to determine the appropriate action.
- Seek expert advice on interpreting in vitro data and the proposed action.

Decision point: There are 3 outcomes in this step of the framework:

1. No or minimal fold change in neutralising activity of a drug against a viral variant relative to the ancestral variant: no action needed; continue to monitor.
2. No or minimal neutralising activity at very high concentrations: determine if need to update recommendation.

3 Some neutralisation at higher concentrations, but substantial fold change compared with ancestral variant: insufficient information to make a decision; seek expert input and ask companies for dose-failure data.

Appendix 1: IVAG members

Amanda Adler (Chair)	Director, Diabetes Trials Unit, University of Oxford
David Bauer	Group Leader & Head, RNA Virus Replication Laboratory. The Francis Crick Institute
Rupert Beale	Clinician Scientist Group Leader, Consultant Nephrologist, The Francis Crick Institute, UCL Division of Medicine
Sanjay Bhangani	Consultant Physician and Honorary Associate Professor, Royal Free Hospital and University College London
Neil Ferguson	Director, MRC Centre for Global Infectious Disease Analysis, Imperial College London
Neil Hawkins	Professor of Health Technology Assessment, University of Glasgow
Mark Jit	Professor of Vaccine Epidemiology, London School of Hygiene and Tropical Medicine
Saye Khoo	Professor in Pharmacology, Hon Consultant Physician in Infectious Diseases, University of Liverpool
David Lalloo	Director, Liverpool Tropical School of Medicine
Siraj Misbah	Consultant Clinical Immunologist, Oxford University NHS Foundation Trust
Andrew Owen	Professor of Pharmacology, University of Liverpool
Derek Smith	Professor of Infectious Disease Informatics, Zoology Department at Cambridge University
David Stuart	MRC Professor of Structural Biology, University of Oxford
Mark Sutton	Scientific Leader - Healthcare Biotechnology, and Professor for Antimicrobial Therapy, UKHSA and King's College London
Laurie Tomlinson	NIHR Research Professor, Honorary Consultant Nephrologist, London School of Hygiene and Tropical Medicine
Erik Volz	Reader in Population Biology of Infectious Diseases, Faculty of Medicine, School of Public Health, Imperial College London

Appendix 2: Search strategy

Pubmed: (omicron[TI] OR XBB[TI] OR BQ.1[TI] OR BQ1[TI] OR BA4[TI] OR BA5[TI] OR BA.4[TI] OR BA.5[TI] OR BA4/5[TI] OR BA.4/5[TI])OR BA2.75[TI] OR BA.2.75[TI])AND (mabs[ti] OR antibod*[ti] OR neutral*[ti] OR vitro[TI] OR in-vitro[TI] OR sotrovimab[ti] OR casirivimab[ti] OR imdevimab[ti] OR tixagevimab[ti] OR cilgavimab[ti])

Europe PMC: ((TITLE:"omicron" OR (TITLE:"XBB") OR (TITLE:"BQ.1") OR (TITLE:"BQ1") OR (TITLE:"BA4") OR (TITLE:"BA5") OR (TITLE:"BA.4") OR (TITLE:"BA.5") OR (TITLE:"BA4/5") OR (TITLE:"BA.4/5") OR (TITLE:"BA2.75") OR (TITLE:"BA.2.75")) AND ((TITLE:"mabs") OR (TITLE:"antibody") OR (TITLE:"antibodies") OR (TITLE:"neutralising") OR (TITLE:"neutralizing") OR (TITLE:"neutralisation") OR (TITLE:"neutralization") OR (TITLE:"vitro") OR (TITLE:"in-vitro") OR (TITLE:"sotrovimab") OR (TITLE:"casirivimab") OR (TITLE:"imdevimab") OR (TITLE:"tixagevimab") OR (TITLE:"cilgavimab")) AND (SRC:PPR))

Appendix 3: Appraisal of the evidence

The risk of bias assessment is to be completed using the adapted Toxicological data reliability assessment tool (TOXRTOOL). The following 23 questions are allocated a score of 0 or 1.

Criteria		
No	**Criteria I: Test substance identification (monoclonal antibody)**	**Score**
1	Was the monoclonal antibody named/described in the study?	
2	Is information on the source/origin of the monoclonal antibody given? *Generally, only authentic product provided by the manufacturer should be accepted for interpretation of the findings. This should include manufacturer name.*	
3	Does the test substance accurately reflect monoclonal antibodies used in clinical practice?	
		0
	Criteria II: Test system characterisation (neutralisation assay)	
4	Is the test system described**?** *At a fundamental level, comparison of in-vitro data across laboratories is hampered by the use of different cell lines that may be infected by SARS-CoV-2 variants to different extents.* *Emerging evidence suggests that MAbs binding outside of the RBD may be sensitive to ACE2 expression levels and this should be considered.*	
5	Was the neutralisation assay appropriate? *It is expected that all neutralisation assays would be ELISA assays conducted in at least two independent experiments.*	
6	Is information given on the source/origin of the test system, and is there data available on the validity of that test system? *This could include:* • *Laboratory/scientist providing cell lines* • *Commercial provider of test systems* • *A description of how the reactivity of the nMAB was validated* • *Origin of tissues and primary cells*	
7	Are necessary information on test system properties, and on conditions of cultivation and maintenance given? (Type of assay, type of virus, type of cell line, type of media) *There is broad agreement that in vitro methodology should employ authentic SARS-CoV-2 isolates, and that routine sequencing of virus stocks is needed*	

	since cell culture adaptation and mutations can occur and can change replication of virus in cells. It is currently unclear whether variants isolated from different countries will behave the same in cell culture since a large study comparison has not been reported. There is evidence that some methods to propagate the virus have led to additional mutations. *Pseudovirus assays present several advantages over live virus which include the speed at which data can be generated after emergence of a new variant, and the lack of reliance upon BSL-3 facilities, and the controlled evaluation of the effect of specific mutations. However, limitations are also evident since the pseudovirus may not contain the full suite of mutations or may not function like an authentic virus in every way. Therefore, it is suggested that data from pseudovirus assays should be considered based on a clear understanding of the inherent benefits and limitations of the data.* *Widely available cell lines should be used such as VeroE6 and VeroE6-TMPRSS2, Calu-3 cells and A549 cells.*	
8	Has sufficient detail been reported on the methods to replicate the study?	
9	Does the study confirm that an appropriate cell line has been used? *Investigators may use cell lines which have been shown to be inappropriate for assaying certain classes of monoclonal antibodies.*	
		0
	Criteria III: Study design description	
10	Are doses administered or concentrations of test substances analysed given?	
11	Are frequency and duration of exposure as well as time-points of observations explained? (duration of incubation with virus, duration of assay) *Timing of assay readouts should be validated.*	
12	Have a range of antibody concentrations been tested that are relevant to those required for neutralisation in serum? *A limitation of many in-vitro studies is the range of antibody concentrations tested, which are often lower than the average maximum serum concentrations.*	
13	Were negative controls included?	
14	Were positive controls included?	
15	Is the number of replicates (or complete repetitions of experiment) given?	
16	Is the study methodology likely to produce reliable comparison data? *For example, have the study investigators utilised an assay calibrated with the WHO International Standard for anti-SARS-CoV-2 immunoglobulin and reporting of neutralisation titres in International Units – an assay useful for standardised comparisons of different monoclonal antibodies against various variants.*	

	Testing should be conducted on an ancestral strain of the virus or reference strain used in an RCT in parallel to the variant under investigation.	
		0
	Criteria IV: Study results documentation	
17	Are the study endpoint(s) and their method(s) of determination clearly described? *A 4-paramater, variable slope dose response analysis has been proposed as the most effective way to determine EC_{50} and EC_{90} parameters.* *Luciferase endpoints for pseudovirus assays and nucleocapsid measurements (anti-N with high content imaging) for authentic live virus have been highlighted as providing reliable readouts.* *Cytopathic effect (e.g. measured by cell titer glo) has been reported to be heterogeneous between different variants studied to date.* *qPCR readouts have an excellent signal to noise ratio but may not be applicable to pseudovirus assays.*	
18	Is the description of the study results for all endpoints investigated transparent and complete?	
19	Are the outcomes appropriate, and clearly and transparently reported? *EC_{50} and EC_{90} values should be generated as outcomes from the in vitro testing.*	
20	Were the study outcomes determined prior to analysis?	
21	Are the statistical methods for data analysis given and applied in a transparent manner?	
22	Are confidential intervals included? *CIs are important in evaluating the uncertainty of any possible changes in neutralisation; particularly when considering IC_{90} values, which lie close to the plateau of the dose–response curve and are inherently noisy.*	
		0
	Criteria V: Plausibility of study design and data	
23	Are the quantitative study results reliable?	
		0
	Total score	0

Based on the total score, studies are allocated to category 1, 2 or 3 as indicated below. Category 1 is assigned if the total score is ≥20, category 2 is assigned for scores >16, and for all scores <16, category 3 is assigned.

Category	Definition

1- Reliable without restrictions	“Studies or data from the literature or reports which were carried out or generated according to generally valid and/or internationally accepted testing guidelines (preferably performed according to GLP) or in which the test parameters documented are based on a specific (national) testing guideline (preferably performed according to GLP) or in which all parameters described are closely related/comparable to a guideline method.”
2- Reliable with restrictions	“Studies or data from the literature, reports (mostly not performed according to GLP), in which the test parameters documented do not totally comply with the specific testing guideline, but are sufficient to accept the data or in which investigations are described which cannot be subsumed under a testing guideline, but which are nevertheless well documented and scientifically acceptable.”
3- Not reliable	“Studies or data from the literature/reports in which there were interferences between the measuring system and the test substance or in which organisms/test systems were used which are not relevant in relation to the exposure (e.g., unphysiologic pathways of application) or which were carried out or generated according to a method which is not acceptable, the documentation of which is not sufficient for assessment and which is not convincing for an expert judgment.”

Appendix 4: Glossary of terms used

Ancestral: the original strain of SARS-CoV-2 identified in Wuhan.

Cell line: a defined population of cells that can be maintained in culture for an extended period of time and can be used for in vitro experiments.

Clonal selection: the process of generating cell lines from a single cell.

Conserved epitope: is an epitope retained by multiple strains of virus as a key target of a broadly neutralising antibody.

EC50: concentration needed to neutralise 50% of the virus population leaving the remaining 50% of the virus to be able to replicate.

EC90: concentration needed to neutralise 90% of the virus population. Concentration is at least 9-fold higher compared with EC50.

Effector functions: antibodies can induce innate and adaptive immune responses beyond neutralisation, including antibody-dependent cellular cytotoxicity.

Epitope: structure on the surface of an antigen that is recognised by and can bind to a specific antibody.

Immune escape: this occurs when the immune system of a host is unable to respond to an infectious agent, such as a virus.

In vitro*:* tests and experiments that researchers perform outside of a living organism in a controlled environment, for example a test tube or petri dish.

Neutralising monoclonal antibodies: ‘mAbs’ that bind to and ‘neutralise’ SARS-CoV-2.

Neutralisation curves: Y axis percentage inhibition, x axis is concentration of drug; different curves for different variants including ‘ancestral’ line (for example, Delta). Different graphs for each drug.

PK/PD data: pharmacokinetic and a pharmacodynamic model which describes exposure response in vivo.

Quality-adjusted life year: ‘generic’ measure of effectiveness used in cost-utility analysis.

Receptor binding domain: a part of the SARS-CoV-2 virus located on its ‘spike’ protein that allows it to dock to body receptors to gain entry into cells and cause infection.

Overview

Explanation

This page details the Managed Access Team's overall assessment on whether a medicine could be suitable for Managed Access and if data collection is feasible. The feasibility assessment does not provide any guidance on whether a medicine is a cost-effective, or plausibly cost-effective, use of NHS resources. This document should be read alongside other key documents, particularly the company's evidence submission and External Assessment Centre (EAC) report. Further detail for each consideration is available within the separate tabs.

Whilst a rationale is provided, in general the ratings for each area:
Green - No key issues identified
Amber - Either outstanding issues that the Managed Access team are working to resolve, or subjective judgements are required from committee / stakeholders (see key questions)
Red - The managed access team does not consider this topic suitable for a managed access recommendation.

The Managed Access Team may not assess other areas where its work has indicated that topic is not suitable for a managed access recommendation

The feasibility assessment indicates whether the Managed Access team have scheduled to update this document, primarily based on whether it is undertaking actions to explore outstanding issues. There may be other circumstance when an update is required, for example when the expected key uncertainties change or a managed access proposal is substantially amended. In these cases an updated feasibility assessment should be requested from the Managed Access team.

Topic name: **Tixagevimab–cilgavimab for preventing COVID-19**
Topic ID: **6136**
Managed Access Lead: **Catrin Austin**
Date of assessment(s): **14/12/2022**

Is Managed Access appropriate - Overall rating	Comments / Rationale
No managed access proposal	Tixagevimab–cilgavimab (Evusheld) for preventing COVID-19 is not a suitable candidate for managed access. Data collection is not expected to be feasible to set-up and would be not resolve the key uncertainties. There are several other substantive barriers to an MAA, some independent from data collection. In addition no managed access proposal has been recieved. To consider managed access, a committee will need a managed access proposal, along with a feasibility assessment from the NICE managed access team. Currently no managed access proposal has been submitted. The managed access team should be contacted if a managed access proposal is expected to be requested or submitted at a later point in the NICE evaluation process.

Area	Rating	Comments / Rationale
Is the technology considered a potential candidate for managed access?	Yes	Tixagevimab–cilgavimab covers an area of high unmet need, has possible significant clinical benefits, and is a step change in treatment as there is currently no other licenced COVID-19 prevention drug.
Is it feasible to collect data that could sufficiently resolve key uncertainties?	No	Further data collection, regardless of feasibility, is unlikely to resolve all key uncertainties. In particular effectiveness against unpredictable landscape changes including changes to baseline rates of infections and hospitalisations and emergence of new variants would not be resolved through further data collection and would remain a signficant issue impacting all other uncertainties. No specific evidence can be collected to account for unpredictable landscape changes, and this would require constant surveillance of clinical practice, and reactive updating of guidance. The feasibility of setting up effective data collection is low. An effective real-world data collection, addressing the identified key uncertainties for this technology is very challenging. A particularly significant challenge is the need for routine testing of patients receiving the technology to determine if they have contracted COVID-19 and genomic testing to identify the particular variant. Furthermore, complications of data collection within primary care such as a lack of national coverage and varied data collection practices mean that an effective collection would require significant amendments to existing, large scale data sources or the creation of a new one.

Can data collection be completed without undue burden on patients or the NHS system	No	Additional burden on the system because coordinating the service between primary and secondary care would be complex. Ethical approval and patient consent is not in place to collect the data needed to resolve uncertainties. Clinicians and patients likely to be burdened by additional data collection through managed access.
Are there any other substantive issues (excluding price) that are a barrier to a MAA	Yes - Major	RWE sources would need amending and significant changes to clinical practice and this would cause a delay to setting up any MAA. Ethical approval and patient consent is not in place to collect the data needed to resolve uncertainties. Unclear if technology would get a routine recommendation at any price.

Further managed access activity	Rating	Comments / Rationale
pre-committee feasibility assessment update	Unclear	Updates to the feasibility assessment may be required as the technology progresses through the NCIE process and futher information from system partners is received.
pre-committee data collection working group	No	No managed access proposal. The managed access team will continue to have informal conversations with potential data providers and system partners
pre-committee patient involvement meeting	No	

Key questions for committee if Managed Access is considered	
1	Is Evusheld likely to be as effective against current and future strains of COVID-19?
2	Would there be undue burden on patients and the system to collect the RWE needed to resolve key uncertainties?
3	Would evidence collected be expected to sufficently resolve uncertainty to enable a routine recommendation at the end of managed access

Early Identification for Managed Access

Explanation on criteria
Companies interested in managed access must engage early with NICE and demonstrate that their technology is suitable for the Innovative Medicines Fund

Date agreed with NHSE	09/12/2022

Is the technology a potential candidate for managed access?	
Rating	**Rationale**
Yes	This technology could address a high unmet need, could provide significant clinical benefits and is a step change for patients. The uncertainties section describes whether new evidence could be generated that is meaningful and would sufficiently reduce uncertainty

IMF prioritisation criteria	Supporting Evidence
Potential to address a high unmet need	Large number of people who are clinically vulnerable and cannot have vaccines against COVID-19 are still shielding and at risk of severe disease. Preventative treatment would be beneficial for this group.
Potential to provide significant clinical benefits to patients	Large differences in infection rate, hospitalisations, and mortality are seen between people who did and did not have tixagevimab–cilgavimab. However, the PROVENT RCT was conducted early in the pandemic and may not be as relevant now. Current evidence was sought but many of the found studies are observational. Therefore, only associations can be made.
represents a step-change in medicine for patients and clinicians	First PrEP for COVID-19 infection, hospitalisation and mortality in the UK.
new evidence could be generated that is meaningful and would sufficiently reduce uncertainty	Explored in uncertainties section.

Uncertainties

Explanation

This page details the Managed Access Team's assessment on whether data collection could sufficiently resolve key uncertainties through further data collection within managed access. The overall assessment is the key judgement from the Managed Access Team.

The Managed Access Team will justify it decision, but broadly it is a matter of judgement on whether the further data collection could lead to a positive NICE decision at the point the technology exits managed access. For this reason individual uncertainties that have a higher impact on the ICER have a greater impact on the overall rating.

Further detail is available on each uncertainty identified primarily informed from a company's managed access proposal, the External Assessment Group (EAG) report, judgements from the NICE Managed Access Team, and where available directly from NICE committee deliberations. The likelihood that data could sufficiently resolve each specific outcome is informed both by the expected primary data source in general (as detailed in the separate tab) and specifically whether the data collected is expected to sufficiently resolve that uncertainty.

Likelihood data collection could sufficiently resolve key uncertainties?	
Rating	**Rationale**
Low	Further data collection, regardless of feasibility, is not expected to sufficently resolve the key uncertainties. In particular uncertainties that are due to unpredictable landscape changes including changes to baseline rates of infections and hospitalisations and emergence of new variants would not be resolved through further data collection and would remain a significant issue at any future guidance update. These uncertainties impact all others. No specific evidence can be collected to account for unpredictable landscape changes, and this would require constant surveillance of clinical practice, and reactive updating of guidance. Most uncertainties cannot be resolved through any further data collection and require committee judgement on its preferred assumptions. RWE could feasibly resolve some uncertainty in the risk of long COVID in non-hospitalised patients and in patients experiencing post year one cases of COVID. Some uncertainties could be resolved or partially resolved by RWE, however there are substantial barriers to setting up RWE data collection in practice and any data collected would be subject to bias (see RWE data sources tab). Data from the ongoing trials could resolve some uncertainty in the assumption of a constant treatment effect for 6 months after each dose of Evusheld and the risk of long COVID for patients experiencing post year one cases of COVID.

Key Uncertainties

Issue	Key uncertainty	Company preferred assumption	ERG preferred assumption	Impact on ICER	Data that could sufficiently resolve uncertainty	Proposed primary data source	Likelihood data collection could sufficiently resolve uncertainty	Rationale / Notes

MAT1+ EAG2	Uncertainty regarding the efficacy of Evusheld against current and future variants	Company assumes the treatment will be equally effective against future variants as previous variants.	The EAG say it is very uncertain. The EAG conducted exploratory analyses that varied the relative risk reduction (RRR) and annual risk of COVID-19. These showed combined impact of uncertainty around the efficacy of Evusheld against future variants and the future risk of COVID-19 which is uncertain and dependent on many factors.	High	None possible	N/A	No further data collection possible / proposed	•Committee judgement required. •Managed access cannot collect data for unpredictable future variants. Managed access collects data to resolve identified committee uncertainty. While a future variant may substantially change the value proposition of the medicine no data could currently be collected to address this uncertainty. In addition the uncertainty around additional future variants is very likely to remain a key issue in the future. •Managed access collects data over a time limited period rather than continual, indefinite data collection and surveillance. Data collection through managed access would not allow live updates of clinical and cost-effectiveness of the technology against new emerging variants. •Collecting data in clinical practice on the effectiveness against specific variants requires national testing, including genotype testing (see RWE data sources page)
EAG1	Economic analysis assumes two doses of Evusheld are administered 6 months apart	The economic analysis assumes one year of Evusheld treatment consisting of an initial 600mg dose, followed 6 months later by a second 600mg dose and assumes equal efficacy with the first. There is no safety or efficacy data for repeat dosing.	The company could provide a threshold analysis to explore the range of risk of COVID-19 in the SoC arm that results in an ICER under the range of £20,000 to £30,000 per QALY when assuming a single dose of Evusheld.	Unquantified	None possible	N/A	No further data collection possible / proposed	It may be possible to collect data on dosing in clinical practice if the medicine is centrally commissioned. However, any outcome data would have a very high risk of selection bias. No meaningful data on efficacy of repeated dosing could be collected in clinical practice.

EAG3	Exclusion of studies for specific subpopulations with the target population for Evusheld	The clinical effectiveness review described in the CS excluded some studies which recruited specific subgroups such as solid organ transplant recipients.	The EAG suggests that any studies conducted in groups that fall within the marketing authorisation for Evusheld should have been included in the CS	Unquantified	A cost-effectiveness analysis using any RWE studies available for specific subgroups of patients	N/A	No further data collection possible / proposed	These data can be collected outside of managed access. Managed access is used to collect prospective data.
EAG4	Risk of COVID-19 in the target population without Evusheld	The company's economic analysis uses the average risk of reporting a positive test for SARS-CoV-2 in the general public between August 2021 to August 2022 as the estimate of risk in the model. This may overestimate the risk of COVID-19. In addition, there is an inherent uncertainty regarding the risks of COVID-19 in the future.	The EAG has conducted a scenario analysis using the EAG's corrected company base case to test how sensitive the cost-effectiveness estimates are to uncertainty regarding the risk of infection.	Medium	None	N/A	No further data collection possible / proposed	•Committee judgement required. •This data is not auto-collected by HES or GP data and no RWE alternative has been identified. •This risk is likely to change over time and with the emergence of new variants •Any data collected to understand baseline rates of infections in the target population would require a widespread testing regime. In addition, if this medicine was available as part of managed access any data from people not taking the medicine would be of very high selection bias. •This uncertainty could be addressed through expert elicitation to provide a range of plausible risks that the committee may wish to consider, although this will not reduce the inherent uncertainty of trying to predict future risks.
EAG5	The implementation of adjustments to capture post year one cases of COVID-19	The EAG identified several errors in how post year one cases were implemented	The EAG has corrected the errors identified.	Medium	None	N/A	No further data collection possible / proposed	Not applicable

EAG6	Estimation of the direct utility gain attributable to Evusheld	The company has applied a direct utility gain to patients receiving Evusheld with the intention of capturing the impact of Evusheld on shielding and other infection avoidance behaviours, but only 13% in the target population are continuing to shield.	The EAG suggests that the direct utility gain should only apply to the 13% of patients in the target population who are currently continuing to follow shielding advice. In patients who experience COVID-19 after receiving Evusheld this should only apply for 6 months.	Medium	A RWE study measuring EQ-5D-3L prospectively in patients receiving Evusheld might reduce this uncertainty.	None.	Low	•This data is not routinely collected within clinical practice by RWE and no existing RWE source has been proposed. •Patient reported outcomes collected within managed access are likely to have bias associated with them as participants are not blinded and also are aware that continued access to the medicine is conditional on the guidance update following a period of managed access. •As there are no existing data sources the company would be expected to establish this if recommended within managed access •Utilities are highly variable and dependent on variant type. This makes utilities very uncertain and heavily impacted by the unpredictable future variants (see issue MAT1).

EAG7	Risk of long COVID in non-hospitalised patients	Company base case uses figures from Augustin et al., but seem much higher than ONS survey estimate. There was also a high drop out rate, which is not accounted for when calculating proportions. Estimated from a study that did not compare rates of long COVID in people who had and did not have COVID infection. May be overestimated as long COVID symptoms can be experienced by people without COVID infection.	EAG base-case used a source from the Netherlands, which may overestimate rates since it was conducted during Alpha variant when vaccination rates were low. ONS data for triple vaccinated people who had variant Omicron BA.2 was used as low estimate.	High	Current data on risk of long COVID in non-hospitalised patients; comparative study of people who did and did not have COVID-19	The COVID-19 Infection Survey and GPES	Low	•RWE data collection is not set up to address the uncertainties in this topic and no alternative RWE set up has been proposed. •Data likely to be confounded with vaccine uptake. Any prospective data within managed access would also be confounded with Evusheld treatment. •Probability of long COVID will be dependent on the dominating variant and the protection a COVID vaccine provides. In the unvaccinated population, who are very relevant in this indication, there would likely be a higher proportion experiencing long COVID.
EAG8	Administration costs for Evusheld	The only resources required to administer Evusheld will be 30 minutes of GP Practice Nurse time per patient receiving Evusheld	The EAG has used the costs of administering COVID-19 therapeutics through CMDUs as a proxy for the costs required to administer Evusheld.	Medium	None	N/A	No further data collection possible / proposed	Committee judgement required.

EAG9	Duration of long COVID for hospitalised and non-hospitalised patients	Average duration of long COVID, hospitalised: 8.5 years; non-hospitalised: 8.9-12.2 years depending on mortality. The company's extrapolations may overestimate time to recovery from 5 months to 1 year. Also assumes that the proportion recovering from long COVID was higher in people who were hospitalised than people who were not.	Average duration of long COVID, hospitalised: 1.4 years; non-hospitalised: 1.4-1.7 accounting for mortality. The EAG preferred to use the company scenario analysis which incorporated more recent ONS data to estimate the duration of long COVID without the calibration to adjust for the 1-year data from the PHOSP-COVID cohort. The EAG also removed the adjustment at 6 months in the hospitalised group in their base case scenario.	High	Longer term data for long COVID	The COVID-19 Infection Survey	Low	•RWE data collection is not set up to address the uncertainties in this topic and no alternative RWE set up has been proposed. •It is reasonably likely that further evidence on the duration of long COVID would become available during any managed access period. However, specific evidence that would sufficiently resolve this uncertainty cannot currently be identified. •The duration of long COVID is likely to be impacted by future variants (see MAT issue 1). The duration of long COVID at the point of any managed access exit could be substantially different and therefore this uncertainty would likely not be resolved at a guidance update. •COVID infection survey caries info on people's hospitalisation for COVID status https://www.ndm.ox.ac.uk/files/coronavirus/covid-19-infection-survey/crf5participantfollowupvisitv14-0_26-01-22clean.pdf
EAG10	Long COVID costs	The company's updated post clarification base case analysis applied a cost for long COVID (£2,500) that was used in an exploratory analysis in the ScHARR COVID-19 MTA model, instead of the cost used in the ScHARR COVID-19 MTA base case which was a cost estimate for chronic fatigue syndrome (£1128).	The EAG's preference is to use the estimate for the cost of chronic fatigue (£1128) as a proxy for the cost of long COVID	Medium	None	N/A	Medium	•It is reasonably likely that further evidence on the costs of managing long COVID would become available during any managed access period, however specific evidence that would sufficiently resolve this uncertainty cannot currently be identified.

EAG11	Long COVID utilities	The company estimated utility decrements by comparing 5-month EQ-5D utility scores in the PHOS-COVID cohort with retrospectively estimated pre-COVID EQ-5D utility scores. Patients were stratified by amount of hospital care given. Disutility based on people who were not recovered at 1 year only. Assumed disutilities for long COVID are constant for the duration of long COVID.	The EAG adjusted the disutility values taken from the PHOSP-COVID UK cohort (Evans 2022), to reflect the weighted average across patients stating either that they were not recovered or unsure at 1 year. Assumed that the utility decrements for long COVID linearly decline over 5 years to 50% of their starting value	Medium	Estimates of the impact of long COVID on health utility measured in patients who did not require hospitalisation for their COVID-19	None.	No further data collection possible / proposed	•RWE data collection is not set up to address the uncertainties in this topic and no alternative set up has been proposed. •COVID infection survey caries info on people's hospitalisation for COVID status •https://www.ndm.ox.ac.uk/files/coronavirus/covid-19-infection-survey/crf5participantfollowupvisitv14-0_26-01-22clean.pdf •No utilities available from RWE https://www.ndm.ox.ac.uk/covid-19/covid-19-infection-survey •Utilities are highly variable and dependent on variant type. This makes utilities very uncertain. •Patient reported outcomes collected within managed access are likely to have bias associated with them as participants are not blinded and also are aware that continued access to the medicine is conditional on the guidance update following a period of managed access.
EAG12	Hospitalisation risk for patients with COVID-19	The company has estimated the risk of hospitalisation (18%) in patients having COVID-19 from an immunocompromised cohort across different variants, reported by Shield et al.	The EAG has applied a lower estimate for the risk of hospitalisation in immunocompromised patients (9.9%) to reflect the reduced risk of hospitalisation for patients with COVID-19 during the period when the Omicron variant was dominant compared with those infected during earlier waves.	Low	None	N/A	No further data collection possible / proposed	•RWE data collection is not set up to address the uncertainties in this topic and no alternative set up has been proposed. •The proportion of patients with COVID-19 requiring hospitalisation may change in the future if the dominant variant changes and therefore this model parameter is inherently uncertain (see issue MAT1).

EAG13	Risk of long COVID for patients experiencing post year 1 cases of COVID	The company model does not allow for incidences of long COVID occurring after the post year 1 cases of COVID-19.	The EAG has estimated the impact of including a risk of long COVID for cases of COVID-19 occurring after the first year	Medium	Data >1-year for long COVID	Ongoing trial and The COVID-19 Infection Survey	Medium	•RWE data collection is not set up to address the uncertainties in this topic and no alternative set up has been proposed. See issue EAG7 for further details on the feasibility of collecting data in clinical practice. •However, ongoing data collection within managed access from the ongoing trials could increase follow-up length and number of people in analyses.
EAG14	Assumption of a constant treatment effect for 6 months after each dose of Evusheld	The economic analysis assumes proportional hazards for 6 months post-dose but the RWE source Young-Xu et al. only follows up for 4 months	The EAG has explored a scenario in which the RRR is reduced to two-thirds of its base case value to explore the impact of a worst-case assumption of zero treatment effect from 4 to 6 months. However, this was not incorporated in the EAG's preferred base case.	Medium	Data that could explore the impact of redosing at 6 months	Ongoing trials	High	There are analyses that could be conducted outside of managed access: •The company could provide further assessment of the proportional hazard assumption from the PROVENT study such as a quantitative test of the proportional hazard's assumption, and an assessment of the Schoenfeld residuals. •If further data collection through managed access was sought, there would need to be confirmation from the company that efficacy data can be collected across the whole 6 months period to resolve this uncertainty.

EAG15	Heterogeneity with the target population for Evusheld	The company's model has used average patient characteristics from the PROVENT study in their base case. However, the subset of patients classified as immunocompromised within the PROVENT study had a higher mean age. The company has included adjustments for all-cause mortality and utility in patients not experiencing COVID-19 or long COVID to account for the prevalence of comorbidities in the target population for Evusheld.	The EAG has conducted a scenario analysis in which the patient characteristics for the immunocompromised group from PROVENT are used.	Low	Efficacy in different subgroups	None.	No further data collection possible / proposed	•This data is not routinely collected in clinical practice by RWE and no RWE alternative has been proposed.
MAT2	Behaviour of population in real world may differ to trial population	People in trial still shield. However, people who receive drug in clinical practice may be confident enough to not shield leading to the drug being prescribed under different circumstances to what occurred in trial.	The EAG prefers to assume that it applies only to the proportion of patients who are continuing to follow shielding advice	Unquantified	Data on efficacy in real world	None.	No further data collection possible / proposed	•RWE data collection is not set up to address the uncertainties in this topic and no alternative set up has been proposed. •Without a unified RWE framework, it is not possible to follow people's progress through the health system. Therefore, it is not possible to estimate how much of an impact having the technology, stopping shielding, and any resulting hospitalisations or long COVID has on the system. •Observational data is likely to have significant confounding, collinearity and missing data, making it difficult to assess if any differences in effectiveness between people who do and do not take the drug is down to the drug.

MAT3	Population in company submission narrower than scope	Company have submitted evidence for people are at the highest risk of an adverse COVID-19 outcome, namely hospitalisation and death, as described in the McInnes report.	The EAG's clinical advisors were satisfied that the McInnes report would identify the groups mostly likely to benefit from Evusheld and that they fall within the scope and the marketing authorisation	Unquantified	Data in other subgroups who cannot have the vaccine or who are unlikely to mount an immune response to the vaccine	None.	No further data collection possible / proposed	•RWE data collection is not set up to address the uncertainties in this topic and no alternative set up has been proposed. •Observational data is likely to have significant confounding, collinearity and missing data, making it difficult to assess if any differences in effectiveness between people who do and do not take the drug is down to the drug.
MAT4	Placebo arm had higher proportion of people who received vaccine	Over double the number of participants in the placebo arm chose to be vaccinated compared to those in the Evusheld arm (31.0% vs 12.3%, respectively)	None provided.	Unquantified	None.	N/A	No further data collection possible / proposed	•Committee judgement required. •When people were called up to have their vaccines, people were unblinded. People on placebo could receive the vaccine immediately and people in treatment arm had to wait 6 months. •It is not known what proportion of people who receive the technology will get vaccinated and how this will affect their COVID-19 outcomes. •RWE data collection is not set up to address the uncertainties in this topic and no alternative set up has been proposed. Any data collected in clinical practice as part of managed access would not be comparative.

Trial Data

Are there further relevant trial data that will become available after the NICE evaluation?	
Rating	**Rationale/comments**
High	Two trials are ongoing until November 2023 and September 2024 and may be able to contribute data towards resolving some uncertainties.

Clinical trial data - PROVENT	
Anticipated completion date	Dec-22
Link to clinicaltrial.gov	https://clinicaltrials.gov/ct2/show/NCT04625725
Start date	Nov-20
Data cut presented to committee	May-21
Link(s) to published data	https://pubmed.ncbi.nlm.nih.gov/35443106/
Description of trial	This randomised trial assesses the safety and efficacy of a single dose of AZD7442(× 2 IM injections) compared to placebo for the prevention of COVID-19, n=5197. People were included who could "benefit from passive immunization with antibodies". The primary outcome is incidence of the first case of SARS CoV-2 confirmed with PCR within 183 days of first dose. PROVENT is ongoing until the end of this year. There is a substudy that is assessing the efficacy of a second dose at either 6 or 12 months after first but the company have not included this in their submission. It includes 503 people from PROVENT. This substudy is ongoing until November 2023.

Clinical trial data - ENDURE	
Anticipated completion date	Sep-24
Link to clinicaltrial.gov	https://clinicaltrials.gov/ct2/show/NCT05375760?term=D8850C00010
Start date	Jun-22
Data cut presented to committee	None
Link(s) to published data	
Description of trial	This dose-ranging randomised trial assesses the safety and immunogenicity, pharmacokinetics, and pharmacodynamics of AZD7442(× 2 IM injections) to prevent COVID-19 in people who are moderately to severely immunocompromised, n=251. Arm A were given a smaller dose but had more doses than arm B. The primary outcome is adverse events with 2 years, there are no outcomes relating to COVID-19 infection or illness.

Data collected in clinical practice

Is RWE data collection within managed access feasible?	
Overall Rating	**Rationale/comments**
Low	It is unlikely that any real-world data collection will be able to sufficiently resolve the uncertainties identified by the NICE committee. For several of the uncertainties it is not possible to collect the information and where it may be possible there are significant hurdles that would need to be overcome. Key hurdles in implementing data collection arise from the planned delivery of the treatment across primary and secondary care and the need to monitor patients across those settings over time. There is no single unified dataset that could be used across both settings. Collecting information about clinical outcomes is possible but has significant limitations. For example, a widespread testing mechanism for COVID-19 would be needed, additional data collection from primary care providers may require new contracts, and there is no national primary care data collection. Patient consent and ethical approval was not set up to cover using data across clinical practice in this way and presents a significant barrier to conducting RWE that would resolve the uncertainties. If prescription of the technology could be restricted to primary care (or excluded those prescribed elsewhere) some information (hospital admissions, length of stay in hospital, mortality) could be collected through GPES (GDPPR), Opensafely and CPRD, all of which have potential shortcomings including missing data and confounding. An effective real-world data collection addressing the key identified uncertainties for this technology is very challenging. A particularly significant challenge is the need for routine testing of patients receiving the technology to determine if they have contracted COVID-19 and genomic testing to identify the particular variant. Furthermore, complications of data collection within primary care such as a lack of national coverage and varied data collection practices mean that an effective collection would require significant amendments to existing, large scale data sources or the creation of a new one. Even if effective real-world data collection for this technology is established, any data collected as part of managed access would not be comparative, would be subject to potentially substantial bias, and may not be relevant for an unpredictable changing landscape - including changes to baseline rates of infections and hospitalisations and emergence of new variants.

Data Source	COVID-19 Infection Survey	
Relevance to managed access		
Existing, adapted, or new data collection	Existing	
Prior experience with managed access	Low	
Relevance of existing data items	Medium	Lists basic data items are available but it does not list more complex items, such as immunocompromised status
If required, ease that new data items can be created / modified	Low	Finding out immunocompromised status would require significant retrospective work
How quickly could the data collection be implemented	Normal timelines	

Data quality		
Population coverage	Medium	Coverage large and fairly broad, but may miss out hard to reach populations who may also be more likely to experience health inequalities
Data completeness	Low	Unlikely to obtain high completeness with a survey dependent on people's availability/willingness
Data accuracy	High	
Data timeliness	Low	Collating all data may take time
Quality assurance processes	Yes	
Data availability lag	High	
Data sharing / linkage		
New data sharing arrangements required?	Yes	Data would have be shared between registries to have a complete dataset.
New data linkages required?	Yes	
If yes, has the governance of data sharing been established	No	
Analyses		
How easily could collected data be incorporated into an economic model	High	
Existing methodology to analyse data	Yes	
If no, is there a clear process to develop the statistical analysis plan	Not applicable	
Existing analytical capacity	Low	The analytical capacity of this data collection is unknown and the NICE MA team does not believe it can be assumed to be sophisticated enough to contribute to a managed access agreement.
Governance		
Lawful basis for data collection	Unclear	Complexity due to using multiple sources
Privacy notice & data subject rights	Unclear	Complexity due to using multiple sources
Territory of processing	Yes	
Data protection registration	Yes	
Security assurance	Yes	
Existing relevant ethics/research approvals	Unclear	Complexity due to using multiple sources
Patient consent	Unclear	Complexity due to using multiple sources
Funding		
Existing funding	Yes	
Additional funding required for MA	Unclear	
If yes, has additional funding been agreed in principle	Not applicable	
Service evaluation checklist - registry specific questions		
HRA question 2. Does the study protocol demand changing treatment/care/services from accepted standards for any of the patients/service users involved?		
Does data collection through registry require any change from normal treatment or service standards?	Yes	There is no uniform test for COVID-19 so patients are likely to have to undergo more tests than otherwise would be needed so each registry can retrieve data.
Are any of the clinical assessments not validated for use or accepted clinical practice	No	
HRA question 3. Is the study designed to produce generalisable or transferable findings?		
Would the data generated for the purpose of managed access be expected to be used to make decisions for a wider patient population than covered by the marketing authorisation / NICE recommendation	No	
Additional considerations for managed access		

Are the clinical assessments and data collection comparable to current clinical practice data collection?	Yes	
Burden		
Additional patient burden	Yes	Patients would have to undergo additional testing and monitoring
Additional clinical burden	Yes	Additional items may be required
Other additional burden	Unclear	Unclear how much burden will be placed on system to link up RWE.

Data Source	**OpenSafely**	
Relevance to managed access		
Existing, adapted, or new data collection	Existing	
Prior experience with managed access	Low	
Relevance of existing data items	Medium	Lists basic data items are available but it does not list more complex items, such as utilities
If required, ease that new data items can be created / modified	Low	
How quickly could the data collection be implemented	Normal timelines	
Data quality		
Population coverage	Low	Unlikely to get full population coverage
Data completeness	Low	Obtaining complete data from sources may be unlikely without significant burden, or possible at all
Data accuracy	High	
Data timeliness	Low	Collating all data may take considerable time
Quality assurance processes	Yes	
Data availability lag	High	
Data sharing / linkage		
New data sharing arrangements required?	Yes	Data would have be shared between registries to have a complete dataset.
New data linkages required?	Yes	
If yes, has the governance of data sharing been established	No	
Analyses		
How easily could collected data be incorporated into an economic model	High	
Existing methodology to analyse data	Yes	
If no, is there a clear process to develop the statistical analysis plan	Not applicable	
Existing analytical capacity	Low	NICE/NHSE would have to find resource, as OpenSAFELY does not provide this.
Governance		
Lawful basis for data collection	Unclear	Complexity due to using multiple sources
Privacy notice & data subject rights	Unclear	Complexity due to using multiple sources
Territory of processing	Yes	
Data protection registration	Yes	
Security assurance	Yes	
Existing relevant ethics/research approvals	Unclear	Complexity due to using multiple sources
Patient consent	Unclear	Complexity due to using multiple sources
Funding		
Existing funding	Yes	
Additional funding required for MA	Yes	
If yes, has additional funding been agreed in principle	Not applicable	

Service evaluation checklist - registry specific questions		
HRA question 2. Does the study protocol demand changing treatment/care/services from accepted standards for any of the		
Does data collection through registry require any change from normal treatment or service standards?	Yes	There is no uniform test for COVID-19 so patients are likely to have to undergo more tests than otherwise would be needed so each registry can retrieve data.
Are any of the clinical assessments not validated for use or accepted clinical practice	No	
HRA question 3. Is the study designed to produce generalisable or transferable findings?		
Would the data generated for the purpose of managed access be expected to be used to make decisions for a wider patient population than covered by the marketing authorisation / NICE recommendation	No	
Additional considerations for managed access		
Are the clinical assessments and data collection comparable to current clinical practice data collection?	Yes	
Burden		
Additional patient burden	Yes	Patients would have to undergo additional testing and monitoring
Additional clinical burden	Yes	Coordinating delivering the drug across the system
Other additional burden	Unclear	Unclear how much burden will be placed on system to link up RWE; additional data collection from primary care providers may require new contracts

Data Source	General Practice Extraction Service (GPES)	
Relevance to managed access		
Existing, adapted, or new data collection	Existing	
Prior experience with managed access	Low	
Relevance of existing data items	Medium	Very basic data items, complex items not included
If required, ease that new data items can be created / modified	Low	Finding out immunocompromised status would require significant retrospective work
How quickly could the data collection be implemented	Normal timelines	
Data quality		
Population coverage	Low	Only in a select number of trusts/practices who have agreed to be part of the registry leading to potential bias
Data completeness	Low	Large number of individual people who have opted out, may cause confounding
Data accuracy	High	
Data timeliness	Low	May take time to collate data from all participating practices
Quality assurance processes	Yes	
Data availability lag	High	
Data sharing / linkage		
New data sharing arrangements required?	Yes	Data would have be shared between registries to have a complete dataset.
New data linkages required?	Yes	
If yes, has the governance of data sharing been established	No	
Analyses		
How easily could collected data be incorporated into an economic model	High	
Existing methodology to analyse data	Yes	

If no, is there a clear process to develop the statistical analysis plan	Not applicable	
Existing analytical capacity	Low	
Governance		
Lawful basis for data collection	Unclear	Complexity due to using multiple sources
Privacy notice & data subject rights	Unclear	Complexity due to using multiple sources
Territory of processing	Yes	
Data protection registration	Yes	
Security assurance	Yes	
Existing relevant ethics/research approvals	Unclear	Complexity due to using multiple sources
Patient consent	Unclear	Complexity due to using multiple sources
Funding		
Existing funding	Yes	
Additional funding required for MA	Unclear	
If yes, has additional funding been agreed in principle	Not applicable	
Service evaluation checklist - registry specific questions		
HRA question 2. Does the study protocol demand changing treatment/care/services from accepted standards for any of the		
Does data collection through registry require any change from normal treatment or service standards?	Yes	There is no uniform test for COVID-19 so patients are likely to have to undergo more tests than otherwise would be needed so each registry can retrieve data.
Are any of the clinical assessments not validated for use or accepted clinical practice	No	
HRA question 3. Is the study designed to produce generalisable or transferable findings?		
Would the data generated for the purpose of managed access be expected to be used to make decisions for a wider patient population than covered by the marketing authorisation / NICE recommendation	No	
Additional considerations for managed access		
Are the clinical assessments and data collection comparable to current clinical practice data collection?	Yes	
Burden		
Additional patient burden	Yes	More testing of patients
Additional clinical burden	Yes	Additional items may be required
Other additional burden	Unclear	Unclear how much burden will be placed on system to link up RWE; additional data collection from primary care providers may require new contracts

Other issues

Explanation

This page details the Managed Access Team's assessment on whether there are any potential barriers to agreeing a managed access agreement and that any potential managed access agreement operates according to the policy framework developed for the Cancer Drugs Fund and Innovative Medicines Fund.

The items included are informed by the relevant policy documentation, expert input from stakeholders including the Health Research Authority, and the Managed Access team's experience with developing, agreeing and operating managed access agreements. Additions or amendments may be made to these considerations as further experience is gained from Managed Access.

The Managed Access Team will justify it decision, but broadly it is a matter of judgement on whether any issues identified, taken as a whole, are likely to lead to a barrier to a Managed Access Agreement being agreed, or operationalised in the NHS. No assessment is made whether a Commercial Access Agreement is likely to be reached between the company and NHS England, which could be a substantive barrier to managed access.

Are there any substantive issues (excluding price) that are a barrier to a MAA	
Overall rating	**Rationale/comments**
Yes - Major	There are substantial issues that would be a barrier to managed access agreement. Any data collection in clinical practice would lead to potentially substatial additional burden on the system and patients. Its also unclear whether a committee would be willing to recomend this technology into routine commissioning at any price. For these reasons patient consent and ethics approval would be required for any data collection. Above the time required to set up a service to deliver the treatment any data collection in clinical practice would be complex and additional time would be required to set this up. In addition, the budget impact could be much greater than the fixed funding envelope of the IMF.

		Rating	Rationale / comments
Burden	Expected overall additional patient burden from data collection?	High	Patients would likely have to undergo more testing
	Expected overall additional system burden from data collection?	High	Unclear how much burden will be placed on system to link up RWE; additional data collection from primary care providers may require new contracts
	Do stakeholders consider any additional burden to be acceptable	Unclear	
	Would additional burden need to be formally assessed, and any mitigation actions agreed, as part of a recommendation with managed access	Yes	

		Rating	Rationale / comments
Patient Safety	Have patient safety concerns been identified during the evaluation?	No	
	Is there a clear plan to monitor patient safety within a MA?	Yes	Adverse event data
	Are additional patient safety monitoring processes required	No	

		Rating	Rationale / comments
Patient access after MAA	Will existing patients be able to continue to use the technology in the event of negative NICE guidance update	Not applicable	The company has not submitted a managed access proposal so it is unclear whether they would sign-up to the IMF exit principles.

		Rating	Rationale / comments
Service implementation	Is the technology disruptive to the service	Yes	Delivery would have to be planned across primary and secondary care.
	Will implementation subject the NHS to irrecoverable costs?	Yes	Data collection within managed access would require additional widespread testing and monitoring
	Is there an existing service specification which will cover the new treatment?	No	

		Rating	Rationale / comments
Patient eligibility	Are there specific eligibility criteria proposed to manage clinical uncertainty	No	
	If yes, are these different to what would be used if the technology had been recommended for routine use?	Not applicable	

		Rating	Rationale / comments
Service evaluation checklist	HRA question 1. Are the participants in your study randomised to different groups?		
	Will the technology be available to the whole recommended population that meet the eligibility criteria?		N/A
	HRA question 2. Does the study protocol demand changing treatment/care/services from accepted standards for any of the patients/service users involved?		
	Will the technology be used differently to how it would be if it had been recommended for use?		N/A
	Any issues from registry specific questions		N/A
	HRA question 3. Is the study designed to produce generalisable or transferable findings?		
	Any issues from registry specific questions		N/A
	Additional considerations for managed access		
	Is it likely that this technology would be recommended for routine commissioning disregarding the cost of the technology?	Unclear	Data is confounded by dominant variant, shielding, and vaccination status, so it is difficult to assess how effective the technology is within the current landscape.
	Any issues from registry specific questions		N/A

		Rating	Rationale / comments
Equality	Are there any equality issues with a recommendation with managed access	No	

		Rating	Rationale / comments
Timings	Likelihood that a Data Collection Agreement can be agreed within normal FAD development timelines	No	Any RWE data collection would require substantial time to set up. It would likely require patient consent and ethics