Tixagevimab–cilgavimab (tix-cil) for preventing COVID-19 [ID6136]

Slides for public, redacted

Technology appraisal committee C [4 April 2023]

Chair: Richard Nicholas

External assessment group: School of Health and Related Research (ScHARR), Sheffield

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Company: AstraZeneca

Tixagevimab–cilgavimab (tix-cil) for preventing COVID-19

- **Appraisal committee meeting 1 recap**
    - Tixagevimab–cilgavimab
    - Draft guidance recommendation
    - Key issues and committee's conclusions after ACM1
- Appraisal committee meeting 2
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    - Cost-effectiveness results
    - Equality considerations

Tixagevimab–cilgavimab (Evusheld, AstraZeneca)

Marketing authorisation	• Tixagevimab–cilgavimab (tix-cil) received a conditional marketing authorisation from the MHRA on 17 March 2022 • Marketing authorisation wording: "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"
Mechanism of action	• Tix-cil is a combination of tixagevimab and cilgavimab, two recombinant human IgG1k monoclonal antibodies • Both antibodies can simultaneously bind to non-overlapping regions of the spike protein receptor binding domain of SARS-CoV-2
Administration	• The expected dose of 600mg is administered as 2 x 150 mg vials of tixagevimab, and 2 x 150 mg vials of cilgavimab; given as two separate sequential intramuscular injections at different injection sites in different muscles
Price	• The list price of tix-cil is £1,600 per 600 mg dose • There is a commercial arrangement (simple PAS discount) in place

Abbreviations: MHRA, Medicines and Healthcare products Regulatory Agency; PAS, patient access scheme; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Draft guidance recommendation

Tixagevimab plus cilgavimab is **not recommended**, within its marketing authorisation, for preventing COVID-19 in adults who are not currently infected with SARS-CoV-2 and who have not had a known recent exposure to someone infected with SARS-CoV-2, and:

- who are unlikely to have an adequate immune response to COVID-19 vaccination, or
- for whom COVID-19 vaccination is not recommended.

In vitro data suggests that tixagevimab plus cilgavimab is unlikely to prevent infection with most of the relevant variants in the appropriate time period for this evaluation.

Abbreviations: SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

RECAP

Committee's conclusions after ACM1

#	Key issue	Committee's conclusion	Draft guidance section
1	Eligible population and heterogeneity	Population should be aligned with the marketing authorisation – Independent Advisory Group (IAG) cohorts A1, A2 and B	3.5
2	Efficacy against current variants	Tix-cil unlikely to prevent infection with most circulating variants	3.12
3	Repeated dosing of tix-cil	Dosing should be aligned with the marketing authorisation – one dose only	3.6
4	Risk of COVID-19 infection (without tix-cil)	Company estimate of 22.58% based on the general population is too high, scenario analyses requested	3.16
5	Risk of hospitalisation for COVID-19 (without tix-cil)	Company estimate of 15.9% based on Shields et al. is too high, committee preferred to assume hospitalisation rate closer to Patel et al. (2.8%)	3.17
6	Direct utility gain for people receiving tix-cil	Company's direct utility gain is likely to be an overestimate. Relationship between efficacy, changing behaviour and utility is complex and uncertain	3.14
7	Cost of administering tix-cil	CMDU administration cost is more appropriate and conservative, given the uncertainty about how tix-cil would be administered in practice	3.15
8	Long COVID – risk, duration, utility decrement, cost	EAG's assumptions are preferred as these are more closely aligned with estimates used in COVID-19 treatments MTA	3.18

Abbreviations: ACM, appraisal committee meeting; EAG, External Assessment Group; IAG, Independent Advisory Group; ICER, incremental cost-effectiveness ratio; MTA, multiple technology appraisal.

Unknown ICER impact
Large ICER impact
Moderate ICER impact

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Consultation comments

Received from:

- **Company:** AstraZeneca
- **9 patient and professional organisations:**
    - CLL support
    - Evusheld for the UK
    - Faculty of Pharmaceutical Medicine
    - Immunodeficiency UK
    - Kidney Care UK
    - Kidney Research UK
    - Leukaemia care
    - LUPUS UK
    - Royal College of Physicians
- **1 patient expert**
- **Web comments (n=8)**

Abbreviations: CLL, chronic lymphocytic leukaemia.

Consultation comments summary (1/3)

Topic	Consultation comments summary
Appraisal process for COVID-19 technologies	• NICE appraisal process is not fit for assessing preventative medicines for COVID-19: • "Delay between the MHRA granting the marketing authorisation for tix-cil and NICE publishing draft guidance is unacceptable" • "Tix-cil may have been able to provide protection to people at high-risk if it had been available when earlier variants were circulating" • "A more flexible and responsive appraisal process which will enable faster access to effective COVID-19 prophylactic treatments would be welcomed" • "A system needs to be in place to monitor current variant mix and adapt to changing variants … tix-cil may regain efficacy against future variants" • "Conclusion that tix-cil will not be effective against variants that will be prevalent in 6 months' time is flawed - no-one knows how COVID-19 will mutate" • "A similar approach to the FDA of reintroducing tix-cil if efficacy is at least 10% would be appropriate – NICE should define a suitable effectiveness threshold" • "The revised appraisal process should apply when updating existing recommendations **and** to new appraisals for future treatments"

Abbreviations: FDA, United States Food and Drug Administration; MHRA, Medicines and Healthcare products Regulatory Agency

Consultation comments summary (2/3)

Topic	Consultation comments summary

Standard of evidence / comparison to vaccination	• Differences in the standard of evidence for vaccinations and tix-cil:
	  • "There was a lack of evidence for the effectiveness of COVID vaccination when first given and for new variants, but mass vaccination was still provided"
	  • "There is disparity with which prophylactic protection for the disabled immunocompromised (tix-cil) was forced down a different process than that of the prophylactic protection for the immunocompetent (vaccines)"
	  • "The threshold of evidence to enter a COVID-19 treatment into clinical practice is unrealistically high, but to withdraw the same treatment it is much lower when based on in-vitro neutralising evidence alone"

Inequity	• Should be equitable opportunity for protection from COVID-19 regardless of disability: • "It is not fair that the burden of protection relies solely on the individual's behaviour"

Usefulness of clinical trials / ongoing data collection	• Mixed responses on usefulness of trials for preventative medicines for COVID-19:
	  • Some supported suggestion of entering tix-cil into an ongoing platform trial
	  • Others argued that trials have limited use for COVID-19 treatments because the moment when a treatment could have been effective will have passed

Consultation comments summary (3/3)

Topic	Consultation comments summary

Efficacy	• Mixed responses on the efficacy data for tix-cil:
	  • Some stakeholders agreed with the committee's recommendation and concluded that tix-cil is not currently anticipated to be efficacious from the data
	  • Some concerns about relying solely on in vitro data when it is unclear how this relates to in vivo efficacy

Changing behaviour	• Stakeholders argued that it is unlikely that patients will put themselves at greater risk following treatment but they should also be informed of potential limitations of treatment:
	  • "For many, aim of treatment is to lower risk … within their home or work which they cannot do anything about, whilst doing everything possible to mitigate these risks"
	  • "NICE should ensure that people are offered advice and guidance on appropriate levels of activity / social mixing following preventative treatment"
	  • "A study into patient behaviour would be of limited use – asking people if they are still shielding when a fair proportion do not realise they are still at high risk is meaningless"

Cost offsets	• Concerns that cost offsets may not have been fully accounted for in the analysis: • "A transplant patient may lose their transplant. The ongoing costs of this are huge and would massively outweigh the costs of prophylaxis"

Further comments related to specific key issues in the draft guidance are summarised later in slides

Overview of company response

In response to consultation, the company has:

- Optimised the population/circumstances in which, tix-cil should be made available (box below)
- Updated base case for some parameters but not others (see next slide)
- Submitted additional justification where base case was not updated
- Provided additional data supporting the direct utility gain assumption

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, with high-risk reflecting groups A1, A2 and a subset of group B (patients who do not have serological response to vaccination) from the independent advisory group report, or
- For whom COVID-19 vaccination is not recommended
- Where tix-cil displays neutralisation activity against a threshold of circulating variants (company suggesting a threshold of 10% in line with FDA)

Abbreviations: FDA, United States Food and Drug Administration; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Key issues remaining for discussion

#	Key issue	Company base case updated?	Details
1	Eligible population and heterogeneity	No	Additional justification provided
2	Efficacy against current COVID-19 variants	Partially	Assumed tix-cil neutralises 10% of circulating variants
3	Repeated dosing of tix-cil	Yes	Single dose assumed
4	Risk of COVID-19 infection (without tix-cil)	No	Additional justification provided
5	Risk of hospitalisation (without tix-cil)	No	Additional justification provided
6	Direct utility gain for people receiving tix-cil	Partially	Utility gain applied to 82% rather than 100%
7	Cost of administering tix-cil	Partially	NHSE cost of £216 used
8	Long COVID – risk, duration, utility decrement, cost	Partially	Cost and utility assumptions updated

Abbreviations: NHSE, NHS England.

Key issue 1: Eligible population and heterogeneity (1/3)

Draft guidance conclusions:

- *"The committee would have preferred to see an analysis that included the whole population covered by the marketing authorisation (Independent Advisory Group [IAG] cohorts A1, A2 and B), in addition to a subgroup analysis in those with the highest risk (A1 and A2)." See back up slides 38 & 39 for cohort details*

Company response:

- Agreed that the IAG report is appropriate for stratifying the need for preventative treatment
- The target population includes people in IAG group A1, A2 and people in group B without serological response to vaccination (the highest risk subset of the high-risk population)
  - This ensures that tix-cil is available to people with the highest unmet need, who will benefit most from treatment, whilst ensuring tix-cil represents a cost-effective use of NHS resources
- Company provided additional justification that the inputs used are appropriate / do not have a substantial impact on the ICER

Consultation comments:

- All immunocompromised people should be given the right to treatments, not just those at highest risk
- It is important to analyse benefit at a defined patient cohort level – this is especially relevant where people have a single identifiable characteristic such as a donated heart or lungs.

Abbreviations: IAG, Independent Advisory Group; ICER, incremental cost-effectiveness ratio.

Key issue 1: Eligible population and heterogeneity (2/3)

EAG response:

- The company's proposed target population is still a subset of marketing authorisation and does not fully address the committee's preferences expressed in the draft guidance
- The target population is now **more** narrowly defined than at the time of submission as it restricts group B to people without a serological response
  - It is not clear how serological response should be defined – the costs for serological testing have not been included in the modelling and are likely to be high
- Maintains that many model inputs are not specific to the target population, or are specific to a single subgroup and do not reflect heterogeneity within the target population
  - Company has not provided cost-effectiveness analysis for specific subgroups of interest
  - The EAG has provided comments on the relevance of various parameter sources to the target population (see next slide)

Clinical experts: How would serological response be determined in clinical practice?

Abbreviations: EAG, External Assessment Group.

Key issue 1: Eligible population and heterogeneity (3/3)

Model parameter	Company's source	Population	IAG cohorts	EAG comments
Baseline characteristics	PROVENT trial (age, weight, percentage male)	Adults at increased risk of inadequate response to vaccination or at increased risk of SARS-CoV-2 infection	A1, A2, B, C and uncategorised	ICER is not sensitive but benefit likely to be considerably heterogeneous
Risk of COVID-19 infection (without tix-cil)	UK government	General population of England between August 2021 and August 2022	Mostly uncategorised	No new evidence presented, explored in scenario analysis
Efficacy of tix-cil in preventing infection	66% reduction based on RWE study by Young-Xu et al. 2022.	US veterans (aged ≥18 years), immunocompromised or otherwise at high-risk for COVID-19.	Not stated by company	See key issue 2 - the EAG would prefer to see the model populated for specific subgroups
Risk of hospitalisation for COVID-19 (without tix-cil)	Shields et al. 2022	Patients with primary and secondary immunodeficiency (receiving immunoglobin replacement therapy)	A2	See key issue 5 – represents only 2 of the 8 groups in A2
Direct utility gain for people receiving tix-cil	Gallop et al. 2022 commissioned by company	Immunocompromised individuals	Majority A2	No evidence those in A1 would be more vulnerable
All-cause mortality	Odnoletkova et al., 2018 common variable immunodeficiency disorders	All-cause mortality in the general population taken from UK life tables with standardised mortality ratio of 1.7	A1 and A2	All cause mortality may be considerably heterogeneous, this is not explored in scenarios

Key issue 2: Efficacy against current COVID-19 variants (1/3)

Draft guidance conclusions:

- *"Tix-cil is unlikely to retain sufficient neutralisation activity against most circulating variants, and this is the most useful estimate of effect against future variants."*
- *"There is uncertainty in relying solely on in vitro evidence but in the context of changing variants, in vitro data is more relevant to decision making than the older real-world studies"*

Company response:

- Accept that in the absence of clinical effectiveness evidence, for the purpose of decision making today, it is reasonable to assume that total loss of neutralisation in vitro means no clinical effectiveness
- However, a more flexible framework for decision making is required:
  - NICE should monitor the situation recommend tix-cil if it neutralises at least 10% of circulating variants at any time, this is in line with the approach taken by the FDA
  - The appropriate neutralisation threshold should be an IC50 of <10,000 ng/mL

FDA position, 26 January 2023:

- The FDA has revised the Emergency Use Authorization for tix-cil to limit its use to when the combined frequency of non-susceptible SARS-CoV-2 variants nationally is less than or equal to 90% (that is,10% or more are susceptible to neutralisation by tix-cil). Based on this revision, tix-cil is not authorised for use in the US until further notice

Abbreviations: FDA, United States Food and Drug Administration; IC50, half maximal inhibitory concentration; ng/ml; nanograms per millilitre; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Key issue 2: Efficacy against current COVID-19 variants (2/3)

Consultation comments:

- There were mixed responses on the efficacy data for tix-cil:
  - Some stakeholders agreed with the committee's recommendation and concluded that tix-cil is not currently anticipated to be efficacious from the data
  - Others were concerned about relying solely on in vitro data when it is unclear how this relates to in vivo efficacy
- Most stakeholders agreed that a more flexible approach to the appraisal of COVID-19 treatments and preventative medicines was required as tix-cil may regain efficacy in the future
  - Stakeholders agreed with company that FDA's approach of reintroducing tix-cil if efficacy is at least 10% would be more appropriate

Company's updated base case:

- Base case been amended to assume tix-cil neutralises 10% circulating variants:
  - Model applies 10% multiplier to the relative risk reduction (RRR) for symptomatic infection based on the real-world evidence study by Young-Xu et al. (66%)
  - This results in a relative risk reduction for infection of 6.6%
- Scenarios tested where tix-cil neutralises up to 30% circulating variants
- Company state that tix-cil may also have an immunomodulatory function beyond neutralisation, so base case may be conservative

Abbreviations: FDA, United States Food and Drug Administration; RRR, relative risk reduction.

Key issue 2: Efficacy against current COVID-19 variants (3/3)

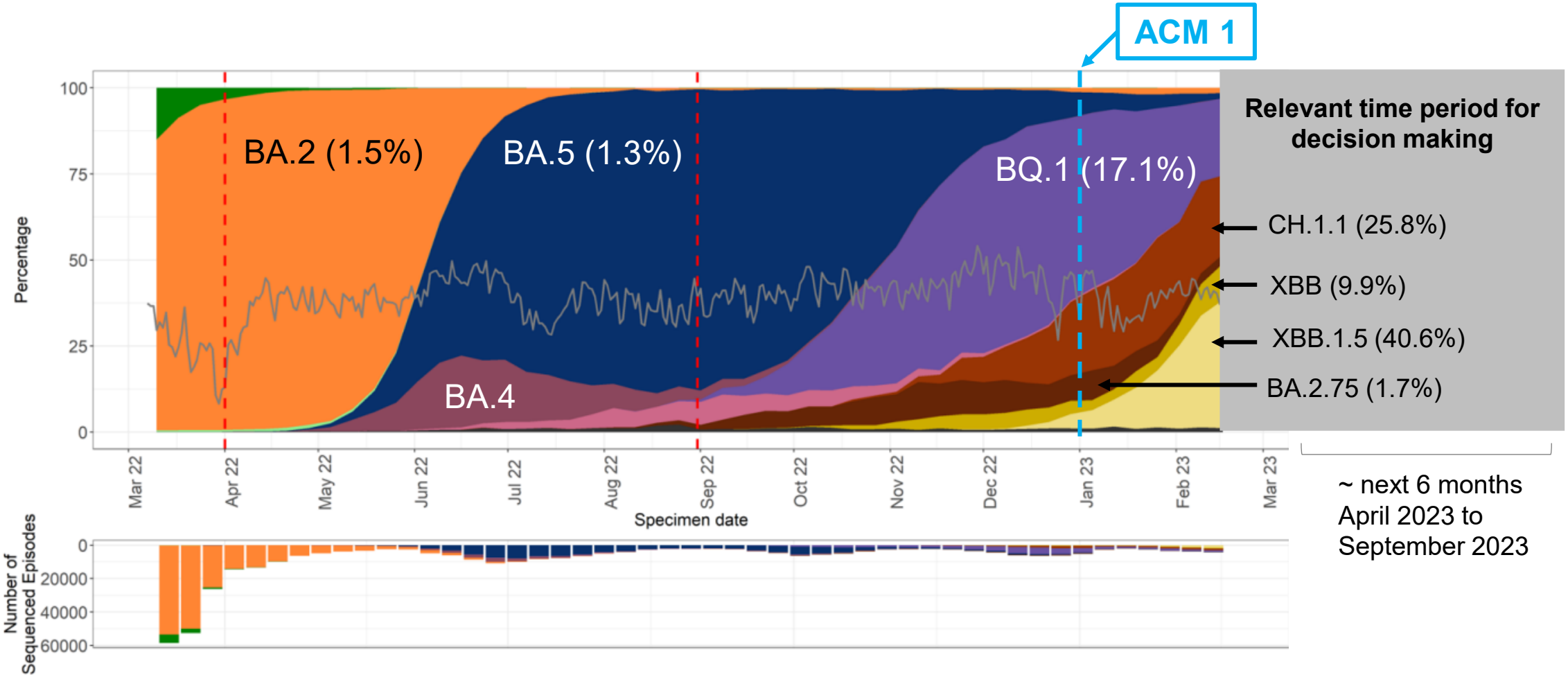
EAG response:

- The company has not provided evidence that tix-cil has an immunomodulatory function beyond neutralisation, so company's base case should not be considered conservative
- The EAG cannot comment on NICE process issues or whether an IC50 of <10,000 ng/mL is an appropriate neutralisation threshold
- The company has only updated the RRR for infection, the RRR for COVID-19 requiring hospitalisation remains the same as in the real-world evidence (62%, Young-Xu et al. 2022)
  - This approach has the unexpected effect of increasing the absolute proportion experiencing COVID-19 without hospitalisation compared to no prophylaxis (shown in table below in **blue**)
  - The EAG prefers to apply the 10% multiplier to both the risk of infection and risk of hospitalisation due to COVID-19, which fixes this issue:

Clinical outcome	No tix-cil	Tix-cil		
		Company base case (ACM1)	Company base case (updated)	EAG preferred base case
No COVID-19	88.0%	95.9%	88.8%	88.8%
Any COVID-19	12.0%	4.1%	11.2%	11.2%
COVID-19 without hospitalisation	**10.1%**	3.8%	**10.5%**	9.6%
COVID-19 with hospitalisation	1.9%	0.3%	0.7%	1.7%

Abbreviations: ACM, appraisal committee meeting; EAG, External Assessment Group; IC50, half maximal inhibitory concentration; ng/ml; nanograms per millilitre; RRR, relative risk reduction.

Changing Omicron variants of concern



Source: UKHSA technical briefing 51, 10 March 2023. **Notes:** Percentages in brackets indicate the variant prevalence - proportion of variants from sequenced episodes between 20 February 2023 and 26 February 2023. The first red dashed line denotes the start of England's 'Living with COVID' plan at the start of April 2022 and the second indicates the pause of asymptomatic testing for high-risk settings at the end of August 2022. **Abbreviations:** ACM, appraisal committee meeting; UKHSA, UK Health Security Agency.

Real world evidence RECAP - Young Xu et al. 2022

Compared to propensity-matched controls, treated patients had a lower incidence of infection, hospitalisation and all-cause mortality

	Matched controls (n=6,354), number of events (%)	Tix-cil recipients (n=1,733), number of events (%)	Propensity-score analysis hazard ratio (95% CI)
Individual component outcomes (overall cohort)			
SARS-CoV-2 infection	69 (1%)	(<0.5%)*	0.34 (0.13, 0.87)
COVID-19-related hospitalisation	38 (0.5%)	(<0.5%)*	0.13 (0.02, 0.99)
All-cause mortality	99 (2%)	(<0.5%)*	0.36 (0.18, 0.73)

EAG comments

- Considers the propensity matching approach to be reasonable, however there is the potential for residual confounding despite matching
- Highlights wide confidence intervals for individual outcomes
- Study may lack generalisability to current UK context:
  - Conducted in a unique population (mostly male and elderly)
  - Coincided with Omicron BA.1 surge

Notes: *Numbers not shown to protect patient information. **Abbreviations:** CI, confidence interval. EAG, External Assessment Group.

Key issue 3: Repeated dosing of tix-cil

Draft guidance conclusions:

- *"Technology appraisal guidance recommendations must be within the marketing authorisation, therefore the economic analysis should include a single dose of tix-cil only."*

Company response:

- The Summary of Product Characteristics (SmPC) recommends a specific dosing criterion, which does not explicitly prohibit any subsequent dosing
- However, the model has been updated to reflect a single dose of tix-cil in line with the committee's preference

EAG response:

- Satisfied that the company's single dose approach is in line with the committee's preference
- There are minor issues relating to the implementation of the approach in the model including adjustment of:
  - adverse event rates, and
  - COVID-19 cases occurring after the period in which tix-cil is assumed to be effective
- However, correcting these is unlikely to have a significant impact on the ICER

Abbreviations: EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; SmPC, Summary of Product Characteristics.

Key issue 4: Risk of COVID-19 infection without tix-cil (1/2)

Draft guidance conclusions:

- *"Infection risk in the group eligible for tix-cil would likely be lower than general population… because people eligible for tix-cil modify their behaviour, which remains an effective way to reduce risk of infection, despite the substantial burden."*

Company response:

- Using the infection risk for the general population between Aug '21 and Aug '22 of 22.58% is conservative as most of general population have immunity to COVID-19 through vaccination or prior infection
- Based on expert clinical feedback, the target population are at a higher risk of infection and severe outcomes compared to the general population, even with shielding methods in place
- Scenario analysis was conducted to assess the impact on the ICER when varying this parameter ± 20%

Consultation comments:

- Draft guidance implies that because some people continue to modify their behaviour, their true risk cannot be fully considered in the model
- It is unreasonable to expect people to continue to modify their behaviour and many are unable to do this.
- An individual's infection risk is also dependent on other household members

Abbreviations: ICER, incremental cost-effectiveness ratio.

Key issue 4: Risk of COVID-19 infection without tix-cil (2/2)

EAG response:

- No additional evidence has been presented on the risk of infection in the company's proposed population
- The risk range (± 20%) explored in the company's scenario analysis is not sufficient to cover the broad uncertainty regarding future risk of infection
- The period used by the company to estimate risk includes the large peak of cases in late '21 and early '22
  - Restricting this period to estimate the risk in the last 3 months of data provided by the company (May '22 – Aug '22) provides an annual risk of 8%
  - This is much lower than the lower bound estimate tested in the company's scenario analysis
  - The EAG explored impact of scenarios halving and doubling the risk assumed in company base case

Period	Annualised infection risk
Aug '21 – Aug '22	22.58%
May '22 – Aug '22	8%
Dec '22 – Mar '23	~2%*

Note: Access to testing restricted from April '22 onwards

Source: Gov. UK coronavirus cases in England. Accessed 29/03/2023. **Notes:** Calculated by NICE technical team. **Abbreviations:** EAG, External Assessment Group.

Key issue 5: Hospitalisation risk for COVID-19 without tix-cil (1/2)

Draft guidance conclusions:

- *"The rate of hospitalisation is uncertain, but the company's estimate based on Shields et al. [15.9%] is high. A rate of hospitalisation closer to Patel et al. [2.8%] is preferred. However, the hospitalisation rate would be dependent on the risk group under consideration"*

Final assumptions in COVID-19 treatments MTA:

- Committee considered hospitalisation rates between 2.4% and 2.8% for the McInnes cohort, and 4.0% for people at very high risk (with stage 4 kidney disease) contraindicated to Paxlovid

Company response:

- Patel et al. was a preferred source in the MTA, but the population in the MTA is not the same as in the current STA which is narrower in comparison and at significantly greater risk
- Alternative sources show a greater hospitalisation risk (during the Omicron wave) for individual patient groups ranging from 7.7% for people with CLL to 31.9% in people with solid organ transplants
- A study by Lee et al. (2023) has also shown a relationship between antibody response (to vaccination) and severity in people with cancer, those with lymphoma and leukaemia had both the highest risk of hospitalisation and the lowest level of antibody response

Abbreviations: CLL, chronic lymphocytic leukaemia; MTA, multiple technology appraisal; STA, single technology appraisal.

Key issue 5: Hospitalisation risk for COVID-19 without tix-cil (2/2)

Consultation comments:

- Subgroup analysis should be conducted as committee may have underestimated hospitalisation risk in certain high-risk patient groups
- Both hospitalisation and mortality statistics should be considered, studies in people who have had a transplant report hospitalisation rates of up to 27% and mortality rates of up to 15.5%
- The MELODY study investigated antibody response to vaccination in immunocompromised people – solid organ transplant recipients were most likely to have no detectable antibodies following vaccination

EAG response:

- Agrees that specific patient groups may have a higher hospitalisation risk
- The company's model does not consider specific subgroups, therefore the best approach is to use the average risk reported across the target population as provided by Patel et al.
- Assumes a hospitalisation risk of 2.8% based on Patel et al. in its base case, but explores rates of up to 31.9% in its scenario analysis reflect the potential higher risk in some specific groups
- Notes that the estimate of 31.9% for people with solid organ transplants is also uncertain as it is based on a small single-centre study in the US, and may not be representative of risk within the NHS

Key issue 6: Direct utility gain for people receiving tix-cil (1/3)

Draft guidance conclusions:

- *"The committee considered that the vignette [used in the company's utility study] describing someone having tix-cil did not align with the evidence for effectiveness or patient expert testimony, and is likely to overestimate the direct utility gain associated with tix-cil."*

Company response:

- The direct utility gain applied in the model of 0.098 based on the vignette study by Gallop et al. appropriately captures the QoL impact for people treated with tix-cil and is based on the best available data
- Company base case is also conservative as it does not account for a caregiver utility improvement
- Even if the clinical trial collected quality of life data, it would likely not show any difference between treatment arms due to blinding – the utility gain is dependent on being aware of taking tix-cil
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  - [redacted]
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Key issue 6: Direct utility gain for people receiving tix-cil (2/3)

EAG response:

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  - [redacted]
  - [redacted]
- No evidence has been presented on utility benefit for caregivers, so the model should not be considered conservative
  - Discussion of results relating to caregivers were omitted from the company's vignette study

Abbreviations: SACT, systemic anti-cancer therapy.

Key issue 6: Direct utility gain for people receiving tix-cil (3/3)

EAG's updated base case:

- The EAG's original base case at ACM1 included a direct utility gain of 0.098 applied to the 82% of the population who were shielding or partially shielding (**Note:** this is also the company's current base case)
- Company's vignette study reported that 50% of patients would return to their pre-treatment behaviour if there was a new variant which tix-cil was not effective against
- Given the in vitro data, EAG has updated its base case to apply direct utility gain to 50% of the population
- Company's vignette did not include situation where there was no efficacy against 90% circulating variants
- It is plausible that if tix-cil was known to neutralise only 10% of variants, then this would not provide sufficient reassurance for most people to stop shielding
- Therefore, the EAG has explored a scenario assuming direct utility gain applies to only 10% of people

Consultation comments:

- The EAG's original base case is not appropriate. The utility gain should be applied to 100% of patients (those shielding, partially shielding **and** not shielding)
- This is because people who not shielding are often unable to shield and have significant anxiety because of this. These individuals would experience a utility gain from treatment

Abbreviations: ACM, appraisal committee meeting; EAG External Assessment Group.

Key issue 7: Cost of administering tix-cil

Draft guidance conclusions:

- *"The committee considered that there was a substantial gap between company and CMDU estimates of administration cost [£41 and £410, respectively], but concluded that the more conservative estimate using the CMDU costs was more appropriate, given the uncertainty about how tix-cil would be delivered."*

Company response:

- The CMDU cost is not appropriate as CMDUs are an acute service
- Tix-cil is expected to be prescribed upon specialist advice and administered as part of routine specialist care in a hospital, or via secondary care led community services
- Updated cost to align with that used by NHSE in the revised budget impact test (£216 based on administration in an outpatient setting)

EAG response:

- Maintains original estimate of £410 as the eligible population is large and may not be attending hospital appointments regularly enough to provide timely administration
- People also need to be monitored for 1 hour following administration in an environment that does not place them at an additional risk of infection
- However, the company's preferred cost of £216 is explored in the scenario analysis

Consultation comments:

- The CMDU cost is not appropriate as CMDU's will no longer be in place after April 2023. The cost for administering other preventative treatments, such as hep B vaccination for kidney patients should be used

Abbreviations: CMDU, COVID Medicines Delivery Unit; NHSE, NHS England.

Key issue 8: Long COVID risk, duration, utility decrement, cost

Draft guidance conclusions:
"Substantial uncertainty about the effects of long COVID. Committee preferred to align with the EAG's estimates as these are more closely aligned with the estimates used in MTA on COVID-19 treatments."

Company response:

- The base case has been updated to use the EAG's assumptions for long COVID cost and utility, however the company would like to highlight that there is no evidence to support a utility waning assumption

Long COVID parameter	Company (ACM1)	EAG
Risk (not hosp.)	34.8% - Augustin et al. '22	12.7% - Ballering et al. '22
Duration	Lognormal curve from MTA – ONS May '22, with adjustment to account for lower proportion recovering between 5 months and 1 year in PHOSP-COVID cohort (Evans et al. '22)	Lognormal curve from MTA – ONS October '22, without Evans et al. adjustment – company's extrapolations counterintuitive and result in longer duration of long COVID than would be expected based on latest ONS data
Utility decrement	Based on Evans et al. '22 (not recovered) Utility decrement assumed constant over duration of long COVID ***Updated to align with EAGs approach***	Based on Evans et al. '22 (not recovered and unsure) Assumed linear improvement over duration of long COVID (50% utility decrement at y5)
Cost	£2,500 – from MTA exploratory scenario ***Updated to align with EAGs approach***	£2,267 - chronic fatigue syndrome (Hunter et al. '17)

Other issues – proportion requiring invasive mechanical ventilation

Background

- The key issues already presented cover all differences between the company's and EAG's base case except for the proportion of people hospitalised who require invasive mechanical ventilation (IMV)

Table 1: Company and EAG assumptions, hospitalisation distribution and proportion requiring invasive mechanical ventilation

	Company (Cusinato et al.)	EAG (Gov.uk Oct 2022 and Cusinato et al. 2nd wave)
No oxygen	26.10%	29.40%
Low-flow oxygen	40.70%	41.42%
NIV / high-flow oxygen	17.80%	24.26%
IMV or ECMO	**15.40%**	**4.92%**

EAG comments:

- The company used data averaged across first and second waves of COVID-19
- The proportion requiring IMV in the Omicron wave is much lower
- The EAG prefers to use estimates based on the general population of 4.92% for year up to Oct 2022 and 2.51% for most recent 3 months
- Upper estimate of 4.92% used as EAG acknowledges proportion on IMV may be higher in target population

Final assumption in COVID-19 treatments MTA:

- The proportion requiring invasive mechanical ventilation was assumed to be 4.12% based on gov.uk data

What proportion of people hospitalised are likely to require invasive mechanical ventilation?

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Abbreviations: EAG, External Assessment Group; ECMO, extra corporeal membrane oxygenation; IMV, invasive mechanical ventilation; MTA, multiple technology appraisal; NIV, non-invasive ventilation.

Key company and EAG base case assumptions

Assumption	Company	EAG
Efficacy	Tix-cil effective against 10% circulating variants – multiplier applied to RRR infection only	Tix-cil effective against 10% circulating variants – multiplier applied to RRR infection **and** hospitalisation
Direct utility gain	0.098 for 82% of target population	0.098 for 50% of target population
Administration cost	£216 (NHSE)	£410 (CMDU)
Risk of hospitalisation	15.9% - Shields et al. 2022	2.8% - Patel et al. 2022
Risk of infection	12.01% (6 month risk)	
Proportion requiring IMV	15.40%	4.92%
Long COVID risk (not hospitalised)	34.8% - Augustin et al. 2022	12.7% - Ballering et al. 2022
Long COVID duration	Lognormal curve from MTA – ONS May ‘22, with Evans et al. adjustment	Lognormal curve from MTA – ONS October ‘22, without Evans adjustment
Long COVID cost	£2,267 annually - chronic fatigue syndrome (Hunter et al. 2017)	
Long COVID disutility	Based on Evans et al. ‘22 (not recovered and unsure). Assumed linear HRQoL improvement over time for 5 years	

Abbreviations: CMDU, COVID Medicines Delivery Unit; EAG, External Assessment Group; HRQoL, health-related quality of life; MTA, multiple technology appraisal; NHSE, NHS England; ONS, Office for National Statistics; RRR, relative risk reduction.

Company and EAG base case results, PAS price

Company deterministic incremental base case results

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
No prophylaxis	[redacted]	[redacted]			
Tix-cil	[redacted]	[redacted]	[redacted]	[redacted]	£15,201

EAG deterministic incremental base case results

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
No prophylaxis	[redacted]	[redacted]			
Tix-cil	[redacted]	[redacted]	[redacted]	[redacted]	£54,668

Abbreviations: EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; QALY, quality-adjusted life year.

Company deterministic scenario analysis – PAS price

Key issue	Scenario (applied to company base case)	ICER (£)
0	**Company base case**	£15,201
#6	Apply utility gain to 50% of patients	£20,143
#4	Increase risk of infection (without tix-cil) by 20%	£13,668
#4	Reduce risk of infection (without tix-cil) by 20%	£16,969
#4, #6	Increase risk of infection (without tix-cil) by 20% and apply utility gain to 50% of patients	£17,694
#4, #6	Reduce risk of infection (without tix-cil) by 20% and apply utility gain to 50% of patients	£23,110
#2	Tix-cil effective against greater proportion of circulating variants (30% threshold)	£12,911

Abbreviations: ICER, incremental cost-effectiveness ratio; PAS, patient access scheme.

EAG deterministic scenario analysis – PAS price

Key issue	Scenario (applied to EAG base case)	Inc. costs (£)	Inc. QALYs	ICER (£)
0	**EAG base case**	[redacted]	[redacted]	£54,668
#2	Tix-cil effective against greater proportion of circulating variants (30% threshold)	[redacted]	[redacted]	£50,716
#5	Higher risk of hospitalisation without tix-cil (31.9%)	[redacted]	[redacted]	£43,212
#7	Lower administration cost (£216)	[redacted]	[redacted]	£46,514
#4	Risk of infection without tix-cil halved (6% in 6 months)	[redacted]	[redacted]	£54,083
#4	Risk of infection without tix-cil doubled (24% in 6 months)	[redacted]	[redacted]	£56,083
#6	Direct utility gain applied to smaller proportion (10%)	[redacted]	[redacted]	£242,097
#4, #6	Risk of infection without tix-cil halved (6% in 6 months) and direct utility gain applied to smaller proportion (10%)	[redacted]	[redacted]	£253,085
#2 #5	Tix-cil effective against greater proportion of circulating variants (30% threshold) and higher risk of hospitalisation without tix-cil (31.9%)	[redacted]	[redacted]	£28,796

Abbreviations: EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; QALY, quality-adjusted life year.

Equality considerations

New equality issues raised in response to consultation:

- The draft guidance discriminates on the grounds of disability:
    - People who are immunocompromised should be able to have the same level of protection as the general population has through vaccines, which were approved much more quickly
    - The decision has denied the ability for immunocompromised people to return to a more normal life, addressing the risk of COVID-19 in people who are immunocompromised must be prioritised
    - Immunocompromised people are most likely to need to attend care settings, and the current danger of COVID-19 in addition to reduced mask wearing in these settings places them at an unacceptable risk
- A disproportionate number of those unable to shield are from minority ethnic groups, due to the higher likelihood that they are in employment without remote working options

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Back up slides

Key issue 1: Eligible population and heterogeneity (2/5)

Independent Advisory Group (IAG) report – Group A1, A2

Group	Description
Group A1 – Known failure of vaccination	• Person in any risk group unable to complete vaccination schedule according to contemporaneous recommendations[1] • 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[2] • 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 A1: People who have not been vaccinated or have been admitted to hospital for moderate or severe COVID-19 despite vaccination

Group A2: Primary or secondary immunodeficiency, B-cell depleting therapy, HSCT in last 12 months, CAR-T, specific haematological malignancies or solid organ transplant

Abbreviations: CAR-T, Chimeric antigen receptor T-cell therapy. HSCT, haematopoietic stem cell transplant.

Key issue 1: Eligible population and heterogeneity (3/5)

Independent Advisory Group (IAG) report – Group B, C

Group B – Anticipated sub-optimal vaccination response: physician discretion advised	• Any person with haematological malignancies 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[3] within 12 months • People who have had cancer resected [4]within 3 months and who received no adjuvant chemotherapy or radiotherapy • People with immune mediated inflammatory diseases (IMIDs) on biologics[5] 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
Group B – Anticipated sub-optimal vaccination response: physician discretion advised	• 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 ≥ 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) • 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

Group B: Most other cancers, chemotherapy, biologics, immunosuppressants, kidney or liver disease, HSCT beyond last 12 months, HIV (CD4 < 350), Down's syndrome

Group C: Inherited anaemia, rare neurological conditions, cancer (resected within 3-12 months, no adjuvant therapy), HIV (CD4 > 350)

Abbreviations: HIV, human immunodeficiency virus; HSCT, haematopoietic stem cell transplant.

In vitro data

In vitro data that will be considered by the committee:

Lead	Title	Date	Tix-cil neutralisation versus…		
			BQ.1	BQ.1.1	XBB
Planas 2022	Resistance of Omicron subvariants BA.2.75.2, BA.4.6 and BQ.1.1 to neutralizing antibodies	Nov 22			
Arora 2023	Omicron sublineage BQ.1.1 resistance to monoclonal antibodies	Nov 22			
Wang 2022	Alarming antibody evasion properties of rising SARS- CoV-2 BQ and XBB subvariants	Dec 22			
Cao 2022	Imprinted SARS-CoV-2 humoral immunity induces convergent Omicron RBD evolution	Dec 22			
Imai 2023	Efficacy of Antiviral Agents against Omicron Subvariants BQ.1.1 and XBB	Jan 23			

Not evaluated

No neutralisation

Abbreviations: RBD, receptor-binding domain.