NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Amivantamab for treating EGFR exon 20 insertion mutation-positive advanced non-small-cell lung cancer after platinum-based chemotherapy [ID3836]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Amivantamab for treating EGFR exon 20 insertion mutation-positive advanced non-small-cell lung cancer after platinum-based chemotherapy [ID3836]

Contents:

The following documents are made available to consultees and commentators:

The **final scope** and **final stakeholder list** are available on the NICE website.

Pre-technical engagement documents

1. **Company submission** from **Janssen-Cilag**

2. **Clarification questions and company responses**

3. **Patient group, professional group and NHS organisation submissions** from:
   a. EGFR Positive UK
   b. Roy Castle Lung Cancer Foundation

4. **Evidence Review Group report** prepared by Kleijnen Systematic Reviews

5. **Evidence Review Group report – factual accuracy check**

Post-technical engagement documents

6. **Technical engagement response from company**

7. **Technical engagement responses and statements from experts:**
   a. Dr Alastair Greystoke – clinical expert, nominated by British Thoracic Oncology Group & National Cancer Research Institute
   b. Clinical expert, nominated by The Royal College of Pathologists
   c. Mrs Angela Terry – patient expert, nominated by EGFR Positive UK
   d. Miss Deborah Littell – patient expert, nominated by EGFR Positive UK

8. **Evidence Review Group critique of responses to technical engagement** prepared by Kleijnen Systematic Reviews
   a. ERG critique of company response to technical engagement
   b. ERG response to Dr Alastair Greystoke's technical engagement response

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

Amivantamab as a monotherapy for treatment of adult patients with locally advanced or metastatic NSCLC with activating EGFR Exon 20 insertion mutations, whose disease has progressed on or after platinum-based chemotherapy [ID3836]

Document B

Company evidence submission

9th February 2022

File name	Version	Contains confidential information	Date
ID3836_Janssen_Amivantamab_Document B_09Feb22_FINAL [REDACTED]	FINAL	Yes	9th February 2022

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Abbreviations

ADR	Adverse drug reaction
AE	Adverse event
AIC	Akaike Information Criterion
AMI	Amivantamab
AUC	Area under the curve
BIC	Bayesian Information Criterion
BICR	Blinded independent committee review assessed
BMI	Body mass index
BNF	British National Formulary
BSA	Body surface area
BSC	Best supportive care
CBR	Clinical benefit rate
CDF	Cancer Drugs Fund
CEM	Cost-effectiveness model
CI	Confidence interval
CR	Complete response
CRD	Centre for Reviews and Dissemination
CRF	Case report form
CSR	Clinical Study Report
DFS	Disease free survival
DOR	Duration of response
DSA	Deterministic sensitivity analysis
EAS	Efficacy analysis set
ECOG	Eastern Cooperative Oncology Group
ECOG	Eastern Cooperative Oncology Group Performance Status
EGFR	Epidermal growth factor receptor
eMIT	Electronic market information tool
EQ-5D-3L	EuroQoL 5-dimensions 3-levels
EQ-5D-5L	EuroQoL 5-dimensions 5-levels
ESMO	European Society for Medical Oncology
Exon20ins	Exon 20 insertion mutations
FDA	Food and Drugs Administration
GFR	Glomerular filtration rate
HCP	Healthcare professional
HIV	Human immunodeficiency virus
HRQoL	Health-related quality of life
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
ILAP	Innovative Licensing and Access Pathway
ILD	Interstitial lung disease
INV	Investigator-assessed

IPW	Inverse probability weighting
IRR	Infusion-related reaction
LOT	Line of therapy
LS	Least squares
MAD	Maximum administered dose
MET	Mesenchymal epithelial transition
MHRA	Medicines and Healthcare Products Regulatory Agency
MTD	Maximum tolerated dose
NCCN	National Comprehensive Cancer Network
NCRAS	National Cancer Registration and Analysis Service
NE	Not evaluable
NGS	Next-generation sequencing
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
NR	Not reported
NSCLC	Non-small cell lung cancer
ORR	Overall response rate
OS	Overall survival
PAS	Patient Access Scheme
PCR	Polymerase chain reaction
PD	Progressed disease
PFS	Progression-free survival
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
PHE	Public Health England
PPS	Post-progression survival
PR	Partial response
PRO	Patient-reported outcome
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALY	Quality-adjusted life year
RCT	Randomised controlled trial
RECIST	Response Evaluation Criteria in Solid Tumours
RP2D	Recommended Phase 2 dose
RWE	Real world evidence
SACT	Systemic Anti-Cancer Therapy
NSCLC-SAQ	Non-small cell lung cancer Symptom Assessment Questionnaire
SAS	Statistical Analysis System
SCLC	Small cell lung cancer
SD	Stable disease
SLR	Systematic literature review

SoD	Sum of diameters
TBD	To be decided
TEAE	Treatment-emergent adverse event
TKI	Tyrosine kinase inhibitor
TTD	Time to treatment discontinuation
TTF	Time to treatment failure
TTNT	Time to next treatment
EQ-5D-5L VAS	EuroQol-5 dimensions 5-levels visual analogue score
WTP	Willingness-to-pay

Submission Summary

Amivantamab is the first targeted treatment in EGFR Exon 20 insertion mutated NSCLC

- This submission considers amivantamab in patients with epidermal growth factor receptor (EGFR) Exon 20 insertion (Exon20ins) mutated non-small cell lung cancer (NSCLC) after platinum-based chemotherapy. EGFR Exon20ins mutations are amongst the rarest and most harmful lung cancer mutations, and effective treatment is urgently needed by patients. It is especially needed for those in second line and later, for whom conventional chemotherapy has failed and therefore no effective treatment options exist.
- There is no established standard of care (SoC) for this population, meaning that treatment is piecemeal and lacking clinical justification. Amivantamab is the first targeted therapy to demonstrate efficacy in patients with EGFR Exon20ins NSCLC after progression on or after platinum based chemotherapy.[1] In an adjusted comparison of CHRYSALIS trial data versus real-world evidence (RWE) data, amivantamab statistically significantly extended progression-free survival (PFS) by [redacted] months and overall survival (OS) by [redacted] months versus SoC (see Section B.2.9).
- Given the urgent and unmet need for an effective targeted therapy in the EGFR Exon20ins population, we argue that the uncertainties associated with the submission could be best managed in the Cancer Drugs Fund (CDF). This will allow patients access to amivantamab while collecting further data to confirm the clinical outcomes for amivantamab in UK patients and the comparative effectiveness of amivantamab versus UK SoC.

EGFR Exon 20 insertion mutated NSCLC patients have an urgent and acute unmet need for a safe, effective, targeted treatment

- There is significant evidence that patients with Exon 20 inserted NSCLC suffer a 'dual burden' of having one of the most severe lung cancer mutations and having no effective treatment for this severe mutation:
    - Real-world data suggest that patients with EGFR Exon20ins mutations have a 75% increased risk of death (HR = 1.75), compared to patients with common EGFR mutations that are sensitive to EGFR-tyrosine kinase inhibitors (TKIs).[2]
    - Unlike patients with common EGFR mutations, those with EGFR Exon20ins mutations respond poorly to EGFR-TKIs and are managed with treatments of limited efficacy, leading to a shorter life expectancy.[3-6]
- Patients with EGFR Exon20ins mutated NSCLC are also subject to stigma, partially as a result of lung cancers being associated with smoking behaviours,[7] despite the comparatively large number of these patients who are never-smokers compared to patients with EGFR-wild-type NSCLC.[8] This stigma can result in decreased symptom reporting,[9] and delays in presentation, diagnosis and treatment,[10] which increases the social value of addressing the unmet need of the population.
- Feedback from clinical experts confirmed that there is no established UK SoC, and that patients with EGFR Exon20ins mutations are treated in a manner broadly similar to patients without gene mutations per NICE Guideline 122.[11, 12] Therefore, this submission considers UK SoC, a basket of treatments comprising chemotherapy, immuno-oncology agents (IOs), and EGFR-TKIs, as the most relevant comparator that would be displaced by any new treatments due to:
    - The lack of specific clinical guidelines for the EGFR Exon20ins population

- Data from RWE studies that show the lack of a definitive SoC therapy (see Section B.2.9)
- Feedback from clinical experts that treatment decisions are often made on a case-by-case basis based on physician and patient choice, taking into account factors such as prior treatments received.[12]

Amivantamab is an innovative product

- Amivantamab is the first targeted treatment for adult patients with EGFR Exon20ins mutated NSCLC.[1] This is a population with a high unmet need and a particularly poor prognosis, in part due to the lack of approved, targeted therapies available. Amivantamab offers substantial efficacy benefits versus existing therapies (see Section B.2.9).
- In addition to offering an innovative, targeted and meaningful treatment for patients with an immense unmet need and leading to benefits with regards to alleviating their clinical burden, the introduction of amivantamab to UK clinical practice has the potential to improve health inequity related to the stigma that can be associated with a lung cancer diagnosis, the relevance of cultural differences on treatment-seeking behaviours, and the impact of the COVID-19 pandemic on time to diagnosis (see Section B.1.4). These equity considerations are not inherently captured within the cost per quality-adjusted life year (QALY) or budget impact frameworks but should be considered as part of the decision-making process.

B.1 Decision problem, description of the technology and clinical care pathway

B.1.1 Decision problem

The submission presents the clinical- and cost-effectiveness for amivantamab, in line with its marketing authorisation. Specifically, this submission positions amivantamab for the treatment of adult patients with locally advanced or metastatic NSCLC with activating EGFR Exon20ins mutations, whose disease progressed on or after platinum-based chemotherapy. The marketing authorisation was granted on 15th November 2021.[13]

Prior to the marketing authorisation for amivantamab, there were no approved, targeted therapies for patients with advanced EGFR Exon20ins mutated NSCLC in the UK, and no specific treatment recommendations are provided in UK clinical treatment guidelines. Therefore, there is substantial unmet need in this patient population, as treatment outcomes remain poor with currently used treatments (see further detail in Section B.1.3.2). Given this, the company applied for an accelerated licence through the Medicines and Healthcare products Regulatory Agency (MHRA) on 1st March 2021 which was assessed under Project Orbis via the accelerated (150-day) procedure.

The decision problem addressed in this submission is largely aligned to that defined in the final scope issued by the National Institute for Health and Care Excellence (NICE), apart from a small change to the population wording to align with the license and the justified exclusion of testing costs for EGFR Exon20ins mutations in the economic analysis. Please see Table 1 for more details.

Cancer Drugs Fund statement

Amivantamab is positioned as a candidate to be recommended for use on the Cancer Drugs Fund (CDF) in this submission. As further described in Section B.1.3.2.2, there is a substantial unmet need for a targeted treatment for EGFR Exon20ins mutated NSCLC. Amivantamab will meet this unmet need by addressing the inconsistency in the availability of effective treatment options and improve prognosis in this subset of the EGFR mutated NSCLC population. Amivantamab offers an innovative, targeted treatment that has demonstrated improved OS and PFS when compared to existing real-world drug therapies (see Section B.2.9). As such, we propose that amivantamab should be recommended for use in the NHS as this will allow patients to have access to an efficacious therapy (with unprecedented OS benefit versus SoC) that specifically targets this rare mutation while allowing for the collection of more data in a real-world setting to definitively demonstrate this OS benefit in the UK setting.

Further details can be found in Section B.2.13.3, and a proposed data collection plan is presented in Section B.2.11.

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 with EGFR Exon 20 insertion-positive NSCLC after previous platinum-based chemotherapy	Adult patients with locally advanced or metastatic NSCLC with activating EGFR Exon20ins, whose disease has progressed on or after platinum-based chemotherapy	Aligned with the licensed indication for amivantamab.
Intervention	Amivantamab	Amivantamab monotherapy, administered via IV infusion • 1,050 mg for patients with body weight <80 kg • 1,400 mg for patients with body weight ≥80 kg	In line with the intervention received by patients falling within the licensed indication in the registrational CHRYSALIS trial.
Comparator(s)	Established clinical management without amivantamab, including but not limited to: • Atezolizumab • Nivolumab (subject to an ongoing NICE appraisal) • Pembrolizumab (for disease with PD-L1 >1%) • Chemotherapy such as docetaxel alone or with nintedanib, pemetrexed and carboplatin	UK standard of care (SoC) consisting of TKIs, IO agents, platinum-based chemotherapy and non-platinum-based chemotherapy.	Aligned with the final NICE scope. Further details can be found in Section B.1.3.2.
Outcomes	The outcome measures to be considered include: • OS • PFS or DFS • Response rate • TTD • AEs • HRQoL	Key outcomes from the CHRYSALIS trial include: • ORR • CBR • DOR • PFS • TTF • OS • AEs	All outcomes requested in NICE's final scope are presented, with additional outcomes included to capture the most important health benefits for amivantamab.

		• HRQoL	
Economic analysis	The reference case stipulates that the cost-effectiveness of treatments should be expressed in terms of incremental cost per QALY. 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 PSS perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. The use of amivantamab is conditional on the presence of an EGFR Exon20ins mutation. The economic modelling should include the costs associated with diagnostic testing for EGFR Exon20ins in people with NSCLC who would not otherwise have been tested. A sensitivity analysis should be provided without the cost of the diagnostic test.	The cost-effectiveness of the treatments evaluated in this appraisal is expressed in terms of incremental cost per QALY. A lifetime time horizon was adopted to capture all relevant costs and health-related utilities. All costs and utilities were discounted at a rate of 3.5% per year in alignment with the NICE guide to the methods of technology appraisal. Costs were considered from an NHS and PSS perspective. The cost of diagnostic testing for EGFR Exon20ins mutations has not been included within the economic analysis.	The genetic test for the EGFR Exon20ins mutation, with a scope covering small variant detection, is included in the National Genomic Test Directory. The directory specifies which genomic tests are commissioned by the NHS in England and is available at: https://www.england.nhs.uk/publication/national-genomic-test-directories/ EGFR Exon20ins mutations can be tested as part of the EGFR test conducted at diagnosis for all NSCLC patients. As such, Janssen, considers there are no additional costs likely to be incurred by the NHS over and above the current standard of care EGFR testing requirements for all NSCLC patients. Thus, the economic modelling excludes the costs associated with diagnostic testing for EGFR in people with NSCLC. This approach is aligned with that taken in previous appraisals in which testing for a specific mutation would be required (such as TA595, TA643 and TA670).[14-16] Some treatments comprising UK SoC (such as atezolizumab, pembrolizumab, nivolumab, afatinib and nintedanib) are subject to Patient Access Schemes (PASs). Due to their confidential nature, these discounts are not taken into account in the base case cost-effectiveness analysis.

Special considerations including issues related to equity or equality	None	Ethnicity, specifically relating to Asian populations, is an equality consideration that is relevant for the committees to consider.	This has been demonstrated through the social and cultural implications of the signs and symptoms of lung cancer in Asian culture,[17, 18] higher rates of diagnosis of NSCLC with activating EGFR Exon20ins in Asian patients,[3] and also direct prejudice and discrimination, at a time when patients are facing even poorer outcomes during the COVID-19 pandemic.[19, 20] As such, Asian patients are disproportionately affected by EGFR Exon20ins driven NSCLC. This raises the prospect of patients being disproportionately disadvantaged on the basis of race. For further discussion of issues related to equality, please see Section B.1.4.
Other considerations	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.	Amivantamab is presented within the full marketing authorisation for the treatment of adult patients with locally advanced or metastatic NSCLC with activating EGFR Exon20ins, whose disease has progressed on or after platinum-based chemotherapy The impact of stigma on people living with lung cancer, including patients and caregivers, is also of relevance to this submission and is not inherently captured in the cost/QALY measure.	The effect of stigma should be included in the decision making process, as it is provided for by the NICE social values judgment principles document.[21] Social value judgement considerations should therefore, be taken into account when deciding whether amivantamab is cost-effective in this underserved population. The impact of stigma on people living with lung cancer can impact symptom reporting,[9] interactions with HCPs and therefore delay in presentation, diagnosis and treatment.[10] Furthermore, lung cancer patients uniquely experience added burden from developing an illness that the public recognises is directly associated with smoking behaviours,[7] despite the fact there is an increasing number of the patient population who are never-smokers.[8] Additionally, EGFR Exon20ins mutations are more commonly seen in never-smokers

			compared with wild-type EGFR.[5] See Section B.1.3.1 for further information. It should further be considered that, since NSCLC and COVID-19 have some overlapping signs and symptoms, messages regarding early diagnosis of NSCLC may be negated by messages necessary to control the pandemic. Due to these overlapping symptoms, patients with NSCLC may be misdiagnosed, and urgent referrals for lung cancer have fallen during the COVID-19 pandemic. These delays in diagnosis will likely lead to an increase in mortality and morbidity from lung cancer, increasing still further the unmet need of these patients.[22]

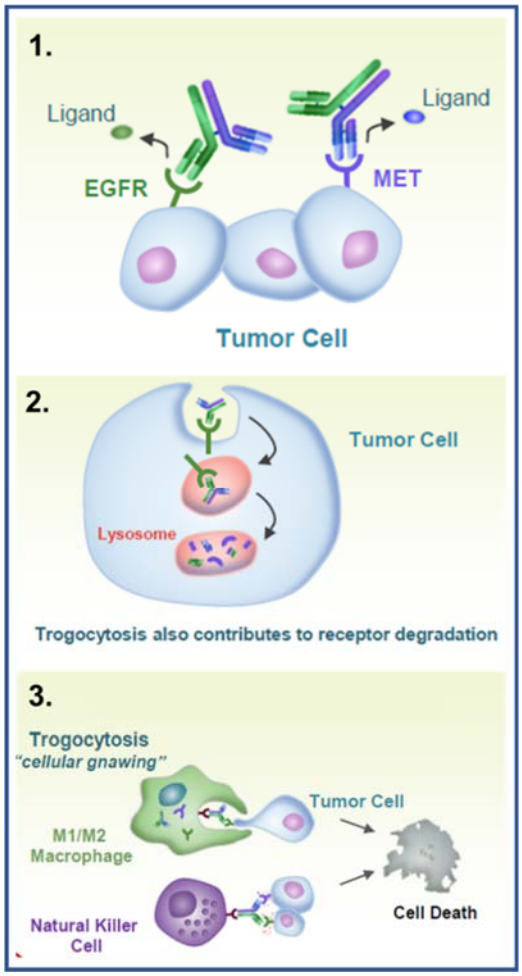
Abbreviations: AE: adverse event; CBR: clinical benefit rate; DFS: disease free survival; DOR: duration of response; EGFR: epidermal growth factor receptor; HCP: healthcare professional; HRQoL: health-related quality of life; IV: intravenous; NHS: National Health Service; NICE: National Institute for Health and Care Excellence; NSCLC: non-small cell lung cancer; ORR: overall response rate; OS: overall survival; PAS: patient access scheme; PFS: progression free survival; PSS: Personal Social Services; QALY: quality adjusted life year; TTD: time to discontinuation; TTF: time to treatment failure; UK: United Kingdom.
Source: NICE Final Scope.[23]

B.1.2 Description of the technology being appraised

A summary of the mechanism of action, marketing authorisation, costs, and administration requirements for amivantamab are presented in Table 2.

Table 2: Technology being appraised

UK approved name and brand name	Amivantamab (Rybrevant®)
Mechanism of action	Amivantamab (JNJ-61186372) is a novel, fully human, bispecific antibody developed using Genmab's DuoBody® technology that targets both EGFR and the protooncogene protein MET.[24, 25] Amivantamab demonstrates activity against NSCLC tumours via three mechanisms of action inhibiting tumour growth and survival regulatory pathways:[1, 26] 1. Inhibition of ligand binding 2. EGFR/MET receptor degradation 3. Immune cell-directing activity Overall, the presence of EGFR and MET on the surface of tumour cells allows for targeting of these cells for destruction by immune effector cells, such as natural killer cells and macrophages, through antibody-dependent cellular cytotoxicity and trogocytosis mechanisms, respectively (see Figure 1).[27, 28] The EGFR activating mutation was identified as a predictive biomarker in 2004 allowing the selection of patients for treatment with the EGFR tyrosine kinase inhibitors (TKIs).[29] Unlike common EGFR mutations however, the Exon20ins mutation induces unique conformational changes in EGFR that affect TKI affinity which in turn leads to resistance of Exon20ins to most EGFR TKIs.[3, 30, 31] Amivantamab is effective in Exon20ins mutated NSCLC as it binds to EGFR extracellularly such that it is not affected by the conformational changes affecting the TKI binding pocket.[32] In addition, by targeting activating and resistance EGFR mutations and MET mutations and amplifications, amivantamab addresses the two major mechanisms of resistance to TKIs.[32]

	Figure 1: Cellular mechanism of action of amivantamab  **Source:** Sabari *et al.* (2021).[33]
Marketing authorisation/CE mark status	A marketing authorisation application for amivantamab was submitted to the MHRA on 1st March 2021. It was assessed under Project Orbis via the accelerated (150-day) procedure. A marketing authorisation was granted on 15th November 2021. Marketing authorisation was granted by the European Commission on 9th December 2021.[34] In the US, amivantamab received Breakthrough Therapy Designation from the FDA in March 2020 and FDA approval on 25th May 2021.[35, 36]
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	Amivantamab as a monotherapy is licenced for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with activating epidermal growth factor receptor (EGFR) Exon 20 insertion mutations, whose disease has progressed on or after platinum-based chemotherapy. **Contraindications[27]** No contraindications beyond hypersensitivity to the active substance(s) or to any of the excipients.
Method of administration and dosage	Amivantamab monotherapy, administered via IV infusion[35] • 1,050 mg for patients with body weight <80 kg • 1,400 mg for patients with body weight ≥80 kg

	A subcutaneous formulation of amivantamab is currently being explored but this is not considered further in this submission.[37]
Additional tests or investigations	An accurate and validated assay for the presence of EGFR Exon20ins is necessary for the selection of patients for treatment with amivantamab. The presence of an EGFR Exon20ins must be established prior to initiation of treatment with amivantamab.[27] EGFR Exon 20 insertions mutations are included in the National Genomic Test Directory for cancer and can be routinely tested in clinical practice in the Genomic Lab Hubs, as part of the diagnosis and treatment selection for patients with EGFR alterations. This means EGFR Exon 20ins can be tested routinely as part of a panel of genes alongside other oncogenic drivers in a standardised and fully validated approach across different centres throughout the UK. Thus, the cost of mutation testing has not been factored into the economic results of this submission.
List price and average cost of a course of treatment	The list price for amivantamab is £1,079.00 per vial. Based on the base case economic analysis, the mean time on treatment is estimated to be [redacted] months for amivantamab, resulting in an average cost of a course of treatment of £[redacted] (at list price) and £[redacted] (at PAS price).
Patient access scheme (if applicable)	A confidential PAS discount has been proposed for amivantamab of [redacted]%. Therefore, the proposed with-PAS price is [redacted] per vial.

Abbreviations: EGFR: epidermal growth factor receptor; FDA: Food and Drug Administration; IV: intravenous; MET: mesenchymal epithelial transition; MHRA: Medicines and Healthcare products Regulatory Agency; NSCLC: non-small cell lung cancer; SmPC: Summary of Product Characteristics; UK: United Kingdom.

B.1.3 Health condition and position of the technology in the treatment pathway

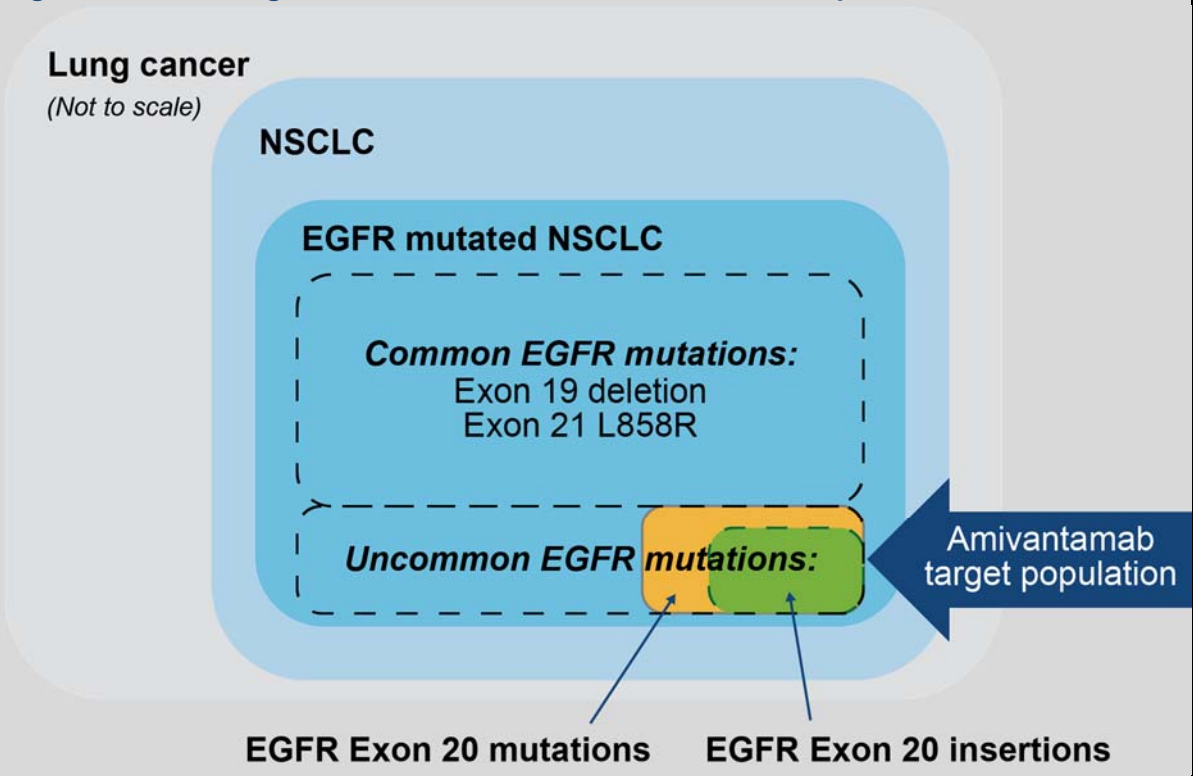
B.1.3.1 Disease overview

Disease overview summary

Disease classification, epidemiology and prognosis

- NSCLC is generally categorised based on characteristic mutations present in tumours, with alterations in EGFR among the most well-established. In the UK, the prevalence of EGFR mutations in any NSCLC histology is estimated to range from 4–17.3%.[38, 39]
- Approximately 10% of EGFR mutations comprise uncommon mutations, including Exon20ins (see Figure 2). Prevalence of EGFR Exon20ins is estimated to be [redacted] in any stage NSCLC and [redacted] in advanced NSCLC.[40]

Figure 2: Positioning of EGFR Exon20ins mutations in NSCLC patients



Abbreviations: EGFR: epidermal growth factor receptor; L858R: leucine-to-arginine substitution at position 858; NSCLC: non-small cell lung cancer.

- This rare mutation is more commonly seen in women, Asian people and never-smokers compared with wild-type EGFR and is associated with a poorer prognosis than patients with common EGFR mutations.[3, 5, 41] Specifically, real-world evidence (RWE) demonstrates that patients with EGFR Exon20ins have a 75% increased risk of death and a 93% increased risk of disease progression or death compared to patients with common EGFR mutations.[42]

Disease burden

- The humanistic burden of NSCLC is substantial and well documented, with patients experiencing reduced health-related quality of life (HRQoL) compared with the general population.[43] While the humanistic burden of patients with EGFR-mutated NSCLC with Exon20ins has not been widely studied, preliminary evidence indicates a significant social, emotional and physical impact on the lives of patients with NSCLC harbouring EGFR Exon20ins.[44]
- A patient and caregiver study identified the main symptoms for patients with EGFR-mutated NSCLC with Exon20ins that impact patient quality of life to be fatigue, cough, breathlessness, nausea and/or vomiting, while carers themselves also reported a reduced quality of life.[45]

Societal perceptions of lung cancer

- Patients with lung cancer uniquely experience an added burden from developing an illness that the public recognises to be directly associated with smoking behaviours, with 86% of patients with EGFR-mutated NSCLC reporting that they feel people with lung cancer are viewed negatively.[7, 45]

- This negative perception may influence the interaction between patients and health care professionals (HCPs), with 42% of patients feeling as though HCPs are less sympathetic towards them as compared with patients with other cancers. Perceived blame by the patient has been reported to lead to higher depression scores in the patient and caregiver alike.[46]
- The impact of having a new treatment option available to patients to alleviate stigma and its effects should be explicitly considered within the decision-making process since the societal, negative perceptions of lung cancer are not inherently captured within the cost per QALY framework.

B.1.3.1.1. Disease classification and prognosis

Classification

There are two major subtypes of lung cancer: small cell lung cancer (SCLC) and NSCLC, with NSCLC accounting for approximately 85% of all lung cancer cases.[3, 47] NSCLC can be further classified into three distinct histological types: squamous-cell carcinoma, adenocarcinoma and large-cell carcinoma. Adenocarcinoma is the most common, comprising 40–43% of all lung cancer cases.[48]

NSCLC is generally categorised based on characteristic mutations present in tumours. Among the most well-established driver mutations (genetic mutations which accelerate cancer progression) in NSCLC are alterations in EGFR, a tyrosine kinase. Approximately 10% of NSCLC tumours harbour a mutation in the EGFR gene, which is involved in cellular processes including cell survival, growth, proliferation and migration. Hence, mutations of this gene contribute to tumour growth and spread.[20, 49]

In NSCLC, mutations in the EGFR gene typically occur in Exons 18–21.[4] Approximately 90% of EGFR mutations comprise Exon 19 deletions and Exon 21 L858R substitutions; these are collectively referred to as the common EGFR mutations. The remaining 10% are made up of uncommon mutations, including Exon20ins. The overall prevalence of EGFR Exon20ins has been found to be [redacted] in any stage NSCLC and [redacted]) in advanced NSCLC based on meta-analysis.[4, 5, 40, 47] No incidence data are currently available for patients with NSCLC with EGFR Exon20ins.

EGFR Exon20ins mutations are heterogeneous at the molecular level with more than 70 types of mutations identified to date.[3, 4, 20, 50, 51]

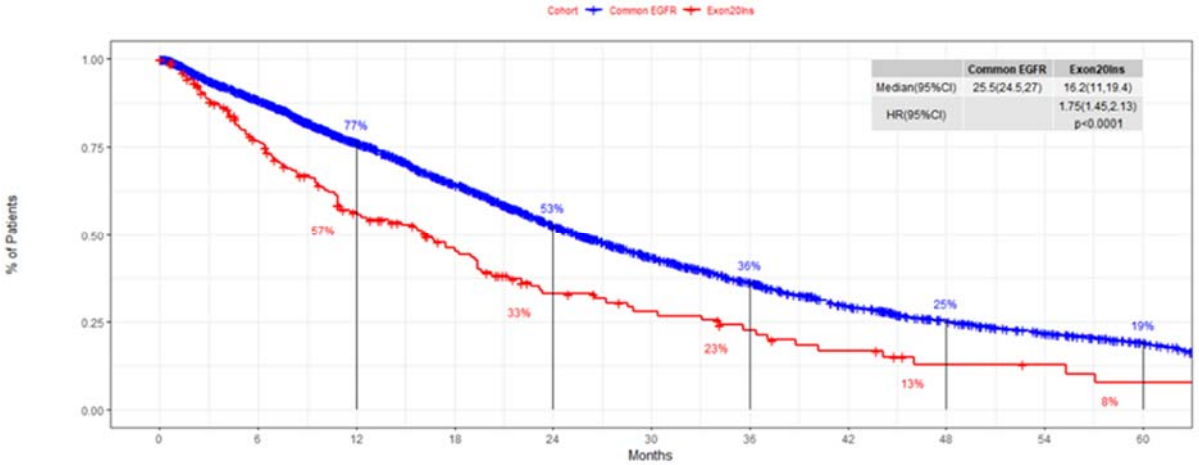
Prognosis

Patients with early-stage NSCLC are often either asymptomatic or present with non-specific symptoms. As such, the majority of patients are diagnosed when the disease is already advanced.[52] In addition, the stigma associated with the disease may also contribute to delayed diagnosis (see Section B.1.3.2.2 for details). Advanced NSCLC refers to both inoperable (unresectable), locally advanced (Stage IIIb/IIIc) and metastatic (Stage IV) disease.[53] The five-year survival rate for patients with metastatic NSCLC is poor and ranges from approximately 0–10%.[54]

Patients with EGFR Exon20ins-mutated NSCLC have a poorer prognosis than those with common EGFR mutations.

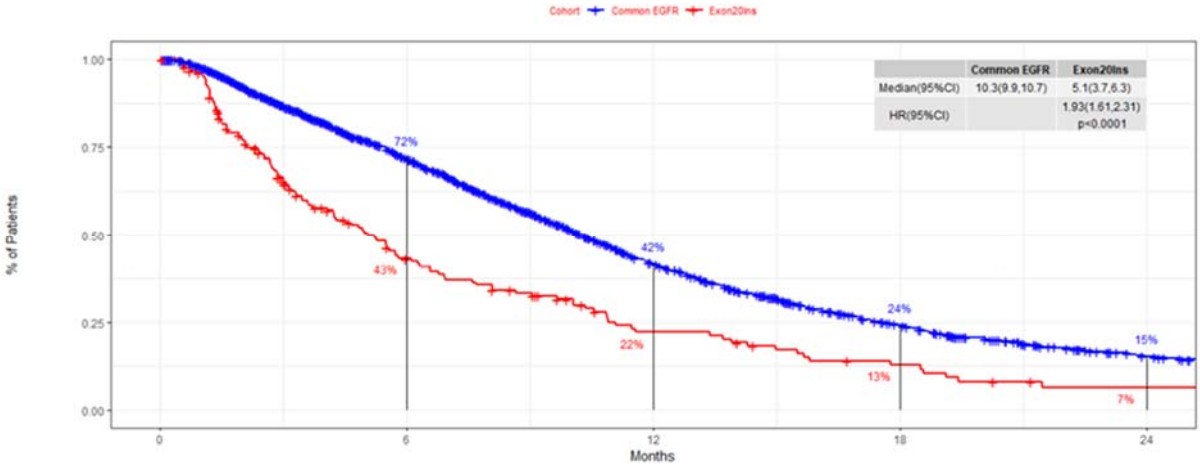
- In a cohort study of 1,086 patients who underwent EGFR genotyping from 2004 to 2012, Oxnard *et al.* (2013) observed a median survival of 16.5 months in patients with EGFR Exon20ins mutated NSCLC, which was similar to the survival of EGFR-wild-type cancers (20.0 months; p=0.60) and shorter than the survival of cancers with common EGFR mutations (33.0 months; p=0.06).[5]
- Moreover, RWE demonstrates that patients with Exon20ins have a 75% increased risk of death (Figure 3) and a 93% increased risk of disease progression or death (Figure 4) compared to patients with common EGFR mutations.[42] This can largely be attributed to the lack of effective targeted treatments in this population compared to other types of common EGFR mutations.[3]

Figure 3: Real world OS data for patients with EGFR Exon20ins (N=181) versus common EGFR mutations (N=2,833)



Abbreviations: CI: confidence interval; EGFR: epidermal growth factor receptor; Exon20ins: Exon 20 insertions; HR: hazard ratio; OS = overall survival.
Source: Bazhenova *et al.* (2021).[42]

Figure 4: Real world PFS data for patients with EGFR Exon20ins (n=181) versus common EGFR mutations (n=2,833)



Abbreviations: CI: confidence interval; EGFR: epidermal growth factor receptor; Exon20ins: Exon 20 insertions; HR: hazard ratio; PFS: progression-free survival.
Source: Bazhenova *et al.* (2021).[42]

In addition, unlike classical EGFR mutations, Exon20ins have been associated with resistance to EGFR-TKIs.[3-6] Specifically, EGFR Exon20ins are associated with a ~170% increased risk of disease progression or death on EGFR TKI treatment compared with patients with common EGFR mutations.[2] Furthermore, there is some evidence suggesting that this population has a

poorer prognosis than patients with wild-type EGFR when treated with immunotherapy.[55] Non-specific, non-selective treatment with chemotherapy is associated with modest survival improvements across all treatment lines at the cost of significant toxicity to the patient.[56, 57]

B.1.3.1.2. Epidemiology

Lung cancer is the most common malignancy and the leading cause of cancer death in the UK, with approximately 48,000 new cases of lung cancer per year (13% of all new cancer cases) and 35,137 lung cancer deaths per year (2016–2018 data).[48, 58] Lung cancer occurs primarily in older individuals, with the highest incidence rates in people aged 75 to 79 for females and 85 to 89 for males (2016–2018 data), and those with a history of smoking.[48, 59] In the UK, the prevalence of EGFR mutations in any NSCLC histology is estimated to range from 4–17.3%.[38, 39] In a RWE study from the National Lung Cancer Audit in collaboration with Public Health England,[60] it was shown that in advanced or metastatic NSCLC, prevalence of EGFR mutations is estimated to be 10.1%. A large-scale study conducted in the UK by Evans *et al.* (2019), which analysed EGFR mutation results of n=18,920 NSCLC patients, found the frequency of EGFR-mutated NSCLC with Exon20ins specifically to be 3.6% among EGFR-mutated patients.[61] As this study utilised polymerase chain reaction (PCR) testing, this estimate may be conservative versus other testing methods such as next-generation sequencing (NGS).[62]

Compared with wild-type EGFR NSCLC, EGFR Exon20ins-mutated NSCLC is more commonly seen in women, Asian people and never-smokers.[3, 5, 41] While specific estimates for each of these populations have not been identified from a UK setting, estimates of the proportion of patients with EGFR-mutated Exon20ins versus those with wild-type EGFR in these demographics from US and Chinese patient populations are presented in Table 3. Of patients with EGFR Exon20ins mutated NSCLC in a Chinese patient population, 47% were female as compared to 28% with EGFR-wild-type NSCLC.[41] In a US population, it was found that 15% of patients with EGFR Exon20ins mutated NSCLC were Asian and 56% were never-smokers, compared to 4% and 20% of EGFR-wild-type NSCLC patients, respectively.[5]

Table 3: Distribution of patients with EGFR Exon20ins mutated NSCLC compared with EGFR-wild-type NSCLC

Patient demographic	Exon20ins	EGFR-wild-type	P value
Female[41]	47%	28%	0.03
Asian[5]	15%	4%	0.02
Never smokers[5]	56%	20%	<0.001

Abbreviations: EGFR: epidermal growth factor receptor; NSCLC: non-small cell lung cancer.
Source: Fang *et al.* (2019);[41] Oxnard *et al.* (2013).[5]

In England, we estimate that 183 patients are diagnosed with EGFR Exon20ins, and 50 patients will be eligible for treatment with amivantamab each year in the licensed indication. See Appendix O for patient number calculations.

B.1.3.1.3. Symptoms and health-related quality-of-life (HRQoL) impact of EGFR Exon20ins mutated NSCLC

A recent RWE study (hereafter referred to as the patient/caregiver survey) was conducted by Janssen between February and April 2021 that aimed to understand the unmet needs and societal burden faced by EGFR-mutated NSCLC patients and supporters in the UK.

The study focused on patients with EGFR mutation positive NSCLC patients and their supporters but had a specific focus on the needs and stigma faced by those patients with EGFR Exon20ins. Insights were gathered via a mix of online surveys and in-depth interviews.

Overall, 53 patients/supporters participated in an online quality of life survey, 44 in an online stigma survey and 20 in in-depth interviews [45]. Specifically, a total of four patients with EGFR Exon20ins mutated NSCLC and four supporters of patients with EGFR Exon20ins mutated NSCLC participated across all approaches (three in the online quality of life survey, two in the online stigma survey and eight in the in-depth interviews). The results of this study are integrated into the subsections below (see also Figure 5).[45]

Disease burden

Whilst the disease burden experienced by patients with EGFR Exon20ins mutated NSCLC specifically has not been well studied, in-depth interviews with these patients in the patient/caregiver survey found that fatigue, cough, breathlessness, nausea and/or vomiting are the main symptoms of lung cancer and its treatment that impact upon quality of life.[45] Patients report that these symptoms and the side effects experienced as a result of treatment serve as a reminder of their cancer, leading to feelings of frustration for being unable to make the most of the time they have left due to feeling too unwell.

These results are supported by preliminary evidence from another qualitative study, where five oncologists and ten of their patients with EGFR Exon20ins mutated NSCLC were interviewed. Patients were identified via the International Cancer Advocacy Network. Patients reported experiencing considerable symptom burden, including shortness of breath, chest pain, bone/other pain and substantial emotional impact.[44] Together, these results highlight the substantial disease burden experienced by patients with EGFR Exon20ins mutated NSCLC and the social, emotional and physical impact experienced as a result of this disease.

Impact on patients

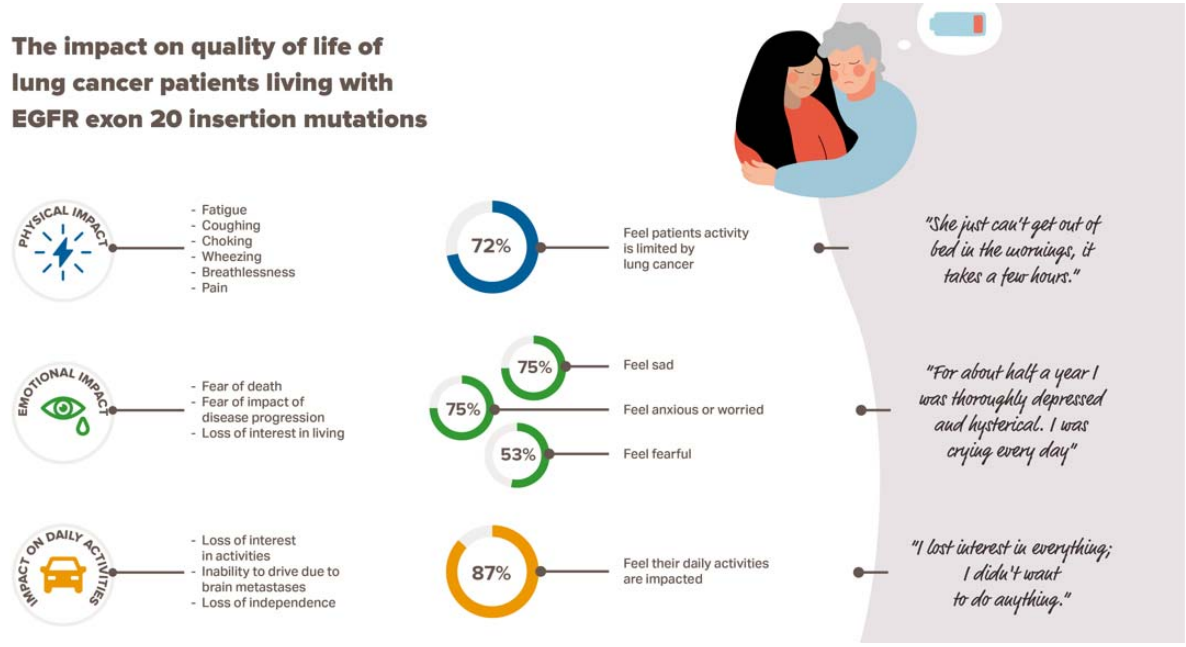
The humanistic burden of NSCLC is substantial, and well documented, with patients experiencing reduced HRQoL compared with the general population. Greater impairments are observed in patients receiving later lines of therapy (LOTs) and in patients with late-stage or progressive disease.[43]

The HRQoL impairment experienced by patients with advanced NSCLC (as measured by the EuroQol-five dimensions-three levels [EQ-5D-3L]) also increases further with worsening performance status.[63] In a European survey (France, Germany and Italy) of patients with Stage IIIb/IV NSCLC, more than 40% of patients reported experiencing some or extreme problems in each domain of the EQ-5D-3L (mobility, self-care, usual activities, pain/discomfort and anxiety/depression). The proportion of patients who experienced some or extreme problems in the five EQ-5D-3L domains significantly increased with worsening Eastern Cooperative Oncology Group (ECOG) performance status ($p<0.05$).[63] These results are supported by the patient/caregiver survey, which showed that EGFR-mutated NSCLC impacted on the activities of 87% patients, including the ability to partake in hobbies (58%), ability to exercise (45%), ability to carry out work or study (43%) and ability to take part in social activities or gatherings (43%).[45]

In-depth interviews with patients with advanced EGFR Exon20ins mutated NSCLC in the patient/caregiver survey indicated that key aspects of quality of life for these patients were: being able to undertake daily activities, maintaining independence and ‘feeling normal’. Patients reported experiencing substantial negative emotions that result in their inability to function

normally (Figure 1). Diagnosis causes high levels of stress and anxiety resulting from a loss of usual role (having to give up work, have family take care of them), worry about the future, and concern for how their family will cope without them. Patients report becoming less interested in activities they once enjoyed, withdrawing socially and feeling isolated from friends and society as a result.[45]

Figure 5: The impact on quality of life of lung cancer patients living with EGFR Exon20ins based on the patient/caregiver survey



Conclusions and quotes based on eight interviews with four patients and four supporters of patients with EGFR NSCLC Exon20ins mutations. Percentage data based on an online survey among 53 respondents comprising 40 surveyed patients and 13 supporters of patients with EGFR NSCLC. Quantitative insights derived from Q12, Q15 and Q17a of the survey.
Abbreviations: EGFR: epidermal growth factor receptor; NSCLC: non-small cell lung cancer.
Source: Janssen Data on File. Impact of EGFR+ NSCLC on quality of life and experiences of stigma (2021).[45]

Impact on caregivers/supporters

As well as having a severe negative impact on the patients diagnosed with EGFR-mutated NSCLC, the caregivers and supporters of these patients are also negatively impacted. The patient/caregiver survey showed that the majority of caregivers and supporters felt anxious and worried (90%), sadness (80%), tense or stressed (50%) and powerless (50%).[45] Furthermore, supporting someone with EGFR-mutated NSCLC impacts on work or study (60%) affects hobbies and leisure interests (40%), ability to plan and/or take part in family events (30%), take part in social activities (30%) and the ability to exercise (30%).[45]

In-depth interviews with caregivers/supporters of patients with EGFR-mutated NSCLC with Exon20ins showed that diagnosis and treatment were also highly distressing for supporters. Caregivers and supporters expressed that managing own emotions as well as supporting the patient was challenging and that they felt responsible for the person that they were caring for in terms of physically taking care of them when unwell, as well as acting as a spokesperson during consultations. Feelings of isolation extend to caregivers/supporters as well. Caregivers expressed that friends and family may not understand their situation, they cannot express their own experiences and feelings and may also feel overlooked by healthcare professionals (HCPs) as the focus is mainly on the patient.[45]

B.1.3.1.4. Societal perceptions of lung cancer

The perception of lung cancer from an individual's perspective, the perspective of those around them and the perspective of the wider community, such as healthcare workers, can lead to direct and indirect consequences for the patient, their loved ones, communities and society itself.

Individual impact

Patients with lung cancer uniquely experience an added burden from developing an illness that the public recognises is directly associated with smoking behaviours.[7] This is particularly unreasonable in the case of patients with EGFR Exon20ins mutated NSCLC as this mutation disproportionately affects never-smokers.[5]

A 2008 qualitative study showed a range of interrelated factors that resulted in patients delaying reporting their symptoms of lung cancer. These included cultural influences, underlying stoical attitudes and blame, and stigma associated with smoking behaviours.[9]

The patient/caregiver survey showed that 86% of patients with EGFR-mutated NSCLC feel that people with lung cancer are viewed negatively, while 93% patients agree some people are less sympathetic to lung cancer than other cancers because it is linked with smoking.[45] In-depth interviews revealed that patients with EGFR Exon20ins mutated NSCLC feel that others assume they are smokers and that the lung cancer is self-inflicted as a result of their assumed smoking behaviours. This results in non-smokers feeling the need to justify themselves and even adopting the negative perceptions of others, while smokers judge themselves harshly for their previous lifestyle choices.[45]

Interpersonal impact

Another qualitative study investigating depressive symptomology in lung cancer patients and their caregivers reported that perceived blame by the patient not only leads to higher depression scores in the patient, but also the caregiver. Furthermore, it showed that caregivers who blamed the patient for developing cancer by not taking better care of themselves had higher depressive symptom scores.[46] The patient/caregiver survey revealed that the caregivers/supporters of patients with EGFR-mutated NSCLC may carry additional emotional burden as a result of the patients reluctance to share the impact of their lung cancer.[45] This research showed that 61% of patients report that they avoid telling people they have lung cancer due to concern that people will treat them differently. As a result, the caregiver/supporter may be the only person who knows the extent of the patient's suffering. Therefore, the negative perception of lung cancer can impact both the patient and their caregiver's outcomes and experiences.[45]

Wider impact

Perceived bias against patients with lung cancer may affect the interactions between patients and some HCPs. Some patients report feeling uncomfortable communicating their symptoms, which can lead to delays in presentation, diagnosis and treatment (or low uptake of treatment).[10] The patient/caregiver survey showed that 42% of patients feel that some HCPs are less sympathetic to people with lung cancer than other cancers, while 55% feel that HCPs assume they are or used to be a smoker. As a result, 15% of patients have delayed seeing a HCP and/or delayed taking treatment as a result of concern about other people's attitudes to lung cancer.[45]

In-depth interviews with patients with EGFR Exon20ins mutated NSCLC revealed that patients anticipate negative views from others and are reluctant to share their diagnosis with their

employers and wider society for fear of being seen as responsible for their illness. Many patients have experienced unfair treatment due to their diagnosis with 55% having experienced stereotypes about people who have lung cancer, 28% have experienced prejudice towards people with lung cancer and 39% worrying or experiencing discrimination in the workplace.[45]

Implications of negative perceptions towards lung cancer

The perceived negative bias against patients with lung cancer can have significant negative consequences on a patient's perception of themselves, impact their interpersonal relationships with caregivers and supporters and impact their interactions with wider society, including with HCPs and people in the workplace. Specifically, perceived negative bias may lead to delays in treatment-seeking behaviours, leading to later diagnosis and management. In turn, this may lead to a high unmet need for treatment options later in the pathway for advanced EGFR Exon20ins mutated NSCLC As such, the impact of having a new treatment option available to patients to alleviate this condition should be explicitly considered within the decision-making process, especially as the negative perceptions of lung cancer are not inherently captured within the cost per QALY framework. In addition, stigma is included in the NICE social value judgements principles document and caregiver burden is also an incredibly important consideration for assessing the wider societal implications of introducing a new treatment option.[21] Therefore, both should be considered when deciding whether amivantamab is cost-effective in this underserved patient population. Overall, the existing evidence supporting the benefits of amivantamab, the importance of mitigating stigma, potential benefits for caregivers, as well the innovative nature of amivantamab in providing a treatment for a population with a high unmet need for effective targeted treatments supports a case for accepting higher levels of uncertainty within the current appraisal (see Section B.2.13.3).

B.1.3.2 Clinical pathway of care

The goal of treatment in advanced NSCLC is to delay disease progression, prolong survival and maintain quality of life, with choice of therapy depending on the presence or absence of driver mutations (EGFR and ALK) and factors such as levels of programmed death-ligand 1 (PD-L1) expression, extent of disease and histology.

Typically, and as part of their diagnosis, patients will undergo genetic screening to identify the presence of driver mutations that are amenable to targeted therapy. As such, EGFR mutation testing is indicated in adults with previously untreated, locally advanced or metastatic NSCLC,[11] which determines eligibility for treatment with EGFR TKIs. EGFR Exon20ins mutations are included in the National Genomic Test Directory for cancer under the EGFR gene panel as part of clinical practice in the UK.[64]

B.1.3.2.1. Treatment pathway

In the NICE lung cancer guidelines, no treatments are recommended specifically for patients with EGFR Exon20ins-mutated NSCLC. Beyond the UK, the most recent US National Comprehensive Cancer Network (NCCN) guidelines do provide specific recommendations for patients with EGFR Exon20ins mutated NSCLC at second-line and beyond (recommendations for first-line treatment are not Exon20ins mutation specific), including recommending amivantamab as a second-line treatment option following initial systemic therapy.[65] Whilst these guidelines are US-based rather than UK-based, the inclusion of amivantamab as a treatment option at second-line supports its use in the treatment pathway within this setting. In the absence of UK-specific guidelines and given the rare nature of EGFR Exon20ins mutations, there is no established standard of care (SoC) in the UK and practice is variable between centres and clinicians.

Feedback from an advisory board with UK clinical experts confirmed that patients with EGFR Exon20ins mutated NSCLC are treated in a manner broadly similar to patients without EGFR or anaplastic lymphoma kinase (ALK) mutations (i.e. no gene mutation or fusion protein), per NICE Guideline 122.[11, 12] Therefore, treatment options for patients in the UK may include the three pathways outlined in Table 4 below.

Table 4: Current treatment pathways for patients with EGFR Exon20ins mutated NSCLC in UK clinical practice

Potential treatment pathway	First line	Second line	Third line	Fourth line
1)	Pembrolizumab + pemetrexed + platinum-based chemotherapy	Docetaxel +/- nintedanib	BSC	
2)	Platinum-based chemotherapy	IO monotherapy[a, b]	Docetaxel +/- nintedanib[b]	BSC
3)	IO monotherapy	Platinum-based chemotherapy	Docetaxel +/- nintedanib	BSC

[a] Atezolizumab (regardless of PD-L1 expression levels),[66] or pembrolizumab (if PD-L1 levels are >1%).[67] [b] Patients may receive either IO monotherapy or docetaxel +/- nintedanib in second line, and then receive the alternative treatment in third line, however clinicians prefer using IO agents at second line due to the toxicity profile of docetaxel +/- nintedanib.[68]
Abbreviations: BSC: best supportive care; EGFR: epidermal growth factor receptor; IO: immuno-oncology agents; NSCLC: non-small cell lung cancer.
Source: Janssen Data on File: Clinical expert opinion;[12] NICE Guidelines 122.[11]

The heterogeneity of treatments administered to patients in UK practice is also supported by RWE from Public Health England (PHE) and from pooled US RWE databases (Flatiron, COTA, ConcertAI), which can be considered a robust source when used alongside input from UK clinicians. Treatments administered to patients with EGFR Exon20ins mutated NSCLC at second-line and beyond in the UK in 2016, 2018 and 2019 and in US patients between December 2009 and October 2020 are presented in Table 5 below. Data from PHE are based on [redacted] treatment lines and have the benefit of being specific to an English population, whereas the US RWE data provides a much larger sample size ([redacted] treatment lines) which is broadly consistent with the patterns observed in England. Note that PHE has now been superseded by NHS Digital, but the database is referred to as 'PHE' throughout this submission to reflect PHE as its original source.

These data are supportive of the fact that patients with EGFR Exon20ins mutated NSCLC do not have a defined treatment class or regimen that is considered standard practice (as demonstrated by the spread of patients between treatment classes). Despite patients receiving platinum-based chemotherapy in the RWE sources, feedback received from a UK-based clinician that re-treatment with platinum-based chemotherapy would be considered only for small subset of patients who had previously responded well to it, typically following failure on at least one therapy in the meantime.[69]

Table 5: RWE on treatments for patients with advanced NSCLC with activating EGFR Exon20ins mutations after failure of platinum-based chemotherapy in the US and England

Treatment class	US RWE[a]	PHE[b]
IO agents	[redacted]	[redacted]
TKIs	[redacted]	[redacted]
Non-platinum chemotherapy	[redacted]	[redacted]

Platinum-based chemotherapy	[redacted]	[redacted]
Other[c]	[redacted]	[redacted]

[a]Based on [redacted] treatment lines from a Janssen RWE Study of US RWE datasets (including Flatiron, COTA, ConcertAI). [b]Based on [redacted] treatment lines from a Janssen RWE Study of PHE data. [c]'Other' includes clinical study drugs, ALK inhibitors, multi-kinase inhibitors, anti-EGFR monoclonal antibodies, mTOR inhibitors, and oestrogen modulators for the US RWE and poziotinib for PHE. Overall, these are considered in this category as they are investigational drugs and drugs not considered to be part of the standard of care (e.g., breast cancer drugs).
Abbreviations: EGFR; epidermal growth factor receptor; IO: immuno-oncology; NSCLC: non-small cell lung cancer; PHE: Public Health England; RWE: real-world evidence; TKI: tyrosine kinase inhibitor.

Taken together the factors discussed in this section support the position that a basket of treatments comprising TKIs, IOs and chemotherapy most accurately reflects what EGFR Exon20ins mutations patients currently receive on the NHS after platinum-based chemotherapy. The basket of treatments (referred to in the submission as UK SoC) is what would be displaced by amivantamab and as such is the most relevant comparator for the submission. To summarise the factors supporting this view:

- There are no specific clinical guidelines in the UK recommending treatments for the EGFR Exon20ins population after platinum-based chemotherapy.
- Data from RWE studies show that there is no definitive SoC therapy as patients were distributed across several treatment classes. Further detail on the RWE sources can be found in Section B.2.9.
- Feedback from clinical experts that treatment decisions are often made on a case-by-case basis based on physician and patient choice, as well as taking into account factors such as prior treatments received.[12]

B.1.3.2.2. Unmet need in patients with EGFR Exon20ins mutated NSCLC

There is substantial evidence that patients with EGFR Exon20ins mutated NSCLC suffer a 'dual burden' of both having poorer prognosis as compared to NSCLC with common EGFR mutations and having no effective, targeted treatment for this severe disease. There is, therefore, a significant unmet need for a treatment which specifically treats patients with EGFR Exon20ins NSCLC, rather than repurposing existing, non-selective, NSCLC treatments which offer only modest survival improvement at the cost of significant toxicity (particularly with chemotherapy regimens). This submission positions amivantamab as addressing both elements of the 'dual burden' suffered by patients, as a targeted treatment that provides significant improvements to PFS, OS and TTNT compared to the current SoC (see Section B.2.9).

Patients with EGFR Exon20ins mutated NSCLC have a poorer prognosis than those with other types of common EGFR mutations.[5] As presented in Section B.1.3.1, RWE demonstrates that patients with Exon 20 insertions have a 75% increased risk of death and a 93% increased risk of disease progression or death as compared with patients with common EGFR mutations.[42] This can largely be attributed to the lack of effective targeted treatments in this population compared to other types of common EGFR mutations.[3] Evidence from a qualitative study involving oncologists and their patients demonstrated that these patients experience considerable symptom burden and highlighted the significant social, emotional, and physical impact on the lives of patients with EGFR Exon20ins mutations.[44] In addition, as well as having a severe negative impact on the patients diagnosed with EGFR-mutated NSCLC, the caregivers and supporters of these patients are also negatively impacted. A patient/caregiver survey conducted by Janssen showed that the majority of caregivers and supporters felt anxious and worried (90%), sadness (80%), tense or stressed (50%) and powerless (50%). Feelings of isolation

extend to caregivers/supporters as well. Caregivers express that friends and family may not understand their situation, they cannot express their own experiences and feelings and may also feel overlooked by healthcare professionals (HCPs) as the focus is mainly on the patient.[45]

In addition, unlike classical EGFR mutations, the EGFR Exon20ins mutations have been associated with resistance to EGFR TKIs.[3-6] Furthermore, there is some evidence suggesting that this population has a poorer prognosis than patients with NSCLC without EGFR mutation (wild-type) when treated with immunotherapy. Non-specific, non-selective treatment with chemotherapy is associated with modest survival improvements across all treatment lines at the cost of significant toxicity to the patient.[56, 57]

When considering all currently available treatment options, treatment outcomes in this patient population are still poor. Treatment with immunotherapies has not been well studied in patients with EGFR Exon20ins mutated NSCLC; however, limited evidence suggests that this population has a poorer prognosis than patients with wild-type (non-mutated) EGFR when treated with immunotherapy.[55] There is also limited evidence on the efficacy of chemotherapy on patients with EGFR Exon20ins mutated NSCLC however, small scale studies have identified that chemotherapy is associated with modest survival improvements as a second (or subsequent) treatment line, with median PFS ranging from 4.1–4.8 months, at the cost of significant toxicity to the patient.[56, 57] Furthermore, patients perceive chemotherapy as intimidating, due to the association with debilitating side effects.[45] The population of interest in this submission will have received platinum-based chemotherapy previously, and therefore patients are likely to be unwilling to be subjected to the significant toxicity profile of platinum-based chemotherapy again, as it serves as a reminder of their disease.[45] Further, based on RWE from the US and England, survival with as basket of SoC therapies is poor. For example, when adjusting data to match the patient population of the key trial for amivantamab, CHRYSALIS, SoC based on US RWE data led to median OS of only [redacted] and median PFS of [redacted]. Further detail on these analyses comparing data from CHRYSALIS and RWE for SoC is provided in Section B.2.9.

While the humanistic burden of patients with EGFR Exon20ins mutated NSCLC not been widely studied, preliminary evidence indicates a significant social, emotional and physical impact on the lives of patients with NSCLC harbouring EGFR Exon20ins.[44] These patients are also subject to stigma, partially as a result of lung cancers being associated with smoking behaviours,[7] despite the comparatively large number of these patients who are never-smokers compared to patients with EGFR-wild-type NSCLC.[8] The effect of stigma experienced by these patients can result in decreased symptom reporting,[9] and delays in presentation, diagnosis and treatment.[10] Furthermore, perceived blame by the patient can lead to increased depression amongst both patients and caregivers.[46] Moreover, while there are limited data on the humanistic burden of patients with EGFR Exon20ins mutated NSCLC , the substantial HRQoL impairment experienced by patients with advanced NSCLC is well documented.[63] Due to the comparatively worse prognosis versus other EGFR-mutated NSCLC,[5] the humanistic burden of EGFR Exon20ins mutated NSCLC can be considered comparable or worse than these other advanced NSCLC populations.

Lung cancer, and advanced NSCLC more specifically, is also associated with a substantial economic burden, via direct costs relating to the treatment of brain metastases and the management of serious adverse events (SAEs),[70, 71] as well as indirect costs such as absenteeism and reduced productivity for both patients and caregivers.[63, 72]

Overall, an urgent unmet need exists for efficacious, targeted therapies that prolong PFS and OS in EGFR Exon20ins mutated NSCLC after platinum-based chemotherapy. This is a patient population with substantial symptom and humanistic burden, poor outcomes, and no specifically recommended targeted treatment options in the UK. The unmet need also extends to supporting caregivers, who also experience a burden associated with this disease.

B.1.3.2.3. Positioning of amivantamab

Amivantamab has received marketing authorisation for the treatment of adult patients with locally advanced or metastatic NSCLC with activating EGFR Exon20 ins, whose disease has progressed on or after platinum-based chemotherapy and is positioned within the full licensed population. In this positioning in UK practice, the relevant comparator to amivantamab is considered to be established clinical management without amivantamab (termed UK SoC), as per the NICE scope. This is appropriate as UK clinical feedback and RWE sources support that there is not a standard treatment approach for patients with EGFR Exon20ins mutations at present, and therefore treatments selected are highly heterogeneous, with decisions taken on a case-by-case basis. Further detail on how a comparison between amivantamab and SoC has been conducted for the purposes of informing the cost-effectiveness model underpinning this submission can be found in Sections B.2.9 and B.3.3 below.

Despite the availability of UK SoC treatments, there remains a substantial unmet need in this setting. Advanced NSCLC patients with EGFR mutations and their caregivers/supporters strongly believe in the need for new treatments that extend the length of life and delay progression.[45] A large proportion of patients and carers would also value a treatment with a manageable side effect profile, and patients with EGFR Exon20ins mutated NSCLC specifically desire treatments that allow them to live normal life for as long as possible, especially those patients who have been subjected to the significant toxicity profile associated with platinum-based chemotherapy.[45]

A positive recommendation from NICE for the use of amivantamab as a treatment in this population in England and Wales would make it the first treatment recommended specifically for patients with EGFR Exon20ins, as the first treatment to show proven clinical benefit in this patient population. This represents a step change in care for patients with locally advanced or metastatic NSCLC with activating EGFR Exon20ins, whose disease has progressed on or after platinum-based chemotherapy.

Amivantamab has already received breakthrough therapy designation and approval by the FDA and marketing authorisation in the UK and Europe and represents an important milestone in advancing the field of precision medicine and the targeted treatment of lung cancer,[34-36] aligning with the aims of the NHS to be world-leading in cutting-edge genomic technologies used to predict, diagnose and treat disease in a personalised manner.[73] Furthermore, amivantamab has also received an innovation passport from the MHRA, confirming its innovative nature.[74]

Therefore, and overall, amivantamab will offer an innovative, targeted and meaningful treatment for patients with an immense unmet need, leading to benefits with regards to alleviating their clinical, economic and humanistic burden, as well as that of their caregivers.

B.1.4 Equality considerations

There is an important equality consideration with respect to the stigma of lung cancer. Lung cancer (of all kinds) is associated with significant stigma, for example the perception that it is in a sense 'self-inflicted' due to the public recognising the link between lung cancer and smoking.[7] As a result of this stigma, people with lung cancer may delay seeking diagnosis and treatment, which means that the disease progresses to a more severe state before it can be properly treated.

This stigma issue is compounded when considering EGFR Exon20ins specifically. EGFR Exon 20ins is more likely than other NSCLC mutations to be associated with never-smokers, and is also particularly associated with being of Asian heritage.[3, 8] The stigma associated with lung cancer may be particularly severe for a never-smoker, and there is some evidence that symptoms of lung cancer are stigmatised in Asian communities, which could reinforce the treatment delaying behaviour seen in lung cancer more generally.[9, 10]

As a result, patients may delay treatment for long enough that their first line options are not effective at managing the disease. This makes access to highly effective second line treatments an equalities issue, since delaying diagnosis may be due to stigma (and mediated through characteristics related to race). Our position is that NICE should therefore consider whether a higher ICER threshold and/or more flexibility around the evidence base and indirect treatment comparison is indicated in order to support the NHS' objective of reducing avoidable health inequalities, particularly as they relate to the stigma of treatment delaying behaviour.

We note that during the COVID-19 pandemic there is also the potential for intersectional discrimination based on race and disease status. Since many symptoms of lung cancer mimic those of COVID-19 (especially the persistent cough), people of Asian heritage who display lung cancer symptoms in public may face race-based prejudice and even outright racism as a result of public misunderstanding about the origins of the virus.[17, 18]

These factors are not inherently captured in the cost/QALY measure. As such, the decision as to whether amivantamab should be recommended should take into account the improvement in health equity that may be seen following its introduction to UK clinical practice and the potential disproportionate disadvantage the lack of an effective treatment option will have on these populations, in addition to benefits in terms of the mitigation of stigma.

B.2 Clinical effectiveness

Clinical effectiveness summary

Summary of clinical effectiveness of amivantamab

- CHRYSALIS is an ongoing Phase 1b, single arm trial. The primary endpoint was overall response rate (ORR). Secondary endpoints included duration of response (DOR), progression-free survival (PFS), time to treatment failure (TTF) and overall survival (OS). Data reported here are from the 30th of March 2021 data cut-off, efficacy analysis set (N=114).
- Amivantamab is efficacious, with deep and durable responses in patients with EGFR Exon20ins who have progressed on or after platinum-based chemotherapy with the following efficacy endpoints by blinded independent committee review (BICR) assessment:[75, 76]
    - The primary endpoint, ORR, was 43.0% (95% CI: 33.7, 52.6).
    - CBR (confirmed complete response + partial response + durable stable disease) was 73.7% (95% CI: 64.6, 91.5).
    - The median DOR was 10.84 months (95% CI: 6.90, 14.98).
    - Median PFS was 6.74 months (95% CI: 5.45, 9.66).
    - Median OS was 22.77 months (95% CI: 17.48, NE), with 64.9% of patients censored.

Summary of the safety of amivantamab

- Safety data are reported for post-platinum patients with Exon20ins at the recommended Phase 2 dose (RP2D) safety population (N=153) from the 30th March 2021 data cut-off.
- The most frequent treatment-emergent adverse events (TEAE) reported were infusion related reaction (97 patients; 63.4%), paronychia (81 patients; 52.9%), rash (66 patients; 43.1%), dermatitis acneiform (60 patients; 39.2%) and hypoalbuminemia (60 patients; 39.2%).
- Grade 3 or higher TEAEs were experienced by 64 patients (41.8%) in this population, of which 30 patients (19.6%) had Grade 3 or higher events reported as related to amivantamab.
- [redacted] in the safety population died at any time on study, with progressive disease being the most common cause of death. For [redacted], death occurred on treatment or within 30 days of the last dose of amivantamab. [redacted] of these deaths were reported as related to study drug by the investigator.
- Overall, amivantamab has a well-characterised and manageable tolerability profile.

Adjusted treatment comparison

- Due to the single-arm nature of the CHRYSALIS trial, an adjusted treatment comparison was conducted to derive comparative efficacy for amivantamab versus UK SoC, a basket of treatments comprising treatments currently used for this population.

- PFS, OS and TTNT data from CHRYSALIS were compared to RWE data, the latter of which was adjusted via IPW or covariate adjustment to account for differences in key prognostic factors between patient populations.
- The main analysis compared amivantamab to SoC based on data from three pooled US RWE databases based on [redacted] LOTs. Supportive data are available from an analysis comparing amivantamab from CHRYSALIS to PHE data from England, where [redacted] LOTs were available. The pooled US analysis provides a larger sample size and is therefore used as a primary analysis.
- The results (Table 6) demonstrate that amivantamab offers statistically significant benefits over SoC in terms of PFS and OS.

Table 6: Results of the adjusted comparison (IPW) for amivantamab versus SoC

Outcome		CHRYSALIS	US RWE cohort
PFS	Median, months (95% CI)	6.74 (5.45, 9.66)	[redacted]
	HR (95% CI)	[redacted]	
	p value	[redacted]	
OS	Median, months (95% CI)	22.77 (17.48, NE)	[redacted]
	HR (95% CI)	[redacted]	
	p value	[redacted]	

Abbreviations: CI: confidence interval; HR: hazard ratio; IPW: inverse probability weighting; NE: not estimable; OS: overall survival; PFS: progression-free survival; RWE: real world evidence; SoC: standard of care.

Summary of innovation

- Amivantamab is the first targeted treatment for adult patients with EGFR Exon20ins mutated NSCLC.[77] This has led to the observed unprecedented efficacy outcomes with an extension in OS of [redacted] months when compared to SoC.
- Amivantamab has already received breakthrough therapy designation by the FDA, marketing authorisation by the MHRA and EMA, and an Innovation Passport designation from the MHRA and therefore represents an important milestone in advancing the treatment of genetically-defined lung cancer.[35]

Conclusion

- Overall, based on the data from CHRYSALIS and the adjusted treatment comparisons conducted to inform this submission, amivantamab will offer an innovative, targeted and meaningful treatment for patients with EGFR Exon20ins, a population with an immense unmet need, leading to benefits with regards to alleviating their clinical, economic and humanistic burden, as well as that of their caregivers.

B.2.1 Identification and selection of relevant studies

A *de novo* clinical systematic literature review (SLR) was conducted in January 2021 to identify relevant clinical evidence on the clinical efficacy and safety outcomes in patients with EGFR Exon20ins mutated NSCLC. The SLR was subsequently updated in September 2021 (using an identical methodological approach) to ensure recently published evidence was included. The SLR was designed to capture data specifically in EGFR Exon20ins mutated NSCLC reported in both interventional (RCT and non-RCT) and observational studies, and considered baseline

characteristics as relevant outcomes, in addition to efficacy and safety and quality of life (QoL) data.

The SLR was conducted according to a pre-specified protocol and performed in accordance with the methodological principles of conduct for systematic reviews as detailed in the York Centre for Reviews and Dissemination (CRD) Handbook recommended by NICE.[78] In total the SLR identified 278 unique interventional studies (reported in 350 records) that met the inclusion criteria of the review. Of these, 88 studies (23 interventional and 65 observational in design) contained quantitative data on patients with EGFR Exon20ins and were fully extracted, and 190 studies (52 interventional and 138 observational in design) contained qualitative data on patients with EGFR Exon20ins and were summarised only.

Full details of the SLR search strategy, study selection process and results are presented in Appendix D.

B.2.2 List of relevant clinical effectiveness evidence

As described above the SLR identified 278 interventional studies. Of the 88 studies considered for full extraction, only one (CHRYSALIS) provides evidence for the clinical efficacy and safety of amivantamab in the patient population of interest for this appraisal (patients with EGFR Exon20ins mutated NSCLC). Studies were not considered for full extraction if they reported only qualitative data on patients harbouring EGFR Exon20ins mutations, contained individual patient data only, or indicated that patients with EGFR Exon20ins mutations had been enrolled but no further details have been provided. Full details of the SLR are presented in Appendix D.

CHRYSALIS

To date, the main body of evidence for amivantamab to address the decision problem is derived from the CHRYSALIS trial, which was used to support the conditional marketing authorisation for amivantamab in the indication of relevance to this submission. CHRYSALIS is a Phase 1b, single arm, first-in-human, open-label, multicentre, 2-part trial investigating the efficacy and safety of amivantamab in patients with EGFR Exon20ins mutated NSCLC. An overview of CHRYSALIS is presented in Table 7. The methodology and results are presented in Section B.2.3 onwards.

Table 7: Clinical effectiveness evidence

Study	CHRYSALIS (NCT02609776)		
Study design	Phase 1b, single arm, first-in-human, open-label, multicentre, 2-part trial (3 UK centres were included)		
Population	Adult patients (aged ≥18 years) with confirmed metastatic or unresectable NSCLC who failed or were ineligible for SoC therapy. Patients in part two of the study had measurable disease, with qualifying EGFR mutations or MET mutations or amplifications. Previous treatment with investigational EGFR Exon 20 ins-targeted TKIs was prohibited in the EGFR Exon20ins expansion cohort. **Note**: The population of relevance to this submission, and whose data is presented in this section, is a subset of the CHRYSALIS population and relates to patients with EGFR Exon20ins mutations who had received previous treatment with platinum-based chemotherapy.		
Intervention(s)	Amivantamab monotherapy, administered via IV infusion • 1,050 mg for patients with body weight <80 kg • 1,400 mg for patients with body weight ≥80 kg		
Comparator(s)	N/A. CHRYSALIS was a single arm trial. See Section B.2.9 for further details on comparative efficacy results generated by adjusted treatment comparison.		
Indicate if trial supports application for marketing authorisation	Yes	**Indicate if trial used in the economic model**	Yes
Rationale for use/non-use in the model	CHRYSALIS represents the primary source of efficacy and safety data for amivantamab in this indication. Data reported from CHRYSALIS are relevant to the decision problem and have therefore been used in the economic model.		
Reported outcomes specified in the decision problem[a]	Measures of disease severity and symptom control: • ORR • DOR • TTF • **PFS** • **OS** Safety outcomes: • **AEs**		
All other reported outcomes	• CBR • The best percentage change from baseline in SoD		

[a] Endpoints in bold are those that are used to inform the cost-effectiveness model.
Abbreviations: AE: adverse event; CBR: clinical benefit rate; DOR: duration of response; EGFR: epidermal growth factor receptor; IV: intravenous NSCLC: non-small cell lung cancer; ORR: overall response rate; OS: overall survival; PFS: progression free survival; SoC: standard of care; SoD: sum of diameters; TKI: tyrosine kinase inhibitor; TTF: time to treatment failure.
Source: Janssen CHRYSALIS CSR (8th June 2020 data cut-off).[79]

B.2.3 Summary of methodology of the relevant clinical effectiveness evidence

Note: All data and trial information to be presented primarily from publications where available and supplemented with data from the clinical overview document and the clinical study report (CSR). Any data not in the public domain are marked as [redacted].

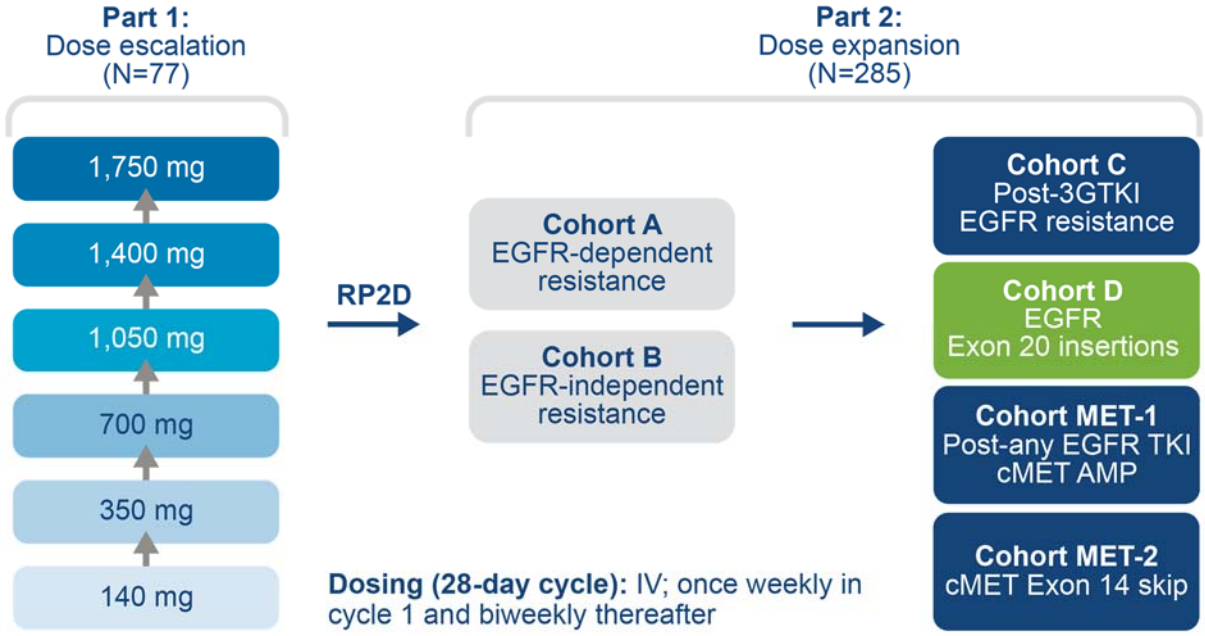
B.2.3.1 Trial design

The clinical evidence base for amivantamab as a treatment for patients with EGFR Exon20ins mutated NSCLC is based on the pivotal CHRYSALIS trial. CHRYSALIS is a Phase 1b, single arm, open-label, multicentre study in patients at least 18 years of age with advanced NSCLC. The study consisted of two parts:

- Part 1 (dose escalation phase), to determine the recommended Phase 2 dose (RP2D) of amivantamab monotherapy in patients with advanced or metastatic NSCLC
- Part 2 (dose expansion phase) to characterise the safety and pharmacokinetics of amivantamab monotherapy at the RP2D and to explore its clinical activity within molecularly defined tumour subgroups

The study design of the CHRYSALIS trial is presented in Figure 6.

Figure 6: Design of the CHRYSALIS study



Cohorts A and B in Part 2 were closed to enrolment upon opening of subsequent cohorts. A weight-based RP2D was added after the initial RP2D determination: 1,050 mg if baseline weight <80 kg and 1,400 mg if baseline weight ≥80 kg.
Abbreviations: EGFR: epidermal growth factor receptor; IV: intravenous; MET: mesenchymal epithelial transition; RP2D: recommended Phase 2 dose; TKI: tyrosine kinase inhibitor.
Source: Janssen CHRYSALIS CSR (8th June 2020 data cut-off).[79]

Part 1 was designed to determine the RP2D of amivantamab monotherapy in patients with advanced NSCLC based on safety, pharmacokinetic, pharmacodynamic, and anti-tumour activity data. Patients enrolled to Part 1 were not required to meet any molecular eligibility requirements. Part 1 started with a standard 3+3 design and investigated doses of 140 mg to 1750 mg. Dose

escalation was to stop when the maximum tolerated dose (MTD) or maximum administered dose (MAD) (in the case where no MTD was determined) was reached.

The goal of Part 2 of CHRYSALIS was to better characterise the safety and pharmacokinetics of amivantamab monotherapy at the RP2D determined in Part 1 and to explore its anti-tumour activity. Patients with locally advanced or metastatic NSCLC who had a previously diagnosed activating EGFR and/or MET mutation, measurable disease, and disease progression following prior systemic anti-cancer therapy were enrolled into separate molecularly defined tumour subgroups. The six separate NSCLC populations with unmet clinical need that were treated with amivantamab monotherapy and evaluated in Part 2 were:

- **Cohort A and B**: Recent progression of EGFR-mutated disease following treatment with a marketed EGFR inhibitor, with the exception for patients diagnosed with mutations associated with *de novo* EGFR inhibitor resistance (e.g., Exon20ins) where only previous treatment with combination platinum-based chemotherapy was required. In Cohort A, patients had to have EGFR-driven tumour progression, while in Cohort B, patients had EGFR-independent tumour progression. Enrolment to both of these cohorts is closed
- **Cohort C**: Patients with documented EGFR alterations (e.g., C797S) mediating resistance to previous treatment with a third generation TKI (e.g., osimertinib). In patients with primary Exon20ins disease, the documented EGFR alteration could have arisen following treatment with a TKI with known activity in Exon20ins disease (e.g., poziotinib)
- **Cohort D**: Patients with previously diagnosed activating EGFR Exon20ins not previously treated with a TKI having known activity in Exon20ins disease (e.g., poziotinib) but previously treated with a platinum-based chemotherapy regimen.
- **Cohort MET-1**: Documented primary EGFR mutation and documented MET amplification or mutation after progression on any EGFR TKI. Patients in this cohort could have either received or been intolerant to prior platinum-based chemotherapy
- **Cohort MET-2**: Documented primary MET Exon 14 skip mutations

Key eligibility criteria are further summarised in Table 8 and a full list of eligibility criteria can be found in the CHRYSALIS protocol.[80]

In line with the decision problem for this submission, the specific population of interest consists largely of a subset of Cohort D and small number of patients in Cohort A i.e. patients with EGFR Exon20ins who had had progressed on or after prior platinum-based chemotherapy and who were treated at the RP2D for amivantamab monotherapy (hereafter referred to as post-platinum patients with EGFR Exon20ins), known as Cohort D+. A full description and schematic describing the relationship between analysis sets is presented in Section B.2.4 and Table 12.

From this point on in the submission, data presented will be from Part 2 of CHRYSALIS only and will concern post-platinum patients with EGFR Exon20ins treated with the RP2D.

B.2.3.2 Trial methodology

A summary of the methodology of CHRYSALIS is presented in Table 8 below. Unless stated otherwise, information pertains to Part 2 of CHRYSALIS only, and is focussed on the population of interest for this appraisal.

Table 8: Summary of the CHRYSALIS trial methodology

Trial name	CHRYSALIS (NCT02609776)
Location	International: 90 sites in 11 countries, including the UK (3 sites)
Trial design	Phase Ib, single arm, first-in-human, open-label, multicentre, 2-part trial
Eligibility criteria for participants	**Key inclusion criteria**: • Adult patients (≥18 years of age) • Histologically- or cytologically-confirmed NSCLC that was metastatic or unresectable • Progressed on or after prior therapy or were not candidates for currently available approved therapeutic options • Must have measurable disease according to RECIST v1.1 • An ECOG performance status of 0 or 1 • Qualifying EGFR mutations or MET mutations or amplifications • Previously diagnosed activating EGFR Exon20ins not previously treated with a TKI having known activity in Exon20ins disease (e.g., poziotinib) but previously treated with a platinum-based chemotherapy regimen • Adequate organ and bone marrow function, as assessed by laboratory measurements of haemoglobin, absolute neutrophil count, platelets, alanine aminotransferase, aspartate aminotransferase, total bilirubin and serum creatine **Key exclusion criteria**: • Prior chemotherapy, targeted cancer therapy, immunotherapy, or treatment with an investigational anti-cancer agent within two weeks or four half-lives whichever is longer, before the first administration of study drug • Untreated or active brain metastases • A history of malignancy other than the disease under study within three years before Screening • A history of clinically significant cardiovascular disease • Known allergies, hypersensitivity, or intolerance to amivantamab or its excipients • Received an investigational drug (not including anti-cancer therapy) or used an invasive investigational medical device within 6 weeks before the planned first dose of study drug • Uncontrolled inter-current illness, including but not limited to poorly controlled hypertension or diabetes, ongoing or active infection, or psychiatric illness/social situation that would limit compliance with study requirements • Any specifically listed comorbidities such as leptomeningeal disease, human immunodeficiency virus (HIV), hepatitis B or C, and interstitial lung disease (ILD) • Any serious underlying medical or psychiatric condition The full list of inclusion and exclusion criteria are presented in the CHRYSALIS protocol.[80]
Intervention	Amivantamab monotherapy, administered via IV infusion • 1,050 mg for patients with body weight <80 kg • 1,400 mg for patients with body weight ≥80 kg

Method of study drug administration	Amivantamab was administered by IV infusion and was given once weekly for the first four weeks (i.e. Cycle 1) and once every two weeks in all subsequent 28-day cycles; with the first dose being split over 2 days. Amivantamab administration occurred on Days 1, 2, 8, 15, and 22 of Cycle 1, and on Days 1 and 15 of each subsequent 28-day cycle.
Permitted and disallowed concomitant medication	Throughout the study, investigators were allowed to prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care except for those listed as prohibited therapies. The medications allowed or disallowed before and during the study, including any exceptions to these requirements, are described below: **Allowed:** • Symptomatic treatment • Prophylactic medications • Localised limited radiotherapy of short duration (e.g., 5 days) for palliative purposes may be permitted but only after discussion with approval by the sponsor's medical monitor **Disallowed:** • Any chemotherapy, anti-cancer therapy (other than study treatment[s]), or experimental therapy • Radiotherapy to tumour lesions being assessed for tumour response prior to radiographic progression • Use of live attenuated vaccines is prohibited • Use of phenytoin or phosphenytoin with carboplatin is not permitted • Nephrotoxic or ototoxic agents should be cautiously used with carboplatin • Caution should be exercised when administering pemetrexed concurrently with a nonsteroidal anti-inflammatory drug to a participant whose creatinine clearance is <80 mL/min For further detail on the permitted and disallowed concomitant medication refer to the CHRYSALIS protocol.[80]
Primary outcomes (Part 2)	ORR: defined as the proportion of patients with a best overall response of a confirmed CR or PR based on RECIST v1.1 criteria (best response as recorded in the CRF from the start of the amivantamab until disease progression, withdrawal of consent, or start of a subsequent anti-cancer therapy, whichever came first). ORR was based on investigator assessment and BICR assessment.
Secondary and exploratory outcomes (Part 2)	• CBR: defined as the percentage of patients achieving CR or PR, or durable stable disease (duration of at least 11 weeks) as defined by RECIST v1.1 • DOR: calculated as time from initial response of CR or PR to PD or death due to underlying disease, whichever comes first, only for patients who achieve CR or PR • PFS: defined as the time from first infusion of amivantamab to PD or death due to any cause • OS: defined as the time from first infusion of amivantamab to death due to any cause

	• TTF: defined as the time from the first infusion of amivantamab to discontinuation of treatment for any reason, including disease progression, treatment toxicity and death • The best percentage change from baseline in SoD: defined as the greatest percentage change in the sum of diameters of target lesions, determined for each patient with measurable disease at baseline based on investigator and BICR assessments • HRQoL (exploratory descriptive analyses): PGIS, PGIC, NSCLC-SAQ and EQ-5D-5L VAS
Pre-planned subgroups	• Age: <65 versus ≥65 years and <75 versus ≥75 years • Sex: male versus female • Race: Asian versus non-Asian (patients with unknown race were not included in the subgroup analysis) • Baseline ECOG performance status: 0 versus ≥1 • History of smoking: yes versus no • Prior immunotherapy: yes versus no • Key EGFR Exon20ins variants (based on ctDNA analysis of pre-treatment samples). The change in SoD for target lesions was also described for these subgroups using a waterfall plot.

Abbreviations: CBR: clinical benefit rate; CR: complete response; ctDNA: circulating tumour deoxyribonucleic acid; DOR: duration of response; ECOG: Eastern Cooperative Oncology Group; EQ-5D-5L VAS: EuroQoL five-dimensions five-levels visual analogue scale; HIV: human immunodeficiency virus; ILD: interstitial lung disease; IV: intravenous; NSCLC: non-small cell lung cancer; NSCLC-SAQ: Non-Small Cell Lung Cancer Symptom Assessment Questionnaire; ORR: overall response rate; OS: overall survival; PFS: progression free survival; PGIC: Patient Global Impression of Change; PGIS: Patient Global Impression of Severity; PRO: patient-reported outcomes; RECIST: Response Evaluation Criteria in Solid Tumours; SoD: sum of diameters; TTF: time to treatment failure.
Source: Janssen CHRYSALIS CSR (8th June 2020 data cut-off);[79] Janssen CHRYSALIS trial protocol.[80]

B.2.3.3 Baseline characteristics

A summary of patient demographics and disease characteristics at baseline, clinical characteristics and prior systemic therapies of interest for the post-platinum patients with Exon20ins at RP2D expanded efficacy analysis set (N=114) population are presented in Table 9, Table 10 and Table 11, respectively. A full description and schematic describing the relationship between analysis sets is presented in Section B.2.4 (Table 12).

The expanded efficacy population (N=114) had a median age of 61.8 years (range: 36–84), 61.4% were female and 51.8% were Asian. Patients in this population predominantly had Stage IV disease (78.9%) at initial diagnosis, with 25.4% having a history of brain metastases. The median time from diagnosis of metastatic disease to the first dose of amivantamab was 15.5 months (range: 0.7–116.4) and the median number of lines of previous therapy was 2 (range: 1–7).

Table 9: Summary of demographics and disease baseline characteristics; post-platinum EGFR Exon20ins RP2D expanded efficacy (N=114)

Characteristic	Post-platinum in patients with Exon20ins at RP2D (N=114)
Age, years	
Mean (SD)	61.8 (10.0)
Median (range)	62.0 (36–84)
<65, n (%)	67 (58.8)

≥65, n (%)	47 (41.2)
<75, n (%)	105 (92.1)
≥75, n (%)	9 (7.9)
Sex	
Female	70 (61.4)
Male	44 (38.6)
Race, n (%)	
Asian	59 (51.8)
Black or African American	3 (2.6)
White	42 (36.8)
Not reported	10 (8.8)
Weight, kg	
Mean (SD)	64.8 (15.8)
Median (range)	62.1 (35.4–115.0)
Body mass index, kg/m^2	
Mean (SD)	24.1 (4.7)
Median (range)	23.5 (14.0–36.9)
Underweight (<18.5), n (%)	11 (9.6)
Normal (18.5–<25), n (%)	65 (57.0)
Overweight (25–<30), n (%)	25 (21.9)
Obese (≥30), n (%)	13 (11.4)

RP2D: 1,050 mg if baseline weight <80 kg and 1,400 mg if baseline weight ≥80 kg.
Abbreviations: RP2D: recommended Phase 2 dose; SD: standard deviation.
Source: Amivantamab EPAR.[75]

Table 10: Summary of baseline clinical disease characteristics; Post-platinum Exon20ins RP2D expanded efficacy population (N=114)

Characteristic	Post-platinum patients with EGFR Exon20ins at RP2D (N=114)
Initial diagnosis NSCLC subtype, n (%)	
Adenocarcinoma	109 (95.6)
Large cell carcinoma	0 (0)
Squamous cell carcinoma	3 (2.6)
Other	2 (1.8)
Histology grade at initial diagnosis, n (%)	
Moderately differentiated	23 (20.2)
Poorly differentiated	19 (16.7)
Well differentiated	7 (6.1)
Other	64 (56.1)
Not reported	1 (0.9)
Cancer stage at initial diagnosis, n (%)	
0	0 (0)
IA	7 (6.1)
IB	1 (0.9)
IIA	2 (1.8)

IIB	4 (3.5)
IIIA	6 (5.3)
IIIB	4 (3.5)
IV	90 (78.9)
Location of metastasis, n (%)	
Bone	51 (44.7)
Liver	13 (11.4)
Brain	29 (25.4)
Lymph Node	62 (54.4)
Adrenal Gland	6 (5.3)
Other	62 (54.4)
Time from initial diagnosis of cancer to first dose, months	
Mean (SD)	22.3 (20.0)
Median (range)	17.5 (1.5–130.1)
Time from metastatic disease diagnosis to first dose, months	
Mean (SD)	18.3 (15.5)
Median (range)	15.5 (0.7–116.4)
Number of prior LOTs	
Mean (SD)	2.1 (1.3)
Median (range)	2 (1–7)
ECOG performance status, n (%)	
0	33 (28.9)
1	80 (70.2)
2	1 (0.9)
History of smoking, n (%)	
Yes	49 (43.0)
No	65 (57.0)

RP2D: 1,050 mg if baseline weight <80 kg and 1,400 mg if baseline weight ≥80 kg.
Abbreviations: ECOG: Eastern Cooperative Oncology Group; LOTs: lines of therapy; NSCLC: non-small cell lung cancer; RP2D: recommended Phase 2 dose; SD: standard deviation.
Source: Amivantamab EPAR. [75]

Table 11: Prior systemic therapies of interest in ≥5% of patients in the post-platinum EGFR Exon20ins RP2D expanded efficacy population (N=114)

Characteristic, n (%)	Post-platinum in patients with EGFR Exon20ins at RP2D (N=114)
Platinum-based chemotherapy	[redacted]
EGFR TKI (1st generation)	[redacted]
EGFR TKI (2nd generation)	[redacted]
EGFR TKI (3rd generation)	[redacted]
IO agents	[redacted]

RP2D: 1,050 mg if baseline weight <80 kg and 1,400 mg if baseline weight ≥80 kg.
Abbreviations: IO: immuno-oncology agent; RP2D: recommended Phase 2 dose; TKI: tyrosine kinase inhibitor.
Source: Janssen CHRYSALIS Clinical Overview.[76]

B.2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

As discussed in Section B.2.3.1, the eligibility criteria for the CHRYSALIS trial were broader than the population of relevance for this submission. For the purposes of analysis, specific datasets were used to evaluate safety and efficacy. The definitions of the primary study populations from CHRYSALIS are presented in Table 12 and the supportive populations in Table 13.

Table 12: Primary trial populations used for the analysis of outcomes of CHRYSALIS

Analysis Set	Definition
Efficacy results	
Post-platinum patients with EGFR Exon20ins RP2D expanded efficacy population **(N=114)**	**Primary population for efficacy results:** This population included all patients with EGFR Exon20ins NSCLC who received the RP2D prior to 04 June 2020 data cut-off with ≥3 disease assessments as of the 08 October 2020 data cut-off
Safety results	
Post-platinum patients with EGFR Exon20ins RP2D safety population **(N=153)**	**Primary population for safety results:** This population included all patients with EGFR Exon20ins NSCLC who received prior chemotherapy at the RP2D prior to the 30 March 2021 data cut-off

RP2D: 1,050 mg if baseline weight <80 kg and 1,400 mg if baseline weight ≥80 kg.
Abbreviations: NSCLC: non-small cell lung cancer; RP2D: recommended Phase 2 dose.
Source: Janssen CHRYSALIS Clinical Overview.[76]

Table 13: Supportive trial populations used for the analysis of outcomes of CHRYSALIS

Analysis Set	Definition
Efficacy results	
Post-platinum patients with EGFR Exon20ins RP2D initial efficacy population **(N=81)**	**Supportive population for efficacy results**: This population included all patients who received the first dose of amivantamab as monotherapy on or before 05 February 2020 and were response-evaluable with ≥3 disease assessments or discontinued treatment for any reason, including disease progression/death, prior to the 08 June 2020 data cut-off
Safety results	
All Treated at RP2D safety population **(N=380)**	**Additional safety population**: All patients enrolled in Part 1 (dose escalation) or Part 2 (dose expansion) irrespective of mutation status or prior chemotherapy, who received at least one dose of amivantamab monotherapy consistent with the RP2D (1,050 mg for body weight <80 kg and 1,400 mg for body weight ≥80 kg).
All Treated safety population **(N=489)**	**Additional safety population**: All patients enrolled in Part 1 or Part 2 who received at least one dose of amivantamab monotherapy at any dose (i.e. RP2D and non-RP2D).

RP2D: 1,050 mg if baseline weight <80 kg and 1,400 mg if baseline weight ≥80 kg.
Abbreviations: NSCLC: non-small cell lung cancer; RP2D: recommended Phase 2 dose.
Source: Janssen CHRYSALIS Clinical Overview.[76]

Only efficacy data from the post-platinum EGFR Exon20ins at RP2D expanded efficacy population (N=114) will be presented in Section B.2.6. Safety data from the EGFR post-platinum Exon20ins at RP2D safety population (N=153) will be presented in Section B.2.10, with supportive safety data from the All Treated at RP2D safety population (N=380) and All Treated

safety population (N=489) presented in Appendix F to provide safety information for a population with a larger sample size.

Statistical methods

The statistical methods for the primary analysis for CHRYSALIS are presented in Table 14.

Table 14: Statistical methods for the primary analysis of CHRYSALIS

Hypothesis objective	The null hypothesis was that the ORR for amivantamab per RECIST v1.1 was ≤15%; the alternative hypothesis was that the ORR was ≥30%
Sample size, power calculation	The maximum total sample size at a RP2D for Part 2 was set to be approximately 460 patients, including approximately 40 patients in Cohort A, 20 patients in Cohort B, and up to 100 patients each if sufficient efficacy was observed in Cohorts C, D, MET-1, and MET-2 at a RP2D of amivantamab monotherapy With a one-sided alpha of 2.5%, and a power of 87.5%, the total number of patients needed for each cohort was 86 response-evaluable patients. Assuming a non-evaluable rate of 15%, approximately 100 patients were to be enrolled within each cohort, although the number of patients was to be expanded beyond 100 patients (maximum of approximately 150) to further characterise activity for subpopulations within a cohort The interim analysis was to be performed when approximately 30 patients were enrolled in each cohort and have sufficient data (i.e., post-baseline disease assessment) to be evaluable for response. Future enrolment into each cohort could have been terminated if it was determined during the first stage that the treatment was considered as ineffective as compared to other treatment options and/or not well tolerated The sample size consideration for the subgroup in Cohort D who required to have had previous therapy with a combination platinum-doublet chemotherapy regimen was based on the null hypothesis of ORR ≤12%, and the alternative hypothesis of ORR >25%. To have a power of 80% to reject the null hypothesis with a one-sided alpha of 0.025, at least 60 patients were required to be enrolled in the subgroup; approximately 100 patients were targeted for enrolment to characterise the activity of amivantamab in this population
Statistical analysis	Primary efficacy analysis of ORR with confirmed best overall responses was performed approximately 12 weeks after the last patient received the first infusion or at the end of study, whichever came first. The data cut-off was communicated to the sites. Any additional data were reported to the appropriate health authorities when all patients had finalised treatment with amivantamab ORR was defined as the proportion of patients who achieved either a CR or PR in all treated analysis set (or response evaluable analysis set for interim monitoring) each expansion cohort (Part 2), as defined by investigator assessment using RECIST v1.1. Observed ORR along with their two-sided 95% exact CIs were presented for each cohort and dose level as appropriate. The null hypothesis for Cohort D was that the ORR was less than or equal to 15%, which was rejected if the lower bound of the 95% CI was greater than 15% To control the overall type I error rate at 5% within each cohort, a sequential testing strategy was used. The hypotheses testing for subgroup within each cohort was only performed after null hypothesis for the whole cohort was rejected. The null hypothesis for the subgroup in Cohort D who require at least one prior line of platinum-containing chemotherapy is ORR ≤12%, which was rejected if the lower bound of the 95% CI was greater than 12% and was only tested after the null

	hypothesis for Cohort D (ORR ≤15%) was rejected
Data management, patient withdrawals	A patient was withdrawn from the study for any of the following reasons: • Lost to follow-up • Withdrawal of consent for follow-up If a patient was lost to follow-up, every reasonable effort was made by the study site personnel to contact the patient and determine the reason for discontinuation/withdrawal. The measures taken to follow up were documented. In accordance with local regulations, information from public records were used to collect any missing survival data

RP2D: 1,050 mg if baseline weight <80 kg and 1,400 mg if baseline weight ≥80 kg.
Abbreviations: CI: confidence intervals; CR: complete response; ORR: overall response rate; PR: partial response; RECIST: Response evaluation criteria in solid tumours; RP2D: recommended Phase 2 dose.
Source: Janssen CHRYSALIS CSR (8th June 2020 data cut-off).[79]

B.2.4.1 Participant flow in the relevant randomised controlled trials

The participant flow (CONSORT diagram) for the CHRYSALIS trial is presented in Appendix D.

B.2.5 Quality assessment of the relevant clinical effectiveness evidence

The trials captured in the clinical SLR were assessed for quality using the York CRD QA checklist (for RCTs) and the ROBINS-1 QA checklist (for non-RCTs). The results of these quality assessments are presented in Appendix D, and a summary of the quality assessment for CHRYSALIS is presented in Table 15 below.

Table 15: Quality assessment of the CHRYSALIS trial (NCT02609776)

Source of bias	Risk of bias
Overall bias due to confounding	Low
Overall bias in selection of participants into the study	Low
Overall bias in classification of interventions	Low
Overall bias due to deviations from intended interventions	Low
Overall bias due to missing data	Low
Overall bias in measurement of outcomes	Moderate
Overall bias in selection of the reported results	Low
Overall risk of bias	Moderate

B.2.6 Clinical effectiveness results of the relevant trials

Efficacy results from CHRYSALIS in this submission are presented from for the post-platinum EGFR Exon20ins at RP2D expanded efficacy population (N=114) the most recent data cut-off (30th March 2021). The median follow-up was [redacted] months (range: [redacted]) in this population.

Supportive clinical efficacy data for the N=81 efficacy population (October 2020 and March 2021 data cut-offs) are available in Appendix L.

A summary of the key results is presented in Table 16.

Table 16: Summary of key clinical results from the CHRYSALIS trial

Outcome	Result
ORR, n (%) [95% CI]	BICR: 49 (43.0) [33.7, 52.6] INV: 42 (36.8) [28.0, 46.4]
CBR, n (%) [95% CI]	BICR: 84 (73.7) [64.6, 81.5] INV: 86 (75.4) [66.5, 83.0]
Median DOR,[a] months (95% CI)	BICR: 10.84 (6.90, 14.98) INV: 12.45 (6.54, 16.13)
Median PFS,[b] months (95% CI)	BICR: 6.74 (5.45, 9.66) INV: 6.93 (5.55, 8.64)
Median TTF,[c] months (95% CI)	8.08 (6.67, 10.64)
Median OS,[d] months (95% CI)	22.77 (17.48, NE)

[a] DOR is calculated as the time from initial response (either complete or partial response) to PD or death. [b] PFS is defined as the time from first infusion of amivantamab to PD or death. [c] TTF is defined as the time from the first infusion of amivantamab to discontinuation of treatment for any reason, including disease progression, treatment toxicity and death. [d] OS is defined as the time from first infusion of amivantamab to death due to any cause
Abbreviations: CI: confidence interval; DOR: duration-of-response; INV: investigator assessed; NE: not evaluable; OS: overall survival; ORR: overall response rate; PFS: progression-free survival; TTF: time to treatment failure.
Source: Amivantamab EPAR.[75]

B.2.6.1 Primary endpoint: ORR

The confirmed ORR based on BICR and INV assessment were and 43.0% (95% CI: 33.7, 52.6) and 36.8% (95% CI: 28.0, 46.4) respectively, as summarised in Table 17.

Table 17: Summary of best overall response based on RECIST v1.1; Post-platinum EGFR Exon20ins RP2D expanded efficacy population (N=114)

	Post-platinum Exon20ins RP2D expanded efficacy population (N=114, 30th March 2021 data cut-off)	
	BICR	INV
Best overall response, n (%)		
CR	3 (2.6)	0 (0)
PR	46 (40.4)	42 (36.8)
SD	47 (41.2)	56 (49.1)
PD	15 (13.2)	14 (12.3)
Not evaluable/unknown	3 (2.6)	2 (1.8)
ORR, n (%) [95% CI]	49 (43.0) [33.7, 52.6]	42 (36.8) [28.0, 46.4]
CBR, n (%) [95% CI]	84 (73.7) [64.6, 81.5]	86 (75.4) [66.5, 83.0]

CBR is defined as the percentage of patients achieving confirmed complete or partial response, or durable stable disease (duration of at least 11 weeks). RP2D is defined as 1,050 mg if baseline weight <80 kg and 1,400 mg if baseline weight ≥80 kg.
Abbreviations: CBR: clinical benefit rate; CR: complete response; CI: confidence interval; EGFR: epidermal growth factor receptor; ORR: overall response rate; PD: progressed disease; PR: partial response; RP2D: recommended Phase 2 dose; SD: stable disease.
Source: Amivantamab EPAR.[75]

B.2.6.2 Secondary endpoint: DOR

The DOR data based on BICR and INV assessment are summarised in Table 18, and the Kaplan-Meier curves for these outcomes are presented in Figure 7 and Figure 8 respectively.

Based on BICR, a total of 49 responders were identified in the post-platinum patients with EGFR Exon20ins at RP2D efficacy population. The median DOR was 10.84 months (95% CI: 6.90, 14.98) and 27 (55.1%) had a DOR ≥6 months. Based on INV, a total of 42 responders were identified in the post-platinum patients with EGFR Exon20ins at RP2D efficacy population. The median DOR was 12.45 months (95% CI: 6.54, 16.13) and 27 (64.3%) had a DOR ≥6 months.

Table 18: Summary of duration of response; Post-platinum EGFR Exon20ins RP2D expanded efficacy population (N=114)

	Post-platinum EGFR Exon20ins RP2D expanded efficacy population (N=114, 30th March 2021 data cut-off)	
	BICR	**INV**
Responders, n	49	42
Event, n (%)	27 (55.1)	21 (50.0)
Censored, n (%)	22 (44.9)	21 (50.0)
Time to event (months)		
25th percentile (95% CI)	5.13 (4.07, 8.21)	4.96 (4.14, 8.31)
Median (95% CI)	10.84 (6.90, 14.98)	12.45 (6.54, 16.13)
75th percentile (95% CI)	21.65 (11.04, NE)	16.13 (12.68, NE)
Range	1.1+, 21.7	1.1+, 19.0+
Duration of response ≥6 months, n (%)	27 (55.1)	27 (64.3)
Duration of study treatment (months)		
N	49	42
Mean (SD)	12.13 (5.77)	12.77 (5.09)
Median	13.37	13.59
Range	1.7, 23.9	2.3, 23.9

RP2D is defined as 1,050 mg if baseline weight <80 kg and 1,400 mg if baseline weight ≥80 kg.
Abbreviations: BICR: blinded independent review; CI: confidence interval; EGFR: epidermal growth factor receptor; INV: investigator; NE: not evaluable; RP2D: recommended Phase 2 Dose; SD: standard deviation.
Source: Amivantamab EPAR.[75]

Figure 7: Kaplan-Meier plot of DOR – expanded efficacy population (N=114) by BICR assessment

Abbreviations: BICR: blinded independent review; DOR: duration of response.
Source: Janssen Data on File: Additional CHRYSALIS Data.[81]

Figure 8: Kaplan-Meier plot of DOR – expanded efficacy population (N=114) by INV assessment

Abbreviations: DOR: duration of response; INV: investigator.
Source: Janssen Data on File: Additional CHRYSALIS Data.[81]

B.2.6.3 Secondary endpoint: PFS

The PFS data based on BICR and INV assessment are summarised in Table 19 with the associated Kaplan-Meier curves for this outcome presented in Figure 9 and Figure 10.

With a median follow up of [redacted] months (range: 0.23, 30.52), the median BICR-assessed PFS was 6.74 months (95% CI: 5.45, 9.66) and the 6-month and 12-month PFS rates were 55% (95% CI: 45, 64) and 29% (95 CI: 21, 39), respectively. The median INV-assessed PFS was 6.9 months (95% CI: 5.6, 8.6) and the 6-month and 12-month PFS rates were 55% (95% CI: 45, 64) and 35% (95 CI: 26, 44), respectively.

Table 19: Summary of PFS; Post-platinum EGFR Exon20ins RP2D expanded efficacy population (N=114)

	Post-platinum EGFR Exon20ins RP2D expanded efficacy population (N=114, 30th March 2021 data cut-off)

	BICR	INV
Event, n (%)	80 (70.2)	81 (71.1)
Censored, n (%)	34 (29.8)	33 (28.9)
Time to event (months)		
25th percentile (95% CI)	3.94 (2.66, 4.83)	3.71 (2.60, 4.34)
Median (95% CI)	6.74 (5.45, 9.66)	6.93 (5.55, 8.64)
75th percentile (95% CI)	12.45 (10.87, NE)	16.56 (12.58, NE)
Range	(0.0+, 23.3)	0.0+, 24.1
3-month event-free rate (95% CI)	0.78 (0.69, 0.85)	0.77 (0.68, 0.84)
6-month event-free rate (95% CI)	0.55 (0.45, 0.64)	0.55 (0.45, 0.64)
9-month event-free rate (95% CI)	0.41 (0.31, 0.50)	0.39 (0.30, 0.48)
12-month event-free rate (95% CI)	0.29 (0.21, 0.39)	0.35 (0.26, 0.44)
15-month event-free rate (95% CI)	0.22 (0.14, 0.31)	0.28 (0.19, 0.37)
18-month event-free rate (95% CI)	0.14 (0.06, 0.26)	0.18 (0.09, 0.30)
21-month event-free rate (95% CI)	0.14 (0.06, 0.26)	0.18 (0.09, 0.30)
24-month event-free rate (95% CI)	0 (NE, NE)	0.18 (0.09, 0.30)
27-month event-free rate (95% CI)	NR	0 (NE, NE)

RP2D is defined as 1,050 mg if baseline weight <80 kg and 1,400 mg if baseline weight ≥80 kg.
Abbreviations: CI: confidence interval; PFS: progression-free survival; NE: not evaluable; NR: not reported; RP2D: recommended Phase 2 dose.
Source: Amivantamab EPAR.[75]

Figure 9: Kaplan-Meier plot of PFS – expanded efficacy population (N=114) by BICR assessment

RP2D is defined as 1,050 mg if baseline weight <80 kg and 1,400 mg if baseline weight ≥80 kg.
Abbreviations: BICR: blinded independent committee review; PFS: progression-free survival; RP2D: recommended Phase 2 dose.
Source: Janssen Data on File: CHRYSALIS Clinical Overview (30th March 2021 data cut-off).[76]

Figure 10: Kaplan-Meier plot of PFS – expanded efficacy population (N=114) by INV assessment

RP2D is defined as 1,050 mg if baseline weight <80 kg and 1,400 mg if baseline weight ≥80 kg.
Abbreviations: PFS: progression-free survival; RP2D: recommended Phase 2 dose; INV: investigator.
Source: Janssen Data on File: CHRYSALIS Clinical Overview (30th March 2021 data cut-off).[76]

B.2.6.4 Secondary endpoint: TTF

The TTF reflects the time from the first infusion of study drug to discontinuation of treatment for any reason, and thus reflects clinical benefit for subjects continuing treatment beyond RECIST-defined disease progression. The median TTF for the post-platinum patients with EGFR Exon20ins at RP2D efficacy population was [redacted] (95% CI: [redacted]). The 9-month and 12-month event-free rates for TTF in this population were [redacted] (95% CI: [redacted]) and [redacted] (95% CI: [redacted]), respectively (Table 20; Figure 11).

Table 20: Summary of TTF; Post-platinum EGFR Exon20ins RP2D expanded efficacy population (N=114)

	Post-platinum EGFR Exon20ins RP2D expanded efficacy population (N=114, 30th March 2021 data cut-off)
Event, n (%)	[redacted]
Censored, n (%)	[redacted]

Time to event (months)	
25th percentile (95% CI)	[redacted]
Median (95% CI)	[redacted]
75th percentile (95% CI)	[redacted]
Range	[redacted]
3-month event-free rate (95% CI)	[redacted]
6-month event-free rate (95% CI)	[redacted]
9-month event-free rate (95% CI)	[redacted]
12-month event-free rate (95% CI)	[redacted]
15-month event-free rate (95% CI)	[redacted]
18-month event-free rate (95% CI)	[redacted]
21-month event-free rate (95% CI)	[redacted]
24-month event-free rate (95% CI)	[redacted]
27-month event-free rate (95% CI)	[redacted]

RP2D is defined as 1,050 mg if baseline weight <80 kg and 1,400 mg if baseline weight ≥80 kg.
Abbreviations: CI: confidence interval; EGFR: epidermal growth factor receptor; NE: not evaluable; RP2D: recommended Phase 2 dose; TTF: time-to-treatment failure.
Source: Janssen Data on File: CHRYSALIS Clinical Overview (30th March 2021 data cut-off).[76]

Figure 11: Kaplan-Meier plot of TTF – expanded efficacy population (N=114)

[redacted]

RP2D is defined as 1,050 mg if baseline weight <80 kg and 1,400 mg if baseline weight ≥80 kg.
Abbreviations: PFS: progression-free survival; RP2D: recommended Phase 2 dose; INV: investigator.
Source: Janssen Data on File: CHRYSALIS Clinical Overview (30th March 2021 data cut-off).[76]

B.2.6.5 Secondary endpoint: OS

As of the 30th March 2021 data cut-off (median follow-up of [redacted] [range: [redacted], [redacted]]), 45 patients (29.4%) in the post-platinum patients with EGFR Exon20ins at RP2D expanded efficacy population had died. The median OS was 22.77 months (95% CI: 17.48, NE), with 64.9% of patients censored. In this population, the estimated 12-month survival rate was 73% (95% CI: 63, 80), while the estimated 18-month survival rate was 61% (95% CI: 49, 71). The Kaplan–Meier curve of OS for this population is presented in Figure 12.

Table 21: Summary of OS; Post-platinum EGFR Exon20ins RP2D expanded efficacy population (N=114)

	Post-platinum EGFR Exon20ins RP2D expanded efficacy population (N=114, 30th March 2021 data cut-off)
Event, n (%)	40 (35.1)
Censored, n (%)	74 (64.9)
Time to event (months)	
25th percentile (95% CI)	9.95 (8.48, 14.59)
Median (95% CI)	22.77 (17.48, NE)
75th percentile (95% CI)	NE (23.00, NE)
Range	(0.2, 30.5+)
3-month event-free rate (95% CI)	0.95 (0.89, 0.98)
6-month event-free rate (95% CI)	0.90 (0.83, 0.94)
9-month event-free rate (95% CI)	0.79 (0.70, 0.86)
12-month event-free rate (95% CI)	0.73 (0.63, 0.80)
15-month event-free rate (95% CI)	0.66 (0.55, 0.75)
18-month event-free rate (95% CI)	0.61 (0.49, 0.71)
21-month event-free rate (95% CI)	0.53 (0.39, 0.66)
24-month event-free rate (95% CI)	0.40 (0.21, 0.58)
27-month event-free rate (95% CI)	0.40 (0.21, 0.58)
30-month event-free rate (95% CI)	0.40 (0.21, 0.58)

RP2D is defined as 1,050 mg if baseline weight <80 kg and 1,400 mg if baseline weight ≥80 kg.
Abbreviations: CI: confidence interval; NE: not evaluable; RP2D: recommended Phase 2 dose; OS: overall survival.
Source: Amivantamab EPAR.[75]

Figure 12: Kaplan-Meier plot of OS – expanded efficacy population (N=114)

RP2D is defined as 1,050 mg if baseline weight <80 kg and 1,400 mg if baseline weight ≥80 kg.
Abbreviations: OS: overall survival; RP2D: recommended Phase 2 dose; INV: investigator.
Source: Janssen Data on File: CHRYSALIS Clinical Overview (30th March 2021 data cut-off).[76]

B.2.6.6 Exploratory endpoint: HRQoL

Patient reported outcome (PRO) measures were not included in the original study design and were a late addition to the trial (Protocol Amendment 7). As the PRO measures were added after some patients had already been enrolled and treated, the available PRO data from CHRYSALIS are limited and only available for a small subset of the expanded efficacy population (n=[redacted]/114 [[redacted]%]).

As detailed in Table 8, four PRO measures were added to CHRYSALIS. However, only ED-5D visual analogue scale (VAS) and NSCLC-SAQ results are presented here for brevity. Results are for the N=114 population from the latest data cut-off (30th March 2021).

The NSCLC-SAQ is a 7-item PRO measure intended for use in advanced NSCLC clinical trials that addresses the concept of NSCLC symptom severity.[82] Using a 7-day recall period and verbal rating scales (5-point Likert scale, 0–4), the questionnaire assessed cough, pain, dyspnoea, fatigue and poor appetite. The total score ranges between 0 and 20, results for CHRYSALIS patients are presented in Figure 13.

The ED-5D-5L VAS is a PRO measure that records patients' self-rated health on a vertical VAS where endpoints are labelled 'best imaginable health state' and 'worst imaginable health state'.[83] ED-5D-5L VAS scores for CHRYSALIS patients are presented in Figure 14.

Overall, completion rates for PROs in CHRYSALIS were limited, particularly at later timepoints as indicated in the figures below. Nevertheless, when considering the results for both scales, scores remain relatively constant across cycles demonstrating maintenance of HRQoL at baseline with no evidence of a decline based on the available data.

Figure 13: Change from baseline of NSCLC-SAQ total score over time – expanded efficacy population (N=114)

Abbreviations: LS: least squares; NSCLC-SAQ: Non-Small Cell Lung Cancer Symptom Assessment Questionnaire.
Source: Janssen Data on File: Additional CHRYSALIS Data.[81]

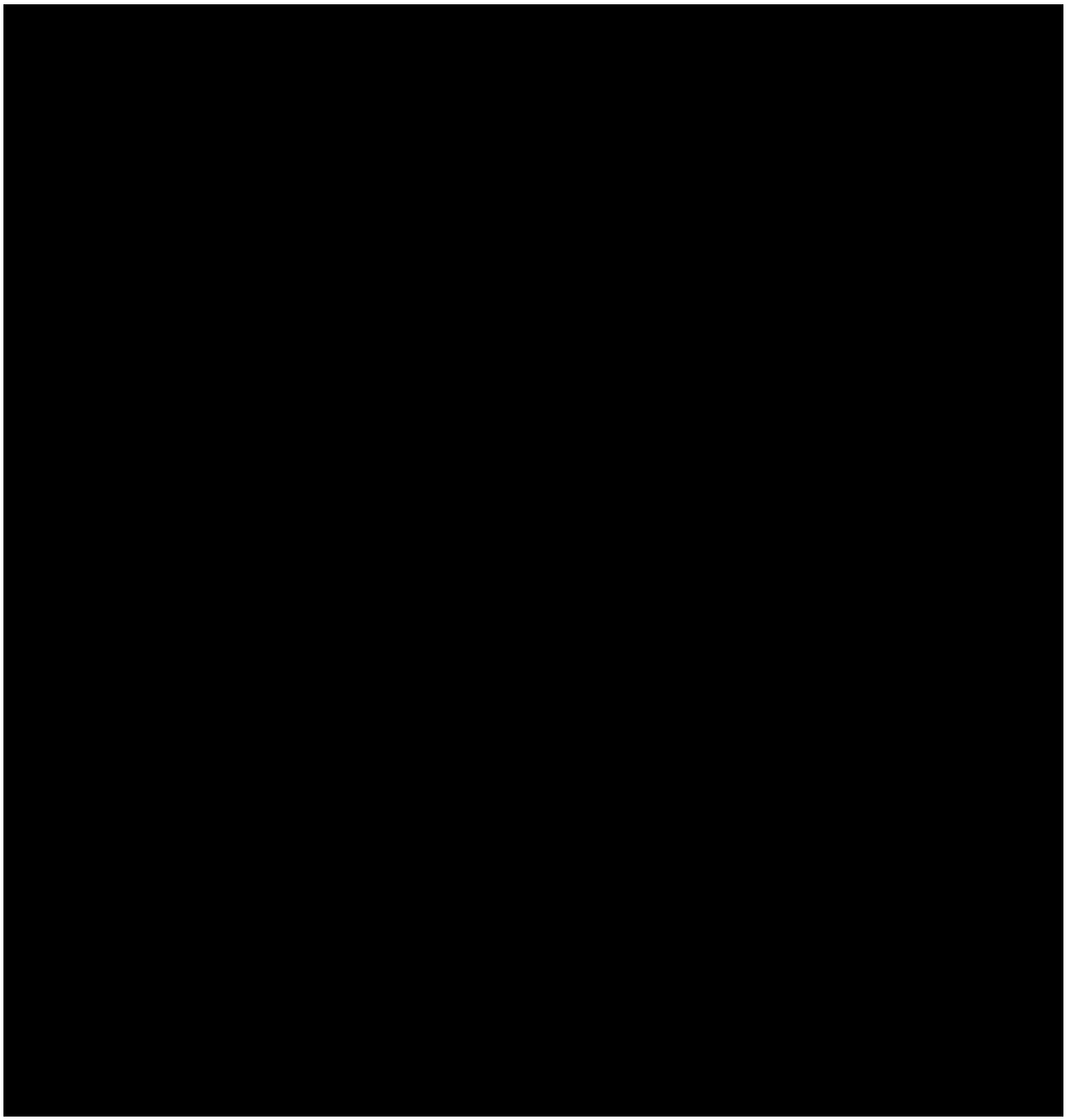
Figure 14: Change of baseline of EQ-5D-5L VAS over time – expanded efficacy population (N=114)

Abbreviations: EQ-5D-5L: EuroQoL five-dimensions five-levels; VAS: visual analogue scale.
Source: Janssen Data on File: Additional CHRYSALIS Data.[81]

B.2.7 Subgroup analysis

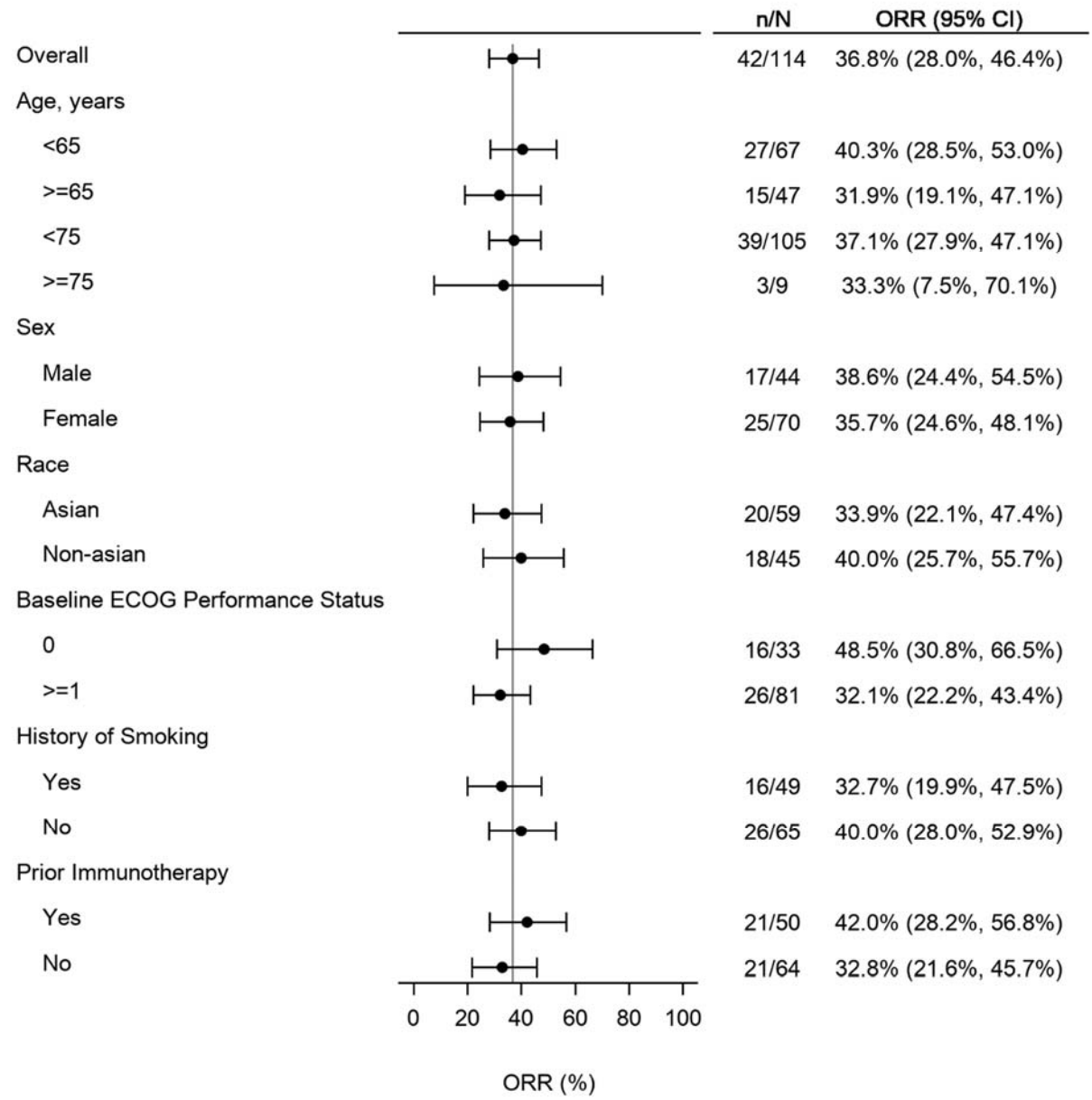
INV- and BICR-assessed ORR in the post-platinum patients with EGFR Exon20ins at RP2D efficacy population (N=114; March 2021 data cut-off) were analysed by several demographic variables, to identify any differences in the efficacy of amivantamab in specific subgroups. Amivantamab demonstrated consistent outcomes and clinical benefit across all pre-specified subgroups (Figure 16 and Figure 15). Notably, results from the CHRYSALIS trial show similar efficacy for Asian versus non-Asian patients; therefore, although a reasonably high proportion of patients in CHRYSALIS were Asian (51.8%), it is not anticipated that this would influence the generalisability of results.

Figure 15: Forest plot of ORR based on RECIST v1.1; efficacy population (N=114) by BICR assessment



n = Confirmed CR + Confirmed PR. If race was not reported, then that patient is excluded from the race subgroup. Chinese patients enrolled beyond the initial global cohort enrolment are excluded.
Abbreviations: CR: complete response; CI; confidence interval; ECOG: Eastern Cooperative Oncology Group; ORR: overall response rate; PR: partial response.
Source: Janssen CHRYSALIS Clinical Overview (30th March 2021 data cut-off).[76]

Figure 16: Forest plot of ORR based on RECIST v1.1; efficacy population (N=114) by INV assessment



n = Confirmed CR + Confirmed PR. If race was not reported, then that patient is excluded from the race subgroup. Chinese patients enrolled beyond the initial global cohort enrolment are excluded.
Abbreviations: CR: complete response; CI; confidence interval; ECOG: Eastern Cooperative Oncology Group; ORR: overall response rate; PR: partial response.
Source: Amivantamab EPAR.[75]

B.2.8 Meta-analysis

CHRYSALIS was the only trial identified evaluating amivantamab in this setting. As such, no meta-analysis is required.

B.2.9 Indirect and mixed treatment comparisons

CHRYSALIS is a single-arm trial, and no other trials were identified in the clinical SLR comparing amivantamab to the relevant comparator (or that could be used to conduct an unanchored

indirect comparison in the specific population of relevance to this submission [adult patients with locally advanced or metastatic NSCLC with activating EGFR Exon20ins, whose disease has progressed on or after platinum-based chemotherapy]). Therefore, an adjusted treatment comparison was conducted to inform the relative efficacy estimates for amivantamab versus SoC utilising comparator data from RWE sources.

Adjusted treatment comparisons were conducted to compare amivantamab from the CHRYSALIS trial versus a pooled SoC treatment basket. Two RWE sources were included in the analyses:

- A US cohort that included pooled data from Flatiron Health Spotlight, ConcertAI and COTA data sources. This is referred to as US RWE throughout the submission
- Data from Public Health England (PHE) using routine population-level data available through PHE (now NHS Digital)'s National Cancer Registration and Analysis Service (NCRAS). These data are referred to as PHE throughout the submission

To account for differences in patient populations between CHRYSALIS and the RWE data sources, the comparisons adjusted for key prognostic variables and baseline characteristics, which were identified *a priori* by an SLR and validated by clinical experts.[84] The following covariates were considered: [redacted]

Different statistical approaches were explored to conduct the adjusted comparisons: namely, covariate adjustment and inverse probability weighting (IPW). IPW was selected as the base case analysis for the US RWE cohort. Conversely, covariate adjustment was selected for the PHE cohort comparison as IPW estimates were unstable due to the small sample size.

Given the larger sample size of the data from the US RWE sources, and clinical expert feedback confirming that the US population and outcomes are generalisable to UK practice, the comparison of amivantamab versus SoC using US RWE was selected as the main analysis to inform the base case of the cost-effectiveness model.[12] The analysis comparing amivantamab to SoC data from PHE is provided as supportive comparative effectiveness evidence and is included as a scenario analysis in the economic section of the submission; see Section B.3.8.3. The PHE analysis is of relevance as it provides results from patients treated in English clinical practice specifically.

Further details on the analysis can be found below and are supplemented by information in Appendix M.

Analysis methods

Naïve comparisons between clinical studies are typically biased due to confounding arising from imbalances between study populations in baseline characteristics prognostic for the outcomes of interest. In these situations, established methods such as propensity score analyses are routinely used to estimate relative treatment effects while adjusting for observed differences between populations of interest.[85]

As described above, to account for differences in patient populations between CHRYSALIS and the RWE data sources, IPW and covariate adjustment methodologies were used in the treatment comparisons to adjust for key prognostic variables and baseline characteristics identified by an SLR and validated by clinical experts.

The methodology of these analyses is described below and summarised in Table 22.

Table 22. Summary of adjusted comparisons methods adopted

Treatment/ comparator	Source	Evidence level	Method (Analysis)	Outcomes
Amivantamab	CHRYSALIS	IPD	-	-
vs SoC	US RWE	IPD	IPW (Base case)	PFS, TTNT, OS, ORR[a]
			Covariate adjustment (scenario)	PFS, TTNT, OS, ORR[a]
	PHE	IPD	Covariate adjustment (Base case)	TTNT, OS

[a] ORR results do not inform the economic model and as such are not presented within the main body of the submission but are included in the appendices for completeness.
Abbreviations: IPD: individual patient level data; IPW: inverse probability weighting; OS: overall survival; PFS: progression-free survival; PS: propensity score; RW: real world; SoC: standard of care; TTNT: time to next treatment.

Data sources and population

The patient cohort from the CHRYSALIS trial, comprising the efficacy analysis set (EAS), N=114, presented in Section B.2.6 was used to derive data for amivantamab for the analyses, as per the relevant marketing authorisation. In order to compare patients from CHRYSALIS Cohort D+ with similar patients from the US and PHE datasets, the same inclusion and exclusion criteria used for the CHRYSALIS trial were used to identify patients in the RWE datasets where possible. The inclusion and exclusion criteria applied to all RWE sources are presented in Appendix M.

Some real-world patients in all data sources satisfied the eligibility criteria at multiple times during their follow-up. Therefore, to achieve an unbiased comparison, in this situation patients satisfying the eligibility criteria in more than one line setting are included multiple times in an analysis, once for each qualifying line setting.[86-88] Further information on this is provided in Appendix M.

Once LOTs with missing ECOG scores had been excluded (see below for rationale), the US RWE cohort was made up of [redacted] LOTs and the PHE cohort of [redacted] LOT. As the PHE cohort contains limited LOTs, the US RWE cohort is considered the main analysis.

Treatments of interest

The treatments of interest were amivantamab (for patients in CHRYSALIS at the RP2D i.e., 1,050 mg if the patient weighed less than 80 kg, or 1,400 mg if the patient weighed ≥80 kg) and a basket of SoC treatments from RWE sources.

Selection of covariates

In order to identify potential confounders in the NSCLC setting, an SLR of prognostic patient and disease characteristics was performed and subsequently validated by clinical expert feedback.

The SLR identified determinants of OS (variables statistically significantly related to the endpoint) as potential confounders in patients with EGFR-mutated NSCLC. Expert interviews were then conducted to validate these potential confounders, particularly with regard to the specific target population, patients with advanced EGFR Exon20ins mutated NSCLC after failure of platinum-based therapy.[84]

Variables for the analyses were therefore selected based on an evidence-informed process considering the strength of the prognostic factor, degree of imbalance between studies, clinical expert opinion and data availability.

The covariates included in the adjusted analyses for the US RWE and PHE cohorts are presented in Table 23. The covariates actually adjusted for in each real world data source were based on the confounders identified by the SLR, clinical expert opinion and data availability (i.e., that data from relevant data sources were available for that covariate, and that data were available for a sufficient sample size [at least five to nine events per confounder]).[89] Overall, clinical experts agreed that key prognostic factors had been considered in the adjustment.[12] Further details regarding justification for covariate inclusion/exclusion is provided in Appendix M.

Table 23: Baseline characteristics adjusted for in comparative analyses

Baseline characteristics	US RWE cohort	PHE cohort
[redacted]	✓	✓
[redacted]	✓	✓
[redacted]	✓	
[redacted]	✓	
[redacted]	✓	✓
[redacted]	✓	✓
[redacted]	✓	✓
[redacted]	✓	
[redacted]		✓
[redacted]		✓

Abbreviations: BMI: body mass index; ECOG: Eastern Cooperative Oncology Group; PHE: Public Health England.

Endpoints of interest

The endpoints of interest included ORR, PFS, OS and TTNT. Due to limitations in the data recorded in the PHE datasets, it was not possible to collect PFS for the PHE cohort. As ORR results do not inform the economic model, the results are presented in Appendix M not the main body of the submission for conciseness. A summary of the endpoints, their definitions and additional information relating to their use in the analyses is provided in Appendix M.

BICR- and INV-assessed PFS were available from CHRYSALIS and INV-assessed PFS was available from RWE sources. Therefore, analyses considering both BICR- and INV-assessed PFS from CHRYSALIS were conducted. BICR results are presented here and INV results are presented in Appendix M.

General analysis specifications

Analysis results are presented as an effect measure with a 2-sided 95% CI and corresponding p value. A p value <0.05 was considered statistically significant.

For the US RWE and PHE cohorts, LOTs with missing ECOG values were excluded from the analysis and for the US RWE cohort no left truncation was applied to the data. Treatment lines with missing ECOG were excluded from the US analysis as the large sample size allowed for this. They were also excluded from the PHE analysis because the OS/TTNT HR for treatment lines with missing ECOG was above that of patients with ECOG of 1 (estimated from a multivariable Cox PH model with all other covariates included). Further information regarding missing data and data handling are presented in Appendix M.

Propensity score based adjusted analysis

Propensity score (PS) methods are used to mimic the effect of randomisation by creating a balance between two treatment groups in respect to important baseline covariates. The PS for an individual describes the probability of being assigned to a particular treatment, conditional on all relevant pre-treatment covariates, and is estimated using a multiple logistic regression model. These PS scores represent a summary of all characteristics included in the model for each patient.

Following calculation of the PS for each patient, IPW was used to adjust for baseline confounding variables. The IPW approach involves generating a pseudo-population in which each covariate combination is balanced between treatment groups, allowing for a population-based interpretation of results; this enables comparison to the trial population as if it had undergone a randomised control trial in which, counter to fact, both treatments were applied to each subject. Balance in covariates across both cohorts, before and after PS adjustment, was assessed by computing the standardised differences for each covariate. These standardised differences informed judgement of the most appropriate weighting approach for each data source.

The following weighting schemes were considered for the IPW approach:

- The Average Treatment effect on the Treated (ATT) approach attempts to generate a comparative arm reflecting the population enrolled in CHRYSALIS by reweighting the RWE cohort to match the amivantamab patients of CHRYSALIS. Treatment lines of treated patients receive a weight of 1, whilst control patients are reweighted by PS/(1-PS). ATT based estimates represent the relative treatment effect in the CHRYSALIS population, and for these analyses, a scaled ATT (sATT) approach was taken. In order to maintain the original sample size for the weighted populations and to properly reflect the associated uncertainty, the ATT weights were multiplied by the ratio of the original sample size versus the sum of the ATT weights making the sum of these recalculated weights equal to the original sample size. This approach is referred to as the ATT approach throughout the submission (although some figures may still be labelled as sATT).

- The Average Treatment Effect (ATE) approach estimates the ATE across both cohorts, as it weights up both propensity score distributions towards the middle. Weights are assigned to patients in the amivantamab cohort and the RWE cohort, creating a more similar distribution of the covariates between the two cohorts. Weights applied are

Pr(treated)/PS for patients for the treated cohort and Pr(control)/(1-PS) for patients in the control cohort.

- The Average Treatment Effect for the Overlap Population (ATO) approach applies weights of 1-PS for patients in the amivantamab cohort and PS for patients in the control cohort. This approach downweights patients at both extremes of the distributions.

The ATT approach is the primary PS-weighting approach and as such, only results from this analysis are presented. Appendix M presents further information on the ATT approach and IPW diagnostic results.

Multivariable regression approach with direct adjustment for covariates

Covariate adjustment based on a multivariable regression (Cox regression for time to event endpoints and logistic regression for binary endpoints) was considered as an alternative to PS based adjustment in adjusting for covariate imbalance and potential confounding for the US RWE cohort. Multivariable regression was used as the main adjustment approach for the PHE database due to the small sample size.

The unbiased treatment effects were estimated using a multivariable model which included all relevant prognostic variables as covariates together with the treatment group indicator. The selected set of prognostic variables as covariates was specified in line with those described above. An advantage of covariate adjustment over the PS approach described in the previous section is that it provides a predictive model (including treatment) for the risk (hazard) of the outcome, which gives insight as to which covariates have the strongest influence on risk.

Statistical software

All analyses were conducted using Statistical Analysis System (SAS) version 9.4 with SAS/Stat 14.2 or higher (SAS Institute Inc., Cary, NC, US) and R version 3.6.1 or higher (R Foundation for Statistical Computing, Vienna, Austria).

Results

Results presented below are for the US RWE cohort and PHE data sets. As described above, IPW was undertaken for the US pooled analysis utilising an ATT approach. Covariate adjustment results for the US RWE cohort are presented in Appendix M. For PHE, only covariate adjustment was undertaken as, due to the small sample size, the ATT approach did not achieve a good covariate balance.

The naïve and adjusted baseline characteristics of treatment lines of patients in the CHRYSALIS and US RWE cohorts are presented in Table 24, and the naïve CHRYSALIS and PHE characteristics are presented in Table 25 (as the covariate adjustment method does not produce adjusted baseline characteristics). These baseline characteristics are largely aligned to UK practice, as validated by UK clinicians at an advisory board.[12]

Table 24: Baseline characteristics of treatment lines for patients in CHRYSALIS and the US RWE cohort

Characteristic, n (%)	CHRYSALIS EAS	US RWE cohort	IPW ATT weighted US RWE cohort
N	114	[redacted]	[redacted]
Prior lines of treatment			

1	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]
4+	[redacted]	[redacted]	[redacted]
Brain metastasis			
No	85 (74.6)	[redacted]	[redacted]
Yes	29 (25.4)	[redacted]	[redacted]
Age			
<60	48 (42.1)	[redacted]	[redacted]
60–70	38 (33.3)	[redacted]	[redacted]
≥70	28 (24.6)	[redacted]	[redacted]
ECOG PS			
0	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]
Number of metastatic locations			
1	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]
Haemoglobin			
Normal/high	[redacted]	[redacted]	[redacted]
Low	[redacted]	[redacted]	[redacted]
Sex			
Male	44 (38.6)	[redacted]	[redacted]
Female	70 (61.4)	[redacted]	[redacted]
Cancer stage at initial diagnosis			
I	[redacted]	[redacted]	[redacted]
II	[redacted]	[redacted]	[redacted]
IIIA	[redacted]	[redacted]	[redacted]
IIIB/IV	[redacted]	[redacted]	[redacted]

Abbreviations: ECOG PS: Eastern Cooperative Oncology Group performance score; EAS: efficacy analysis set.
Source: Amivantamab EPAR.[75]

Table 25: Baseline characteristics of treatment lines for patients in CHRYSALIS and the PHE data source

Characteristic, n (%)	CHRYSALIS EAS	PHE cohort[a]
N	114	[redacted]
Prior lines of treatment		
1	[redacted]	[redacted]
2	[redacted]	[redacted]
3+	[redacted]	[redacted]
Brain metastasis		
No	85 (74.6)	[redacted]

Yes	29 (25.4)	[redacted]
Age		
≤55	[redacted]	[redacted]
55–≤60	[redacted]	[redacted]
> 60	[redacted]	[redacted]
ECOG PS		
0	33 (28.9)	[redacted]
1	80 (70.2)	[redacted]
Liver metastasis		
No	101 (88.6)	[redacted]
Yes	13 (11.4)	[redacted]
Sex		
Male	44 (38.6)	[redacted]
Female	70 (61.4)	[redacted]
BMI		
Underweight (<18.5)	11 (9.6)	[redacted]
Normal (18.5- <25)	65 (57.0)	[redacted]
Overweight (25- <30)	25 (21.9)	[redacted]
Obese (>30)	13 (11.4)	[redacted]

[a] Adjusted baseline characteristics are not available for the PHE cohort as only covariate adjustment was applied.
Abbreviations: BMI: body mass index; ECOG PS: Eastern Cooperative Oncology Group performance score; EAS: efficacy analysis set; PHE: Public Health England.
Source: Amivantamab EPAR.[75]

B.2.9.1 Progression-free survival

US RWE cohort

Results presented in this section are based on BICR-assessed PFS from CHRYSALIS versus PFS from US RWE. Results for the comparison based on INV-assessed CHRYSALIS PFS versus PFS from US RWE are presented in Appendix N.

Unadjusted results

For the US RWE cohort, the median PFS of amivantamab was [redacted] (95% CI: [redacted]) versus [redacted] (95% CI: [redacted]) for the unadjusted SoC cohort. The unadjusted HR for amivantamab versus SoC was [redacted] (95% CI: [redacted]). The unadjusted Kaplan-Meier plot for PFS for amivantamab versus SoC is shown in Figure 17.

Figure 17: Kaplan-Meier curve for PFS for CHRYSALIS versus US RWE cohort (amivantamab vs SoC) – unadjusted results

Abbreviations: CI: confidence interval; HR: hazard ratio; PFS: progression-free survival; RW: real world; SoC: standard of care.

Adjusted results

For the US pooled cohort, the median PFS of amivantamab is [redacted] (95% CI: [redacted]) versus [redacted] (95% CI: [redacted]) for the ATT-weighted SoC cohort. The adjusted HR for amivantamab versus SoC is [redacted] (95% CI: [redacted]) demonstrating that amivantamab is statistically significantly favoured over SoC in terms of PFS. The Kaplan-Meier plot of PFS for amivantamab versus the ATT-weighted SoC cohort is presented in Figure 93. Covariate adjustment results for this comparison are presented in Appendix M.

Figure 18: Kaplan-Meier curve for PFS for CHRYSALIS versus US RWE cohort (amivantamab vs SoC) – IPW (ATT)

Abbreviations: ATT: average treatment effect among the treated; CI: confidence interval; HR: hazard ratio; PC: physician's choice; PFS: progression-free survival; PS: propensity score; RW: real world; SoC: standard of care.

B.2.9.2 Overall survival

US RWE cohort

Unadjusted results

For the US RWE cohort, the median OS of amivantamab was [redacted] (95% CI: [redacted]) versus [redacted] (95% CI: [redacted]) for the unadjusted SoC cohort. The unadjusted HR for amivantamab versus SoC was [redacted] (95% CI: [redacted]). The unadjusted Kaplan-Meier plot for OS for amivantamab versus SoC is shown in Figure 19.

Figure 19: Kaplan-Meier curve for OS for CHRYSALIS versus US RWE cohort (amivantamab vs SoC) – unadjusted results

Abbreviations: CI: confidence interval; HR: hazard ratio; OS: overall survival; PS: propensity score; RW: real world; SoC: standard of care.

Adjusted results

For the US pooled cohort, the median OS of amivantamab is [redacted] (95% CI: [redacted]) versus [redacted] (95% CI: [redacted]) for the ATT-weighted SoC cohort. The adjusted HR for amivantamab versus SoC is [redacted] (95% CI: [redacted]) demonstrating that amivantamab is statistically significantly favoured over SoC in terms of OS. The Kaplan-Meier

plot of OS for amivantamab versus the ATT-weighted SoC cohort is presented in Figure 20. Covariate adjustment results for this comparison are presented in Appendix M.

Figure 20: Kaplan-Meier curve for OS for CHRYSALIS versus US RWE cohort (amivantamab vs SoC) – IPW (ATT)

Abbreviations: ATT: average treatment effect among the treated; CI: confidence interval OS: overall survival; HR: hazard ratio; IPW: inverse probability weighting; PS: propensity score; RW: real world; SoC: standard of care.

PHE cohort

Unadjusted results

For the PHE cohort, the median OS of amivantamab was [redacted] (95% CI: [redacted]) versus [redacted] (95% CI: [redacted]) for the unadjusted SoC cohort. The unadjusted HR for amivantamab versus SoC was [redacted] (95% CI: [redacted]).

Adjusted results

For the PHE cohort, following covariate adjustment, the adjusted HR for amivantamab versus SoC was [redacted] (95% CI: [redacted]) demonstrating that amivantamab is statistically significantly favoured over SoC in terms of OS.

B.2.9.3 Time-to-next treatment

US RWE cohort

Unadjusted results

For the US pooled cohort, the median TTNT of amivantamab is [redacted] (95% CI: [redacted]) versus [redacted] (95% CI: [redacted]) for the unadjusted SoC cohort. The unadjusted HR for TTNT for amivantamab versus SoC is [redacted] (95% CI: [redacted]). The unadjusted Kaplan-Meier curve for TTNT for amivantamab versus SoC is shown in Figure 21.

Figure 21: Kaplan-Meier curve for TTNT for CHRYSALIS versus US RWE cohort (amivantamab vs SoC) – unadjusted results

Abbreviations: CI: confidence interval; HR: hazard ratio; PS: propensity score; RW: real world; TTNT: time-to-next-treatment; SoC: standard of care.

Adjusted results

The median TTNT of amivantamab is [redacted] (95% CI: [redacted]) versus [redacted] (95% CI: [redacted]) for the ATT-weighted SoC cohort. The adjusted HR for amivantamab versus SoC is [redacted] (95% CI: [redacted]) demonstrating that amivantamab is statistically significantly favoured over SoC in terms of TTNT. The Kaplan-Meier plot of TTNT for amivantamab versus the ATT-weighted SoC cohort is presented in Figure 22. Covariate adjustment results for this comparison are presented in Appendix M.

Figure 22: Kaplan-Meier curve for TTNT for CHRYSALIS versus US RWE cohort (amivantamab vs SoC) – IPW (ATT)

Abbreviations: ATT: average treatment effect among the treated; CI: confidence interval; HR: hazard ratio; IPW: inverse probability weighting; PS: propensity score; RW: real world; TTNT: time-to-next treatment; SoC: standard of care.

PHE cohort

Unadjusted results

For the PHE cohort, the median TTNT of amivantamab was [redacted] (95% CI: [redacted]) versus [redacted] (95% CI: [redacted]) for the unadjusted SoC cohort. The unadjusted HR for amivantamab versus SoC was [redacted] (95% CI: [redacted]).

Adjusted results

For the PHE cohort, following covariate adjustment, the adjusted HR for amivantamab versus SoC was [redacted] (95% CI: [redacted]) demonstrating that amivantamab is statistically significantly favoured over SoC in terms of TTNT.

B.2.9.4 Uncertainties in the indirect and mixed treatment comparisons

The evidence base for amivantamab as a treatment for patients with advanced NSCLC with activating EGFR Exon20ins, after failure of platinum-based therapy is derived from Cohort D+ of the CHRYSALIS trial, which is a Phase 1b single-arm trial, and therefore provides no comparative efficacy versus currently used treatments for this population. As such, the adjusted analyses presented above provide valuable evidence for key clinical outcomes on the comparative efficacy of amivantamab versus current SoC treatments, which is necessary for the

cost-effectiveness analysis underpinning this submission and would otherwise not be available. The US RWE cohort provides the most robust results given the larger sample size and as such, is considered the main analysis. Results from the smaller PHE cohort were largely consistent with the US results and demonstrate the generalisability of these results to UK clinical practice.

In addition, these analyses provided comparative efficacy for amivantamab versus UK SoC, which is the most relevant comparator, reflecting the heterogeneity of the treatment lines and treatments received by this patient population. Due to small sample sizes, comparisons versus specific individual treatments were not feasible to conduct in a robust manner and therefore have not been undertaken.

Whilst the sample sizes from the PHE data are small, the use of the US RWE data as a primary analysis and consistency of results from both sources supports that amivantamab is a valuable treatment option in a population relevant to UK clinical practice. In addition, outcomes from the US pooled analysis have been validated with UK clinicians as generalisable to expected SoC outcomes in UK practice (see Section B.3.3 for more details).[12]

Despite the treatment comparisons being unanchored, the adjusted treatment comparisons were conducted using robust statistical methodology. The prognostic baseline characteristics adjusted for between treatment cohorts were identified by an SLR and subsequently validated by clinical expert feedback with regard to the specific target population of interest.[90] Despite this, adjustment for baseline characteristics via covariate adjustment and IPW cannot guarantee accounting for all imbalances in any unobserved variables, which randomisation would account for and bias due to residual confounding cannot be entirely excluded as with any non-randomised comparison. Due to limited data availability, it was not feasible to adjust for all baseline characteristics identified as relevant prognostic factors. However, where at all possible, key covariates were adjusted for.

Conclusions

These adjusted treatment comparisons provide valuable data on the comparative efficacy of amivantamab versus current treatments, and they provide valuable and strong evidence more generally for a consistent and significant treatment benefit in favour of amivantamab versus current SoC treatments. The use of two data sources (US RWE and PHE) to provide the comparative data, combined with the statistical methodologies accounting for differences in key prognostic variables, mean the adjusted treatment comparison provides robust comparative evidence for amivantamab versus current SoC that is generalisable to the UK.

Results from the adjusted comparison demonstrate a consistent benefit with amivantamab monotherapy over SoC across all tested efficacy endpoints (PFS, OS and TTNT) as demonstrated by the hazard ratios derived from these analyses. In the base case analysis, amivantamab statistically significantly reduced the risk of death by 50% when compared to SoC: HR = [redacted] (95% CI, [redacted]). This translated to an extension of median OS by an unprecedented [redacted] months. The robustness of these findings is demonstrated by the consistency in results across the two data sources investigated.

B.2.10 Adverse reactions

Safety results from CHRYSALIS in this submission are presented from the 8th October 2020 and 30th March 2021 data cut-offs. Results are presented for the post-platinum patients with Exon20ins at RP2D safety population (N=153) from the 30th March 2021 data cut-off. Supportive data from the All Treated at RP2D safety population (N=380) and All Treated safety population (N=489) at the latest data cut-off are presented in Appendix F.

B.2.10.1 Treatment duration and dosage

Patient disposition and completion/withdrawal information

Table 26 summarises study and treatment disposition for the post-platinum patients with EGFR Exon20ins at RP2D safety population at the 30th of March 2021 data cut-off. As of the latest data cut-off date (median follow-up: [redacted] months), [redacted] of patients had completed the study, 62.1% (95/153) of patients were still in the study and [redacted] had terminated study participation prematurely. As this time, 36.6% (56/153) of patients were still receiving amivantamab and 63.4% (97/153) had discontinued treatment with amivantamab; the most common reason for treatment discontinuation was progressive disease. Twelve patients (7.8%) were identified as discontinuing treatment due to AEs and three patients (2.0%) discontinued treatment due to death.

The majority of patients (62.1%) remained on study as of the data cut-off date, with some patients in this population terminating study participation.

Table 26: Study and treatment disposition; Post-platinum patients with EGFR Exon20ins at RP2D safety population (N=153)

Event, n (%)	Safety population (N=153, 30th March 2021 data cut-off)
Study disposition	
Patients ongoing	[redacted]
Completed study participation	[redacted]
Terminated study participation prematurely	[redacted]
Treatment disposition	
Patients ongoing	56 (36.6)
Discontinued study treatment	97 (63.4)
Reason for discontinuation	
Progressive disease	73 (47.7)
AE	12 (7.8)
Withdrawal by patient	7 (4.6)
Physician decision	2 (1.3)
Death	3 (2.0)

RP2D is defined as 1,050 mg if baseline weight <80 kg and 1,400 mg if baseline weight ≥80 kg. [a] Patient is considered to have completed the study if the patient died prior to the end of study.
Abbreviations: AE: adverse event; RP2D: recommended Phase 2 dose.
Source: Janssen CHRYSALIS Clinical Overview (30th March 2021 data cut-off).[75, 76]

Extent of exposure

The extent of exposure for the post-platinum patients with EGFR Exon20ins at RP2D safety population is summarised in Table 27. In this population, the median duration of treatment was 5.6 months with 46.4% (71/153) patients having received treatment for ≥6 months, and a maximum of duration of treatment of 23.9 months. The median number of treatment cycles was 7.0, with 34.0% (52/153) subjects having received treatment for ≥10 cycles, and the maximum number of treatment cycles was 27.

Table 27: Summary of treatment with amivantamab; Post-platinum patients with EGFR Exon20ins at RP2D safety population (N=153)

	Safety population (N=153, 30th March 2021 data cut-off)
Duration of study treatment, months[a]	
Mean (SD)	7.28 (5.81)
Median	5.52
Range	(0.03; 23.89)
Duration of study treatment, n (%)	
<2 months	31 (20.3)
2 –<4 months	26 (17.0)
4 –<6 months	25 (16.3)
≥6 months	71 (46.4)
Total number of cycles[b]	
Mean (SD)	8.5 (6.2)
Median	7
Range	(1, 27)

RP2D is defined as 1,050 mg if baseline weight <80 kg and 1,400 mg if baseline weight ≥80 kg. [a] Treatment duration is defined as the duration from the date of the first dose of amivantamab to the date of last dose of amivantamab+1 divided by 30.4375. [b] A patient is considered as treated in a cycle if the patient received any non-zero dose of study agent in that cycle.
Abbreviations: SD: standard deviation; RP2D: recommended Phase 2 dose.
Source: Amivantamab EPAR.[75]

B.2.10.2 Adverse events

Overview of treatment-emergent AEs

An overall summary of treatment-emergent AEs (TEAEs) for the post-platinum patients with EGFR Exon20ins at RP2D safety population at the 30th March 2021 (N=153) data cut-off is presented in Table 28.

All patients experienced at least one TEAE and most patients 150/153 (98.0%) had at least one TEAE reported by the investigator to be related to amivantamab. Grade 3 or higher TEAEs were experienced by 64 patients (41.8%) in this population, of which 30 patients (19.6%) had Grade 3 or higher events reported as related to amivantamab. Forty-four patients (28.8%) had serious TEAEs (8.5% reported related by investigator). Four patients (2.6%) had Grade 4 TEAEs. Grade 5 (fatal) TEAEs were reported for 11 patients (7.2%) (all assessed as unrelated to amivantamab).

Table 28: Overall summary of TEAEs; Post-platinum patients with EGFR Exon20ins at RP2D safety population (N=153)

Event, n (%)	Safety population (N=153, 30th March 2021 data cut-off)
Patients with ≥1 AE	153 (100.0)
Related AEs[a]	150 (98.0)
AEs leading to death[b]	11 (7.2)
Related AEs leading to death[a,b]	0
Serious AEs	44 (28.8)
Related serious AEs[a]	13 (8.5)
AEs leading to discontinuation of amivantamab	18 (11.8)
Related AEs leading to discontinuation of amivantamab[a]	8 (5.2)
AEs leading to dose reduction	22 (14.4)
Related AEs leading to dose reduction[a]	22 (14.4)
AEs leading to infusion modification[c]	91 (59.5)
Related AEs leading to infusion modification[a, c]	90 (58.8)
AEs leading to dose interruption[d]	55 (35.9)
Related AEs leading to dose interruption[a, d]	32 (20.9)
Grade ≥3 AEs	64 (41.8)
Related grade ≥3 AEs[a]	30 (19.6)
Grade 1	4 (2.6)
Grade 2	85 (55.6)
Grade 3	49 (32.0)
Grade 4	4 (2.6)
Grade 5	11 (7.2)

RP2D: 1,050 mg if baseline weight <80 kg and 1,400 mg if baseline weight ≥80 kg. [a] An AE is categorised as related if assessed by the investigator as possibly, probably, or very likely related to study agent. [b] AEs leading to death are based on AE outcome of Fatal. [c] AEs leading to infusion modification of study agent are based on infusion interrupted, infusion rate decreased, and infusion aborted due to adverse event on the infusion eCRF page. [d] Excludes infusion related reactions.
Abbreviations: AE: adverse event; RP2D: recommended Phase 2 dose.
Source: Amivantamab EPAR.[75]

Treatment-emergent AEs by preferred term

Common TEAEs (i.e., frequency of 10% or higher in All Treated at RP2D population) for the post-platinum patients with EGFR Exon20ins at RP2D safety population (N=153) at 30th March 2021 data cut-off are summarised in Table 29. The most frequently reported TEAE was infusion related reactions (IRRs; 63.4%). Common on-target events associated with EGFR inhibition, included dermatitis acneiform (39.2%), rash (43.1%), paronychia (52.9%), and stomatitis (22.2%). Common on-target events associated with MET inhibition included hypoalbuminemia (39.2%). Constipation (23.5%) was also reported in >20% of patients in this population.

Other TEAEs associated with the EGFR inhibition, such as dry skin (13.7%) and diarrhoea (13.7%) or MET inhibition such as peripheral oedema (22.9%), were also observed in at least 10% of patients in this population. Of note, other TEAEs associated with EGFR inhibitors were uncommon in this population. Keratitis occurred in 2 subjects (1.3%). Both instances were non-

serious and did not result in treatment discontinuation. ILD/pneumonitis occurred in 6 subjects (3.9%). Other TEAEs associated with EGFR inhibitors were uncommon in this population.

Table 29: Number of patients with TEAEs with a frequency of at least 10% by system organ class and preferred term; Post-platinum patients with EGFR Exon20ins at RP2D safety population (N=153)

Event, n (%)	Safety population (N=153, 30th March 2021 data cut-off)
Patients with 1 or more AEs	153 (100.0)
Skin and subcutaneous tissue disorders	136 (88.9)
Dermatitis acneiform	60 (39.2)
Rash	66 (43.1)
Pruritus	24 (15.7)
Dry skin	21 (13.7)
Gastrointestinal disorders	114 (74.5)
Constipation	36 (23.5)
Nausea	38 (24.8)
Stomatitis	34 (22.2)
Vomiting	21 (13.7)
Diarrhoea	21 (13.7)
Injury, poisoning and procedural complications	102 (66.7)
Infusion related reaction	97 (63.4)
Infections and infestations	107 (69.9)
Paronychia	81 (52.9)
Respiratory, thoracic and mediastinal disorders	88 (57.5)
Dyspnoea	30 (19.6)
Cough	26 (17.0)
General disorders and administration site conditions	96 (62.7)
Oedema peripheral	35 (22.9)
Fatigue	30 (19.6)
Pyrexia	26 (17.0)
Metabolism and nutrition disorders	92 (60.1)
Hypoalbuminaemia	60 (39.2)
Decreased appetite	27 (17.6)
Musculoskeletal and connective tissue disorders	73 (47.7)
Myalgia	18 (11.8)
Back pain	25 (16.3)
Nervous system disorders	50 (32.7)
Dizziness	18 (11.8)
Headache	11 (7.2)
Investigations	63 (41.2)
Alanine aminotransferase increased	34 (22.2)
Aspartate aminotransferase increased	25 (16.3)

Blood alkaline phosphatase increased	16 (10.5)
Psychiatric disorders	29 (19.0)
Insomnia	16 (10.5)

RP2D: 1,050 mg if baseline weight <80 kg and 1,400 mg if baseline weight ≥80 kg. Patients are counted only once for any given event, regardless of the number of times they actually experienced the event.
Abbreviations: TEAE: treatment emergent adverse event.
Source: Amivantamab EPAR.[75]

Treatment-emergent AEs Grade ≥3 by preferred term

TEAEs at Grade ≥3 for the post-platinum patients with EGFR Exon20ins at RP2D safety population (N=153) at the 30th March 2021 data cut-off are summarised in Table 30. These are the AEs feeding into the cost-effectiveness model informing this submission (see Section B.3.3.3). Overall, [redacted] patients experienced one or more Grade ≥3 AEs with Grade ≥3 TEAEs considered by the investigator to be related to amivantamab reported for [redacted] ([redacted]) patients; however, none of these AEs occurred in ≥5% patients. The most common Grade ≥3 AEs were pulmonary embolism and hypokalaemia, occurring in [redacted] and [redacted] patients, respectively.

Table 30: Number of patients with grade 3 or higher TEAE by preferred term: Post-platinum patients with EGFR Exon20ins at RP2D safety population (N=153)

Event, n (%)	Safety population (N=153, 30th March 2021 data cut-off)
Subjects with 1 or more Grade ≥3 AEs	[redacted]
Preferred term	
Pulmonary embolism	[redacted]
Hypokalaemia	[redacted]
Pneumonia	[redacted]
Dyspnoea	[redacted]
Hypoalbuminaemia	[redacted]
Paronychia	[redacted]
Diarrhoea	[redacted]
Infusion related reaction	[redacted]
Neutropenia	[redacted]
Hyponatraemia	[redacted]
Alanine aminotransferase increased	[redacted]
Hypophosphataemia	[redacted]
Hypotension	[redacted]
Gamma-glutamyltransferase increased	[redacted]
Rash	[redacted]
Respiratory failure	[redacted]
Anaemia	[redacted]
Respiratory tract infection	[redacted]
Sepsis	[redacted]
Acne	[redacted]
Cellulitis	[redacted]
Fatigue	[redacted]

Event, n (%)	Safety population (N=153, 30th March 2021 data cut-off)
Hypoxia	[redacted]
Pleural effusion	[redacted]
Pericardial effusion	[redacted]
Aspartate aminotransferase increased	[redacted]
Dermatitis acneiform	[redacted]
Headache	[redacted]
Hypertension	[redacted]
Oedema peripheral	[redacted]
Syncope	[redacted]
Abdominal pain	[redacted]
Atrial fibrillation	[redacted]
Blood alkaline phosphatase increased	[redacted]
Blood creatine phosphokinase increased	[redacted]
Decreased appetite	[redacted]
Lymphopenia	[redacted]
Mental status changes	[redacted]
Nausea	[redacted]
Pneumonia aspiration	[redacted]
Pneumonitis	[redacted]
Stomatitis	[redacted]
Vomiting	[redacted]
Aspiration	[redacted]
Hypocalcaemia	[redacted]
Infected dermal cyst	[redacted]
Insomnia	[redacted]
International normalised ratio increased	[redacted]
Muscular weakness	[redacted]
Pulmonary sepsis	[redacted]
Pulseless electrical activity	[redacted]
Rash papular	[redacted]
Renal vein thrombosis	[redacted]
Sudden death	[redacted]
Thrombocytopenia	[redacted]
Toxic epidermal necrolysis	[redacted]
Transitional cell carcinoma	[redacted]

Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event. The event experienced by the subject with the worst toxicity is used. RP2D: 1,050 mg if baseline weight <80 kg and 1,400 mg if baseline weight ≥80 kg.
Abbreviations: RP2D: recommended Phase 2 dose; (TE)AE: (treatment-emergent) adverse event.
Source: Janssen Data on File: Additional CHRYSALIS data.[81]

Treatment-related AEs

A total of [redacted] patients in the post-platinum patients with EGFR Exon20ins at RP2D safety population (N=153) had AEs reported by the investigator to be related to amivantamab. The most frequently reported related treatment-related AE was IRR ([redacted]). Aside from IRRs, treatment-related AEs in this population were comprised predominantly of on-target events associated with EGFR or MET inhibition. Frequently reported (≥20%) treatment-related AEs were EGFR-associated events of paronychia (50.3%), rash ([redacted]) and dermatitis acneiform (39.2%). On-target MET-associated events of hypoalbuminemia and peripheral oedema were reported as related to amivantamab in [redacted] and [redacted] of patients, respectively.

Table 31: Number of patients with treatment-related AEs by system organ class and preferred term; Post-platinum patients with EGFR Exon20ins at RP2D safety population (N=153)

Preferred term, n (%)	Safety population (N=153, 30th March 2021 data cut-off)
Patients with 1 or more related AEs	[redacted]
Skin and subcutaneous tissue disorders	[redacted]
Dermatitis acneiform	[redacted]
Rash	[redacted]
Pruritus	[redacted]
Dry skin	[redacted]
Injury, poisoning and procedural complications	[redacted]
Infusion related reaction	[redacted]
Gastrointestinal disorders	[redacted]
Stomatitis	[redacted]
Nausea	[redacted]
Infections and infestations	[redacted]
Paronychia	[redacted]
General disorders and administration site conditions	[redacted]
Fatigue	[redacted]
Oedema peripheral	[redacted]
Metabolism and nutrition disorders	[redacted]
Hypoalbuminaemia	[redacted]
Investigations	[redacted]
Alanine aminotransferase increased	[redacted]
Aspartate aminotransferase increased	[redacted]

RP2D: 1,050 mg if baseline weight <80 kg and 1,400 mg if baseline weight ≥80 kg. Patients are counted only once for any given event, regardless of the number of times they actually experienced the event.
Abbreviations: AE: adverse event; RP2D: recommended Phase 2 dose.
Source: Janssen Data on File: Additional CHRYSALIS data.[81]

Serious treatment-emergent AEs

The incidence of treatment-emergent AEs reported by the investigator to be serious for the post-platinum patients with EGFR Exon20ins at RP2D safety population (N=153) is summarised in Table 32.

A total of [redacted] patients in the post-platinum patients with EGFR Exon20ins at RP2D safety population (N=153) had TEAEs reported by the investigator to be serious. The most frequently reported serious TEAE was interstitial lung disease, reported in [redacted] patients ([redacted]).

Table 32: Incident of serious treatment-emergent AEs by system organ class, preferred term; Post-platinum patients with EGFR Exon20ins at RP2D safety population (N=153)

System organ class/Preferred term, n (%)	Safety population (N=153, 30th March 2021 data cut-off)
Subjects with any serious treatment-emergent AEs	[redacted]
Skin and subcutaneous tissue disorders	[redacted]
Rash	[redacted]
Toxic epidermal necrolysis	[redacted]
Injury, poisoning and procedural complications	[redacted]
Infusion related reaction	[redacted]
Gastrointestinal disorders	[redacted]
Diarrhoea	[redacted]
Abdominal pain	[redacted]
Respiratory, thoracic and mediastinal disorders	[redacted]
Interstitial lung disease	[redacted]

RP2D: 1,050 mg if baseline weight <80 kg and 1,400 mg if baseline weight ≥80 kg. Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event. The event experienced by the subject with the worst toxicity is used.
Abbreviations: ADR: adverse drug reaction; RP2D: recommended Phase 2 dose.
Source: Janssen Data on File: CHRYSALIS Clinical Overview (30th March 2021 data-cut).[76]

Deaths

OS is a secondary efficacy endpoint in this study, and survival data continues to be collected on all patients even after discontinuation of amivantamab during the Follow-up Period. In all cases of patient death, regardless of timing, the cause of death was separately reported. For all deaths that occurred during the Treatment Period (and up through 30 days after last dose), specific information regarding the cause of death was to be reported as a Grade 5 TEAE. Thus, patient deaths that are due to progressive disease, if occurring on treatment or within 30 days of the last dose, are also separately reported as an AE having an outcome of death.

A summary of deaths that occurred at any time during the study through the data cut-off for the post-platinum patients with EGFR Exon20ins at RP2D safety population (N=153) at the 30th March data cut-off is presented in Table 33. Separately summarised in this table are deaths that occurred during the Treatment Period (or within 30 days of last dose of amivantamab). The median follow-up was [redacted] months (range: [redacted]). Of note, none of these deaths were reported as related to amivantamab by the investigator, and the fatal events reflect consequences associated with the patients' underlying NSCLC.

In the post-platinum patients with EGFR Exon20ins at RP2D safety population (N=153), [redacted] patients ([redacted]) died at any time on study, with progressive disease being the most common cause of death (n=[redacted]). For [redacted] patients ([redacted]), death occurred on treatment or within 30 days of the last dose of amivantamab, including [redacted] patients who died due to a TEAE and [redacted] patients who died due to progressive disease. A summary of these deaths is presented in Table 34.

Table 33: Summary of deaths during study; Post-platinum patients with EGFR Exon20ins at RP2D safety population (N=153)

Preferred term, n (%)	Safety population (N=153, 30th March 2021 data cut-off)
Deaths during study	[redacted]
PD	[redacted]
AE	[redacted]
Other	[redacted]
Deaths during treatment	[redacted]
AE	[redacted]
PD	[redacted]
Other	[redacted]

RP2D: 1,050 mg if baseline weight <80 kg and 1,400 mg if baseline weight ≥80 kg. Deaths during treatment are presented for patients who died within 30 days of last amivantamab dose.
Abbreviations: AE: adverse event; PD: progressive disease; RP2D: recommended Phase 2 dose.
Source: Janssen Data on File: CHRYSALIS Clinical Overview (30th March 2021 data-cut).[76]

Table 34: Number of patients with TEAEs leading to death by system organ class and preferred term; Post-platinum patients with Exon20ins at RP2D safety population (N=153)

Preferred term, n (%)	Safety population (N=153, 30th March 2021 data cut-off)
Patients with 1 or more AEs leading to Death	[redacted]
Infections and infestations	[redacted]
Pneumonia	[redacted]
Adenovirus infection	[redacted]
Pulmonary sepsis	[redacted]
Respiratory, thoracic and mediastinal disorders	[redacted]
Respiratory failure	[redacted]
Dyspnoea	[redacted]
Aspiration	[redacted]
Pneumonia aspiration	[redacted]
Cardiac disorders	[redacted]
Cardio-respiratory distress	[redacted]
General disorders and administration site conditions	[redacted]
Sudden death	[redacted]

RP2D: 1,050 mg if baseline weight <80 kg and 1,400 mg if baseline weight ≥80 kg. AEs leading to death are based on AE outcome of Fatal. Patients are counted only once for any given event, regardless of the number of times they actually experienced the event.
Abbreviations: AE: adverse event; RP2D: recommended Phase 2 dose; TEAE: treatment emergent adverse event.
Source: Janssen Data on File: CHRYSALIS Clinical Overview (30th March 2021 data-cut).[76]

Infusion-related reactions

In the All Treated at RP2D safety population (N=[redacted]), IRRs occurred in 67.4% of post-platinum patients with Exon20ins. In general, IRR events (characterised predominantly by symptoms of dyspnoea, flushing, chills, nausea, chest discomfort, and vomiting) were of mild or moderate

severity, non-serious, and not treatment limiting: 97.4% of IRR events were Grade 1 or 2 and 98.8% of IRRs occurred at the first infusion, with a median time to onset of 60 minutes. The overall rates of IRRs per infusion (regardless of toxicity grade) fell from 66.3% for Cycle 1 Day 1 to 3.5% for Cycle 1 Day 2, after which they continued to fall, with 0.1% of patients experiencing IRRs for Cycle 2 onwards. IRRs were prophylactically managed through use of split dosing of the first dose (Cycle 1) over Days 1 and 2 and the administration of select drugs such as corticosteroids, antihistamines, and antipyretics prior to the scheduled amivantamab infusion.[75]

B.2.11 Ongoing studies

The CHRYSALIS trial is ongoing; however, there are currently no plans for additional data availability in the patient populations with EGFR Exon20ins mutations following platinum-based chemotherapy. Given amivantamab is a likely candidate for the CDF, a proposed data collection plan is presented in Table 35. The objective of further data collection is to address the degree of uncertainty around the following areas of the submission:

- **Confirmation of clinical outcomes for amivantamab in UK patients.** The submission proposes further collection of OS data for amivantamab whilst in use within the NHS in order to confirm that the clinical outcomes observed in the CHRYSALIS trial are representative of those expected in typical UK clinical practice. Data on baseline characteristics, OS, time to treatment discontinuation (TTD), and subsequent therapies, would be collected via the Systemic Anti-cancer Therapy (SACT) dataset.

- **The comparative effectiveness of amivantamab versus UK SoC.** Due to the single arm nature of the CHRYSALIS trial and the sample size limitations in the most relevant real-world dataset to UK clinical practice (the PHE dataset), uncertainty exists around the comparative efficacy of amivantamab versus UK standard of care. Further retrospective data collection of covariates is required to increase the sample size and reduce the uncertainty in the adjusted comparison analysis. Data on baseline characteristics, OS and TTNT, would be collected via an existing Janssen study using NCRAS and linked datasets. This will rely on molecular data linkage to the NCRAS dataset and will cover the years 2017, 2021 and 2022. The planned data collection duration avoids any overlap with the time period covering the SACT data collection detailed in the previous point.

Table 35: Key areas of uncertainty and proposed approach to data collection

Key uncertainty	Issues addressed	Data source	How data will address the uncertainty	Data availability
Generalisability of OS data for amivantamab from CHRYSALIS to UK clinical practice	• Collection of OS data for amivantamab in UK practice whilst available on the NHS	SACT	Reduce uncertainty in the generalisability to UK clinical practice of OS estimates for amivantamab	TBD[a]
Comparative effectiveness of amivantamab versus UK SoC	• Further UK-specific data for UK SoC over an extended timeframe. Outcomes collected will be OS and TTNT • Increase the sample size of the PHE study	NCRAS datasets	Reduce uncertainty in the relative efficacy estimates for amivantamab versus SoC for key efficacy outcomes informing the model, including OS and PFS	31st December 2023

[a] The timeline for data availability will be determined in collaboration with NICE and will be dependent on the timing of the anticipated recommendation of amivantamab for use on the CDF following the appraisal of this submission by NICE.
Abbreviations: NCRAS: National Cancer Registration and Analysis Service; NHS: National Health Service; OS: overall survival; PHE: Public Health England; SACT: Systemic Anti-cancer Treatments; SoC: standard of care; TBD: to be decided; TTNT: time to next treatment.

B.2.12 Innovation

While significant advancements in the treatment of the common EGFR mutations have been made in the last two decades (notably the introduction of EGFR TKIs), targeted treatment options have not been available for patients with EGFR Exon20ins mutations, which are rarer and are associated with resistance to EGFR TKI treatment. As such, treatment options for EGFR Exon20ins mutated NSCLC after platinum-based chemotherapy are currently non-targeted and associated with limited efficacy. Consequently, prognosis for these patients is poor and there remains a significant unmet need for novel treatment options that can extend PFS and life expectancy.

Amivantamab is the first targeted treatment for adult patients with EGFR Exon20ins mutated NSCLC after platinum-based chemotherapy and represents an important milestone in advancing the treatment of genetically-defined lung cancer.[35, 77] In CHRYSALIS, amivantamab is the first targeted therapy to demonstrate efficacy in patients with EGFR Exon20ins NSCLC after progression on platinum based chemotherapy,[1] with a median PFS of 6.74 months (95% CI: 5.45, 9.66), and a median OS of 22.77 months (95% CI: 17.48, NE). In an adjusted treatment comparison, amivantamab showed statistically significantly lengthened PFS (HR: 0.53; 95% CI: 0.40, 0.70; p≤0.001) and OS (HR: 0.50; 95% CI: 0.35, 0.73; p=0.0003) as compared with therapies currently used in the real world. Further, amivantamab has a manageable and predictable safety profile, consistent with the inhibition of the EGFR and MET pathways. These data demonstrate that amivantamab monotherapy represents a step-change in the management of this underserved population and its availability would align with the aims of the NHS to be world-leading in cutting-edge genomic technologies used to predict, diagnose and treat disease in a personalised manner. The innovative nature of amivantamab is further confirmed by its receipt of an innovation passport from the MHRA and breakthrough therapy designation from the FDA.[35, 73, 74]

In addition to offering an innovative, targeted and meaningful treatment for patients with an immense unmet need and leading to benefits with regards to alleviating their clinical burden, economic and humanistic burden, as well as that of their caregivers, the introduction of amivantamab to UK clinical practice has the potential to improve health inequity for the reasons discussed in Section B.1.4. These include the stigma that can be associated with a lung cancer diagnosis, the relevance of cultural differences on treatment-seeking behaviours, and the impact of the COVID-19 pandemic on time to diagnosis. These equity considerations are not inherently captured within the cost per QALY or budget impact frameworks and should be explicitly considered within the decision-making process.

Finally, the Genomic Medicines Service is an NHS innovation that, among other things, aims to “match people to the most effective medications and interventions”. It is unique to the UK, and reflects a UK-specific social value judgement of the importance of prioritising and funding targeted therapies. Amivantamab provides a treatment option for patients identified via a genetic test and as such - if recommended - can be a contributor in driving forward the use of the Genomic Medicines Service and testing pathways. This demonstrates that amivantamab is innovative in a way which matters to patients and the UK public, by providing a targeted therapeutic option in response to information gathered from a genetic diagnostic test.

B.2.13 Interpretation of clinical effectiveness and safety evidence

B.2.13.1 Principal findings from the clinical evidence base

Amivantamab is a clinically effective treatment for patients with locally advanced or metastatic NSCLC with EGFR Exon20ins, after failure with platinum-based chemotherapy. This is a disease which has a substantial impact on both patient and caregiver quality of life with a poor prognosis and limited treatment options. As the first bi-specific antibody to show efficacy in this population, amivantamab is an innovative therapy that represents an important milestone in advancing the treatment of lung cancer driven by genetic alterations in EGFR.

The Phase 1b, single arm clinical trial CHRYSALIS provides the main evidence base for amivantamab in this population. Evidence from the CHRYSALIS trial demonstrates that amivantamab produces robust responses with a well-characterised and manageable safety profile. After a median follow-up of [redacted] months (range: [redacted]), BICR-assessed ORR for amivantamab was 43.0% (95% CI: 33.7, 52.6) and the median DOR was 10.84 months (95% CI: 6.90, 14.98). Median BICR-assessed PFS was 6.74 months (95% CI: 5.45, 9.66) and the median OS 22.77 months (95% CI: 17.48, NE). Overall, outcomes from CHRYSALIS exceed those for SoC, as presented in Section B.2.9 and below. At the latest data cut-off, 98.0% of patients had experienced at least one TEAE related to amivantamab, 19.6% of patients had Grade 3 or higher AEs related to amivantamab. The most frequently reported related TEAE was IRR which occurred in 63.4% of patients. Grade 5 (fatal) TEAEs were reported for 11 patients (all assessed as unrelated to amivantamab).

The adjusted treatment comparison showed that, after adjustment for key prognostic factors, amivantamab provided a statistically significant treatment benefit versus SoC in terms of PFS, OS and TTNT. In the US RWE cohort, the adjusted HR for amivantamab versus SoC for PFS was [redacted] (95% CI: [redacted]), for OS was [redacted] (95% CI: [redacted]) and for TTNT was [redacted] (95% CI: [redacted]) demonstrating that amivantamab offers a statistically significant benefit over SoC. Results from the US RWE cohort are supported by largely consistent results from the comparison to the smaller PHE cohort, a smaller sample that supports the generalisability of the results to UK clinical practice.

Amivantamab thus allows patients with EGFR Exon20ins mutations who have progressed on or after platinum-based chemotherapy to achieve clinical outcomes closer to those achieved in the second-line by patients with common EGFR mutations who received first-line platinum-based chemotherapy (median PFS [redacted] months and median OS [redacted] months).[91]

B.2.13.2 Strengths and limitations of the clinical evidence base

The CHRYSALIS trial provides valuable efficacy and safety data in the specific population relevant to this submission and is therefore highly generalisable to the patient population; having this data in the licensed population is a considerable strength. As the trial includes patients from UK centres, the results are also generalisable to the UK population. This assumption was validated by UK clinicians at an advisory board.[12]

The wide range of endpoints considered in the trial (ORR, CBR, DOR, PFS, TTF and OS) are all clinically relevant and important to both patients and clinicians. The benefits demonstrated in the trial will therefore translate to meaningful improvements for patients in clinical practice.

As discussed in Section B.2.5, the CHRYSALIS trial was methodologically robust and well reported. The results were considered to be at a low-moderate risk of bias in all categories considered.

Limitations

As the CHRYSALIS trial was single-arm and the SLR uncovered no other relevant RCTs, there was no direct comparative efficacy evidence available from RCTs assessing amivantamab. Comparative evidence for this submission was therefore obtained through an adjusted treatment comparison using RWE sources. These comparisons used robust statistical methodology with key prognostic baseline characteristics (identified through an evidence-based process) adjusted for to reduce confounding. Despite comparative analyses being adjusted for available clinically important prognostic variables, bias due to residual confounding cannot be entirely excluded as with any non-randomised comparison.

The supportive PHE data used in the adjusted treatment comparison were collected from a relatively small sample size which may limit the robustness of the results. However, these results do not inform the base case for the model. The results are also largely consistent with the bigger US RWE cohort considered to be the main analysis, supporting the conclusion that these results are highly relevant to UK practice.

As HRQoL data was only collected from a small number of patients, the robustness of the results may be limited. However, the general trend suggests that HRQoL did not worsen over the measured period.

B.2.13.3 CDF considerations

As described in Section B.1.3.2.2, there is a significant unmet need for a robust treatment option in UK clinical practice for patients with EGFR Exon20ins-mutated NSCLC after platinum-based chemotherapy. Amivantamab will meet this unmet need by addressing the inconsistency in the availability of effective treatment options and improving prognosis in this subset of the EGFR mutated NSCLC population. Amivantamab offers an innovative, targeted treatment that has demonstrated improved OS and PFS when compared to existing real-world drug therapies. As such, we propose that amivantamab should be recommended for use in the NHS despite some uncertainties in the data package, in order to allow patients to benefit from this breakthrough technology while more data are being collected.

In Section B.1.4, we propose that the Committee should consider whether the principle of requiring NICE's usual standard of data should override the principle of minimising avoidable health inequalities. The case for baseline commissioning of amivantamab in spite of the limits of the CHRYSALIS trial is strong, since it will reduce the inequity of outcomes due to stigma in a heavily stigmatised space, as well as addressing the ethnicity-driven inequality in treatment seeking behaviour. Nevertheless, we note that NICE have conventionally positioned technologies like amivantamab as candidates for the CDF.

As highlighted in Section B.2.11, uncertainties related to the confirmation of clinical outcomes for amivantamab in UK patients and the comparative effectiveness of amivantamab versus UK SoC have the potential to be resolved with further data. Therefore, given the potential for future data collection to reduce uncertainty, amivantamab is an ideal candidate for the CDF, as this innovative treatment has the potential to demonstrate cost-effectiveness with the collection of further data. A full outline of the data collection plan is presented in Section B.2.11.

B.2.13.4 End-of-life criteria

Amivantamab should be considered as an end-of-life treatment for adult patients with locally advanced or metastatic NSCLC with activating EGFR Exon20ins, whose disease has progressed on or after platinum-based chemotherapy, given (a) these patients currently have a short life expectancy of <24 months on UK SoC and (b) that amivantamab offers an extension to life of at least an additional three months as compared with current UK SoC.

Further details to support amivantamab as an end-of-life treatment are provided below.

The treatment is indicated for patients with a short life expectancy of <24 months

Median OS data for patients with EGFR Exon20ins mutated NSCLC after failure of platinum-based chemotherapy are not available in the literature. However, based on the base case analysis for the cost-effectiveness model, the predicted median OS for patients with EGFR Exon20ins mutated NSCLC on SoC is [redacted] months (based on the base case assumptions outlined in Section B.3). Therefore, as predicted median OS is less than 24 months, amivantamab meets this NICE end of life criterion for the licensed indication under review.

There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional three months, as compared with current NHS treatment

There are no direct comparisons between amivantamab and current clinical management. However, the median OS of amivantamab the post-platinum patients with Exon20ins at RP2D efficacy population was 22.77 months (95% CI: 17.48, NE). Further, data from the cost-effectiveness model predicts median OS with amivantamab in the base case analysis to be [redacted] months (ranging from [redacted] months).

Consequently, there is sufficient evidence to indicate that amivantamab offers an extension of life of at least an additional three months compared with current NHS treatment.

Table 36: End-of-life criteria

Criterion	Data available			Section in Document B
	Comparator	Median OS	Mean undiscounted life years	
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	UK SoC	US RWE: [redacted] CEM: [redacted]	1.38 LYs	B.2.9 (61), B.3.3 (100)
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment	Amivantamab	CHRYSALIS: 22.77 (17.48, NE) CEM: [redacted]	2.31 LYs	B.2.6 (47), B.3.3 (100)
	Difference versus amivantamab	US RWE: [redacted] CEM: [redacted]	0.93 LYs	

[a] Median OS is presented based on adjusted comparison with US data (US RWE), unadjusted comparison with UK data (PHE), the output of the cost-effectiveness model (CEM) or the CHRYSALIS trial (CHRYSALIS).
Abbreviations: NE: not evaluable; NHS: National Health Service; IO: immuno-oncology agent; OS: overall survival; TKI: tyrosine kinase inhibitor.

B.3 Cost effectiveness

Cost effectiveness summary

Cost effectiveness model methodology

- An SLR of economic evaluations did not identify any prior cost-effectiveness analyses for pharmacologic interventions in locally advanced or metastatic NSCLC with activating EGFR Exon20ins. Accordingly, relevant previous NICE appraisals of treatment options in second-line EGFR mutated NSCLC populations were reviewed (see Table 37) to inform the development of a *de novo* cost-utility analysis to assess the cost-effectiveness of amivantamab versus current treatment options in this patient population.[66, 92-95]
- The cost effectiveness model adopted a partitioned survival approach. At the start of the model, all patients were within the PFS health state. Each cycle, patients could remain in the PFS state, move to the post-progression survival (PPS) state or die based on treatment-specific PFS and OS functions. Costs and health benefits were accrued each cycle for each health state.
- In line with the NICE reference case, the analysis was conducted from the perspective of the NHS and PSS over a 15-year (i.e., lifetime) time horizon.[96]
- Due to considerable heterogeneity in treatments due to lack of specifically recommended treatments in the UK, evidence from real-world data sources of variability in treatments received and clinical expert feedback, amivantamab was compared to a basket of treatments termed UK SoC within the model.
- OS and PFS data for amivantamab were sourced directly from the CHRYSALIS trial. Data to inform UK SoC were sourced from a US RWE database in the base case, with use of data from PHE explored in a scenario analysis.
- Utility values associated with the PFS and PPS health states and AEs were sourced from previous NICE appraisals where possible (TA484 and TA520, respectively), and from the literature where necessary.[93, 97]
- Health state unit costs and resource use were sourced from TA520 and AE management costs were applied in alignment with the approach taken in TA653.[66, 95] Unit costs were sourced from the NHS reference costs or the PSSRU.[98, 99]

Cost effectiveness model results

- At the confidential PAS price, the ICER for amivantamab versus UK SoC fell within the range considered to be cost-effective. At £39,764/QALY gained, it is below the NICE willingness-to-pay (WTP) threshold of £50,000 (considering amivantamab meets the NICE end-of-life criteria, see Section B.2.13.4).
- These results demonstrate amivantamab to be a cost-effective option for the treatment of patients with locally advanced or metastatic NSCLC with activating EGFR Exon20ins mutations following progression on or after platinum-based chemotherapy as compared with UK SoC.
- Results of the sensitivity analyses demonstrate that the base case cost-effectiveness results exhibit little variation when the combined distributional uncertainty across model parameters is taken into account. The three most influential parameters driving the model

when the amivantamab with-PAS price was considered were PFS data for UK SoC, drug costs in subsequent cycles for amivantamab and the health state utility value for the PPS state.

Cost-effectiveness model conclusions

- Overall, the introduction of amivantamab into UK clinical practice is anticipated to bring substantial benefits to patients with Exon20ins for whom current treatment options (UK SoC) are unable to fulfil a substantial unmet need for an effective, well tolerated treatment that is able to delay progression and improve survival rates.
- This analysis demonstrates that amivantamab is a cost-effective treatment option that would offer value for money for the NHS. If recommended, amivantamab would represent the first treatment available that is specifically for the treatment of this patient population in the UK.

B.3.1 Published cost-effectiveness studies

A *de novo* economic SLR was conducted on 4th May 2020 and updated on 4th February 2021 and 2nd November 2021 to identify cost-effectiveness, health-state utility values (HSUVs) and cost and healthcare resource use data to populate missing parameters for the cost-effectiveness analysis. The databases and hand searches were conducted simultaneously for these three data streams, and each record identified in these searches was assessed for eligibility across all three streams.

In total, the cost-effectiveness SLR included 270 articles reporting on 248 unique studies. Of these, 75 articles reporting on 60 unique studies were conducted from a UK perspective. Full details of the cost-effectiveness SLR methods and results, including a summary of published economic evaluations identified in the review, are presented in Appendix G.

Given that the economic SLR did not identify any evaluations investigating the cost-effectiveness of amivantamab in this patient population, a *de novo* cost-effectiveness analysis of amivantamab versus the comparator relevant to the decision problem for this submission was performed.

B.3.2 Economic analysis

The objective of this economic analysis was to assess the cost-effectiveness of amivantamab versus current treatment options in adult patients with locally advanced or metastatic NSCLC with activating EGFR Exon20ins whose disease has progressed on or after platinum-based chemotherapy. The perspective of the model was the UK National Health Service (NHS) including direct medical costs and Personal Social Services (PSS) over a lifetime time horizon (i.e. 15 years) of the patient cohort from the initiation of treatment. Sections B.3.2.1, B.3.2.2 and B.3.2.3 present details on the patient population, the model structure and the included interventions and comparators, respectively.

B.3.2.1 Patient population

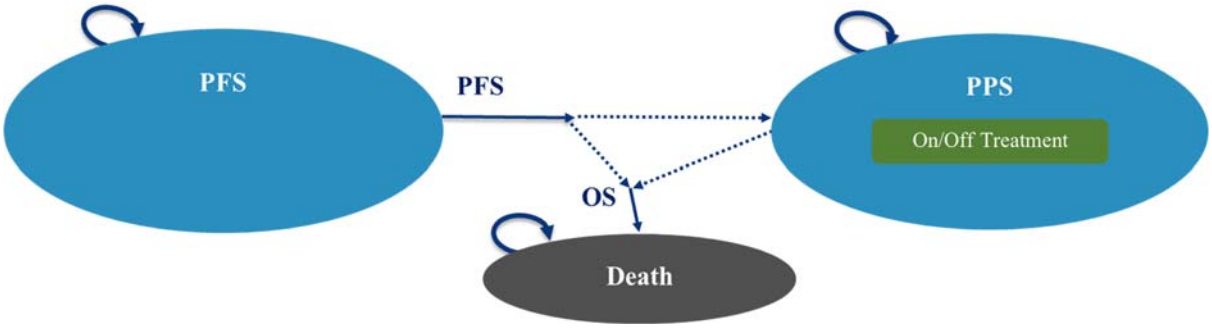
The patient population of relevance considered in this economic evaluation was adult patients with locally advanced or metastatic NSCLC with activating EGFR Exon20ins, whose disease has progressed on or after platinum-based chemotherapy. As set out in the decision problem in Section B.1 (Table 1), the population considered in this model is in line with the full marketing authorisation for amivantamab and is reflective of the post-platinum patients with EGFR

Exon20ins at RP2D efficacy population (N=114) as of the 30th March 2021 data-cut from CHRYSALIS.

B.3.2.2 Model structure

An economic model was developed to conduct a cost-effectiveness analysis of amivantamab versus the relevant comparator for the target patient population. The model was developed using a partitioned survival approach to track a cohort's costs and health outcomes over time from the beginning of current-line treatment until death. The model includes a progression-free survival (PFS) state, a post-progression survival (PPS) state, and death. All patients started in the PFS health state, and in each cycle, the cohort was distributed into three health states (i.e., PFS, PPS, and death) as shown in Figure 23.

Figure 23: Partitioned survival model structure



Abbreviations: OS: overall survival; PFS: progression free survival; PPS: post-progression survival.

Partitioned survival model

The partitioned survival approach was selected given that it permits the use of outcome data from the adjusted treatment comparison presented in Section B.2.9 and permits the clinical benefits of amivantamab to be captured by reflecting the increased proportion of patients expected to be alive and/or progression-free over time. In addition, it has been implemented in previous cost-effectiveness models in metastatic NSCLC with EGFR appraised by NICE.[66, 92-95]

The percentage of patients in a state at any given time were estimated using an area under the curve (AUC) approach. That is, the allocation of patients into health states was based directly on treatment-specific PFS and OS functions. Once progressed, patients could not return to the PFS state; they were assumed to continue living with progressed disease or die. The costs and health benefits were accrued each cycle (i.e., four-week cycle) for each health state to estimate the expected outcomes and costs for the intervention and comparator. Health effects in the model are calculated in terms of both life years (LYs) and QALYs.

In the PFS state, response rates were not considered due to data limitations. Given the small sample size in the CHRYSALIS trial (post-platinum patients with EGFR Exon20ins at RP2D efficacy population [N=114] as of the 30th March 2021 data-cut), stratification by response would further decrease patient numbers and therefore create more uncertainties around long-term extrapolations. In addition, response-stratified data were not available from RWE to inform relative efficacy estimates.

The model considers up to two distinct LOTs (i.e., current-line treatment, while in the PFS state, and a subsequent line, while in the PPS state). The proportion of patients on and off current-line treatment was estimated using the same AUC approach. In the base case, time on treatment is assumed to be equal to progression (see Section B.3.3.2).

The proportion of patients in the PPS health state was estimated by taking the difference of OS and PFS survival functions. In the PPS health state, patients received a basket of subsequent treatments following disease progression. In the base case, the proportion of patients modelled to receive treatments following progression and the composition of the subsequent treatment basket was derived from the US RWE pooled data (see Section B.3.2.3), and feedback received from UK-based clinicians at a Janssen-led advisory board was that the treatment classes received by patients in the pooled US RWE study are broadly aligned with those which would be received by patients in the UK.[12] It was assumed that efficacy of subsequent treatments was implicitly captured in OS extrapolations and, thus, only the costs of subsequent treatments were considered in the model.

Features of the *de novo* analysis

The cost-effectiveness analysis adopts the perspective of the UK healthcare payer, i.e., NHS and PSS, which includes only direct medical costs. The time horizon for the base case was 15 years (i.e., lifetime) which sufficiently captured the lifetime of the targeted population given the starting age of patients in the model (61.75 years, as per the CHRYSALIS trial population) and their poor prognosis. The model tracked the cohort of patients over time in cycles of four weeks. An annual discount rate of 3.5% was applied in the model base case to the costs and health benefits that occurred beyond the first cycle. Given that amivantamab meets one of the criteria under which a discount rate of 1.5% per year may be considered (that it is for patients who would otherwise die or have a severely impaired life), an illustrative scenario in which this discount rate is implemented for costs and benefits beyond the first cycle (Section B.3.8.3).[100]

A summary of the features of the economic analysis can be found in Table 37, as compared to relevant previous NICE appraisals for TA310 (afatinib for treating epidermal growth factor receptor mutation-positive locally advanced or metastatic non-small-cell lung cancer), TA484/TA713 (nivolumab for previously treated non-squamous non-small-cell lung cancer), TA520 (atezolizumab for treating locally advanced or metastatic non-small-cell lung cancer after chemotherapy) and TA653 (osimertinib for treating EGFR T790M mutation-positive advanced non-small-cell lung cancer).[66, 93, 95] Of note, no previous appraisals have been conducted in patients with EGFR Exon20ins mutations; as such, adjustments to methodology or sources as compared with the previous examples have been made in this appraisal as appropriate.

Table 37: Features of the economic analysis

Factor	Previous appraisals				Current appraisal	
	TA310[92]	TA484[93] and TA713[94]	TA520[66]	TA653[101]	Chosen values	Justification
Model structure	Partitioned survival model	Partitioned survival model	Partitioned survival model	Partitioned survival model	Partitioned survival model	Captures the clinical benefits of amivantamab, utilises the outcome data available from the adjusted treatment comparison and aligned with previous similar submissions
Time horizon	10 years	20 years	25 years	15 years	15 years	Expected to sufficiently capture the lifetime of targeted population given their poor prognosis
Cycle length	1 month	1 week	1 week	3 weeks	4 weeks	In line with the dosing regimens for amivantamab and expected to be sufficiently short to capture time-to-event outcomes
Discount	3.5%	3.5%	3.5%	3.5%	3.5%	NICE reference case[96]
Health effects measure	QALYs	QALYs	QALYs	QALYs	QALYs	NICE reference case[96]
Perspective	NHS/PSS	NHS/PSS	NHS/PSS	NHS/PSS	NHS/PSS	NICE reference case[96]
Source of health state utilities	PF: EQ-5D results collected in the LUX-Lung trials PD: Published literature (Chouaid *et al.* 2013)[102]	*TA484:* EQ-5D results collected in CheckMate 057 *TA713:* Combination of EQ-5D values from CheckMate 057 with a Dutch lung cancer study (van den	EQ-5D results collected in OAK trial	EQ-5D results collected in AURA/IMPRESS and AURA3 trials	TA484/TA713	Due to low sample size in the EQ-5D-3L data collected in the CHRYSALIS trial (data are available for only [redacted]% of the population due to the late introduction of the QoL questionnaire), published sources were required to estimate the utility values in patients with advanced EGFR Exon20ins mutated NSCLC

		Hout *et al*. 2006)[103]				
Source of costs	• NHS National Reference costs • PSSRU • eMIT[a] • BNF					NICE reference case[96]
Modelling approach for subsequent treatments	NR	Applied as a one-off cost to patients who transitioned out of the PFS health state	Applied as a one-off cost for all patients moving out of the "on treatment" health state for all comparators included in the mode	NR	Applied as a one-off cost to patients who transitioned out of the PFS health state	Based on the time spent (undiscounted LYs) by patients in the PPS health state in the model, patients receiving amivantamab spend 1.47 years and those on UK SoC spend 0.86 years in this state. Therefore, it is not unreasonable to assume only one line of subsequent treatment. There are also limited data on the subsequent treatments that patients would receive in the long-term.

[a] TA310 does not source costs from eMIT.

Abbreviations: AE: adverse event; BNF: British National Formulary; eMIT: electronic market information tool; EGFR: epidermal growth factor receptor; EQ-5D(-3L): EuroQol five-dimensions (three-levels) instrument; Exon20ins: Exon 20 insertion mutations; LY: life years; NHS: National Health Service; NSCLC: non-small-cell lung cancer; NICE: National Institute for Health and Care Excellence; NR: not reported; PFS: progression-free survival; PPS: post-progression survival; PSS: personal social services; QALYs: quality-adjusted life years; SoC: standard of care.

B.3.2.3 Intervention technology and comparators

Intervention

The intervention of interest is amivantamab monotherapy, at 1,050 mg for patients with body weight <80 kg and 1,400 mg for patients with body weight ≥80 kg administered once weekly for the first four weeks and then once every two weeks starting at Week 5, in line with the regimen used in the CHRYSALIS trial informing the submission as well as the SmPC for amivantamab.[27]

Comparators

As the CHRYSALIS trial is a single arm study, data informing comparator efficacy were derived from a US RWE database study. Further detail regarding the approach for determining relative efficacy is described in Section B.2.9 above, and how these data are utilised in the cost-effectiveness model is described in Section B.3.3 below.

As discussed in Section B.1.3.2, clinical expert feedback received from UK clinicians is that there is no established standard treatment pathway for patients with EGFR Exon20ins mutated NSCLC in the UK, with treatment decisions often made on a case-by-case basis due to a lack of national guidelines and no licensed treatment options for these patients previously available. The UK clinicians further confirmed that treatment decisions are typically not defined by specific patient characteristics such as age or disease stage at diagnosis, with previous treatment received and patient or clinician preferences being more heavily weighted in the decision-making process.[12]

Due to considerable heterogeneity in treatments due to lack of specifically recommended treatments in the UK, evidence from real-world data sources of variability in treatments received and clinical expert feedback, amivantamab was compared to a basket of treatments termed UK SoC within the model. This approach reflects and accounts for the heterogeneity in the treatments being prescribed to patients with EGFR Exon20ins mutated NSCLC in current UK clinical practice.

Feedback received from UK-based clinicians at a Janssen-led advisory board was that the treatment classes received by patients in the pooled US RWE study are broadly aligned with those which would be received by patients in the UK.[12] Patients in the pooled US RWE database received a variety of treatments across several treatment classes, reflecting the heterogeneity of the treatment lines and treatments received in current clinical practice. Therefore, and given that these patient characteristics in the pooled US RWE are aligned with the licensed population for amivantamab, the composition of UK SoC was derived from these patients (Table 38). As outlined in Section B.1.3.2.1 (Table 5), treatment distribution data are also available from PHE for [redacted] patients (representing [redacted] LOTs). While these data are not considered in the economic model due to the uncertainty introduced by the limited sample size, the broad alignment between the treatment class proportions received by patients in the US RWE cohort and in the PHE dataset supports the generalisibility of the US RWE dataset to current UK clinical practice.

Of the treatment classes received by patients in the pooled US RWE database, the most frequently received were IO agents, EGFR TKIs, platinum-based chemotherapy regimens and non-platinum-based chemotherapy regimens. As such, in the base case, the costs and safety data inputs proportion of each of these treatment classes considered for UK SoC is informed by the pooled US RWE study data reweighted to consider these four treatment classes. Of note, the EGFR TKI, IO agent and platinum-based chemotherapy categories include any treatment (monotherapy or combination therapy) that contains an EGFR TKI, IO agent or platinum-based

chemotherapy, respectively, while the non-platinum-based chemotherapy category is any combination (excluding the above three) that includes a non-platinum chemotherapy drug. As noted in Section B.1.3.2, although the RWE indicates a small proportion of patients receiving platinum-based chemotherapy, feedback received from a UK-based clinician that re-treatment with platinum-based chemotherapy would be considered only for small subset of patients who had previously responded well to it, typically following failure on at least one therapy in the meantime.[69]

Table 38: Standard of care treatment class distribution

Treatment class	Pooled US RWE[a]
IO agents	[redacted]
EGFR TKIs	[redacted]
Platinum-based chemotherapy	[redacted]
Non-platinum-based chemotherapy	[redacted]

[a] Patients from the pooled US RWE study who received treatments in other classes (9%) have been distributed amongst the four classes presented.
Abbreviations: EGFR: epidermal growth factor receptor; IO: immuno-oncology; RWE: real-world evidence; TKI: tyrosine kinase inhibitor.
Source: Janssen RWE Study of US RWE datasets.

For costing purposes, the individual treatments considered in each of these four treatment classes were as follows:

- IO agents: atezolizumab (45%), pembrolizumab (45%) and nivolumab (10%)
- EGFR TKIs: afatinib (100%)
- Platinum-based chemotherapy: carboplatin + gemcitabine (33.3%), carboplatin + pemetrexed (33.3%) and carboplatin + vinorelbine (33.3%)
- Non-platinum-based chemotherapy: docetaxel + nintedanib (75%) and docetaxel monotherapy (25%)

The treatments included within each class, and their proportions, were based on consideration of therapies within each class that are currently approved by NICE for routine commissioning in the patient population of interest and feedback from UK-based clinical experts at a Janssen-led advisory board regarding the specific treatments within each treatment class that would typically be offered to these patients in current UK clinical practice.[11, 12, 92, 97, 104, 105]

Three scenario analyses were performed to assess the impact of varying the treatments and treatment proportions implemented in the model:

1. EGFR TKIs: osimertinib (100%)
2. Platinum-based chemotherapy: carboplatin + gemcitabine (50%) and carboplatin + vinorelbine (50%)
3. Non-platinum-based chemotherapy: docetaxel + nintedanib (50%) and docetaxel monotherapy (50%)

Subsequent treatments

In the base case, the composition of the basket for subsequent treatments received following amivantamab or UK SoC was sourced from the subsequent treatment distribution of patients

receiving third-line or later therapy in the pooled US RWE database. In line with this study, [redacted]% of patients are modelled to receive subsequent treatments (calculated from the proportion of second line patients receiving a third-line treatment upon progression), with the remaining [redacted]% of patients receiving no active treatment and assumed to receive best supportive care (BSC). Based on expert opinion received from UK clinicians, patients who failed on a treatment class are not modelled to receive the same treatment class as a subsequent therapy given that this would not reflect typical UK clinical practice.[12]

The subsequent treatment compositions for patients in the amivantamab and UK SoC arms in the base case are presented in Table 39. The proportions for the UK SoC arm are derived from a weighted average of the individual treatment class data from the pooled US RWE, as presented in Table 40. The average duration of each treatment is presented in Table 41.

A scenario analysis was explored in which the subsequent treatment composition for patients following amivantamab was sourced from the subsequent treatment distribution of patients receiving third-line or later therapy in the CHRYSALIS trial (the subsequent treatment composition for patients for UK SoC remained aligned with the base case). A similar approach was taken to derive the proportion of patients modelled to receive subsequent treatments in this scenario analysis as was taken in the base case, but with data derived from CHRYSALIS specifically: [redacted]% of patients in both arms (amivantamab and UK SoC) are modelled to receive subsequent treatments based on the proportion of second line patients receiving a third-line treatment upon progression in the CHRYSALIS trial, with [redacted]% of patients receiving no active treatment and assumed to receive BSC.[81] The subsequent treatment compositions for patients in the amivantamab and UK SoC arms in this scenario analysis are presented in Table 42.

Table 39: Subsequent treatment composition (base case)

Treatment class	Proportion of patients, %	
	Amivantamab	UK SoC
IO agents	[redacted]	[redacted]
EGFR TKIs	[redacted]	[redacted]
Platinum-based chemotherapy	[redacted]	[redacted]
Non-platinum-based chemotherapy	[redacted]	[redacted]

Abbreviations: EGFR: epidermal growth factor receptor; IO: immuno-oncology; Pt: platinum; SoC: standard of care; TKI: tyrosine kinase inhibitor.
Source: Janssen RWE Study of US RWE datasets.

Table 40: Calculation of subsequent treatment composition for UK SoC

Treatment class	Proportion of patients, %				
	IO agents	EGFR TKIs	Pt-based chemotherapy	Non-Pt-based chemotherapy	Weighted average (UK SoC)
IO agents	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EGFR TKIs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pt-based chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-Pt-based chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: EGFR: epidermal growth factor receptor; IO: immuno-oncology; Pt: platinum; SoC: standard of care; TKI: tyrosine kinase inhibitor.
Source: Janssen RWE Study of US RWE datasets.

Table 41: Duration of subsequent treatments

Treatment class	Average duration (cycles)	Source
IO agents	4.6	Migliorino *et al*. (2017)[106]
EGFR TKIs	4.2	Park *et al.* (2019)[107]
Platinum-based chemotherapy	3.0	Park *et al*. (2019)[107]
Non-platinum-based chemotherapy	3.0	Park *et al.* (2019)[107]

Abbreviations: EGFR: epidermal growth factor receptor; IO: immuno-oncology; TKI: tyrosine kinase inhibitor.

Table 42: Subsequent treatment composition (scenario analysis)

Treatment class	Proportion of patients, %	
	Amivantamab	UK SoC
IO agents	[redacted]	[redacted]
EGFR TKIs	[redacted]	[redacted]
Platinum-based chemotherapy	[redacted]	[redacted]
Non-platinum-based chemotherapy	[redacted]	[redacted]

Abbreviations: EGFR: epidermal growth factor receptor; IO: immuno-oncology; Pt: platinum; SoC: standard of care; TKI: tyrosine kinase inhibitor.
Source: Janssen RWE Study of US RWE datasets; Janssen Data on File: Additional CHRYSALIS data.[81]

B.3.3 Clinical parameters and variables

B.3.3.1 Baseline characteristics

The baseline characteristics of the modelled cohort are based on the CHRYSALIS trial and are presented in Table 43. Expert clinicians consulted at the advisory board indicated that the CHRYSALIS trial population was largely generalisable to patients presenting in UK clinical practice.[12] Age and gender are included in the model in order to inform general mortality inputs, whilst body weight, body surface area (BSA) and the proportion of patients below 80 kg in body weight are included to inform drug acquisition costs of treatments that are dosed based on these characteristics. No differences in population characteristics are assumed between interventions.

Table 43: Baseline characteristics for the base case population

Component	Base case value
Mean age, years (SE)	61.8 [redacted]
Male, %	38.6
Mean weight, kg (SE)	64.8 (1.5)
Mean BSA, m^2 (SE)	[redacted]
Patients <80kg, %	[redacted]

Abbreviations: BSA: body surface area; SE: standard error.

B.3.3.2 Survival inputs and assumptions

The key efficacy inputs in the model were OS and PFS. In the base case, amivantamab efficacy data are informed by blinded independent committee review (BICR) results. To account for differences in patient populations between CHRYSALIS and the RWE used to inform comparator efficacy (US RWE for the base case and PHE data in a scenario analysis), treatment comparisons between amivantamab and UK SoC were adjusted for differences in key prognostic

variables at baseline, which were identified *a priori* by an SLR and validated by clinical experts.[12] Efficacy data from the US RWE database (OS and PFS) were adjusted utilising an ATT (IPW) approach, and those from PHE using a covariate adjustment approach (see Section B.2.9).

The parametric distributions for amivantamab (and, for scenario analyses, UK SoC) extrapolations were selected based on a rigorous process to avoid bias and were selected to reflect clinical plausibility in the long term, based on feedback from UK clinicians, as well as statistical goodness of fit to the short-term observed data. Therefore, the process of selecting a "best-fitting" distribution involved two elements; goodness-of-fit to the observed data and clinical plausibility of results.[108]

1. **Graphical assessment of fit:** focuses on how well the predicted curve captures the shape of the observed Kaplan-Meier curve
2. **Fit statistics** (Akaike Information Criterion [AIC] and Bayesian Information Criterion [BIC]): statistically, the best fit to the observed data is the curve with the lowest AIC and BIC
3. **Clinical plausibility of long-term projections:** this was assessed by examining the prediction estimates and checking that these do not contradict known disease trends, which would indicate an inappropriate statistical model.

Extrapolation of the US RWE data informing efficacy for UK SoC was not deemed necessary due to the maturity of the available data. As such, Kaplan-Meier curves are considered directly for UK SoC in the base case. However, a scenario analysis is explored in which the US RWE data are extrapolated. The parametric distribution selection for the US RWE curves used in this scenario analysis were selected as described above.

As discussed in Section B.2.9, data are available from PHE for a cohort of patients treated in the UK ([redacted] patients representing [redacted] LOTs). However, OS and PFS data from PHE do not inform efficacy for UK SoC in the base case due to the uncertainty introduced by the limited sample size. However, a supportive scenario analysis is presented in which these Kaplan-Meier data are considered to inform efficacy for UK SoC since these data are directly generalisable to UK clinical practice and the specific patient population of interest.

B.3.3.2.1. Overall survival

Amivantamab

The OS Kaplan-Meier curve for amivantamab was generated based on data from the CHRYSALIS clinical trial (30th March 2021 data cut, N=114) (Figure 24).

Figure 24: OS Kaplan-Meier curve for amivantamab

Abbreviations: OS: overall survival.

Six parametric distributions were fitted to the trial data. A summary of all the AIC and BIC values is presented in Table 44 and the extrapolations for OS are presented in Figure 25 below.

Table 44: AIC and BIC values for amivantamab OS extrapolations

Distributions	AIC	BIC
Exponential	376.8	**379.5**
Generalised gamma	377.8	386.0
Gompertz	376.5	382.0
Log-logistic	376.3	381.7
Log-normal	379.9	385.4
Weibull	**375.8**	381.3

AIC is corrected for small sample sizes (AICc). A smaller AIC or BIC value represents a better goodness of fit. The lowest AIC and BIC value for each response is **bolded**.
Abbreviations: AIC: Akaike's Information Criterion; AICc: sample size corrected Akaike's Information Criterion; BIC: Bayesian Information Criterion; OS: overall survival.

Figure 25: Extrapolations for amivantamab OS, based on data from the CHRYSALIS trial

Abbreviations: KM: Kaplan Meier; OS: overall survival.

UK clinicians stated that a five-year OS of around 7–8% for amivantamab-treated patients would approximately align with their clinical expectations for these patients.[12] Therefore, based on this clinical plausibility and the statistical fit data (lowest AIC), the Weibull curve was selected for use in the base case. The generalised gamma curve, considered by clinicians to be similarly plausible but showing less good statistical fit as per the AIC/BIC statistics, was explored in a scenario analysis.[12]

UK SoC (base case)

OS for UK SoC is informed by data from the US RWE dataset due to its robust size (N=206) and UK clinicians confirmation that it is generalisable to UK clinical practice.[12] Due to the maturity of the data meaning that all patients in the cohort have died or been censored within the timeframe of data collection, Kaplan-Meier data are implemented directly in the model (Figure 26).

Figure 26: OS Kaplan-Meier curve for UK SoC OS (base case, US RWE)

Abbreviations: OS: overall survival; RWE: real-world evidence; SoC: standard of care.

The base case approach to the implementation of OS for amivantamab and UK SoC, is presented in Figure 27. For reference, the Kaplan-Meier curve for amivantamab is also included in the figure.

Figure 27: Base case OS approach for amivantamab (based on data from the CHRYSALIS trial) and UK SoC (based on US RWE data)

Abbreviations: KM: Kaplan-Meier; OS: overall survival; RWE: real-world evidence; SoC: standard-of-care.

UK SoC (scenario analysis, US RWE extrapolations)

In the base case, extrapolation of the US RWE data to inform efficacy for UK SoC was not deemed necessary due to the maturity of the available data. However, a scenario analysis was performed to explore the impact on the cost-effectiveness results of extrapolating these US RWE data. Six parametric distributions were fitted to the US RWE data. A summary of all the AIC and BIC values is presented in Table 45 and the extrapolations for OS are presented in Figure 28 below.

Table 45: AIC and BIC values for UK SoC OS extrapolations (US RWE scenario)

Distributions	AIC	BIC
Exponential	1063.6	1066.9
Generalised gamma	1055.3	1065.3
Gompertz	1060.1	1066.7
Log-logistic	1059.9	1066.6
Log-normal	1060.3	1066.9
Weibull	**1054.6**	**1061.3**

AIC is corrected for small sample sizes (AICc). A smaller AIC or BIC value represents a better goodness of fit. The lowest AIC and BIC value for each response is **bolded**.
Abbreviations: AIC: Akaike's Information Criterion; AICc: sample size corrected Akaike's Information Criterion; BIC: Bayesian Information Criterion; OS: overall survival; RWE: real-world evidence; SoC: standard of care.

Figure 28: Extrapolations for UK SoC OS, based on US RWE data

Abbreviations: OS: overall survival; RWE: real-world evidence; SoC: standard of care.

UK clinicians estimated that a five-year survival rate of approximately 1–2% for UK SoC-treated patients would be clinically plausible.[12] Based on this feedback and the statistical fit data, the generalised gamma (preferred choice during clinical expert feedback elicitation) and Weibull (best statistical fit and second choice during clinical expert feedback elicitation) curves were selected for use in the scenario analyses.

The selected extrapolation curves for amivantamab and UK SoC in the US RWE scenario analyses are presented in Figure 29 (Weibull curve for UK SoC) and Figure 30 (generalised gamma curve for UK SoC).

Figure 29: Extrapolated OS curves for amivantamab (based on data from the CHRYSALIS trial, Weibull curve) and UK SoC (based on US RWE data, Weibull curve), scenario analysis

Abbreviations: OS: overall survival; RWE: real-world evidence; SoC: standard-of-care.

Figure 30: Extrapolated OS curves for amivantamab (based on data from the CHRYSALIS trial, Weibull curve) and UK SoC (based on US RWE data, generalised gamma curve), scenario analysis

Abbreviations: OS: overall survival; RWE: real-world evidence; SoC: standard-of-care.

UK SoC (scenario analysis, PHE)

Due to the direct relevance of the UK PHE dataset ([redacted] patients representing [redacted] LOTs) to the population of interest, a scenario analysis was performed to explore the impact of using PHE data to inform the UK SoC comparator. Given the maturity of the data, and in alignment with the base case approach, the PHE Kaplan-Meier data are implemented directly in this scenario (Figure 31).

Figure 31: OS Kaplan-Meier curve for UK SoC OS (scenario analysis, UK PHE data)

Abbreviations: OS: overall survival; PHE: Public Health England; SoC: standard of care.

B.3.3.2.2. Progression-free survival

Amivantamab (base case, BICR)

The PFS Kaplan-Meier curve for amivantamab was generated based on data from the CHRYSALIS clinical trial (30th March 2021 data cut, N=114) (Figure 32). PFS was BICR assessed and defined as the time from the first infusion of the study to disease progression or death due to any cause.

Figure 32: PFS Kaplan-Meier curve for amivantamab (base case, BICR)

Abbreviations: BICR: blinded independent committee review; PFS: progression-free survival.

Six parametric distributions were fitted to the trial data. A summary of all the AIC and BIC values is presented in Table 46 and extrapolations for PFS are presented in Figure 33 below.

Table 46: AIC and BIC values for amivantamab PFS extrapolations (base case)

Distributions	AIC	BIC
Exponential	547.6	550.4
Generalised gamma	543.5	551.7
Gompertz	547.3	552.7
Log-logistic	**542.4**	**547.9**
Log-normal	543.3	548.7
Weibull	543.7	549.1

AIC is corrected for small sample sizes (AICc). A smaller AIC or BIC value represents a better goodness of fit. The lowest AIC and BIC value for each response is **bolded**.
Abbreviations: AIC: Akaike's Information Criterion; AICc: sample size corrected Akaike's Information Criterion; BIC: Bayesian Information Criterion; PFS: progression-free survival.

Figure 33: Extrapolations for amivantamab PFS, based on data from the CHRYSALIS trial

Abbreviations: PFS: progression-free survival.

Feedback received from UK clinicians was that the five-year PFS rate would be expected to be low (less than 1%) for both amivantamab- and UK SoC-treated patients. At the two-year timepoint, however, a higher proportion of patients treated with amivantamab would be expected to be progression free (approximately 10% as compared with 3–4% of patients who received UK SoC).[12] As such, the generalised gamma curve was selected for use in the base case given that it is associated with two- and five-year progression-free rates of 8.50% and 0.3%, respectively.[12]

UK SoC (base case)

In line with the approach taken for the OS endpoint, PFS Kaplan-Meier data from the US RWE database are implemented directly in the model due to their maturity, robust size and generalisability to the UK (Figure 34).

Figure 34: PFS Kaplan-Meier curve for UK SoC (base case, US RWE)

Abbreviations: PFS: progression-free survival; RWE: real-world evidence; SoC: standard of care.

The base case approach to implementing PFS for amivantamab and UK SoC is presented in Figure 35 alongside the Kaplan-Meier curve for amivantamab, which is included for reference.

Figure 35: Base case PFS approach for amivantamab (based on data from the CHRYSALIS trial, BICR) and UK SoC (based on US RWE data)

Abbreviations: BICR: **b**linded independent committee review; KM: Kaplan-Meier; OS: overall survival; RWE: real-world evidence; SoC: standard-of-care.

Amivantamab (scenario analysis, INV)

The impact of using investigator-assessed (INV) PFS from the CHRYSALIS trial to inform amivantamab PFS was explored in a scenario analysis. These Kaplan-Meier data are presented in Figure 36.

Figure 36: PFS Kaplan-Meier curves for amivantamab (base case, INV)

Abbreviations: INV: investigator-assessed; PFS: progression-free survival.

Six parametric distributions were fitted to the trial data. A summary of all the AIC and BIC values is presented in Table 47 and extrapolations for PFS are presented in Figure 37 below.

Table 47: AIC and BIC values for amivantamab PFS extrapolations (scenario)

Distributions	AIC	BIC
Exponential	568.9	571.7
Generalised gamma	565.2	573.5
Gompertz	570.9	576.4
Log-logistic	563.9	569.4
Log-normal	**563.3**	**568.8**
Weibull	568.9	574.4

AIC is corrected for small sample sizes (AICc). A smaller AIC or BIC value represents a better goodness of fit. The lowest AIC and BIC value for each response is **bolded**.
Abbreviations: AIC: Akaike's Information Criterion; AICc: sample size corrected Akaike's Information Criterion; BIC: Bayesian Information Criterion; PFS: progression-free survival.

Figure 37: Extrapolations for amivantamab PFS, based on data from the CHRYSALIS trial (scenario analysis, INV)

Abbreviations: INV: investigator-assessed; PFS: progression-free survival.

Based on the statistical fit data and in alignment with the feedback received from UK clinicians that two- and five-year PFS rates of 3–4% and less than 1%, respectively, for patients receiving UK SoC would be clinically plausible, the Weibull curve was selected for use in the PFS (INV) scenario analysis.[12]

UK SoC (scenario analysis, US RWE extrapolations)

In the base case, extrapolation of the US RWE data informing efficacy for UK SoC was not deemed necessary due to the maturity of the available data. However, a scenario analysis was performed to explore the impact on the cost-effectiveness results of extrapolating these US RWE data. Six parametric distributions were fitted to the US RWE data. A summary of all the AIC and BIC values is presented in Table 48 and the extrapolations for OS are presented in Figure 38 below.

Table 48: AIC and BIC values for UK SoC PFS extrapolations (US RWE scenario)

Distributions	AIC	BIC
Exponential	940.3	943.7
Generalised gamma	901.8	911.8
Gompertz	925.9	932.5
Log-logistic	**899.4**	**906.1**
Log-normal	901.1	907.8
Weibull	942.1	948.7

AIC is corrected for small sample sizes (AICc). A smaller AIC or BIC value represents a better goodness of fit. The lowest AIC and BIC value for each response is **bolded**.
Abbreviations: AIC: Akaike's Information Criterion; AICc: sample size corrected Akaike's Information Criterion; BIC: Bayesian Information Criterion; OS: overall survival; RWE: real-world evidence; SoC: standard of care.

Figure 38: Extrapolations for UK SoC PFS, based on US RWE data

Abbreviations: PFS: progression-free survival; RWE: real-world evidence; SoC: standard of care.

Given the similarity between the curves, the log logistic curve was selected for use in the scenario analysis based on best statistical fit as per the AIC/BIC statistics.

These selected extrapolation curves for amivantamab and UK SoC in the US RWE scenario analysis are presented in Figure 39.

Figure 39: Extrapolated PFS curves for amivantamab (based on data from the CHRYSALIS trial) and UK SoC (based on US RWE data), scenario analysis

Abbreviations: PFS: progression-free survival; RWE: real-world evidence; SoC: standard-of-care.

UK SoC (scenario analysis, PHE)

In line with the OS endpoint, the use of data from the UK PHE dataset ([redacted] patients representing [redacted] LOTs) to inform the PFS implementation for UK SoC was explored in a scenario analysis given the direct relevance of this population to the UK. However, PFS data are not available from this dataset; as such, TTNT data were utilised as a proxy. Given the maturity of the data, and in alignment with the base case approach, the PHE Kaplan-Meier data are implemented directly in this scenario (Figure 40).

Figure 40: TTNT Kaplan-Meier curve for UK SoC PFS (scenario analysis, UK PHE data, proxy for PFS

Abbreviations: PFS: progression-free survival; PHE: Public Health England; SoC: standard of care; TTNT: time to next treatment.

B.3.3.2.3. Time to treatment discontinuation

Amivantamab

As per the protocol of the CHRYSALIS clinical trial, patients could continue to receive treatment following disease progression. As such, median time to discontinuation (TTD) of amivantamab was longer than median PFS ([redacted] months and [redacted] months, respectively). However, feedback received from UK clinical experts at a Janssen-led advisory board was that this does not reflect expected clinical practice, where patients would stop current treatment upon progression.[12] As such, an assumption is made that time on treatment is equal to PFS.

UK SoC

In line with the approach taken for amivantamab, it is assumed that UK SoC time on treatment is equal to UK SoC progression-free survival to reflect clinical feedback that patients would be expected to stop current treatment following progression.[12]

B.3.3.3 Adverse events

The model includes Grade ≥3 AEs that were reported in more than 5% of patients in key trials, except for incidence of diarrhoea, which was considered at any grade due to its clinical relevance. Clinical expert opinion received by Janssen supports that these AEs are relevant for inclusion and that no relevant events expected to affect more than 5% of patients have been omitted.[12] AEs were only considered for current-line treatments, and AEs associated with subsequent-line treatments were not included. The treatment-related AE data were derived from clinical trials (CHRYSALIS for amivantamab, AURA3 for platinum-based chemotherapy [as per TA653] and LUX-Lung-8 for TKIs) or previous NICE appraisals (TA520 for IO agents and non-platinum-based chemotherapy).[97, 109, 110] The consequences of AEs were modelled in terms of the accrual of associated management costs and disutilities. The percentage of patients who

experienced AEs was calculated at the start of the model and one-off costs and disutilities were incurred at this stage.

In alignment with Section 4.2.17 of the NICE health technology evaluations manual (PMG36) in which it is stated that treatments may form a class of treatments if evidence is available to support their clinical equivalence, it is assumed that treatments within the same treatment class, and therefore with the same mechanism of action, have similar safety profiles.[100] In discussion with clinical experts, safety profiles were considered and compared in the context of treatment classes rather than individual treatments, validating this approach.[12]

Table 49: Incidence of Grade ≥3 AEs occurring in ≥5% of patients

AE, %	AMI	UK SoC				
		IO agents	EGFR TKIs	Pt-based chemotherapy	Non-Pt-based chemotherapy	Weighted average
Anaemia	[redacted]	0.5	0.0	11.8	3.8	3.2
Diarrhoea[a]	[redacted]	15.4	69.9	11.0	24.4	28.4
Fatigue	[redacted]	1.6	1.3	0.7	3.5	2.1
Febrile neutropenia	[redacted]	0.0	0.0	0.0	9.4	3.4
Neutropenia	[redacted]	0.5	0.0	11.8	14.6	7.2
Neutrophil count decreased	[redacted]	0.0	0.0	0.0	11.1	4.0
Rash	[redacted]	0.0	5.9	0.0	0.0	1.1
Thrombo-cytopaenia	[redacted]	0.0	0.0	7.4	0.0	1.1

[a] Due to its clinical relevance, the incidence of diarrhoea was considered at any grade.
Abbreviations: AE: adverse event; AMI: amivantamab; IO: immuno-oncology; Pt: platinum; SoC: standard of care; TKI: tyrosine kinase inhibitor.
Source: Janssen Data on File: Additional CHRYSALIS data;[81] TA520;[97] Goss *et al.* (2018);[110] Mok *et al*. (2016).[109]

B.3.4 Measurement and valuation of health effects

B.3.4.1 Health-related quality-of-life data from clinical trials

EQ-5D-5L data were collected in CHRYSALIS at Day 1 of each cycle, at the end of treatment and during post-treatment follow-up.[80] However, patient reported outcome (PRO) assessments were not introduced until Amendment 7 (August 2019) and as a result, the number of responses to the EQ-5D-5L questionnaire was low at the time of data cut-off. As such, EQ-5D-3L utility values used in the model were not derived from EQ-5D-5L data from CHRYSALIS.

B.3.4.2 Mapping

As stated in Section B.3.4.1, EQ-5D-5L data from CHRYSALIS were not used to derive utility values in the model; therefore, mapping was not applicable.

B.3.4.3 Health-related quality-of-life studies

As described in Section B.3.1, a *de novo* economic SLR was conducted to identify cost-effectiveness, health-state utility values (HSUVs) and cost and healthcare resource use data to populate missing parameters for the cost-effectiveness analysis.

In total, the utilities SLR found 50 articles reporting on 47 unique studies. Full details on the methods and results of this SLR are presented in Appendix H.

Health state utility values used in the model have been sourced from TA484/TA713, a previous NICE appraisal in advanced non-squamous NSCLC after chemotherapy.[94, 105] This was considered a suitable source for utility data given the similarity of this population to the population of interest in this submission. UK clinical experts consulted as part of this appraisal confirmed that the values used are appropriate and in line with their clinical understanding of the population of interest.[12]

B.3.4.4 Adverse reactions

AEs considered in the model were Grade ≥3 TEAEs with an incidence ≥5% in any treatment arm in key trials except for diarrhoea, which was considered at any grade due to its clinical relevance (see Section B.3.3.3). A summary of the AE disutilities applied in the cost-effectiveness model, sourced from TA520, TA484/TA713 and the published literature, is presented in Table 50. Disutilities associated with AEs were applied in the model in the first cycle.

Table 50: Summary of AE disutilities applied in the cost-effectiveness model

AE	Disutility (SE)	Source
Anaemia	−0.073 (0.018)	Nafees *et al.* (2008), as per TA484/TA713 and TA520[94, 97, 105, 111]
Diarrhoea	−0.047 (0.016)	Nafees *et al.* (2008), as per TA484/TA713[94, 105, 111]
Fatigue	−0.073 (0.018)	Nafees *et al.* (2008), as per TA484/TA713 and TA520[94, 97, 105, 111]
Febrile neutropenia	−0.090 (0.016)	Nafees *et al.* (2008), as per TA484/TA713 and TA520[94, 97, 105, 111]
Neutropenia	−0.090 (0.015)	Nafees *et al.* (2008), as per TA484/TA713 and TA520[94, 97, 105, 111]
Neutrophil count decreased	0	TA484/TA713 and TA520[94, 97, 105]
Rash	−0.032 (0.012)	Nafees *et al.* (2008)[111]
Thrombocytopaenia	−0.108 (0.011)	Tolley *et al.* (2013)[112]

Abbreviations: AE: adverse event.

B.3.4.5 Health-related quality-of-life data used in the cost-effectiveness analysis

A summary of health state utility values included in the base case analysis and sourced from TA484/TA713 is presented in Table 51. Given that the time horizon of the model is relatively short, the impact of age-adjustment on results is likely to be marginal; as such, utilities are not age-adjusted.

Table 51: Summary of utility values for the base case cost-effectiveness analysis

State	Utility value	95% CI
Progression-free survival	0.713	0.0713
Post-progression survival	0.569	0.0569

Abbreviations: CI: confidence interval.
Source: TA484/TA713.[93]

B.3.5 Cost and healthcare resource use identification, measurement and valuation

An SLR was conducted to identify any relevant cost or resource use data that could be incorporated into the model. The SLR was originally conducted on 4th May 2020 with updates conducted in February 2021 and November 2021 using the same methodology. Full details of the SLR search strategy, study selection process and results are presented in Appendix I.

In total, the SLR identified seven articles reporting on seven unique studies in patients with lung cancer. However, no studies reporting on cost and healthcare resource use were conducted in the population considered in this submission (adult patients with locally advanced or metastatic NSCLC with activating EGFR Exon20ins, whose disease has progressed on or after platinum-based chemotherapy).

The cost-effectiveness analysis was conducted from the perspective of the NHS and PSS in England and therefore included only costs that would be incurred by the health system. Appropriate sources of unit costs, such as NHS Reference costs 2019/20, British National Formulary (BNF) and drugs and pharmaceutical electronic market information tool (eMIT) were used for cost inputs in the model.

The following cost types were included in the model: drug acquisition and administration costs for first-line and subsequent treatments, follow-up and monitoring costs, AE management costs and end-of-life costs.

B.3.5.1 Intervention and comparators' costs and resource use

Drug acquisition costs

Drug acquisition costs per four-week model cycles were calculated for each treatment based on the dosing schedule and the UK list price of each pack or vial. Drug costs per treatment regimen were extracted from the England based eMIT and BNF databases. Where multiple pack sizes were available, the cheapest option was assumed. In the base case, no vial sharing is assumed given the small patient population, but a scenario analysis in which vial sharing is considered was explored. The drug acquisition costs and dosing regimens are presented in Table 52 and Table 53, respectively.

Drug administration costs

All drugs administered orally or via intravenous (IV) infusion were assumed to be administered in an outpatient setting. The administration-related costs were derived according to data available from the NHS Reference Costs 2019/20 and are presented in Table 54. The cost of chemotherapy administration was applied to all therapies administered intravenously (IV): the administration of combination and monotherapy chemotherapy regimens were costed as complex and simple IV chemotherapy, respectively. Oral administration of afatinib and nintedanib was assumed be associated with a one-off oral administration cost applied at treatment initiation. The frequency and cost of drug administration are summarised in Table 55.

Table 52: Drug acquisition costs for intervention and comparators, inclusive of amivantamab PAS discount

Treatment	Dependency	Vial sharing	Strength per unit (mg)	Units per pack	Cost per pack
Amivantamab	Fixed dose	No	350	1	£[redacted]
EGFR TKIs					
Afatinib	Fixed dose	No	40	28	£2,023.28
Osimertinib[a]	Fixed dose	No	80	30	£5,770.00
IO agents					
Atezolizumab	Fixed dose	No	1,200	1	£3,807.69
Pembrolizumab	Fixed dose	No	100	1	£2,630.00
Nivolumab	Fixed dose	No	100	1	£1,097.00
Platinum-based chemotherapy regimens					
Carboplatin	Fixed dose	No	450	1	£13.51
Carboplatin	Fixed dose	No	150	1	£6.08
Gemcitabine	BSA	No	1,000	1	£7.89
Gemcitabine	BSA	No	200	1	£2.56
Pemetrexed	BSA	No	100	1	£125.00
Vinorelbine	BSA	No	50	10	£159.46
Non-platinum-based chemotherapy regimens					
Docetaxel	BSA	No	80	1	£8.90
Nintedanib	Fixed dose	No	100	120	£2,151.10

[a] Osimertinib was considered in a scenario analysis only.
Abbreviations: BSA: body surface area; EGFR: epidermal growth factor receptor; IO: immuno-oncology; TKI: tyrosine kinase inhibitor.

Table 53: Dosing regimens and cost per model cycle of intervention and comparators, inclusive of amivantamab PAS discount

Treatment	Dosing regimen	Stopping rule	Cost per dose	Admins per cycle	Cost per treatment cycle	Weeks per cycle	Cost per model cycle
Amivantamab (1,050 mg)	1,050 mg or 1,400 mg (weight dependent) weekly for four weeks and bi-weekly thereafter	Treat to progression	£[redacted]	Initial cycle: 4 Subsequent cycles: 2	Initial cycle: £[redacted] Subsequent cycles: £[redacted]	4	Initial cycle: £[redacted] Subsequent cycles: £[redacted]
Amivantamab (1,400 mg)		Treat to progression	£[redacted]		Initial cycle: £[redacted] Subsequent cycles: £[redacted]	4	Initial cycle: £[redacted] Subsequent cycles: £[redacted]
EGFR TKIs							
Afatinib	Oral, 40 mg daily	Treat to progression	£72.26	28	£2,023.28	4	£ 2,023.28
Osimertinib[a]	Oral, 80 mg daily	Treat to progression	£192.33	28	£5,385.33	4	£5,385.33
IO agents							
Atezolizumab	1,200 mg every 3 weeks	Treat to progression	£3,807.69	1	£3,807.69	3	£5,076.92
Pembrolizumab	200 mg every 3 weeks	Treat to progression	£5,260.00	1	£5,260.00	3	£7,013.33
Nivolumab	240 mg every 2 weeks	Treat to progression	£3,291.00	1	£3,291.00	2	£6,582.00
Platinum-based chemotherapy regimens							
Carboplatin + gemcitabine							Initial cycle: £84.92 Subsequent cycles: £0
Carboplatin	Area under curve 6 mg/mL per min administered every 3 weeks[b]	Four treatment cycles or progression	£27.03	1	£108.10	12	Initial cycle: £36.03 Subsequent cycles: £0
Gemcitabine	1,250 mg/m^2 on Days 1 and 8 every 3 weeks		£18.33	2	£146.65	12	Initial cycle: £48.88 Subsequent cycles: £0

Carboplatin + vinorelbine							Initial cycle: £76.74 Subsequent cycles: £0
Carboplatin	Area under curve 5 mg/mL per min administered every 3 weeks[b]	Four treatment cycles or progression	£25.67	1	£102.66	12	Initial cycle: £34.22 Subsequent cycles: £0
Vinorelbine	25 mg/m^2 on Days 1 and 8 every 3 weeks		£15.95	2	£127.56	12	Initial cycle: £42.52 Subsequent cycles: £0
Carboplatin + pemetrexed							Initial cycle: £1,459.22 Subsequent cycles: £0
Carboplatin	Area under curve 5 mg/mL per min administered every 3 weeks[b]	Four treatment cycles or progression	£25.67	1	£102.66	12	Initial cycle: £34.22 Subsequent cycles: £0
Pemetrexed	500 mg/m^2 on Day 1 every 3 weeks		£1,068.75	1	£4,275.00	12	Initial cycle: £1,425.00 Subsequent cycles: £0
Non-platinum-based chemotherapy regimens							
Docetaxel + nintedanib							First six cycles: £1,935.83 Subsequent cycles: £1,912.09
Docetaxel	75 mg/m^2 repeat cycle every 3 weeks	Fixed duration (six cycles)	£17.81	1	£18.26	3	£24.35
Nintedanib	200 mg twice daily on Days 2–21 of cycle.	Treat to progression	£35.85	40	£1,434.07	3	£1,912.09
Docetaxel	75 mg/m^2 repeat cycle every 3 weeks	Treat to progression	£17.81	1	£18.26	3	£24.35

[a] Osimertinib was considered in a scenario analysis only. [b] Carboplatin dose was estimated based on the Calvert formula described in the carboplatin SmPC.[113] Due to lack of baseline serum creatinine data for patients in the CHRYSALIS trial, the maximum dose was assumed in the model. The maximum dose was based on a GFR estimate that is capped at 125 mL/min for patients with normal renal function as per the NCCN guidelines.[114]
Abbreviations: EGFR: epidermal growth factor receptor; IO: immuno-oncology; IV: intravenous; TKI: tyrosine kinase inhibitor.

Table 54: Administration unit costs

	Cost per admin	Source
One-off oral administration	£207.79	NHS Reference Costs 2019/20: SB11Z deliver exclusively oral chemotherapy
IV administration of simple chemotherapy	£221.35	NHS Reference Costs 2019/20: SB12Z deliver simple parenteral chemotherapy at first attendance
IV administration of complex chemotherapy	£352.24	NHS Reference Costs 2019/20: SB14Z deliver complex chemotherapy, including prolonged infusional treatment, at first attendance

Abbreviations: IV: intravenous; NHS: National Health Service.

Table 55: Frequency and cost of administration

	Frequency of administration per model cycle			Administration cost per model cycle
	Oral administration	Simple chemotherapy, IV	Complex chemotherapy, IV	
Amivantamab				
Amivantamab	-	Initial cycle: 4 Subsequent cycles: 2	-	Initial cycle: £885.39 Subsequent cycles: £442.70
IO agents				
Atezolizumab	-	1.33	-	£295.13
Nivolumab	-	2	-	£442.70
Pembrolizumab	-	1.33	-	£295.13
EGFR TKIs				
Afatinib	1	-	-	Initial cycle: £207.79 Subsequent cycles: £0
Osimertinib[a]	1	-	-	Initial cycle: £207.79 Subsequent cycles: £0
Platinum-based chemotherapy				
Carboplatin + gemcitabine[b]				First three cycles: £764.79 Subsequent cycles: £0

Carboplatin	-	-	1.33	£469.66
Gemcitabine	-	1.33	-	£295.13
Carboplatin + pemetrexed	-	-	1.33	First three cycles: £469.660 Subsequent cycles: £0
Carboplatin + vinorelbine[b]				First three cycles: £764.79 Subsequent cycles: £0
Carboplatin	-	-	1.33	£469.66
Vinorelbine	-	1.33	-	£295.13
Non-platinum-based chemotherapy				
Docetaxel	-	1.33	-	£295.13
Docetaxel + nintedanib[c]	1	1.33	-	Initial cycle: £502.92 Subsequent four cycles: £295.13 Subsequent cycles: £0

[a] Osimertinib was considered in a scenario analysis only. [b] The administration cost for combination therapy is applied once. Half of the administrations are monotherapy (gemcitabine or vinorelbine only); this is calculated as the cost of IV administration of simple chemotherapy (£221.35) multiplied by the frequency of administration per cycle divided by two (2.6666/2), resulting in an administration cost of £295.13. [c] Docetaxel is administered in combination with nintedanib for a maximum of six weeks. As such, IV administration costs apply for this time period only. The initial cycle cost is inclusive of the one-off oral administration cost.
Abbreviations: EGFR: epidermal growth factor receptor; IO: immuno-oncology; IV: intravenous; TKI: tyrosine kinase inhibitor.

Subsequent treatments

Following progression in the model, patients were assumed to immediately switch to subsequent-line treatments and to incur associated costs while in the PPS health state. The subsequent treatments were calculated as a basket treatment that included all the therapy class options in the current line. Both drug acquisition and administration costs were considered in the calculation of cost per 4-week cycle for each subsequent treatment.

The composition of the subsequent treatment basket and the derivation of these distributions are presented in Section B.3.2.3 (Table 39 and Table 40, respectively).

B.3.5.2 Health-state unit costs and resource use

The types of resource use incorporated in the model were based on TA520.[66] This was considered to be a suitable source for healthcare resource use given that it is a relatively recent NICE appraisal that considered a patient population analogous to that of this submission: locally advanced or metastatic NSCLC after chemotherapy. According to clinical expert opinion, it is expected that monitoring and resource use for patients in the PFS state would vary dependent upon the administration schedule of the treatment received.[12] As such, resource use in the PFS state is adjusted based on whether treatments are administered once every three weeks (amivantamab and EGFR TKIs) or once every four weeks (IO agents and chemotherapies), as presented in Table 56. The unit costs were based on NHS Reference Costs 2019/20 (Table 57).

Table 56: Monitoring and resource use per model cycle

	Drugs administered Q3W (amivantamab and EGFR TKIs)		Drugs administered Q4W (IO agents and chemotherapies)	
	PFS	PPS	PFS	PPS
Liver function test	1.00	0.61	1.33	0.61
Renal function test	1.00	0.61	1.33	0.61
Full blood test	1.00	1.33	1.33	1.33
Outpatient oncologist visit	0.80	0.61	1.07	0.61
CT scan (chest)	0.28	0.37	0.37	0.37
GP surgery visit	0.63	1.33	0.84	1.33
GP home visit	0	0.33	0	0.33
Non-admitted monitoring consultation	1	0	1.33	0
Palliative care	2	2.67	2.67	2.67

Abbreviations: PFS: progression-free survival; PPS: post-progression survival.
Source: NICE TA520.[66]

Table 57: Summary of monitoring and resource use costs

	Unit cost	Source
Liver function test	£1.20	NHS Reference Costs 2019/20: DAPS04 clinical biochemistry
Renal function test	£1.20	
Full blood test	£2.53	NHS Reference Costs 2019/20: DAPS05 haematology
Outpatient oncologist visit	£200.20	NHS Reference Costs 2019/20: WF01A non-admitted face-to-face attendance, follow up; Medical Oncologist

CT scan (chest)	£114.36	NHS Reference Costs 2019/20: RD24Z CT scan of two areas, with contrast
GP surgery visit	£39.23	PSSRU 2021: GP contact lasting 9.22 minutes, including direct care staff costs, qualification costs and carbon offset
GP home visit	£39.23	PSSRU 2021: GP contact lasting 9.22 minutes, including direct care staff costs, qualification costs and carbon offset
Non-admitted consultation	£200.20	NHS Reference Costs 2019/20: WF01A non-admitted face-to-face attendance, follow up; Medical Oncologist
Palliative care	£113.09	NHS Reference Costs 2019/20: CHS - N21AF, Specialist nurse, palliative care

Abbreviations: CT: computerised tomography; GP: general practitioner; NHS: national health service; PSSRU: Personal Social Services Research Unit.

B.3.5.3 Adverse reaction unit costs and resource use

The cost of managing AEs experienced by patients receiving treatments was included in the model. The costs per event, presented in Table 58, were based on NHS Reference Costs 2019–20 as per TA653.[95] These costs were applied to the proportion of patients experiencing each event in each of the treatment arms in the model and were applied in the first cycle of the model.

Table 58: Summary of AE costs applied in the cost-effectiveness model

AE	Cost	Source
Anaemia	£859.55	Weighted average of NHS Reference Costs (2019/20) SA04G–SA04K
Diarrhoea	£1,366.10	Weighted average of NHS Reference Costs (2019/20) FD01–FD01J
Fatigue	£859.55	Assumed to be the same as anaemia as per TA653
Febrile neutropenia	£2,900.64	Weighted average of NHS Reference Costs (2019/20) SA35A–SA35E (non-elective long stay)
Neutropenia	£705.82	Weighted average of NHS Reference Costs (2019/20) SA35A–SA35E (non-elective short stay)
Neutrophil count decreased	£705.82	Weighted average of NHS Reference Costs (2019/20) SA35A–SA35E (non-elective short stay)
Rash	£586.65	Weighted average of NHS Reference Costs (2019/20) JD07A–JD07K
Thrombocytopaenia	£968.25	Weighted average of NHS Reference Costs (2019/20) SA12G–SA12K

Abbreviations: AE: adverse event; NHS: national health service.

B.3.5.4 Miscellaneous unit costs and resource use

End-of-life costs

A one-off cost representing the cost of terminal care was applied in the model in the first cycle post-death. The cost applied in the model (£3,803.36) was derived as per the assumptions in TA520, using costs from the NHS Reference Costs (2019/20) and PSSRU (2021).[97]

Table 59: Calculation of end-of-life costs

Component	Frequency	Patients, %	Unit cost	Weighted cost	Source

Hospitalisation admission and excess bed days	1	55.8	£4,293.60	£2,395.83	National reference costs 2019/20 (Department of Health 2020) Respiratory Neoplasms without intervention, with CC score 13+ (currency code DZ17S), non-elective long stay
Macmillan Nurse (home setting)	50	27.3	£36.67	£10.01	Assumed two thirds of the cost of a community nurse (£55 per working hour, PSSRU 2021)
Hospice care	1	16.9	£5,367.01	£907.02	Assumed 25% increase on hospitalisation setting
				Total	**£3,803.36**

Abbreviations: PSSRU: Personal Social Services Research Unit.

B.3.6 Summary of base-case analysis inputs and assumptions

B.3.6.1 Summary of base-case analysis inputs

A summary of the base case model inputs and settings are presented in Table 60.

Table 60: Summary of variables applied in the economic model base case

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty (distribution)	Reference to section in submission
Model characteristics			
Time horizon	Lifetime (15 years)	NA	B.3.2
Cycle length	28 days	NA	
Discount rate effects	3.5%	NA	
Discount rate costs	3.5%	NA	
Patient characteristics			
Mean starting age, years	61.8	SE: [redacted] (Normal)	B.3.2.1
Proportion male, %	38.6	0.04 (Beta)	
Mean weight, kg	64.8	NA[a]	
Mean body surface area, m^2	[redacted]	NA[a]	
Proportion <80kg, %	[redacted]	NA[a]	
Efficacy data			
Amivantamab OS	Weibull	Covariance-matrices (Normal/Cholesky decomposition)	B.3.3.2
Amivantamab PFS	Generalised gamma		
UK SoC OS	KM data	NA	
UK SoC PFS			
Drug costs, initial cycle			
Amivantamab	£13,780.99	Assumed to be ±10% of the mean (Gamma)	B.3.5.1
IO agents	£6,098.81		

EGFR TKIs	£2,023.28		
Pt-based chemotherapy	£540.29		
Non-Pt-based chemotherapy	£1,457.81		
Drug costs, subsequent cycles			
Amivantamab	£6,890.49	Assumed to be ±10% of the mean (Gamma)	B.3.5.1
IO agents	£6,098.81		
EGFR TKIs	£2,023.28		
Pt-based chemotherapy	£0.00[b]	-	
Non-Pt-based chemotherapy	£1,440.00	Assumed to be ±10% of the mean (Gamma)	
Administration costs, initial cycle			
Amivantamab	£885.39	Assumed to be ±10% of the mean (Gamma)	B.3.5.1
IO agents	£309.89		
EGFR TKIs	£207.79		
Pt-based chemotherapy	£666.41		
Non-Pt-based chemotherapy	£295.13		
Administration costs, subsequent cycles			
Amivantamab	£442.70	Assumed to be ±10% of the mean (Gamma)	B.3.5.1
IO agents	£309.89		
EGFR TKIs	£0.00	-	
Pt-based chemotherapy	£0.00	-	
Non-Pt-based chemotherapy	£73.78	Assumed to be ±10% of the mean (Gamma)	
AE management costs			
Amivantamab	£242.43	Assumed to be ±10% of the mean (Gamma)	B.3.5.3
UK SoC	£628.82		
Disease management costs, progression-free			
Amivantamab	£648.19	Assumed to be ±10% of the mean (Gamma)	B.3.5.2
UK SoC	£823.35		
Disease management costs, post-progression			
Amivantamab	£536.28	Assumed to be ±10% of the mean (Gamma)	B.3.5.2
UK SoC	£536.28		
Disease management costs, one-off cost			
Mortality	£3,803.36	Assumed to be ±10% of the mean (Gamma)	B.3.5.4
Subsequent treatment costs			
Amivantamab	£8,200.12	Assumed to be ±10% of the mean (Gamma)	B.3.5.1
UK SoC	£8,469.41		
Health state utility values			

PFS	0.713	Assumed to be ±10% of the mean (Beta)	B.3.5.4
PPS	0.569		
AE disutilities			
Amivantamab	−0.012	Assumed to be ±10% of the mean (Beta)	B.3.4.4
UK SoC	−0.028		

[a] Inputs for patient weight, body surface area and proportion <80 kg are not varied in the sensitivity analyses given that they are implicitly varied within the drug cost variations presented. [b] Platinum-based chemotherapy subsequent treatment costs are set to £0 given that these are fixed duration regimes of eight treatment cycles, all of which are costed as "initial cycles".
Abbreviations: AE: adverse event; EGFR: epidermal growth factor receptor; IO: immuno-oncology; KM: Kaplan-Meier; NA: not applicable; OS: overall survival; PFS: progression-free survival; PPS: post-progression survival; Pt: platinum; SE: standard error; SoC: standard of care; TKI: tyrosine kinase inhibitor.

B.3.6.2 Assumptions

A list of the assumptions used in the base case analysis is provided in Table 61 below alongside a list of scenarios to explore the impact of these assumptions on the cost-effectiveness results.

Table 61: List of assumptions for the base case analysis model

Assumption	Description of assumption for the base case	Justification	Addressed in scenario analysis
Efficacy source for UK SoC	US RWE from a pooled analysis of three US-based databases adjusted to the population of the CHRYSALIS trial is used as a source for UK SoC efficacy within the economic model.	Of the available sources for SoC efficacy, the US pooled analysis provided results largely consistent with PHE data from England but derived from a larger sample size. Clinical experts considered patient characteristics and outcomes from the US pooled analysis as generalisable to UK clinical practice.[12]	Y – a scenario has been conducted where data from a PHE analysis has been used to inform efficacy for UK SoC to demonstrate the effect of this on the cost-effectiveness model results.
UK SoC and subsequent treatment distributions	Treatment distributions within UK SoC and for subsequent therapies are based on US RWE.	This was done to align with the efficacy inputs for UK SoC in the cost-effectiveness model. Feedback received from UK-based clinicians at a Janssen-led advisory board was that the treatment classes received by patients in the pooled US RWE study are broadly aligned with those which would be received by patients in the UK.[12]	Y – a scenario has been conducted in which the subsequent treatment composition for patients following amivantamab are sourced from the CHRYSALIS trial to assess the impact of using this alternative data source on the cost-effectiveness results. Since all patients in the CHRYSALIS trial received amivantamab, the subsequent treatment composition for patients following UK SoC remain aligned with the base case.
Non-platinum-based chemotherapy	Of those receiving non-platinum-based chemotherapy, the proportion of patients receiving docetaxel + nintedanib is assumed to be 75% and those on docetaxel monotherapy 25%.	This is based on clinical expert opinion that patients who are fit enough to receive docetaxel are typically fit enough to receive it in combination with nintedanib.[12]	Y – a scenario has been conducted where these proportions are assumed to be 50%/50% to demonstrate the effect of this on the cost-effectiveness model results.
Assessment of progression	BICR as the response measure for progression	The use of BICR assessment aims to address disagreement that may arise between investigators that can lead to ascertainment bias. Results from BICR assessment are included in the SmPC for amivantamab and are consistent with the INV results.[13]	Y – the use of INV-assessed progression is investigated in a scenario analysis to demonstrate the effect of this on the cost-effectiveness model results.

Health state utility values	Utility data collected utilising EQ-5D from CHRYSALIS were sparse, particularly at later timepoints. Therefore, health state utility values are based on those from TA484/TA713.	The utility values used were accepted as part of the NICE appraisal for nivolumab for previously treated non-squamous NSCLC and are in a similarly advanced population with non-squamous NSCLC. UK clinical experts also considered the utility values to be appropriate for the relevant population for this appraisal.[12]	N – no other utility values were considered to be more appropriate than those selected in the base case and therefore a scenario analysis has not been conducted.
AEs within treatment classes	AE incidences are the same for all treatments within a particular treatment class i.e. inputs are specific to a treatment class but not to a specific treatment. AEs for platinum-based chemotherapy are derived from the comparator arm of the AURA3 trial (as per TA653) where a mixture of different platinum-based regimens were given to patients (including both carboplatin and cisplatin-based regimens).	It was considered appropriate to assume that treatments within the same treatment class (and therefore with the same mechanism of action) would have similar safety profiles. In discussion with clinical experts, safety profiles were considered and compared in the context of treatment classes rather than individual treatments, validating this approach.[12] Feedback from clinical experts was that AE incidences for platinum-based chemotherapy where patients received a carboplatin-based regimen and were also at second-line for NSCLC would be an appropriate source.[12] However, a source where patients exclusively received carboplatin-based regimens was not available. Therefore, the approach was taken where a second-line population was used (albeit with a mixture of carboplatin- and cisplatin-based regimens).	N – this was a simplifying assumption and AE inputs are not a key driver of the model results. Therefore, a scenario analysis has not been conducted.
Monitoring and resource use for comparators	Monitoring and resource use is considered to be the same for all treatment classes within UK SoC; however, frequencies are aligned with	This has been validated by clinical expert opinion and is in line with the approach taken in previous NICE appraisals (e.g. TA520).[66, 69]	N – the base case approach is considered the most appropriate based on expert opinion and precedent. In addition, monitoring and resource use

	dosing regimens/treatment cycles based on feedback from UK clinical experts.[12]		inputs are not a key driver of the model results. Therefore, a scenario analysis has not been conducted.
Diagnostic testing costs for EGFR Exon20ins mutations	Testing costs are excluded from the cost-effectiveness model.	The EGFR Exon20ins mutation is tested as part of the mandatory EGFR test conducted at diagnosis for all NSCLC patients. This was validated at a recent advisory board with UK clinical experts and is aligned with the approach taken in previous appraisals in which testing for a specific mutation would be required (such as TA595, TA643 and TA670).[12, 14, 15] As such, there are no additional costs likely to be incurred by the NHS over and above the current EGFR testing requirements for all NSCLC patients receiving UK SoC.	N – it is not appropriate to include testing costs for EGFR Exon20ins mutations in the cost-effectiveness model. Therefore, a scenario analysis has not been conducted.
Subsequent treatment duration	Patients are assumed to only receive one course of subsequent treatment.	Based on the time spent (undiscounted LYs) by patients in the PPS health state in the model, patients receiving amivantamab spend 1.47 years and those on UK SoC spend 0.86 years in this state. Therefore, it is not unreasonable to assume only one cycle of subsequent treatment. There are also limited data on the subsequent treatments that patients would receive in the long-term.	N – in the absence of a suitable alternative, a scenario analysis has not been conducted.
Proportion of patients receiving subsequent treatment	An equal proportion of amivantamab and UK SoC patients ([redacted]%) are assumed to receive subsequent treatments based on data from US RWE.	The proportion of patients anticipated to proceed to subsequent therapy was validated with UK clinical experts in an advisory board and is derived from the same source as the efficacy inputs for the UK SoC arm of the cost-effectiveness model.[12] The cost of BSC	N – there is no evidence to suggest that there would be a different proportion of patients from amivantamab or UK SoC proceeding to subsequent treatments and it is considered the most appropriate approach to not risk double counting BSC costs. Therefore, a

	Patients who don't receive subsequent treatments are assumed to receive BSC, which is assumed to have no associated costs given these costs are captured in existing monitoring and resource use costs.	was not considered to avoid double counting.	scenario analysis has not been conducted.
Re-treatment	Patients are assumed to not receive re-treatment with the same treatment class as a subsequent therapy.	This was considered appropriate based on UK clinical expert opinion where clinicians discussed that treatment options would be based on what patients had received previously and that subsequent treatments would not be from the same treatment class received at a prior line.[12]	N – based on clinical expert opinion, it would not be appropriate to assume re-treatment with the same treatment class and therefore a scenario analysis has not been conducted.
Vial sharing	Vial sharing is excluded.	This approach was taken given the small patient population considered within the model.	Y – a scenario where vial sharing is included has been conducted to demonstrate the effect of this on the cost-effectiveness model results.

Abbreviations: AE: adverse event; BICR: blinded independent committee review; BSC: best supportive care; EGFR: epidermal growth factor receptor; EQ-5D-5L: EuroQoL five-dimensions five-levels; INV: investigator-assessed; NICE: National Institute for Health and Care Excellence; NSCLC: non-small cell lung cancer; PPS: post-progression survival; RWE: real-world evidence; SoC: standard of care.

B.3.7 Base-case results

B.3.7.1 Base-case incremental cost-effectiveness analysis results

A summary of results in the base case analysis are presented in Table 62 (at PAS price) and Table 63 (at list price).

At PAS price, amivantamab and UK SoC accumulated costs of £[redacted] and [redacted], and total QALYs of [redacted] and [redacted], respectively. The with-PAS ICER was within the range considered cost-effective; at £39,764/QALY, it falls below the NICE WTP threshold of £50,000 (considering amivantamab meets end-of-life criteria). These results demonstrate amivantamab to be a cost-effective option for the treatment of patients with NSCLC with activating EGFR Exon20ins whose disease has progressed on or after platinum-based chemotherapy versus UK SoC, the comparator relevant to UK clinical practice.

Disaggregated results of the base case incremental cost-effectiveness analysis and clinical outcomes of the model are presented in Appendix J.

Table 62: Base case results at amivantamab PAS price (deterministic)

	Total			Incremental			ICER (£/QALY)
	Costs	QALYs	LYs	Costs	QALYs	LYs	
UK SoC	[redacted]	[redacted]	1.33	-	-	-	-
AMI	[redacted]	[redacted]	2.17	[redacted]	[redacted]	0.84	£39,764

Abbreviations: AMI: amivantamab; ICER: incremental cost-effectiveness ratio; LY: life years; PAS: patient access scheme; QALYs: quality-adjusted life years; SoC: standard of care.

Table 63: Base case results at amivantamab list price (deterministic)

	Total			Incremental			ICER (£/QALY)
	Costs	QALYs	LYs	Costs	QALYs	LYs	
UK SoC	[redacted]	[redacted]	1.33	-	-	-	-
AMI	[redacted]	[redacted]	2.17	[redacted]	[redacted]	0.84	[redacted]

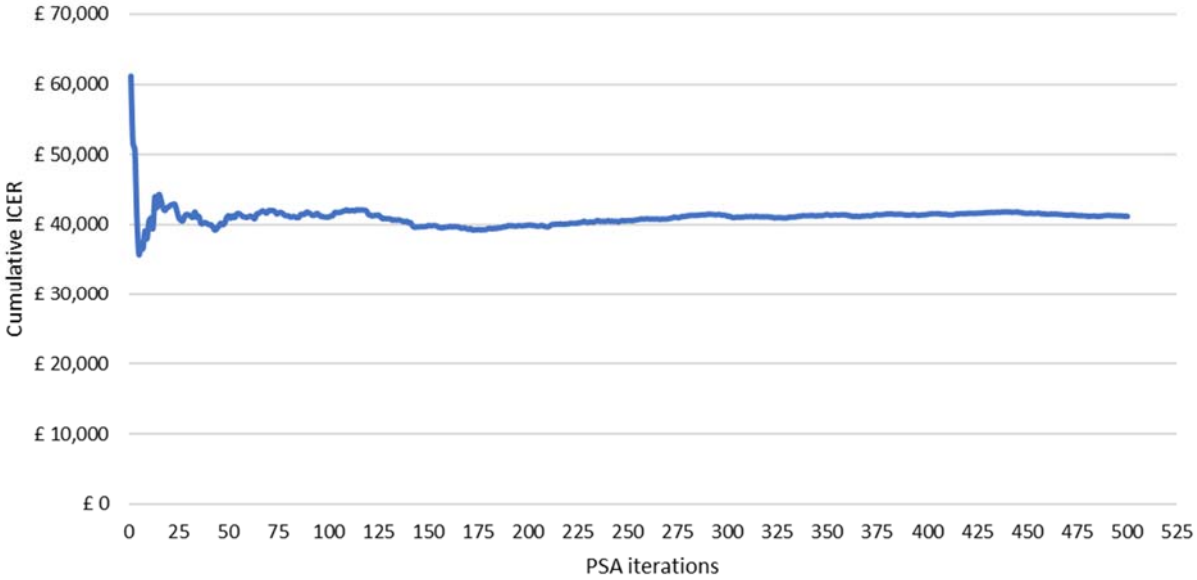
Abbreviations: AMI: amivantamab; ICER: incremental cost-effectiveness ratio; LY: life years; QALYs: quality-adjusted life years; SoC: standard of care.

B.3.8 Sensitivity analyses

B.3.8.1 Probabilistic sensitivity analysis

Probabilistic sensitivity analyses (PSAs) with 1,000 iterations were performed in order to assess the uncertainty associated with model input parameters. Use of 1,000 iterations was deemed appropriate based on the results of an ICER convergence test, shown in Figure 41.

Figure 41: Probabilistic ICER convergence plot at amivantamab PAS price



Abbreviations: ICER: incremental cost-effectiveness ratio; PAS: patient access scheme; PSA: probabilistic sensitivity analysis.

The probabilistic base case results are presented in Table 64 (PAS price) and Table 65 (list price). Cost-effectiveness planes and cost-effectiveness acceptability curves (PAS price) are presented in Figure 42 and Figure 43, respectively. The probabilistic base case results are in close alignment with the deterministic base case results.

Table 64: Base case results at amivantamab PAS price (probabilistic)

	Total			Incremental			ICER (£/QALY)
	Costs	QALYs	LYs	Costs	QALYs	LYs	
UK SoC	[redacted]	[redacted]	1.33	-	-	-	-
AMI	[redacted]	[redacted]	2.21	[redacted]	[redacted]	0.88	£40,246

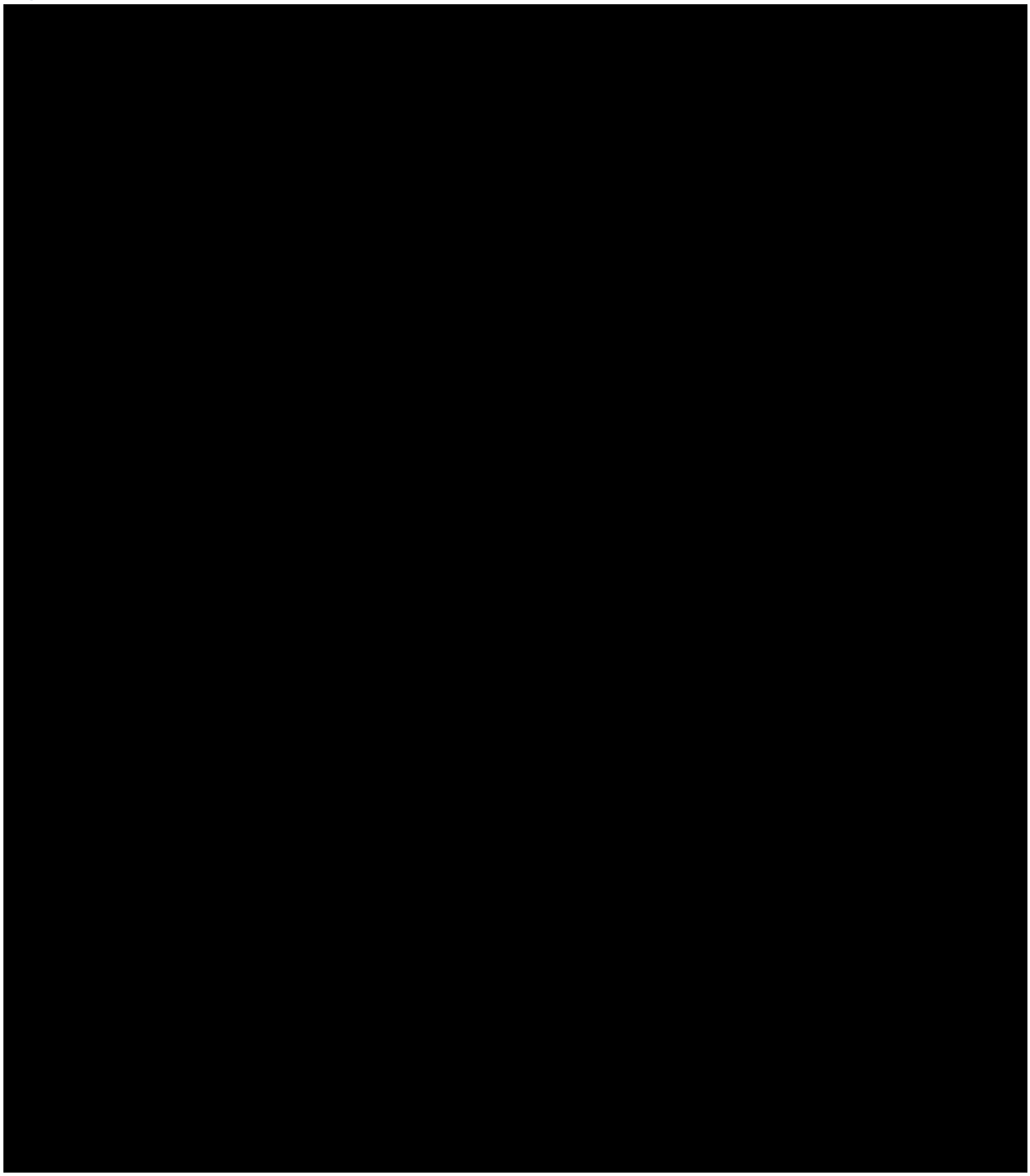
Abbreviations: AMI: amivantamab; ICER: incremental cost-effectiveness ratio; LY: life years; PAS: patient access scheme; QALYs: quality-adjusted life years; SoC: standard of care.

Table 65: Base case results at amivantamab list price (probabilistic)

	Total			Incremental			ICER (£/QALY)
	Costs	QALYs	LYs	Costs	QALYs	LYs	
UK SoC	[redacted]	[redacted]	1.32	-	-	-	-
AMI	[redacted]	[redacted]	2.21	[redacted]	[redacted]	0.89	[redacted]

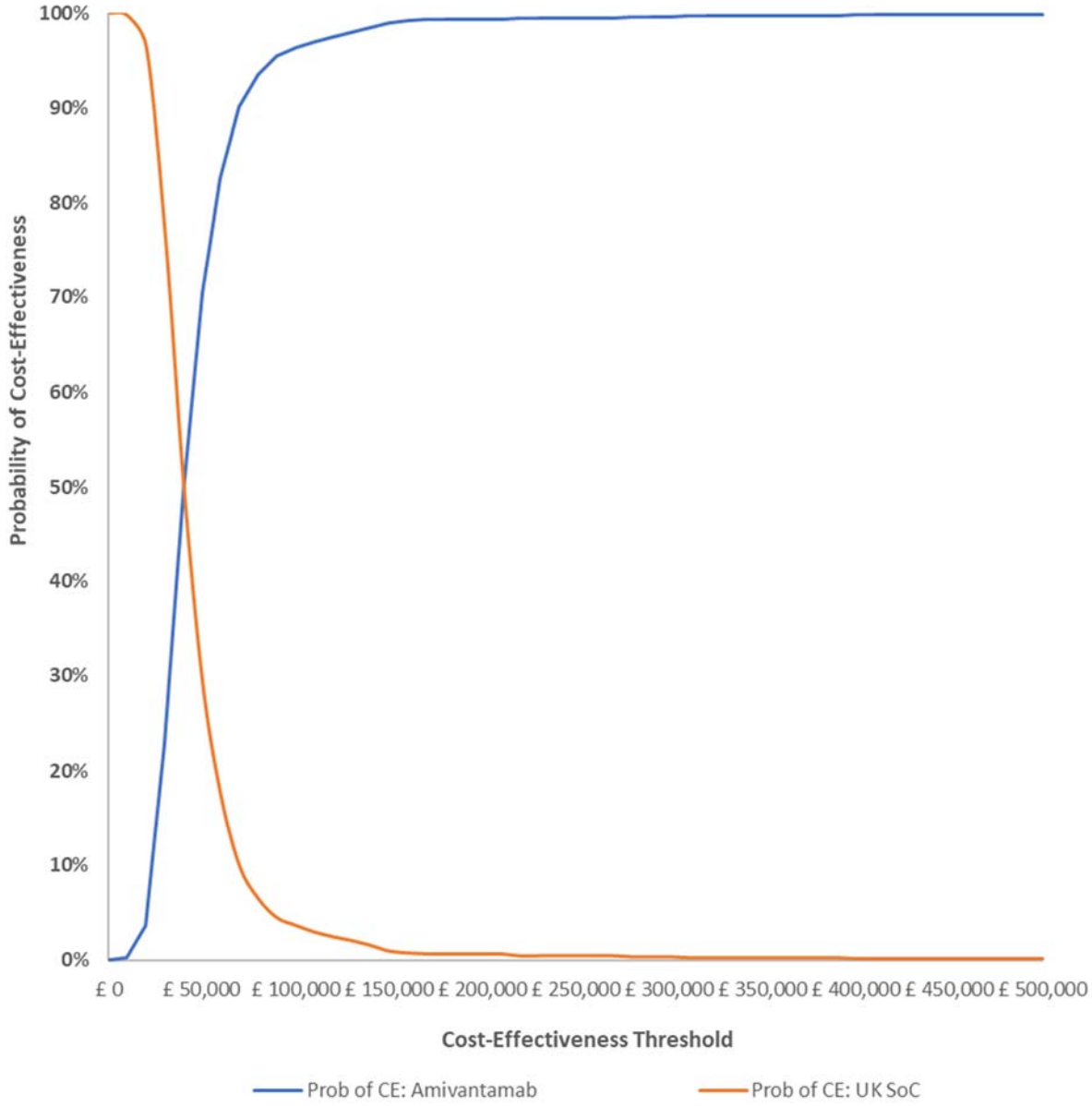
Abbreviations: AMI: amivantamab; ICER: incremental cost-effectiveness ratio; LY: life years; QALYs: quality-adjusted life years; SoC: standard of care.

Figure 42: Cost effectiveness plane scatterplot at amivantamab PAS price



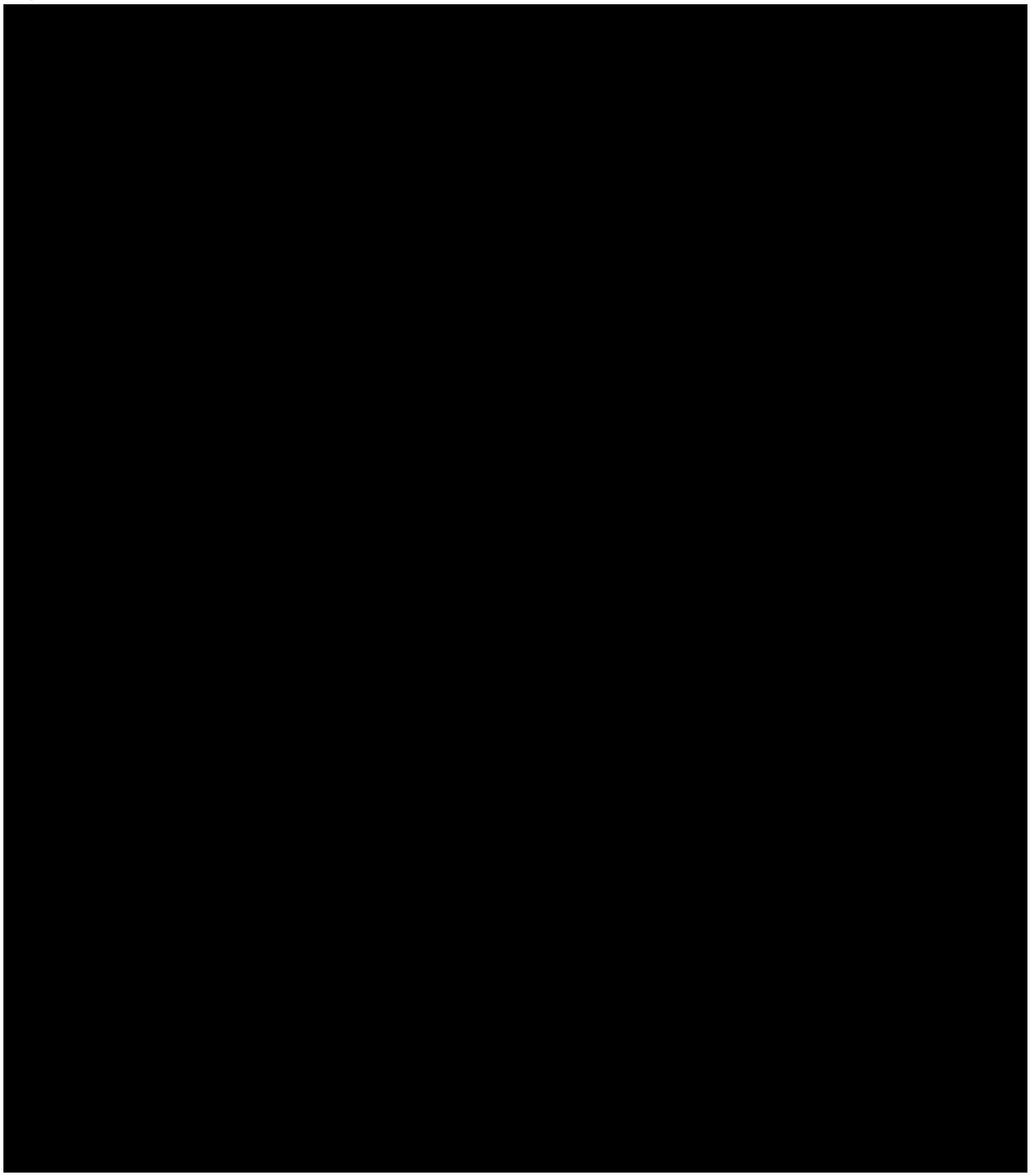
Abbreviations: ICER: incremental cost-effectiveness ratio; PAS: patient access scheme; QALY: quality-adjusted life year; SoC: standard of care.

Figure 43: Cost-effectiveness acceptability curve at amivantamab PAS price



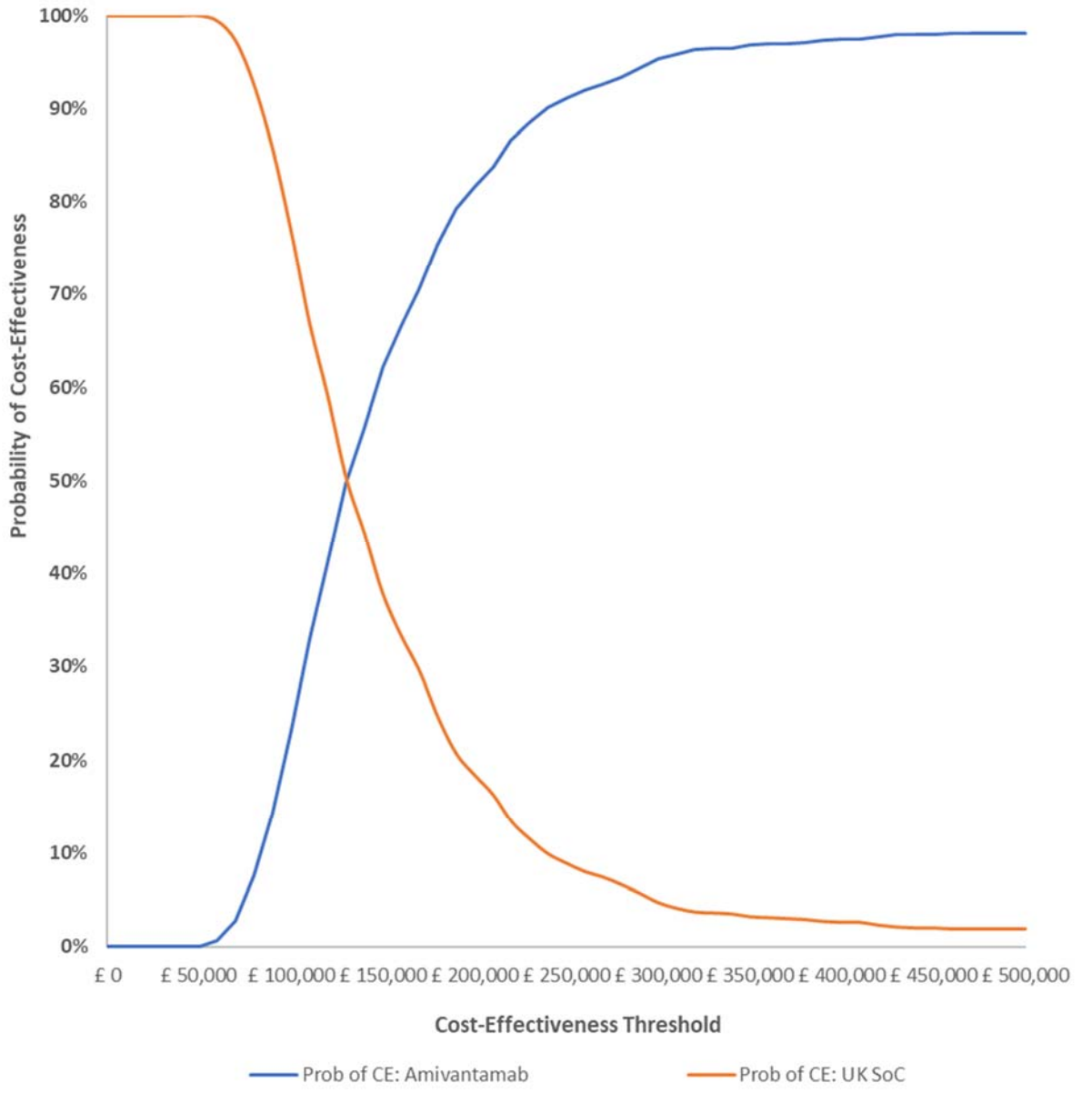
Abbreviations: CE: cost-effectiveness; PAS: patient access scheme; SoC: standard of care.

Figure 44: Cost effectiveness plane scatterplot at amivantamab list price



Abbreviations: ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; SoC: standard of care.

Figure 45: Cost-effectiveness acceptability curve at amivantamab list price

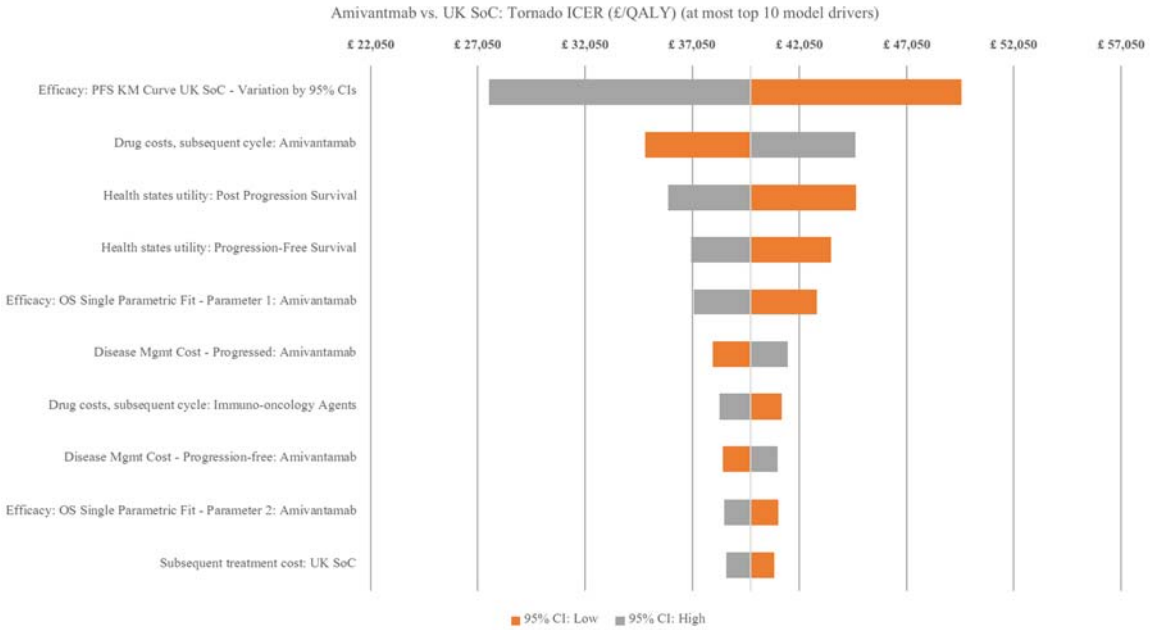


Abbreviations: CE: cost-effectiveness; SoC: standard of care.

B.3.8.2 Deterministic sensitivity analysis

Deterministic sensitivity analyses (DSA) were undertaken to explore the impact of changing assumptions concerning key model parameter values on the base case ICERs. In the DSAs, inputs were varied by their 95% CIs to represent upper and lower bounds where these data were available. Where 95% CIs were not available, a variation of ± 10% of the mean was assumed. The ten most influential variables in the DSA for the analysis of amivantamab (PAS price) versus UK SoC are presented as tornado plot in Figure 46. These results indicate that the three most influential parameters on the ICER results at a £50,000 threshold were PFS data for UK SoC, drug costs in subsequent cycles for amivantamab and the health state utility value for the PPS state. Overall, results were largely robust to parameter uncertainty, demonstrating the stability of the model.

Figure 46: Tornado plot (ICER) at amivantamab PAS price



Abbreviations: AE: adverse event; CI: confidence interval; ICER: incremental cost-effectiveness ratio; OS: overall survival; PAS: patient access scheme; PFS: progression-free survival; QALY: quality-adjusted life year; SoC: standard of care.

Figure 47: Tornado plot (ICER) at amivantamab list price

Abbreviations: AE: adverse event; CI: confidence interval; ICER: incremental cost-effectiveness ratio; OS: overall survival; PFS: progression-free survival; QALY: quality-adjusted life year; SoC: standard of care.

B.3.8.3 Scenario analysis

A number of scenario analyses were explored in which model assumptions or parameters were altered. The rationale and results of the scenario analyses carried out are presented in Table 66.

Table 66: Summary of scenario analyses

#	Scenario analysis	Rationale	LIST PRICE			WITH PAS		
			Incr. costs (£)	Incr. QALYs	ICER (£/QALY)	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)
Base case			[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£39,764
1	Discount rate of 1.5%	In the base case, a discount rate of 3.5% is used in line with the NICE reference case.[96] A scenario has been conducted to assess the impact of a lower discount rate on the cost-effectiveness model results.	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£38,729
2	Proportion of patients receiving docetaxel + nintedanib and docetaxel alone as 50%/50% within non-platinum-based chemotherapy	In the base case, 75% patients are assumed to receive docetaxel + nintedanib based on clinical expert opinion;[12] however, there is a degree of uncertainty in this estimate. Therefore, a scenario has been conducted to assess the impact of a higher proportion of docetaxel monotherapy use.	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£41,897
3	Proportion of patients receiving carboplatin + pemetrexed within platinum-based chemotherapy at 0%	In the base case, platinum-based chemotherapy is comprised of carboplatin + gemcitabine, carboplatin + vinorelbine and carboplatin + pemetrexed (33%/33%/33%). However, based on expert feedback from two UK clinicians, patients may be more likely to receive carboplatin + gemcitabine or carboplatin + vinorelbine.[12] Therefore, a scenario analysis has been conducted where these regimens take a 50%/50% split within platinum-based chemotherapy.	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£40,040
4	Osimertinib as the treatment assumed to represent EGFR TKIs	In the base case, afatinib is assumed to be the TKI of choice based on feedback from UK clinical experts.[12] However, osimertinib is a NICE recommended treatment for treating EGFR T790M mutation-positive locally advanced or metastatic NSCLC in adults;[95] therefore, a scenario has been conducted to show the effect of assuming 100% patients receiving TKIs receive osimertinib rather than afatinib.	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£31,224

5	Subsequent treatment composition for patients following amivantamab	In the base case, US RWE is used to inform the subsequent treatment compositions for patients following amivantamab or UK SoC to ensure alignment with the source of the UK SoC treatment class distribution and UK SoC efficacy. However, given the availability of subsequent treatment data following amivantamab from the CHRYSALIS trial, a scenario has been conducted in which the subsequent treatment composition for patients following amivantamab are sourced from the CHRYSALIS trial. Since all patients in the CHRYSALIS trial received amivantamab, the subsequent treatment composition for patients following UK SoC remain aligned with the base case.	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£39,479
6	UK SoC efficacy from PHE data	In the base case, US RWE is used to inform efficacy inputs for UK SoC based on the larger sample size and clinical expert feedback that these data would be generalisable to UK practice.[12] However, given the availability of data specifically from English practice from PHE, a scenario has been conducted to show the influence of these data on the cost-effectiveness model results. Note that PFS data are not available from PHE; therefore, TTNT data are used as a proxy.	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£25,865
7	Progression measure for amivantamab = INV (Weibull)	In the base case, BICR results for progression are utilised (generalised gamma selection); however, a scenario has been conducted to show the effect of using INV as an alternative measure.	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£42,249
8a	Extrapolations for UK SoC PFS and OS	In the base case, Kaplan-Meier data are used for UK SoC given the maturity of the data. However, a scenario analysis has been conducted to assess the impact of applying parametric extrapolations. In this scenario, PFS is extrapolated based on a log-logistic selection (best statistical fit and in line with clinical expert feedback that all curve choices were clinically plausible) and OS is extrapolated based on a generalised gamma selection (preferred choice during clinical expert feedback elicitation).[12]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£41,742

8b		In the base case, Kaplan-Meier data are used for UK SoC given the maturity of the data. However, a scenario analysis has been conducted to assess the impact of applying parametric extrapolations. In this scenario, PFS is extrapolated based on a log-logistic selection (best statistical fit and in line with clinical exert feedback that all curve choices were clinically plausible) and OS is extrapolated based on a Weibull selection (best statistical fit and second choice during clinical expert feedback elicitation).[12]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£40,863
9	Generalised gamma extrapolation for amivantamab OS	In the base case, Weibull is selected in line with clinical expert feedback.[12] An alternative extrapolation that would also largely align with clinical feedback is the generalised gamma. Therefore, a scenario analysis has been conducted assessing the impact of this selection on the cost-effectiveness model results.	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£41,572
10	Inclusion of vial sharing	In the base case, vial sharing is excluded due to the small patient population considered within the cost-effectiveness model. However, a scenario where vial sharing is included has been conducted to demonstrate the effect of this on the cost-effectiveness model results.	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£40,280

Abbreviations: BICR: blinded independent committee review; EGFR: epidermal growth factor receptor; INV: investigator-assessed; NICE: National Institute for Health and Care Excellence; NSCLC: non-small cell lung cancer; OS: overall survival; PAS: patient access scheme; PFS: progression-free survival; PHE: Public Health England; RWE: real-world evidence; SoC: standard of care; TKI: tyrosine kinase inhibitor; TTNT: time to next treatment.

B.3.8.4 Summary of sensitivity analyses results

Results of the sensitivity analyses demonstrate that the base case cost-effectiveness results exhibit little variation when the combined distributional uncertainty across model parameters is taken into account. The PSA results aligned closely with the deterministic base case results showing that amivantamab is cost-effective versus UK SoC and indicating it to be a cost-effective use of resources in the NHS. As demonstrated by the DSA (with PAS), the three most influential parameters driving the model were PFS data for UK SoC, drug costs in subsequent cycles for amivantamab and the health state utility value for the PPS state. Limited variation was observed in the majority of changes to the modelling approach that were explored in the scenario analyses: across all scenarios conducted, amivantamab was associated with ICERs (with PAS) of less than £50,000 per QALY gained. Altogether, these results demonstrate the robustness of the model to uncertainty.

B.3.9 Subgroup analysis

No economic subgroup analyses were conducted as part of this appraisal.

B.3.10 Validation

B.3.10.1 Validation of cost-effectiveness analysis

Clinical validation

Expert clinical input was sought during the development of the cost-effectiveness model to ensure that the inputs and assumptions used in the analysis were relevant to UK clinical practice and to validate the clinical plausibility of the outcomes predicted by the model. Feedback was obtained in two advisory boards and in total, input was gathered from seven UK clinical experts.

As detailed throughout the submission, the clinical experts were in agreement with the approaches and assumptions taken in the development of the cost-effectiveness model and full details of the clinical validation are provided in the reference pack accompanying this submission. Expert clinical opinion was sought to validate the following model inputs:

- Testing algorithms
- The treatment pathway for NSCLC and relevant comparators
- Appropriate estimates of PFS and OS for amivantamab and UK SoC
- Generalisability of CHRYSALIS and RWE sources
- AE rates
- Utility values
- Monitoring and follow-up resource use assumptions

For survival data for amivantamab and UK SoC where extrapolation was required, clinical expert opinion on the plausibility of long-term extrapolations was sought, and subsequently considered alongside a combination of statistical goodness of fit criteria and visual inspection when determining the most appropriate selections (see Section B.3.3).

Technical validation

The model programming was checked by an analyst who was not involved in the original development of the model using a validation checklist similar that reported in the published literature.[115] This involved a quality control check of the formulae used in the model and stress testing of the model to ensure that it behaves as expected when extreme values are used.

In addition, a model challenge session was held with health economic experts to gain insights and advice regarding the most appropriate assumptions and inputs to consider for the cost-effectiveness model. Advice was sought from four health economic experts and feedback taken into account when developing the cost-effectiveness model for this submission where at all possible.[69]

B.3.11 Interpretation and conclusions of economic evidence

Advanced NSCLC is a life-limiting disease that has a substantial impact on both patient and caregiver quality of life, negatively affecting both physical and psychological health.[43, 63] Additionally, patients with EGFR Exon20ins mutated NSCLC have a particularly poor prognosis compared to other EGFR mutations, in large part due to the lack of approved, targeted therapies available for this population.[5] Furthermore, there is no established SoC pathway in UK clinical practice for these patients, with no targeted therapies for patients with Exon20ins mutations specifically.[11] Importantly, prognosis is extremely poor, and these patients meet NICE's end-of-life criterion of a short life expectancy of <24 months. Based on the observed outcomes in patients treated with amivantamab and patients treated with SoC, amivantamab meets NICE's end of life criteria and should be assessed according to the higher willingness-to-pay threshold of £50,000/QALY gained. Based on the opportunity to address a driver of race and stigma-based discrimination, we argue that the £50,000 end of life threshold should be seen as a lower limit for decision-making, and that the true social value judgement for approving amivantamab could be much higher than this.

In addition to the results of the economic model which focus on the NHS/PSS perspective, lung cancer (and advanced NSCLC more specifically) is also associated with a substantial indirect economic burden of missed work for patients and carers, and time spent travelling between home and hospital for patients and carers. Although not considered in the presented analysis, the indirect costs displaced by introducing an effective, new treatment like amivantamab should be considered as part of the social value judgement of the medicine.

The economic analysis presented in this submission is robust in the context of a very rare and understudied patient population. It makes best use of available data and captures the benefits of amivantamab as compared to the most relevant comparator in this setting, UK SoC. Where required, model extrapolations have been assessed based on consideration of statistical/visual fit and clinical expert opinion on their plausibility. Model inputs and assumptions were also validated with both health economic and clinical experts to maximise robustness and confirm generalisability. It is acknowledged that CHRYSALIS is a single-arm trial, with some uncertainty in long-term outcomes and relative efficacy versus UK SoC. The latter therefore necessitates relative efficacy estimates to be derived from an adjusted analysis comparing to RWE sources from the US and English settings. However, these analyses were based on robust statistical methodology, accounted for differences in key prognostic factors, and outputs were consistent with each other and with clinical expert opinion on predicted outcomes for SoC therapies. Furthermore, uncertainties related to the confirmation of clinical outcomes for amivantamab in UK patients and the comparative effectiveness of amivantamab versus UK SoC can be

addressed with further data collection on the CDF, the ideal route for amivantamab as an innovative and first targeted therapy in this underserved population with a rare mutation and a high unmet need.

The results of the cost-effectiveness model found amivantamab to represent a cost-effective use of NHS resources in England, being associated with an ICER at PAS price of £39,764 per QALY gained versus UK SoC. The model results are considered to be robust, and the inputs and assumptions used in the model have been tested and explored via the use of extensive scenario and sensitivity analyses.

In summary, the results of the cost-effectiveness analysis suggest that the use of amivantamab would represent a cost-effective treatment strategy, being associated with an ICER of less than £50,000 per QALY gained (with PAS). Amivantamab addresses the unmet need for a targeted, effective therapy for patients and is highly innovative in nature, representing a step-change in the management of patients with locally advanced or metastatic NSCLC with activating EGFR Exon20ins after progression on or after platinum-based chemotherapy. In addition, there will be extensive benefits not captured within the cost/QALY framework such as effects on stigmatisation of patients, providing treatment options for distinct epidemiological subgroups that may be underrepresented, and impacting informal carers in terms of reduced anxiety/depression and the ability to return to work. Taken together, these imply that amivantamab could potentially be a good use of NHS resources even at a threshold slightly higher than £50,000/QALY, and any residual uncertainty about this value can be managed through the CDF.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Amivantamab for treating EGFR Exon 20 insertion-positive non-small-cell lung cancer after platinum-based chemotherapy [ID3836]

Clarification questions

February 2022

File name	Version	Contains confidential information	Date
ID3836_Janssen_Amivantamab_Clarification Questions	1	Yes	18th March 2022

Notes for company

Highlighting in the template

Square brackets and grey highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [grey highlighting] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

To delete grey highlighted text, click anywhere within the text and press DELETE.

Section A: Clarification on effectiveness data

Literature searches

A1. Please explain why targeted searches were conducted in addition to the main clinical evidence literature searches, as referred to in Appendix D (section D.1.1.6). Please provide full details of the targeted searches, including the search strategies or search terms used, date searched, and results.

As no search terms specific to Exon 20 insertions (Exon20ins) were included in the database search strategies, additional targeted searches were conducted to increase the comprehensiveness of the review. Ovid (MEDLINE and Embase), Google and Google Scholar were additionally searched using terms for "exon 20 insertions" and "non-small cell lung cancer" to identify any additional, relevant studies for inclusion not identified via the database searches or other supplementary sources.

Full search terms for MEDLINE and Embase are provided below in Table 1. Searches were conducted on 8th March 2021 and updated on 18th October 2021.

Table 1: Search Strategy for targeted searches for Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily and Embase

1	NSCLC.ti,ab,kw,kf.
2	exp Carcinoma, Non-Small-Cell Lung/
3	(lung$ and (non small cell or nonsmall cell) and (carcinoma$ or adenocarcinoma$ or cancer$ or tumo?r$ or neoplasm$)).ti,ab,kw,kf.
4	or/1-3
5	("exon 20" and "insert$").ti,ab.

6	"ex20".ti,ab.
7	"20ins".ti,ab.
8	or/5-7
9	(epidermal growth factor receptor$ or EGFR$ or tyrosine kinase receptor$ or rare mutation$).ti,ab,kw,kf.
10	exp ErbB Receptors/
11	exp mutation/
12	or/9-11
13	4 and 8 and 12
14	("conference abstract" or "conference review").pt.
15	limit 14 to yr="1974-2017"
16	case study/ or case reports/
17	15 or 16
18	13 not 17
19	remove duplicates from 18

A total of 264 and 94 hits were screened in the original systematic literature review (SLR) and update, respectively, and a total of 11 records reporting on nine studies were ultimately included in the original SLR, with a further seven records reporting on seven studies included in the SLR update. Studies included from the targeted searches are shown in Table 2.

Google and Google Scholar were searched on 9th March 2021 and again on 18th October 2021 using the search strings “exon 20 insertions lung cancer” and “ex20ins lung cancer”. The first 20 hits of each search were screened, and no studies were included.

Table 2: Studies included from targeted searches and extracted in the clinical SLR

#	Study name	Reference
Original SLR (May 2020)		
Interventional studies		
1	EXCLAIM	Riely, G. J. N., J. W.; Camidge, D. R.; Spira, A.; Piotrowska, Z.; Horn, L.; Costa, D. B.; Tsao, A.; Patel, J.; Gadgeel, S.; Bazhenova, L.; Zhu, V. W.; West, H.; Mekhail, T.; Gentzler, R.; Nguyen, D.; Bunn, V.; Jin, S.; Feng, Z.; Janne, P. A. Updated results from a phase I/II study of mobocertinib (TAK-788) in NSCLC with EGFR exon 20 insertions (exon20ins) Annals of Oncology 2020;31(Supplement 4);S815-S816
		Riely, G. J., Neal, J. W., Camidge, D. R., Spira, A. I., Piotrowska, Z., Costa, D. B., Tsao, A. S., Patel, J. D., Gadgeel, S. M., Bazhenova, L., Zhu, V. W., West, H. L., Mekhail, T., Gentzler, R. D., Nguyen, D., Vincent, S., Zhang, S., Lin, J., Bunn, V., Jin, S., Li, S. and Janne, P. A. Activity and Safety of Mobocertinib (TAK-788) in Previously Treated Non-Small Cell Lung Cancer With EGFR Exon 20 Insertion Mutations From a Phase 1/2 Trial Cancer discovery 2021;-(-);-
		Riely, G., Neal, J., Camidge, D. R., Spira, A., Piotrowska, Z., Horn, L., Costa, D., Tsao, A., Patel, J., Gadgeel, S., Bazhenova, L., Zhu, V., West, H., Vincent, S., Zhu, J., Jin, S., Zhang, S., Li, S. and Janne, P. P1.01-127 Antitumor Activity of the Oral EGFR/HER2 Inhibitor TAK-788 in NSCLC with EGFR Exon 20 Insertions Journal of Thoracic Oncology 2019;14(10 Supplement);S412-S413
2	Yang 2020a	J.C. Yang1, M. Schuler2, S. Popat3, S. Miura4, S. Heeke5, A. Passaro6, F. de Marinis6, K. Park7, E.S. Kim8 1341P - Afatinib in Asian and non-Asian patients (pts) with EGFR mutation-positive (EGFRm+) NSCLC harboring uncommon mutations ESMO 2020 2020;-(-);-
Observational studies		
3	Chen 2017	Chen, K., Yu, X., Wang, H., Huang, Z., Xu, Y., Gong, L. and Fan, Y. Uncommon mutation types of epidermal growth factor receptor and response to EGFR tyrosine kinase inhibitors in Chinese non-small cell lung cancer patients Cancer Chemotherapy and Pharmacology 2017;80(6);1179-1187
4	Lund-Iversen 2012	Lund-Iversen, M., Kleinberg, L., Fjellbirkeland, L., Helland, A. and Brustugun, O. T. Clinicopathological characteristics of 11 NSCLC patients with EGFR-exon 20 mutations Journal of Thoracic Oncology 2012;7(9);1471-1473
5	Qin 2020	Qin, Y., Jian, H., Tong, X., Wu, X., Wang, F., Shao, Y. W. and Zhao, X. Variability of EGFR exon 20 insertions in 24 468 Chinese lung cancer patients and their divergent responses to EGFR inhibitors Molecular Oncology 2020;14(8);1695-1704
6	Tu 2017	Tu, H. Y., Ke, E. E., Yang, J. J., Sun, Y. L., Yan, H. H., Zheng, M. Y., Bai, X. Y., Wang, Z., Su, J., Chen, Z. H., Zhang, X. C., Dong, Z. Y., Wu, S. P., Jiang, B. Y., Chen, H. J., Wang, B. C., Xu, C. R., Zhou, Q., Mei, P., Luo, D. L., Zhong, W. Z., Yang, X. N. and Wu, Y. L. A comprehensive review of uncommon EGFR mutations in patients with non-small cell lung cancer Lung Cancer 2017;114;96-102

#	Study name	Reference
7	Woo 2014	Woo, H. S., Ahn, H. K., Lee, H. Y., Park, I., Kim, Y. S., Hong, J., Sym, S. J., Park, J., Lee, J. H., Shin, D. B. and Cho, E. K. Epidermal growth factor receptor (EGFR) exon 20 mutations in non-small-cell lung cancer and resistance to EGFR-tyrosine kinase inhibitors Investigational New Drugs 2014;32(6);1311-1315
8	Wu 2018	Wu, J. Y., Shih, J. Y. and Yu, C. J. Effectiveness of treatments in advanced nonsmall cell lung cancer with Exon 20 insertion epidermal growth factor receptor mutations Respirology 2018;23(Supplement 2);168
9	Yamada 2020	Yamada, Y., Tamura, T., Yamamoto, Y., Ichimura, H., Hayashihara, K., Saito, T., Yamada, H., Endo, T., Nakamura, R., Inage, Y., Satoh, H., Iguchi, K., Saito, K., Inagaki, M., Kikuchi, N., Kurishima, K., Ishikawa, H., Sakai, M., Kamiyama, K., Shiozawa, T., Hizawa, N., Sekine, I., Sato, Y., Funayama, Y., Miyazaki, K., Kodama, T., Hayashi, S., Nomura, A., Nakamura, H., Furukawa, K., Yamashita, T., Okubo, H., Suzuki, H., Kiyoshima, M. and Kaburagi, T. Treatment of Patients With Non-small-cell Lung Cancer With Uncommon EGFR Mutations in Clinical Practice Anticancer research 2020;40(10);5757-5764
SLR update (February 2021)		
Interventional studies		
1	Cappuzzo 2018	Chang, G.-C., Lam, D. C.-L., Tsai, C.-M., Chen, Y.-M., Shih, J.-Y., Aggarwal, S., Wang, S., Kim, S.-W., Kim, Y.-C., Wahid, I., Li, R., Lim, D. W.-T., Sriuranpong, V., Chan, R. T.-T., Lorence, R. M., Carriere, P., Raabe, C., Cseh, A. and Park, K. Experience from Asian centers in a named-patient-use program for afatinib in patients with advanced non-small-cell lung cancer who had progressed following prior therapies, including patients with uncommon EGFR mutations International Journal of Clinical Oncology 2021;26(5);841-850
2	CHRYSALIS	Park, K., Haura, E. B., Leighl, N. B., Mitchell, P., Shu, C. A., Girard, N., Viteri, S., Han, J.-Y., Kim, S.-W., Lee, C. K., Sabari, J. K., Spira, A. I., Yang, T.-Y., Kim, D.-W., Lee, K. H., Sanborn, R. E., Trigo, J., Goto, K., Lee, J.-S., Yang, J. C.-H., Govindan, R., Bauml, J. M., Garrido, P., Krebs, M. G., Reckamp, K. L., Xie, J., Curtin, J. C., Haddish-Berhane, N., Roshak, A., Millington, D., Lorenzini, P., Thayu, M., Knoblauch, R. E. and Cho, B. C. Amivantamab in EGFR Exon 20 Insertion-Mutated Non-Small-Cell Lung Cancer Progressing on Platinum Chemotherapy: Initial Results From the CHRYSALIS Phase I Study Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2021;-(-);JCO2100662
3	Riess 2021	Riess, J. W., Kelly, K. A., Gandara, D. R., Lara, P. N., Frankel, P., Longmate, J., Newman, E. M., Weipert, C. M., Raymond, V. M., Mack, P. C., Keer, H. N. and Reckamp, K. L. Erlotinib and Onalespib Lactate Focused on EGFR Exon 20 Insertion Non-Small Cell Lung Cancer (NSCLC): A California Cancer Consortium Phase I/II Trial (NCI 9878): Onalespib Plus Erlotinib in EGFR-Mutant NSCLC Clinical Lung Cancer 2021;-(-);-
Observational studies		

#	Study name	Reference
4	Huang 2021	Huang, C.-H., Ju, J.-S., Chiu, T.-H., Huang, A. C.-C., Tung, P.-H., Wang, C.-C., Liu, C.-Y., Chung, F.-T., Fang, Y.-F., Guo, Y.-K., Scott Kuo, C.-H. and Yang, C.-T. Afatinib treatment in a large real-world cohort of non-small cell lung cancer patients with common and uncommon epidermal growth factor receptor mutation International journal of cancer 2021
5	Metro 2021	Metro, G., Baglivo, S., Bellezza, G., Mandarano, M., Gili, A., Marchetti, G., Toraldo, M., Molica, C., Reda, M. S., Tofanetti, F. R., Siggillino, A., Prosperi, E., Giglietti, A., Di Girolamo, B., Garaffa, M., Marasciulo, F., Minotti, V., Gunnellini, M., Guida, A., Sassi, M., Sidoni, A., Roila, F. and Ludovini, V. Sensitivity to Immune Checkpoint Blockade in Advanced Non-Small Cell Lung Cancer Patients with EGFR Exon 20 Insertion Mutations Genes 2021;12(5)
6	Shah 2021b	Shah, M. P., Aredo, J. V., Padda, S. K., Ramchandran, K. J., Wakelee, H. A., Das, M. S. and Neal, J. W. EGFR exon 20 Insertion NSCLC and Response to Platinum-Based Chemotherapy Clinical lung cancer 2021
7	Wang 2021	Wang, V., Cui, C., Yang, L., Li, G., Schrock, A. B., Li, M., Venstrom, J. M. and Tolba, K. A. Off-label targeted therapy (TT) use in recurrent/metastatic NSCLC Journal of Clinical Oncology 2021;39(15 SUPPL)

A2. Please provide full details of the literature searches for the systematic literature review of prognostic patient and disease characteristics conducted to identify potential confounders for the adjusted treatment comparison referred to in B.2.9 and Appendix M. Reference 84 in Document B.

Methods

The SLR focused on observational studies, guidelines or SLRs of observational studies conducted in adults with epidermal growth factor receptor (EGFR)-mutated non-small cell lung cancer (NSCLC) reporting on the impact of potential confounders on overall survival (OS) and/or quality of life (QoL) published from 2018 to 2020.

Separate searches were conducted for (a) clinical guidelines (b) SLRs, and (c) real-world observational studies, in Embase and MEDLINE via Embase.com on 31st August 2020. The search strategy is presented in Table 3. Articles published before 2018 were manually excluded after the search in order to gain a sufficiently comprehensive literature collection and to avoid the identification of potential confounders, which are no longer considered adequate in the scientific community. The bibliography list of relevant SLRs and meta-analyses identified by means of the real-world observational studies or SLR search strategies were also hand-searched for additional citations of interest not captured by our database search.

A single reviewer evaluated the evidence with 20% quality checks according to the criteria shown in Table 4. Data extraction was conducted in piloted templates in Microsoft Excel. For the purpose of this study, a determinant was defined as a variable that was reported to be statistically significantly related to OS and/or QoL, regardless of the size of the study.

Table 3: Search strategy

Database: Embase and Medline (via Embase.com)		
	Search terms	**Results**
#1 **Population**	'lung tumor'/exp OR 'non small cell lung cancer'/exp OR 'lung carcinoma':ab,ti OR 'lung cancer*':ab,ti OR 'lung neoplasm*':ab,ti OR 'lung tumor*':ab,ti OR 'lung tumour*':ab,ti OR 'non small cell*':ab,ti OR 'nonsmall cell*':ab,ti	473,231
#2 **Population**	egfr*:ab,ti	115,878
#3 **Study design**	'epidemiology'/exp OR 'cohort analysis'/exp OR 'longitudinal study'/exp OR ('prospective study'/exp NOT 'randomized controlled trial'/exp) OR 'cross-sectional study'/exp OR 'case control study'/exp OR cohort*:ab,ti OR registry:ab,ti OR registries:ab,ti OR prospective:ab,ti OR retrospective:ab,ti OR 'chart review':ab,ti OR 'real world':ab,ti OR observational:ab,ti	5,625,029
#4 **Outcomes**	'quality of life'/exp OR 'quality of life':ab,ti OR qol:ab,ti OR HRQOL:ab,ti OR 'quality of life assessment'/exp OR 'SF 36':ab,ti OR 'short form 36':ab,ti OR SF36:ab,ti OR 'EQ5d':ab,ti OR 'EQ 5D':ab,ti OR 'overall survival'/exp OR 'overall survival':ab,ti	984,032
#5 **Non-interventional studies**	#1 AND #2 AND #3 AND #4	3,495
#6	guideline*:ti	103,391
#7 **Guidelines**	#1 AND #6 AND [2019-2020]/py	166

#8	(meta:ti AND analy*:ti OR metaanaly*:ti OR ((systematic NEAR/1 (review* OR overview*)):ti) NOT (random*:ab,ti OR trial*:ab,ti))	121,413
#9 **SLR/MA**	#1 AND #3 AND #4 AND #8 AND [2019-2020]/py	82
#10	#5 OR #7 OR #9	3,739
#11	#10 AND [2015-2020]/py	2,699
#12	#11 NOT (letter:it OR editorial:it)	2,664
#13	#12 NOT ('animals'/exp NOT 'humans'/exp)	2,652
#14	[conference abstract]/lim AND [2015-2018]/py	1,465,168
#15	**#13 NOT #14**	**1,806**
#16 **Non-interventional studies with limits**	#15 AND #5	1,584
#17 **Guidelines with limits**	#15 AND #7	146
#18 **SLR/MA with limits**	#15 AND #9	82

Abbreviations: MA: meta-analysis; SLR: systematic literature review.

Table 4: Study selection criteria

	Inclusion criteria	Exclusion criteria
Population	Adults with EGFR-mutated NSCLC	• Co-morbidities with other diseases (COPD etc.) • NSCLC not restricted to patients with EGFR mutations
Intervention/ comparator	All/none/any	N/A
Outcomes	Data reporting on determinants of OS and/or QoL	Any other outcome
Study design	• Real-world observational research • Clinical guidelines • SLRs	• Studies with any other study design • Studies with sample size <125 patients
Publication year	2018–2020	Prior to 2018

Abbreviations: COPD: chronic obstructive pulmonary disease; EGFR: epidermal growth factor receptor; n/a: not applicable; NSCLC: non-small cell lung cancer; OS: overall survival; SLRs: systematic literature reviews; QoL: quality-of-life.

Results

A total of [redacted] citations were identified across searches, including [redacted] non-interventional studies, [redacted] guidelines and [redacted] SLRs.

- **Non-interventional studies**: A total of [redacted] citations were identified, and [redacted] unique citations were screened at the abstract level. Among these, [redacted] were excluded and [redacted] were retrieved and assessed in full text. After full-text review, [redacted] studies were excluded,

and [redacted] publications were included. An additional publication was included from additional bibliography checks, yielding a total of [redacted] publications.

- **Clinical guidelines**: A total of [redacted] citations were identified, and [redacted] unique citations were screened at the abstract level. Among these, [redacted] were excluded and [redacted] were retrieved and assessed in full text. After full-text review, [redacted] guidelines reported across [redacted] publications were included.
- **SLRs**: The SLR search yielded [redacted] citations of which [redacted] unique citations were screened at the abstract level. Among these, [redacted] were excluded and [redacted] were retrieved and assessed in full text. After full-text review and hand-searching of the bibliography lists, no relevant publications were deemed eligible.

Further details related to the SLR and expert validation of the output are available in the report included in the reference pack to these responses.

Decision problem

A3. Priority question: The NICE final scope defines the population of interest as "*Adults with EGFR Exon 20 insertion-positive non-small-cell lung cancer after previous platinum-based chemotherapy*." The population defined in the company's clinical effectiveness submission is: "*Adult patients (aged ≥18 years) with confirmed metastatic or unresectable NSCLC who failed or were ineligible for SoC therapy*."

a. **Please confirm that the population in this submission is narrower than the NICE final scope population.**

Janssen can confirm that the population in the submission is narrower than the NICE final scope population and is aligned with the licensed indication: adult patients with locally advanced or metastatic NSCLC with activating EGFR Exon20ins mutations, whose disease has progressed on or after platinum-based chemotherapy.

b. **The company states that the changes to the population were made to align with the indication granted an innovation passport by MHRA. Can the company provide a copy of the MHRA documentation that documents this?**

The submission population was selected to align with the marketing authorisation granted by the Medicines and Healthcare products Regulatory Agency (MHRA) as described in the Summary of Product Characteristics (SmPC) for amivantamab. This document is available on the electronic medicines compendium website and can be accessed via this link: https://www.medicines.org.uk/emc/product/13084/smpc. A copy of the SmPC was also provided in the reference pack accompanying this submission.[1]

Note that the innovation passport was granted to amivantamab by the MHRA as part of the Innovative and Licensing and Access Pathway and enabled Janssen to apply for marketing authorisation under the MHRA accelerated regulatory pathway. A copy of the innovation passport award document is also provided in the reference pack.[2]

A4. Priority question: The NICE final scope defines the population of interest as "*Adults with EGFR Exon 20 insertion-positive non-small-cell lung cancer after previous platinum-based chemotherapy*." The inclusion criteria for the population in the CHRYSALIS trial appears to be narrower in at least the two ways listed below

a. **Histologically- or cytologically-confirmed NSCLC that was metastatic or unresectable**

b. **An ECOG performance status of 0 or 1**

Please comment on the two above mentioned inclusion criteria for the CHRYSALIS trial, contrasting it with the population defined in the final NICE scope.

The two inclusion criteria cited above were part of a list of eligibility criteria in CHRYSALIS which, in keeping with most clinical trials, serve the following functions:

- To ensure that people recruited to the trial have the characteristics that will enable the researchers to accomplish the study objectives
- To increase the likelihood of the trial to produce accurate, reliable, and reproducible results
- To help ensure the safety of participants

Thus, while the submission population is narrower than the scope, this is to align with the marketing authorisation, rather than to account for any individual inclusion criteria in the CHRYSALIS trial.

A situation in which the licensed indication is broader than the inclusion criteria of the pivotal clinical trial is not unusual as it permits equitable access to new therapies for patients who are not able to enrol in clinical trials. NICE appraise and make recommendations based on the licensed indication population.[3-6] The differences between the licensed indication and the CHRYSALIS trial population are common for oncology treatments (for example restricting to patients with ECOG status of 0 or 1), and mean that trial populations are generally, slightly fitter than the population in UK clinical practice for the reasons outlined in the bullets above.

A5. Priority question: The comparator chosen by the company is a pooled treatment basket in the form of real-world data to estimate clinical effectiveness and SoC in the cost effectiveness analysis. However, as specified in the scope, established clinical management depends upon line of

therapy (first or later) and PD-L1 status. Please provide separate clinical effectiveness analyses (indirect treatment comparisons) by line of therapy and PD-L1 subgroup using only the comparators that would be standard care for the specific subgroup e.g., only pembrolizumab or nivolumab for PD-L1 positive patients.

Overall, Janssen maintain that a basket of comparators is the most appropriate comparator to amivantamab given expert feedback and the real-world evidence (RWE) indicating the heterogenous mix of treatments that patients receive in practice. Further, it is not considered appropriate to split the RWE data for SoC into subgroups given that this introduces additional uncertainty given the smaller sample sizes involved in such analyses, thus limiting their robustness.

However, in order to provide some of the information requested in the ERGs question, subgroup analyses by line of therapy have been provided below. HRs are consistent with results from the base case (see Table 5 below); however, these relative treatment effects are estimated for a restricted population and are therefore associated with greater uncertainty.

Table 5: Comparison of HRs for overall population and subgroups by LOT

HR (95% CI), ATT approach	OS	PFS (BICR)	TTNT
Base case (2L+)	[redacted]	[redacted]	[redacted]
2L subgroup	[redacted]	[redacted]	[redacted]
3L+ subgroup	[redacted]	[redacted]	[redacted]

Abbreviations: 2L: second line; 3L+: third line and beyond; ATT: average treatment effect among the treated; HR: hazard ratio; BICR: blinded independent committee review; LOT: line of therapy; OS: overall survival; PFS: progression-free survival; TTNT: time to next treatment.

For the PD-L1 subgroup analyses, a test for PD-L1 status was performed for [redacted] patients in the CHRYSALIS population, and [redacted] tested positive. In the US cohort, [redacted] lines of therapy corresponded to patients who tested PD-L1 positive. Of these, only [redacted] lines of therapy consisted of nivolumab or pembrolizumab monotherapies. In the PHE cohort, [redacted] patient had a positive PD-L1 status and was not treated with nivolumab or pembrolizumab monotherapies. It is therefore not feasible to conduct a comparative analysis on this subgroup.

Line of therapy

Clinical effectiveness analyses for patients on 2L therapy in the CHRYSALIS cohort (N=[redacted]) and the US RWE cohort (N=[redacted]) are presented below. The baseline characteristics for the two 2L cohorts are presented in Table 6.

Table 6: Baseline characteristics for 2L LOTs in the CHRYSALIS and US RWE cohorts

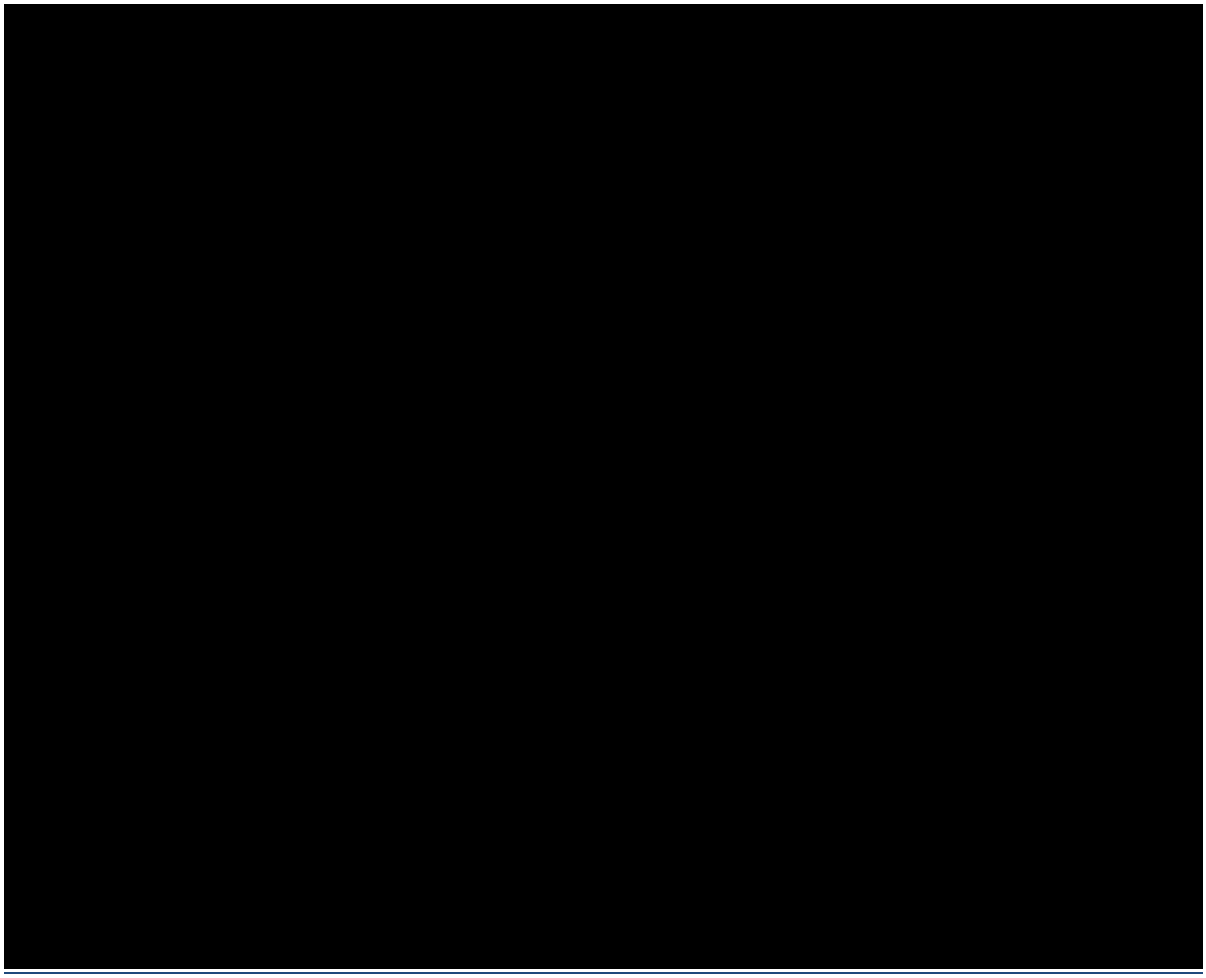
Characteristic, n (%)	Amivantamab (N=[redacted])	UK SoC (N=[redacted])	Total (N=[redacted])
Brain metastasis			
No	[redacted]	[redacted]	[redacted]
Yes	[redacted]	[redacted]	[redacted]
Age			

<60	[redacted]	[redacted]	[redacted]
60-70	[redacted]	[redacted]	[redacted]
≥70	[redacted]	[redacted]	[redacted]
ECOG			
0	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]
Number of metastatic locations			
1	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]
4+	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]
Haemoglobin			
Normal/High	[redacted]	[redacted]	[redacted]
Low	[redacted]	[redacted]	[redacted]
Gender			
Male	[redacted]	[redacted]	[redacted]
Female	[redacted]	[redacted]	[redacted]
Cancer stage at initial diagnosis			
I	[redacted]	[redacted]	[redacted]
II	[redacted]	[redacted]	[redacted]
IIIA	[redacted]	[redacted]	[redacted]
IIIB/IV	[redacted]	[redacted]	[redacted]

Abbreviations: ECOG: Eastern Cooperative Oncology Group; SoC: standard of care.

As shown in Figure 1, there is a good overlap between the propensity score (PS) distributions by treatment of the unweighted populations, where the same variables as in the base case are included in the PS model with the exception of prior lines of treatment (as the populations are restricted to 2L).

Figure 1: Distribution of propensity scores for the unweighted population by treatment; CHRYSALIS and US cohort; 2L



Abbreviations: 2L: second line; PC: physician's choice (alternatively called UK standard of care [SoC]).

After applying ATT weights (including in the PS model the same variables as in the base case, with the exclusion of prior lines of treatment), a good covariate balance is achieved between treatment arms, illustrated by the low standardised mean differences (Figure 2), as well as a good overlap of the ATT-weighted distribution of PS (Figure 3).

Figure 2: Standardised mean difference plot for the unadjusted versus ATT-weighted; CHRYSALIS and US cohort; 2L

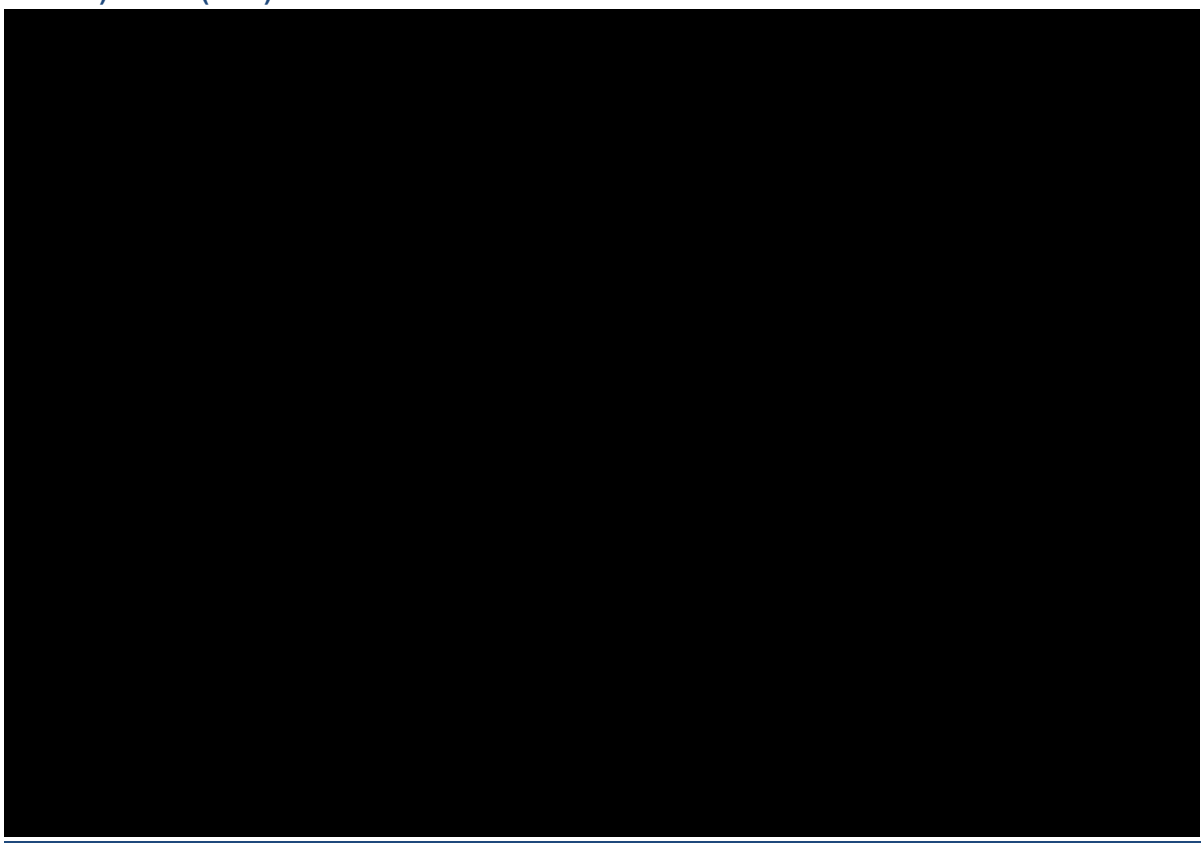
Abbreviations: ATT: average treatment effect among the treated; ECOG: eastern cooperative oncology group; PC: physician's choice.

Figure 3: Distribution of propensity scores for the ATT weighted population by treatment; CHRYSALIS and US cohort; 2L

Abbreviations: ATT: average treatment effect among the treated; PC: physician's choice

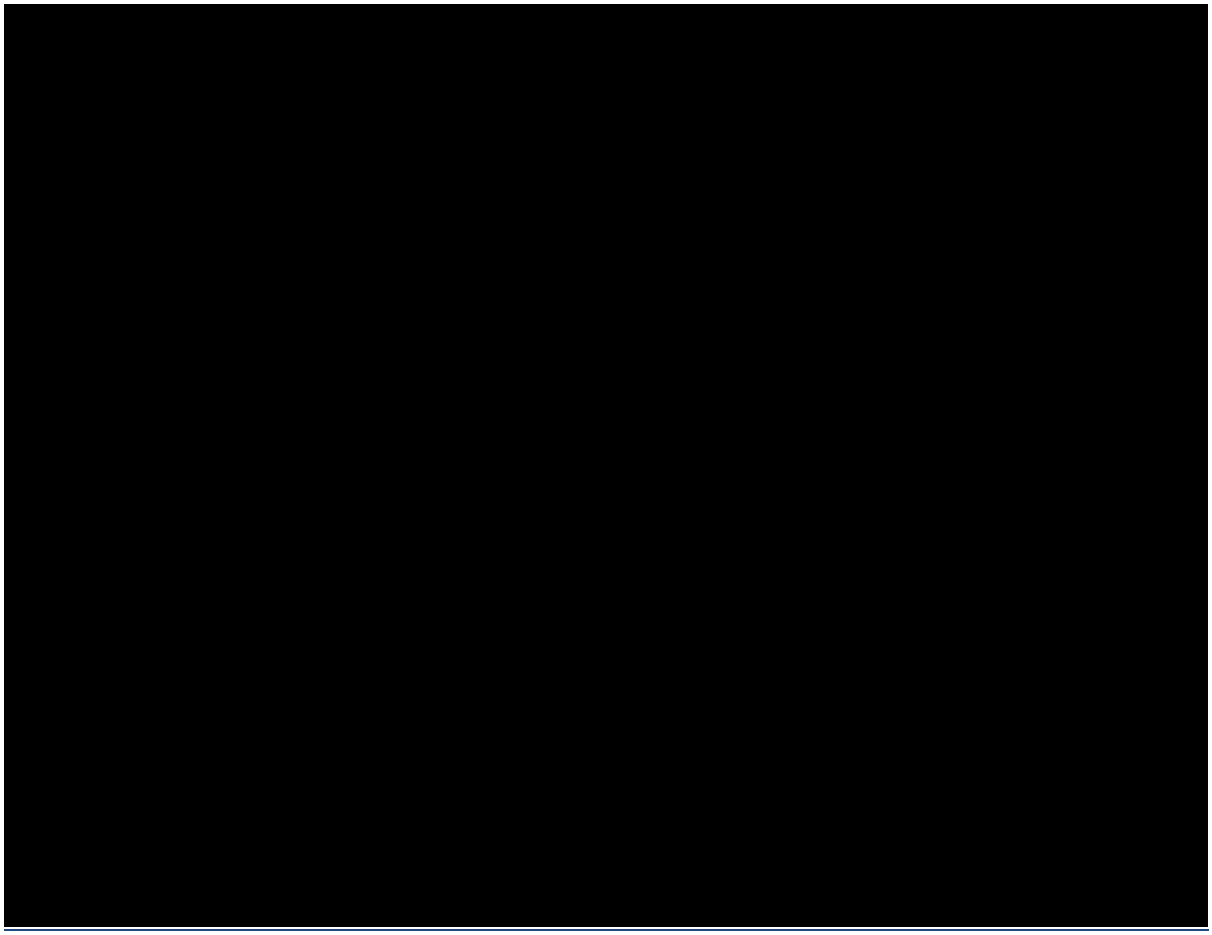
As shown in Figure 4 to Figure 6 below, hazard ratios (HRs) are consistent with results from thefull population as presented in base case.

Figure 4: Kaplan-Meier curve for OS for CHRYSALIS versus US cohort at 2L (amivantamab vs SoC) – IPW (ATT)



Abbreviations: ATT: average treatment effect among the treated; CI: confidence interval OS: overall survival; HR: hazard ratio; IPW: inverse probability weighting; PC: physician's choice; PS: propensity score; RW: real world.

Figure 5: Kaplan-Meier curve for PFS for CHRYSALIS versus US cohort at 2L (amivantamab vs SoC) – IPW (ATT)



Abbreviations: ATT: average treatment effect among the treated; CI: confidence interval; HR: hazard ratio; INV: investigator assessed; PC: physician's choice; PFS: progression-free survival; PS: propensity score; RW: real world.

Figure 6: Kaplan-Meier curve for TTNT for CHRYSALIS versus US cohort at 2L (amivantamab vs SoC) – IPW (ATT)

Abbreviations: ATT: average treatment effect among the treated; CI: confidence interval; HR: hazard ratio; IPW: inverse probability weighting; PC: physician's choice; PS: propensity score; RW: real world; TTNT: time-to-next treatment.

The analysis was repeated for a population restricted to patients at third line and beyond (3L+). This includes N=[redacted] CHRYSALIS patients and N=[redacted] lines of treatment from the US database. Their baseline characteristics distributions are presented in Table 7.

Table 7: Baseline characteristics for CHRYSALIS and US RWE cohorts at 3L+

Characteristic, n (%)	Amivantamab (N=[redacted])	SoC (N=[redacted])	Total (N=[redacted])
Prior lines of treatment			
2	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]
4+	[redacted]	[redacted]	[redacted]
Brain metastasis			
No	[redacted]	[redacted]	[redacted]
Yes	[redacted]	[redacted]	[redacted]
Age, years			
<60	[redacted]	[redacted]	[redacted]
60-70	[redacted]	[redacted]	[redacted]
≥70	[redacted]	[redacted]	[redacted]
ECOG			

0	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]
Number of metastatic locations			
1	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]
4+	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]
Haemoglobin			
Normal/High	[redacted]	[redacted]	[redacted]
Low	[redacted]	[redacted]	[redacted]
Gender			
Male	[redacted]	[redacted]	[redacted]
Female	[redacted]	[redacted]	[redacted]
Cancer stage at initial diagnosis			
I	[redacted]	[redacted]	[redacted]
II	[redacted]	[redacted]	[redacted]
IIIA	[redacted]	[redacted]	[redacted]
IIIB/IV	[redacted]	[redacted]	[redacted]

Abbreviations: ECOG: Eastern Cooperative Oncology Group; SoC: standard of care.

The distribution of PS by treatment arm shows an acceptable overlap (before weighting, Figure 7), and ATT-weighting (adjusted for all variables included in the base case, including prior lines of therapy) shows a good overlap of PS distribution by treatment as well as achieving a good covariate balance (Figure 7 to Figure 9).

Figure 7: Distribution of propensity scores for the unweighted population by treatment; CHRYSALIS and US cohort; 3L+

Abbreviations: 3L+: third line and beyond; PC: physician's choice (alternatively called UK standard of care [SoC]).

Figure 8: Standardised mean difference plot for the unadjusted versus ATT-weighted US cohort; 3L+

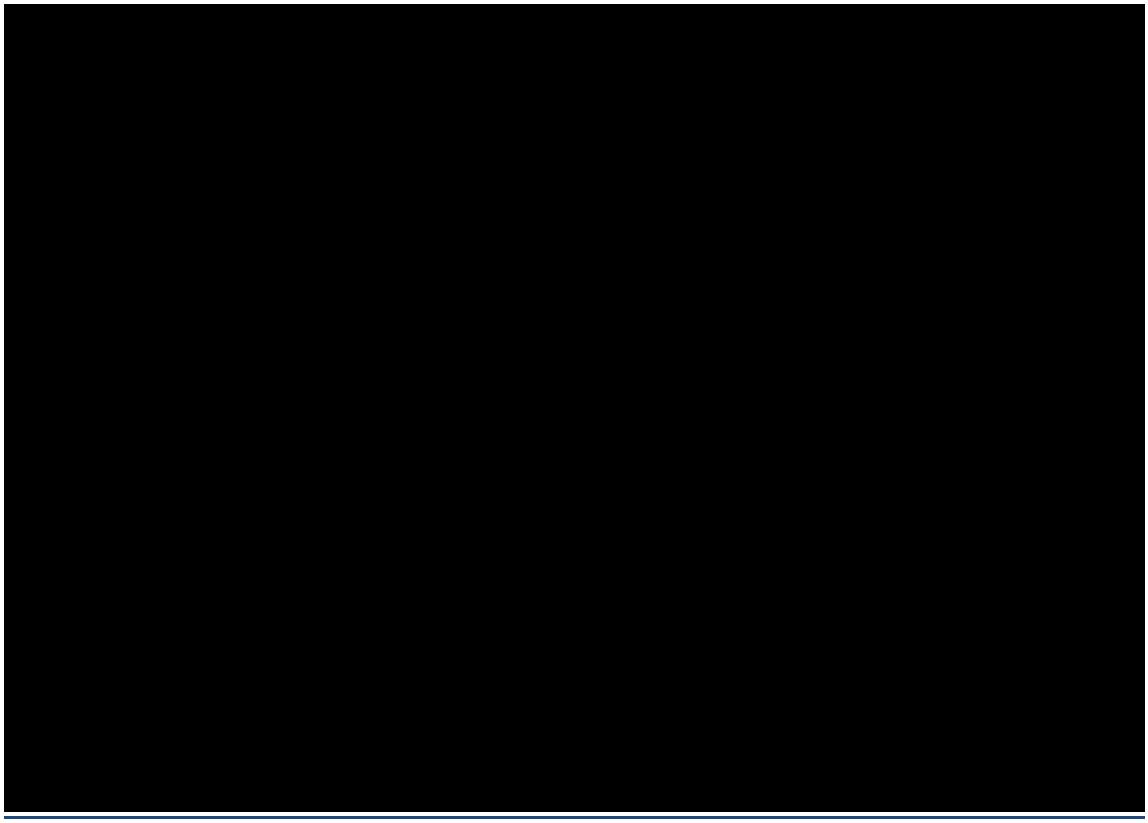
Abbreviations: 3L+: third line and beyond; ATT: average treatment effect among the treated; ECOG: eastern cooperative oncology group; PC: physician's choice (alternatively called UK standard of care [SoC]).

Figure 9: Distribution of propensity scores for the ATT weighted population by treatment; CHRYSALIS and US cohort; 3L+

Abbreviations: 3L+: third line and beyond; ATT: average treatment effect among the treated; PC: physician's choice (alternatively called UK standard of care [SoC]).

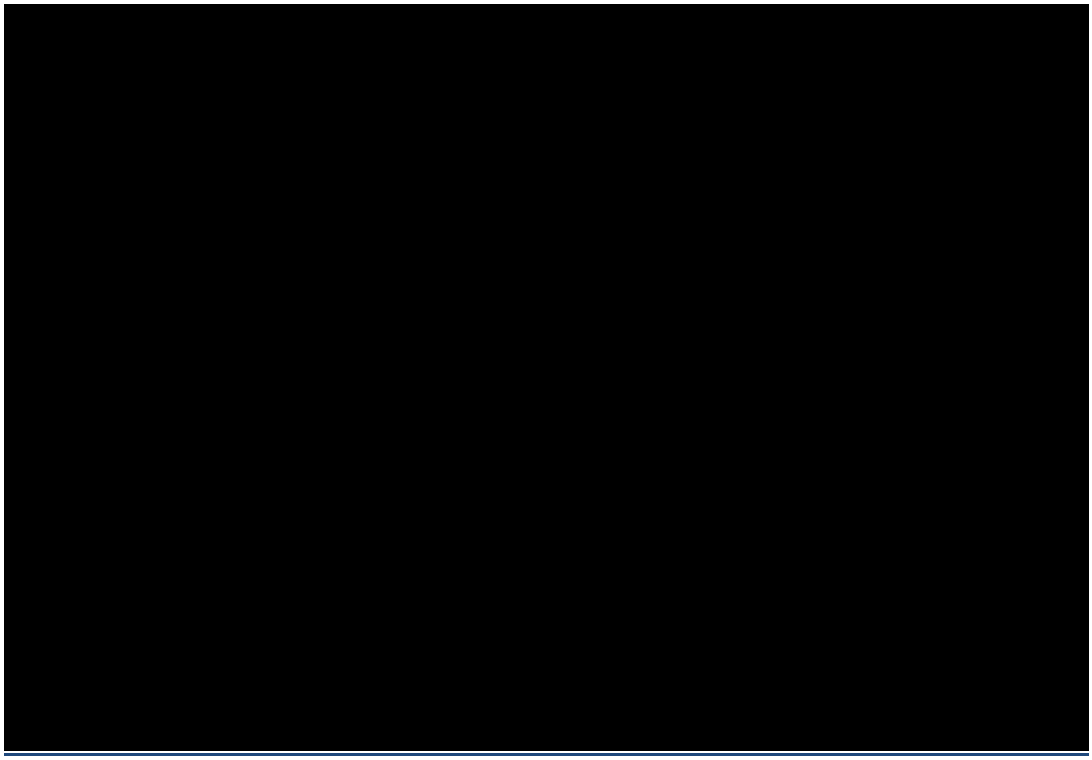
Estimates of the relative treatment effect are generally consistent with the base case. (Figure 10 to Figure 12).

Figure 10: Kaplan-Meier curve for OS for CHRYSALIS versus US cohort at 3L+ (amivantamab vs PC) – IPW (ATT)



Abbreviations: ATT: average treatment effect among the treated; CI: confidence interval OS: overall survival; HR: hazard ratio; IPW: inverse probability weighting; PC: physician's choice; PS: propensity score; RW: real world.

Figure 11: Kaplan-Meier curve for PFS for CHRYSALIS versus US cohort at 3L+ (amivantamab vs PC) – IPW (ATT)



Abbreviations: ATT: average treatment effect among the treated; CI: confidence interval; HR: hazard ratio; INV: investigator assessed; PC: physician's choice; PFS: progression-free survival; PS: propensity score; RW: real world.

Figure 12: Kaplan-Meier curve for TTNT for CHRYSALIS versus US cohort at 3L+ (amivantamab vs PC) – IPW (ATT)

Abbreviations: ATT: average treatment effect among the treated; CI: confidence interval; HR: hazard ratio; IPW: inverse probability weighting; PC: physician's choice; PS: propensity score; RW: real world; TTNT: time-to-next treatment.

A6. In describing the treatment pathway, the CS states that "Taken together the factors discussed in this section support the position that a basket of treatments comprising TKIs, IOs and chemotherapy most accurately reflects what EGFR Exon20ins mutations patients currently receive on the NHS after platinum-based chemotherapy. The basket of treatments (referred to in the submission as UK SoC) is what would be displaced by amivantamab and as such is the most relevant comparator for the submission." TKIs are also listed in the RWE in Table 5. However, the scope and Table 4 do not explicitly mention TKIs other than nintedanib as comparators, and the CS states that "…unlike classical EGFR mutations, Exon20ins have been associated with resistance to EGFR-TKIs". (p.23)

a. Please specify TKIs included in the RWE, and the proportion of patients taking those TKIs.

In the PHE cohort, TKI's were used in 13 % of all treatment lines (afatinib and erlotinib) Table 8.

Despite low patient numbers, this observed TKI use is consistent with what is observed in the US cohort, where 16.5% of treatment lines included TKIs (mainly afatinib and erlotinib as well), Table 9.

Table 8: The TKIs included in the PHE RWE and the proportion of patients being administered them

TKI treatment group	Line of therapy, n (%)
Treatment regimen (detailed)	
Afatanib	[redacted]
Erlotinib	[redacted]

Abbreviations: TKI: tyrosine kinase inhibitor.

In the US RWE, the number of lines of TKI therapy being administered to patients were as follows: [redacted] lines of afatinib; [redacted] lines of osimertinib; [redacted] lines of erlotinib; [redacted] line of afatinib, carboplatin, pemetrexed; [redacted] line of afatinib, paclitaxel; and [redacted] line of erlotinib, pemetrexed (Table 9).

Table 9: The TKI included in the US RWE and the proportion of patients being administered them at each line of therapy

TKI treatment group	Line of therapy, n (%)								
Treatment regimen (detailed)	2	3	4	5	6	7	8	9	Total
Afatinib	[redacted]								
Afatanib, carboplatin, pemetrexed	[redacted]								
Afatanib, padtaxel	[redacted]								
Erlotinib	[redacted]								
Erlotinib, pemetrexed	[redacted]								
Osimertinib	[redacted]								
Subtotal	[redacted]								

Abbreviations: RWE: real-world evidence; TKI: tyrosine kinase inhibitor.

b. Please provide a rationale for the inclusion of TKIs other than nintedanib as comparators.

TKI usage in this patient population is supported by data from real-world studies. [redacted] of the 206 eligible lines of therapy (LOTs) were TKIs, while that figure was [redacted] of the 16 eligible LOTs in the PHE cohort (please note that Table 5 of the company submission has a typographical error; [redacted] LOTs for the US RWE were TKIs and [redacted] were IOs). The PHE data is directly relevant to UK clinical practice as they were derived through the National Cancer Registration and Analysis Service (NCRAS). NCRAS provides linkage to multiple datasets via the Cancer Analysis System (CAS). Identification of patients with the relevant genetic mutation was made possible by linkage to molecular test data from 11 diagnostics laboratories and 132 pathology laboratories across England. The US RWE data is also relevant as the patient and disease characteristics for the cohort are generalisable to UK clinical practice, as detailed in the response to Question A21c.

The inclusion of TKIs in the comparator is also supported by data from a Market Research study conducted by IQVIA on [redacted] oncologists from across the UK. Of the [redacted] second-line plus patients with an EGFR Exon 20 insertion mutation, [redacted] had received a TKI or a regimen including a TKI in the eligible LOT. In addition, the latest NCCN guidelines do highlight that certain Exon20 mutations are exceptions to the general rule that tumours with Exon20ins mutations are associated with lack of response to TKIs.[7]

These data reflect the lack of formal treatment guidelines recommending specific treatments for this patient population and the variability in treatments used by clinicians to manage this difficult to treat condition within the UK.

Further, the final NICE scope refers to “established clinical management without amivantamab” as the submission comparator and provides a non-exhaustive list of the constituent treatments. The compelling RWE described above show that TKIs are used as a treatment option for patients with EGFR Exon20ins mutated NSCLC after platinum-based chemotherapy. A clinical expert consulted during the development of this response document confirmed that the distribution of treatments observed in the two RWE studies was reflective of treatments seen in real life in the UK. [8] As such, Janssen contend that TKIs should be included in the basket of treatments that comprise the relevant comparator for this submission.

c. Please conduct all analyses (Indirect treatment comparisons and cost-effectiveness analyses) excluding TKIs other than nintedanib as comparators.

The indirect treatment comparison results for CHRYSALIS efficacy analysis set excluding TKIs versus US RWE cohort are presented in Table 10, alongside the base case results which were presented in the original submission. Overall, the results are consistent with the base case results, indicating that the base case approach is clinically justified. The comparator US RWE population excluding TKIs (N=[redacted]) and their baseline characteristics relative to the CHRYSALIS cohort are presented in Table 11.

Table 10: Summary of HRs for the base case and scenario analysis excluding TKIs

HR (95% CI)	Base case	Scenario analysis excluding TKIs
PFS BICR	[redacted]	[redacted]
OS	[redacted]	[redacted]
TTNT	[redacted]	[redacted]

Abbreviations: BICR: blinded independent committee review; HR: hazard ratio; OS: overall survival; PFS: progression-free survival; TKI; tyrosine kinase inhibitors; TTNT: time to next treatment.

Table 11: Unadjusted baseline characteristics of the SoC population (N=172) excluding TKIs relative to the CHRYSALIS population

n (%)	Amivantamab (N=114)	US RWE SoC (N=172)	Total (N=286)
Prior lines of treatment			
1	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]
4+	[redacted]	[redacted]	[redacted]
Brain metastasis			
No	[redacted]	[redacted]	[redacted]
Yes	[redacted]	[redacted]	[redacted]
Age			
<60	[redacted]	[redacted]	[redacted]
60- 70	[redacted]	[redacted]	[redacted]
≥70	[redacted]	[redacted]	[redacted]
ECOG			
0	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]
Number of metastatic locations			
1	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]
4+	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]
Haemoglobin			
Normal/High	[redacted]	[redacted]	[redacted]
Low	[redacted]	[redacted]	[redacted]
Gender			
Male	[redacted]	[redacted]	[redacted]
Female	[redacted]	[redacted]	[redacted]
Cancer stage at initial diagnosis			
I	[redacted]	[redacted]	[redacted]
II	[redacted]	[redacted]	[redacted]
IIIA	[redacted]	[redacted]	[redacted]
IIIB/IV	[redacted]	[redacted]	[redacted]

Abbreviations: ECOG: Eastern Cooperative Oncology Group; SoC: standard of care; TKI: tyrosine kinase inhibitor.

The distribution of PS by treatment arms (before weighting) shows good overlap, where the PS model includes all variables included in the base case (Figure 13). ATT weighting leads to good covariate balance and overlap to the weighted PS distribution by treatment. Estimates of the relative treatment effect are consistent with the base case (Figure 14 to Figure 18).

Figure 13: Distribution of propensity scores for the unweighted population; CHRYSALIS and US cohort

Abbreviations: PC: physician's choice.

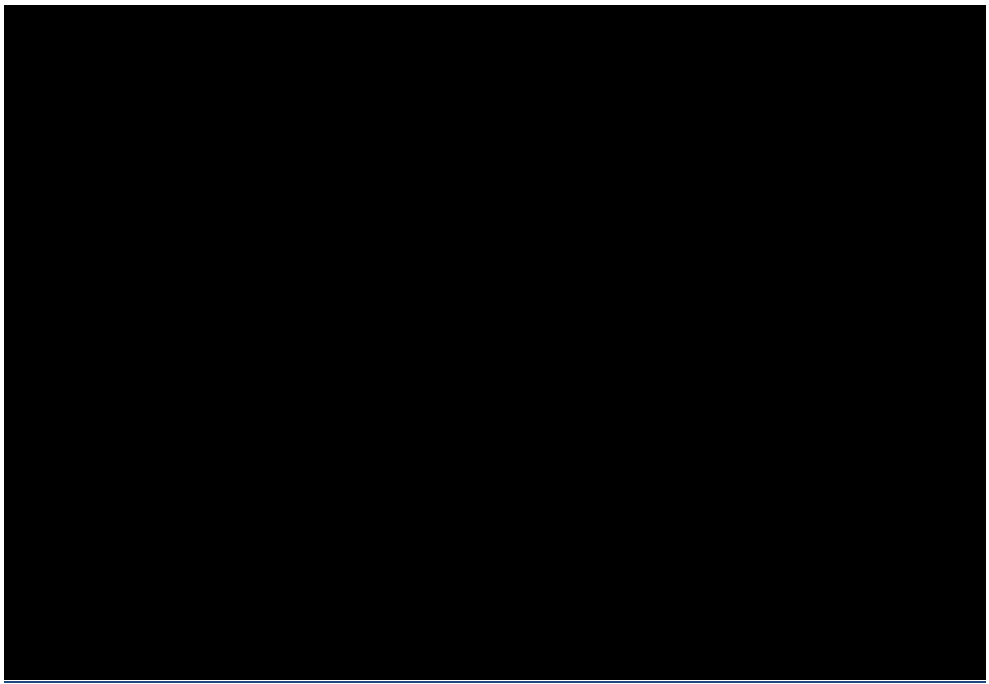
Figure 14: Standardised mean different: ATT (weight PC) for US cohort

Abbreviations: ATT: average treatment effect among the treated; ECOG: eastern cooperative oncology group; PC: physician's choice.

Figure 15: Distribution of ATT propensity scores for the CHRYSALIS and US cohort

Abbreviations: ATT: average treatment effect; PC: physician's choice.

Figure 16: Kaplan-Meier curve for OS for CHRYSALIS versus US cohort, excluding TKIs (amivantamab vs PC) – IPW (ATT)



Abbreviations: ATT: average treatment effect among the treated; CI: confidence interval OS: overall survival; HR: hazard ratio; IPW: inverse probability weighting; PC: physician's choice; PS: propensity score; RW: real world; TKI: tyrosine kinase inhibitor.

Figure 17: Kaplan–Meier curve for PFS for CHRYSALIS versus US cohort, excluding TKIs (amivantamab vs PC) – IPW (ATT)

Abbreviations: ATT: average treatment effect among the treated; CI: confidence interval; HR: hazard ratio; INV: investigator assessed; PC: physician's choice; PFS: progression-free survival; PS: propensity score; RW: real world; TKI: tyrosine kinase inhibitor.

Figure 18: Kaplan-Meier curve for TTNT for CHRYSALIS versus US cohort, excluding TKIs (amivantamab vs PC) – IPW (ATT)

Abbreviations: ATT: average treatment effect among the treated; CI: confidence interval; HR: hazard ratio; IPW: inverse probability weighting; PC: physician's choice; PS: propensity score; RW: real world; TKI: tyrosine kinase inhibitor; TTNT: time-to-next treatment.

A7. The company submission, and the CHRYSALIS protocol list several allowed concomitant medications and disallowed other medications.

a. Please provide a complete list of concomitant medications and the number of patients who took them, and state whether they were all permitted according to the protocol.

A listing of concomitant medicines, all permitted per protocol, and the number of patients who received them is provided in Table 43 in the Appendix to this document.

b. Please comment on the possibility that some of the concomitant medications, including targeted radiotherapy, could have resulted in clinical improvement that is unrelated to the administration of amivantamab.

Section 5.5.2 of the CHRYSLALIS study protocol clearly defines prohibited therapies during study participation, including anti-cancer therapies and radiotherapy to tumour lesions being assessed for response prior to radiographic progression.[9] As such, the administration of these concomitant therapies would not have had an impact on ORR or DOR.

c. According to the company (CHRYSALIS trial protocol), pemetrexed is included as standard of care. Pemetrexed is also listed as a comparator. Can the company please clarify whether pemetrexed is a comparator, or part of standard of care to be used alongside amivantamab, or both?

Data from CHRYSALIS presented in the submission are limited to patients enrolled and treated with amivantamab monotherapy in the dose escalation (Part 1) and dose expansion (Part 2) phases of the clinical trial. Thus, pemetrexed is not included in the intervention technology, and is listed appropriately as an example of treatments comprising "established clinical management without amivantamab" within the scope.

The reference to pemetrexed in the CHRYSALIS protocol relates to a separate cohort which is not relevant for this submission. In one of the three cohorts in the dose escalation phase of the trial, patients were treated with amivantamab in combination with standard of care carboplatin and pemetrexed.

A8. The company cites expert opinion to justify their choice of standard of care. Please provide any additional evidence to support the clinical expert opinion regarding standard of care.

In addition to the clinical expert opinion cited in submission, data from RWE show that there is heterogeneity in the treatments used for this patient population with no definitive standard of care. Table 5 in the submission summarises treatments used in this patient population from the US RWE and PHE datasets where it is clear that no standard of care exists. As noted in

response to Part B of Question A6, Table 5 of the company submission has a typographical error; [redacted] LOTs for the US RWE were TKIs and [redacted] were IOs; this has been corrected below (Table 12).

In response to a question on existing treatment options and utilising the basket of treatments as the relevant comparator, a medical oncologist consulted during the development of this response document stated that:

This is a reasonable approach which takes into account the variability and heterogeneity of the treatments that patients currently receive (TKIs, IOs, non-platinum-based chemotherapy and a small proportion of platinum-based chemotherapy rechallenge). This approach accurately reflects the treatments that would be displaced by amivantamab.[8]

Table 12: RWE on treatments for patients with advanced NSCLC with activating EGFR Exon20ins mutations after failure of platinum-based chemotherapy in the US and England

Treatment class	US RWE[a]	PHE[b]
IO agents	[redacted]	[redacted]
TKIs	[redacted]	[redacted]
Non-platinum chemotherapy	[redacted]	[redacted]
Platinum-based chemotherapy	[redacted]	[redacted]
Other[c]	[redacted]	[redacted]

[a]Based on [redacted] treatment lines from a Janssen RWE Study of US RWE datasets (including Flatiron, COTA, ConcertAI). [b]Based on [redacted] treatment lines from a Janssen RWE Study of PHE data. [c]'Other' includes clinical study drugs, ALK inhibitors, multi-kinase inhibitors, anti-EGFR monoclonal antibodies, mTOR inhibitors, and oestrogen modulators for the US RWE and poziotinib for PHE. Overall, these are considered in this category as they are investigational drugs and drugs not considered to be part of the standard of care (e.g., breast cancer drugs).
Abbreviations: EGFR; epidermal growth factor receptor; IO: immuno-oncology; NSCLC: non-small cell lung cancer; PHE: Public Health England; RWE: real-world evidence; TKI: tyrosine kinase inhibitor

A9. Whereas the final NICE scope lists time to treatment discontinuation as an outcome, the company lists "time to treatment failure" as an outcome. Yet, discontinuation might be initiated for reasons beyond failure.

Please comment on the difference between time to treatment discontinuation and time to treatment failure, and implications of this difference.

In CHRYSALIS, time to treatment failure (TTF) was defined as the time from the first infusion of the study drug to discontinuation of treatment for any reason, including disease progression, treatment toxicity, and death.

As such, TTF is identical to time to treatment discontinuation as it encompasses treatment discontinuation due to "any reason". The full list of reasons for discontinuation captured in the TTF definition (83 [72.8%] events) for the N=114 efficacy population are presented in Table 13.

Table 13. Treatment disposition: Post-platinum patients with EGFR Exon20ins at RP2D efficacy population (N=114)

Event, n (%)	Efficacy population (N=114, 30th March 2021 data cut-off)
Treatment disposition	

Patients ongoing	[redacted]
Discontinued study treatment	[redacted]
Reason for discontinuation	
Progressive disease	[redacted]
AE	[redacted]
Withdrawal by patient	[redacted]
Death	[redacted]
Physician decision	[redacted]

RP2D is defined as 1,050 mg if baseline weight <80 kg and 1,400 mg if baseline weight ≥80 kg.
Abbreviations: AE: adverse event; RP2D: recommended Phase 2 dose.

Systematic literature review (SLR)

A10. Please discuss how the SLR eligibility criteria for population (as documented in Table 7 of Appendix D) is relevant to the NICE final scope population for this submission.

This submission focused on adult patients with locally advanced or metastatic NSCLC with activating EGFR Exon20ins mutations, whose disease has progressed on or after platinum-based chemotherapy. This is in line with the UK marketing authorisation for amivantamab, but is narrower than the population defined in the final scope from NICE as locally advanced or metastatic disease is specified ('Adults with EGFR Exon20ins mutated NSCLC after previous platinum-based chemotherapy'; see Question A3).

Advanced NSCLC refers to both inoperable (unresectable), locally advanced (Stage IIIb/IIIc) and metastatic (Stage IV) disease. To align with this definition, the SLR captured any patients with metastatic or surgically unresectable EGFR Exon20ins mutated NSCLC and specifically included:

- Any patients with Stage IIIB, IIIC or IV disease;
- Any studies where patients were specified as "Stage III" patients, provided Stage IV patients were also included in the study population;
- Any studies where staging was unclear but patients received targeted therapy and were confirmed to harbour EGFR Exon20ins.

This means that any patients with early-stage NSCLC were excluded from the SLR, including any patients with resectable disease, Stage IIIA disease, or patients with unclear disease staging. This ensured that the SLR only included patients with disease staging relevant to the licensed indication.

Whilst disease staging eligibility criteria for the SLR were narrower than that of the final scope, the SLR included a slightly broader population than the NICE scope in terms of treatment experience. Specifically, treatment naïve and chemotherapy naïve patients were included in the SLR; however, studies conducted in patients progressing on or after platinum-based chemotherapy were reported separately in the SLR write-up as these data were considered most relevant to the submission.

A11. Adverse events. Section B.3.3.3 of the CS states: "safety profiles were considered and compared in the context of treatment classes rather than individual treatments, validating this approach."

Please provide adverse events specifically of amivantamab rather than the class of treatments to which amivantamab belongs.

Apologies for the confusion here; the adverse events (AEs) presented in Section B.3.3.3 of the company submission (CS), and included in Table 14 below for completeness, for amivantamab are taken from the CHRYSALIS trial specifically, rather than from a source representing a broader treatment class. The text in the question refers to the approach taken to characterise the safety profile of UK SoC. AE incidence rates for the treatment classes included in the comparator basket were considered and compared in the context of treatment classes rather than individual treatments.

Table 14: Incidence of Grade ≥3 AEs occurring in ≥5% of patients

AE, %	AMI	UK SoC				
		IO agents	EGFR TKIs	Pt-based chemotherapy	Non-Pt-based chemotherapy	Weighted average
Anaemia	[redacted]	0.5	0.0	11.8	3.8	3.2
Diarrhoea[a]	[redacted]	15.4	69.9	11.0	24.4	28.4
Fatigue	[redacted]	1.6	1.3	0.7	3.5	2.1
Febrile neutropenia	[redacted]	0.0	0.0	0.0	9.4	3.4
Neutropenia	[redacted]	0.5	0.0	11.8	14.6	7.2
Neutrophil count decreased	[redacted]	0.0	0.0	0.0	11.1	4.0
Rash	[redacted]	0.0	5.9	0.0	0.0	1.1
Thrombo-cytopaenia	[redacted]	0.0	0.0	7.4	0.0	1.1

[a] Due to its clinical relevance, the incidence of diarrhoea was considered at any grade.
Abbreviations: AE: adverse event; AMI: amivantamab; IO: immuno-oncology; Pt: platinum; SoC: standard of care; TKI: tyrosine kinase inhibitor.
Source: Janssen Data on File: Additional CHRYSALIS data;[10] TA520;[11] Goss *et al.* (2018);[12] Mok *et al.* (2016).[13]

Trials and data analysis

A12. Priority question: In the CHYRSALIS trial, 51.8% of patients in the post-platinum EGFR Exon20ins RP2D expanded efficacy subgroup (also called Cohort D+) were Asian and had 78.9% Stage IV disease at diagnosis.

a. Please provide the number of UK patients in Cohort D+ and present the baseline characteristics of these UK patients.

Given that there were only [redacted] UK patients in Cohort D+ of the CHRYSALIS trial, their baseline demographic characteristics cannot be presented in order to avoid patient identification.

b. Please describe (if available) the breakdown of the characteristics of those participants defined as Asian in the CHRYSALIS study.

The baseline characteristics for patients defined as Asian in the study are presented in Table 15 and Table 16 below.

Table 15: Baseline demographic characteristics for patients defined as Asian in CHRYSALIS; post platinum EGFR Exon20ins RP2D expanded efficacy set (N=114)

Variable	Level / statistic	
Age	N	[redacted]
	Mean (SD)	
	Median	
	Range	
Age (65 years threshold)	N	
	<65	
	≥65	
Age (75 years threshold)	N	
	<75	
	≥75	
Gender	N	
	Male	
	Female	
Race	N	
	Asian	
Ethnicity	N	
	Not Hispanic or Latino	
Weight (kg)	N	
	Mean (SD)	
	Median	
	Range	
Height (cm)	N	
	Mean (SD)	
	Median	
	Range	
BMI (kg/m)	N	
	Mean (SD)	
	Median	
	Range	
BMI category	N	
	Underweight (<18.5)	
	Normal (18.5- <25)	
	Overweight (25- <30)	
	Obese (>30)	

RP2D (recommended phase 2 dose): 1050 mg if baseline weight <80 kg and 1400 mg if baseline weight >= 80 kg. Prior Chemotherapy: subjects whose disease progressed on or after platinum-based chemotherapy. Note: If race was not reported, then that subject is excluded from the race subgroup. Note: N's for each parameter reflect non-missing values.
Abbreviations: BMI: body mass index.

Table 16: Baseline clinical and disease characteristics for patients defined as Asian in CHRYSALIS; post platinum EGFR Exon20ins RP2D expanded efficacy set (N=114)

Variable	Level / statistic	
Initial diagnosis NSCLC subtype	N	[redacted]
	Adenocarcinoma	
	Squamous cell carcinoma	

	Other	[redacted]
Histology grade at initial diagnosis	N	[redacted]
	Moderately differentiated	[redacted]
	Poorly differentiated	[redacted]
	Well differentiated	[redacted]
	Other	[redacted]
Cancer stage at initial diagnosis	N	[redacted]
	IA	[redacted]
	IB	[redacted]
	IIA	[redacted]
	IIB	[redacted]
	IIIA	[redacted]
	IIB	[redacted]
	IV	[redacted]
Bone metastasis	N	[redacted]
	No	[redacted]
	Yes	[redacted]
Liver metastasis	N	[redacted]
	No	[redacted]
	Yes	[redacted]
Brain metastasis	N	[redacted]
	No	[redacted]
	Yes	[redacted]
Lymph node metastasis	N	[redacted]
	No	[redacted]
	Yes	[redacted]
Adrenal gland metastasis	N	[redacted]
	No	[redacted]
	Yes	[redacted]
Other metastasis	N	[redacted]
	No	[redacted]
	Yes	[redacted]
Time from initial diagnosis of cancer to first dose	N	[redacted]
	Mean (SD)	[redacted]
	Median	[redacted]
	Range	[redacted]
Time from metastasis disease diagnosis to first dose	N	[redacted]
	Mean (SD)	[redacted]
	Median	[redacted]
	Range	[redacted]
Prior lines of treatment	N	[redacted]
	Mean (SD)	[redacted]
	Median	[redacted]
	Range	[redacted]
	N	[redacted]

Prior lines of treatment (Category)	1	[redacted]
	2	[redacted]
	3	[redacted]
	4	[redacted]
	5	[redacted]
	6	[redacted]
	7	[redacted]
ECOG	N	[redacted]
	ECOG 0	[redacted]
	ECOG 1+	[redacted]
Smoking history	N	[redacted]
	Yes	[redacted]
	No	[redacted]
Hepatic impairment at baseline	N	[redacted]
	Normal (Total bilirubin ≤ ULN and AST ≤ ULN)	[redacted]
	Mild (Total bilirubin ≤ ULN and AST > ULN) or (ULN < Total bilirubin ≤ 1.5 x ULN)	[redacted]
Renal impairment at baseline	N	[redacted]
	Normal (eGFR: ≥ 90 mL/min/1.73m2)	[redacted]
	Mild (eGFR: 60 to < 90 mL/min/1.73m^2)	[redacted]
	Moderate (eGFR: 30 to < 60 mL/min/1.73m^2)	[redacted]

Abbreviations: ECOG: eastern cooperative oncology group; NSCLC: non-small cell lung cancer.

c. Please discuss the generalisability of the study population (i.e., race and cancer stage) to the UK patient population relevant to this submission. If possible, please supply relevant supporting documents.

Clinical experts consulted by Janssen in the two advisory boards stated that the baseline characteristics of patients recruited to the CHRYSALIS trial broadly reflect those of patients seen in UK clinical practice.

EGFR Exon20ins NSCLC is more prevalent in the Asian population than other races.[14] A clinical expert consulted by Janssen during the development of responses to this question stated that this was the case regardless of geographical location and that the proportion of Asian patients recruited to CHRYSALIS was broadly in line with what is seen in the UK.[8]

Most patients with EGFR Exon20ins NSCLC are Stage IV at initial diagnosis.[15] The clinical expert also stated that the distribution of cancer stage at initial diagnosis seen in CHRYSALIS is reflective of clinical practice in the UK with most patients being Stage IV.[8]

d. Please provide the number of patients comprising Cohort A and Cohort D+.

A breakdown of the patient numbers comprising the efficacy analysis set N=114, patients with EGFR Exon20ins and post platinum chemotherapy who were treated at RP2D is presented in Table 17.

Table 17: Breakdown of patient numbers from CHRYSALIS; post platinum EGFR Exon20ins RP2D expanded efficacy analysis set (N=114)

Part and Cohort	Number of patients (N=114)
Part 1	[redacted]
Part 2 Cohort A	[redacted]
Part 2 Cohort D	[redacted]

Part 1, dose escalation phase and Part 2: dose expansion phase, RP2D: 1,050 mg if baseline weight <80 kg and 1,400 mg if baseline weight ≥80 kg.
Abbreviations: EGFR: epidermal growth factor receptor; RP2D: recommended Phase 2 dose; SD: standard deviation.

A13. Priority question: Despite noting that the CHRYSALIS trial is ongoing, the CS states that "there are currently no plans for additional data availability in the patient populations with EGFR Exon20ins mutations following platinum-based chemotherapy."

Please justify why additional data will not be made available.

Janssen wish to provide an update regarding the expected availability of data from the CHRYSALIS trial. A snapshot look into the data for OS was conducted on 1 March 2022. These OS data could not be processed in time to meet the deadline for the submission of this response document and Janssen expect to submit them during Technical Engagement. Beyond this, we plan to conduct a final database lock and analysis when all patients are fully enrolled across all study cohorts and the study is in close-out. The date for the final database lock is to be determined.

A14. The CS states that in the CHRYSALIS trial, symptomatic treatment, prophylactic medications, and localised limited radiotherapy of short duration for palliative purposes, were permitted concomitant medications.

Did any of the patients in Cohort D+ receive localised radiotherapy for palliative care? If yes:

a. How many patients in Cohort D+ received localised radiotherapy for palliative purposes?

During the on-treatment period, which was the time interval between the first dose of amivantamab and the end of treatment, [redacted] patients in the expanded efficacy analysis set (N=114) received palliative radiotherapy. Out of these [redacted] patients:

- [redacted] patients received palliative radiotherapy beyond the last dose date but before end-of-treatment

- [redacted] patient received on-treatment salvage local therapy
- [redacted] patients received on-treatment primary local therapy

b. What criteria were used to select patients for localised radiotherapy for palliative purposes?

There were no specific criteria for patient selection and the decision was based on investigator judgement.

c. What was the recovery time between receipt of radiotherapy and amivantamab administration?

Among the patients that received on treatment palliative radiotherapy and restarted treatment, treatment with amivantamab was re-started within [redacted] days after the end of radiotherapy.

This does not include the 3 patients who did not restart amivantamab following palliative radiotherapy as mentioned in A15a.

A15. The CS defined the submission safety population (n=153) as "patients with EGFR Exon20ins NSCLC who received prior chemotherapy at the RP2D prior to the 30 March 2021 data cut-off."

Please clarify if this included only patients with EGFR Exon20ins NSCLC whose disease had progressed after platinum-based chemotherapy and had received at least one dose of the study drug, amivantamab.

Janssen can confirm that the safety population (N=153) included only patients with EGFR Exon20ins NSCLC whose disease had progressed after platinum-based chemotherapy and had received at least one dose of the study drug, amivantamab.

A16. A key inclusion/exclusion criterion for patients entering into the CHRYSALIS trial is an ECOG of 0 or 1.

The decision problem does not specify performance status for the population. Please confirm that the evidence included in this submission is for a restricted population (limited to people with ECOG performance status 0 or 1) and does not cover the full population specified in the decision problem.

As noted in response to Question A4, the NICE final scope is slightly broader than the marketing authorisation for amivantamab. As NICE appraise within the marketing authorisation, the marketing authorisation for amivantamab represents the population for the decision problem.

Also as stated in response to Question A4, the CHRYSALIS trial includes patients with an ECOG performance status of 0 or 1; i.e., a narrower population than the marketing authorisation. These data are the data upon which the marketing authorisation was granted and Janssen is requesting access for the licensed indication. That the CHRYSALIS trial, similar to most oncology trials, excludes some patients covered by the marketing authorisation does not mean that this submission is for a restricted population. The decision to treat patients above ECOG 1 is driven by the fitness of the patient and this would be based on the clinical assessment by the oncologist for treatment rather than mandated in the license. In alignment with this, a clinical expert consulted by Janssen during the development of this response document stated that clinicians would consider amivantamab as an option in some patients with ECOG >1.[8]

A17. Regarding the definition of study groups in the relevant clinical effectiveness evidence, section B.2.4 of the CS states that the primary trial population for efficacy results "*included all patients with EGFR Exon20ins NSCLC who received the RP2D prior to 04 June 2020 data cut-off with ≥3 disease assessments as of the 08 October 2020 data cut-off". In section B.2.6 states that "Efficacy results from CHRYSALIS in this submission are presented from for the post-platinum EGFR Exon20ins at RP2D expanded efficacy population (N=114) the most recent data cut-off (30th March 2021)*."

a. Please clarify which date is used for the data cut-off for the efficacy evidence?

The efficacy evidence for the N=114 efficacy population is derived from the 30th of March 2021 data cut-off.

b. The CS also states that the supportive trial population for efficacy is defined by an 8th of June 2020 data cut-off. Can the company confirm that the data cut-off is different than the one used for the primary trial population?

Supportive clinical efficacy data for the N=81 efficacy population is derived from the 8th October 2020 and 30th March 2021 data cut-offs.

A18. Table 17 of the CS report the best overall response according to RECIST v1.1. Please provide additional data on whether the patients were still receiving treatment at the time of the evaluation of best overall response.

Considering INV-assessed best overall response (BOR), all patients for whom a partial response or stable disease was their BOR achieved this whilst receiving treatment. Two patients were recorded as having a non-evaluable BOR since treatment was discontinued before the first disease evaluation.

For BICR-assessed BOR, all patients with a BOR of complete response, partial response or stable disease achieved this whilst receiving treatment. Two patients were recorded as having a non-evaluable BOR since due to discontinuation of treatment before disease evaluation, and one

patient had stable disease on Day 38, but this was not counted given that it did not meet the minimum window of 42 days for standard disease assessment as outlined by the CHRYSALIS trial protocol.

The timing for the assessment of best overall response in relation to treatment is summarised in Table 18 based on BICR and INV assessments.

Table 18: Summary of best overall response based on RECIST v1.1 and timing of assessment; Post-platinum EGFR Exon20ins RP2D expanded efficacy population (N=114)

	Post-platinum Exon20ins RP2D expanded efficacy population (N=114, 30th March 2021 data cut-off)			
	BICR		INV	
BOR	**n (%)**	**Timing of evaluation**	**n (%)**	**Timing of evaluation**
CR	[redacted]	[redacted]	[redacted]	[redacted]
PR	[redacted]	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]	[redacted]
PD	[redacted]	[redacted]	[redacted]	[redacted]
Not evaluable/ unknown	[redacted]	[redacted]	[redacted]	[redacted]
ORR, n (%) [95% CI]	[redacted]		[redacted]	
CBR, n (%) [95% CI]	[redacted]		[redacted]	

CBR is defined as the percentage of patients achieving confirmed complete or partial response, or durable stable disease (duration of at least 11 weeks). RP2D is defined as 1,050 mg if baseline weight <80 kg and 1,400 mg if baseline weight ≥80 kg.
Abbreviations: BOR: best overall response; CBR: clinical benefit rate; CR: complete response; CI: confidence interval; EGFR: epidermal growth factor receptor; ORR: overall response rate; PD: progressed disease; PR: partial response; RP2D: recommended Phase 2 dose; SD: stable disease.

A19. Cohort D+ includes only those patients, from the CHRYSALIS trial, who had tumours with *EGFR* exon20ins mutations.

Please provide details of the method used to identify *EGFR* exon20ins mutations.

Please also provide evidence that this method is comparable (including with respect

to specific mutations detected and limits of detection) with testing currently in place in routine practice in the UK.

In CHRYSALIS, EGFR Exon20ins mutations were assessed by local testing in the respective clinical trial centre locations or centrally using NGS testing for circulating tumour DNA (ctDNA), or tumour tissue where available. For central testing, Guardant was used for ctDNA while ThermoFischer was used for tumour tissue.

The methods used are comparable to those available to patients in the UK as included on the NHS National Genomic Test Directory as part of the services provided by the Genomic Lab Hubs (GLHs

A20. Table 9 of the CS reports summary of demographic baseline characteristics. There are four age categories: <65, ≥65, <75, ≥75. The sum of the four categories comes up to 228 patients which is double of the included population (N=114).

Please provide the corrected population groups.

The values given in Table 9 of the CS are correct as the four age categories are not mutually exclusive. For example, patients can be included in both the <65 age group and the <75 age groups if they are <65 years of age. When examined separately, the sum of both the <65 (n=67) /≥65 (n=47) groups and <75 (n=105)/≥75 (n=9) groups are equal to the included population (N=114).

Indirect treatment comparisons (ITC)

A21. Priority question: To perform their indirect treatment comparison, the company uses the following RWE sources: US RWE (Flatiron, COTA, and ConcertAI) and the PHE cohort.

a. **Please provide the method by which these studies were found, e.g., systematic review.**

The US RWE and the PHE cohort studies were initiated by Janssen with the objective of providing RWE data for patients with EGFR Exon20ins mutations previously treated with platinum-based chemotherapy to inform the external control arm for the CHRYSALIS trial.

b. **Please explain why evidence was limited to these sources.**

As reported in Section D of the Appendices to Document B of the main submission, systematic literature reviews were conducted to identify relevant studies for this population. However, the SLRs did not identify any studies reporting on clinical outcomes for patients with EGFR Exon20ins mutations positive NSCLC previously treated with platinum-based chemotherapy. As a result, individual patient level data derived from the US RWE and PHE studies were used as the only sources for these data for the adjusted comparison analyses.

c. **Please report the demographic characteristics of the patients in the Flatiron, COTA, and ConcertAI databases used in the company's analysis**

and compare them with demographic characteristics of the relevant population in the UK.

The baseline characteristics of patients in the pooled US RWE and PHE cohorts are presented in Section B.2.9 of the CS. Baseline characteristics for patients in each of the three databases (Flatiron, COTA and ConcertAI) are presented in Table 19, Table 20 and Table 21 and for the available characteristics, are similar to those from PHE, indicating generalisability to a UK population.

Furthermore, in an advisory board, UK-based clinical experts emphasised the high degree of alignment in the baseline characteristics of patients included in both of these RWE data sources and the CHRYSALIS trial, with the proportion of patients with brain metastases being the only characteristic highlighted as differing notably between them. As such, although only [redacted] patients from Cohort D+ of the CHRYSALIS trial, plus all of the patients included in the PHE dataset, were recruited from the UK, it is expected that the characteristics and outcomes of the US RWE and PHE databases are generalisable to a UK population as per clinician feedback.

Table 19: Unadjusted baseline characteristics for patients in the Flatiron database

	Amivantamab (N=114)	SoC (N=[redacted])	Total (N=[redacted])
Prior lines of treatment			
1	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]
4+	[redacted]	[redacted]	[redacted]
Brain metastasis			
No	[redacted]	[redacted]	[redacted]
Yes	[redacted]	[redacted]	[redacted]
Age			
<60	[redacted]	[redacted]	[redacted]
60- 70	[redacted]	[redacted]	[redacted]
>=70	[redacted]	[redacted]	[redacted]
ECOG			
0	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]
Number of metastatic locations			
1	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]
4+	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]
Haemoglobin			
Normal/High	[redacted]	[redacted]	[redacted]
Low	[redacted]	[redacted]	[redacted]
Gender			
Male	[redacted]	[redacted]	[redacted]

Female	[redacted]	[redacted]	[redacted]
Cancer stage at initial diagnosis			
I	[redacted]	[redacted]	[redacted]
II	[redacted]	[redacted]	[redacted]
IIIA	[redacted]	[redacted]	[redacted]
IIIB/IV	[redacted]	[redacted]	[redacted]

Abbreviations: ECOG: eastern cooperative oncology group; SoC: standard of care.

Table 20: Unadjusted baseline characteristics for patients in the COTA database

	Amivantamab (N=114)	SoC (N=[redacted])	Total (N=[redacted])
Prior lines of treatment			
1	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]
4+	[redacted]	[redacted]	[redacted]
Brain metastasis			
No	[redacted]	[redacted]	[redacted]
Yes	[redacted]	[redacted]	[redacted]
Age			
<60	[redacted]	[redacted]	[redacted]
60- 70	[redacted]	[redacted]	[redacted]
>=70	[redacted]	[redacted]	[redacted]
ECOG			
0	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]
Number of metastatic locations			
1	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]
4+	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]
Haemoglobin			
Normal/High	[redacted]	[redacted]	[redacted]
Low	[redacted]	[redacted]	[redacted]
Gender			
Male	[redacted]	[redacted]	[redacted]
Female	[redacted]	[redacted]	[redacted]
Cancer stage at initial diagnosis			
I	[redacted]	[redacted]	[redacted]
II	[redacted]	[redacted]	[redacted]
IIIA	[redacted]	[redacted]	[redacted]
IIIB/IV	[redacted]	[redacted]	[redacted]

Abbreviations: ECOG: eastern cooperative oncology group; SoC: standard of care.

Table 21: Unadjusted baseline characteristics of patients in the ConcertAI database

	Amivantamab (N=114)	SoC (N=[redacted])	Total (N=[redacted])
Prior lines of treatment			
1	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]
4+	[redacted]	[redacted]	[redacted]
Brain metastasis			
No	[redacted]	[redacted]	[redacted]
Yes	[redacted]	[redacted]	[redacted]
Age			
<60	[redacted]	[redacted]	[redacted]
60- 70	[redacted]	[redacted]	[redacted]
>=70	[redacted]	[redacted]	[redacted]
ECOG			
0	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]
Number of metastatic locations			
1	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]
4+	[redacted]	[redacted]	[redacted]
Haemoglobin			
Normal/High	[redacted]	[redacted]	[redacted]
Low	[redacted]	[redacted]	[redacted]
Gender			
Male	[redacted]	[redacted]	[redacted]
Female	[redacted]	[redacted]	[redacted]
Cancer stage at initial diagnosis			
I	[redacted]	[redacted]	[redacted]
II	[redacted]	[redacted]	[redacted]
IIIA	[redacted]	[redacted]	[redacted]
IIIB/IV	[redacted]	[redacted]	[redacted]

Abbreviations: ECOG: eastern cooperative oncology group; SoC: standard of care.

d. Please discuss the attempts made to mitigate selection bias associated with the use of a US cohort RWE source and a UK patient RWE source.

Janssen acknowledge that the real-world evidence cohorts are limited to patients with EGFR Exon20ins mutations for whom data are available, and as such, that limitations around geographical coverage may exist; this was highlighted as a possibility by UK clinicians. However, given the rarity of this disease, some degree of selection bias is unavoidable. In order to counteract this as far as possible by minimising any bias at baseline, the US RWE data were adjusted to the CHRYSALIS population in terms of key prognostic variables and baseline

characteristics, as detailed in Section B.2.9 of the CS. In support of this, the UK clinicians confirmed that the characteristics and outcomes broadly aligned with their expectations for the patient population in the UK, and that none of the baseline characteristics showed systematic differences that would confer a substantial selection bias.

A22. Priority question: The submission mentions that covariate adjustment (multivariable regression) and inverse probability weighting (IPW) were explored to conduct the adjusted ITCs.

a. Please refer to NICE TSD 17 and provide justification for the method of adjusting for confounding.

Inverse probability weighting (IPW) and covariate adjustment were considered the most appropriate approaches given the availability of individual patient data (IPD) for both CHRYSALIS and the RWE sources (US and PHE). IPW (specifically the ATT approach) was considered appropriate for the US analysis given the larger sample size and good overlap of the naïve PS distributions by treatment. Moreover, the ATT keeps the CHRYSALIS arm unchanged while weighting only the RWE sources, which provides a counterfactual arm for the observed CHRYSALIS population, which best approaches a randomized trial in the trial population, and allows to use the counterfactual ATT weighted PC curve in the model without any further assumptions. The ATT approach provided good covariate balance, shown, by the overlapping ATT weighted PS distributions by treatment, as well as the Standardized means difference (SMD) plots. Results with alternative IPW approaches (e.g. ATO) and covariate adjustment results were consistent with the ATT results (see Appendix M of CS, Part E of Question A22.e and Part D of Question A22 below for US covariate adjustment results, US ATO results and PHE ATT results, respectively). For PHE, IPW did not achieve a good balance given the small sample size; therefore, covariate adjustment was considered the primary analysis.

b. Please provide details of the method regression analysis and whether there was a single model or separate models for intervention and comparator.

Covariate adjustment based on a multivariable regression (Cox PH regression for time to event endpoints and logistic regression for binary endpoints) was considered as an alternative to PS-based adjustment in adjusting for covariate imbalance and potential confounding. The unbiased treatment effects were estimated using a single, multivariable model, which included all relevant prognostic variables as covariates together with the treatment group indicator. A robust sandwich estimator of the covariance matrix was used, clustered by patient identifier in order to account for potentially multiple lines of treatment per patient in the comparator arm and the weighting of observations; the Breslow method was used for ties.

c. The Average Treatment Effect for the Overlap Population (ATO) approach was mentioned. Please clarify if this was implemented. Whether or not it

was implemented, please provide results for all datasets using this approach.

Table 22 presents a side-by-side comparison of the ATT and ATO results for the US cohort versus CHRYSALIS analysis. The results are highly consistent across both methodologies. This reflects the very similar overlap of the PS distributions by treatment arm as well as the good balance between covariates achieved with the ATT method. Further details on the US ATO results are presented below the table. ATO results have also been presented for PHE below and ATT results for PHE are presented in part d of this question below.

Overall, where IPW was the base case approach, the ATT approach was considered the most appropriate for the base case as it allows you to estimate the relative treatment effect for a counterfactual arm for the CHRYSALIS population and makes the most efficient use of the sample size available (in contrast to methods such as ATO where the population is restricted).

Table 22: Comparison of results following adjustment with ATT and ATO approaches for amivantamab versus the US RWE cohort

	ATT	ATO
PFS		
Amivantamab median; months (95%CI)		
SoC median; months (95%CI)		
Adjusted HR for amivantamab vs SoC (95%CI; p-value)		
OS		
Amivantamab median; months (95%CI)		
SoC median; months (95%CI)		
Adjusted HR for amivantamab vs SoC (95%CI; p-value)		
TTNT		
Amivantamab median; months (95%CI)		
SoC median; months (95%CI)		
Adjusted HR for amivantamab vs SoC (95%CI; p-value)		

Abbreviations: ATT: average treatment effect among the treated; ATO: average treatment effect for the overlap population; CI: confidence interval; HR: hazard ratio; OS: overall survival; SoC: standard-of-care; PFS: progression-free survival; TTNT: time-to-next treatment.

The distribution of ATT PS scores and ATO PS scores by treatment in the US cohort are presented in Figure 19 and Figure 20 respectively. The standardised mean differences after adjusting using the ATT and ATO approaches for the US cohort are presented in Figure 21 and Figure 22, respectively, which shows that the standardised mean differences are typically reduced after weighting and there is a good balance of baseline characteristics between the treatment arms.

Figure 23 shows of the naïve PS scores by treatment in the CHRYSALIS and PHE cohort, which show only a partial overlap. ATO-weighted PS scores, depicted in Figure 24, show that the overlap, while improved, still shows areas of no overlap in the tails, due to the limited sample size available and the initial lack of overlap.

The results of the comparison following ATO adjustment for both the US and PHE cohorts are presented below.

Figure 19: Distribution of ATT propensity scores by treatment; amivantamab vs. US RWE cohort

Abbreviations: ATT: average treatment effect among the treated; PC: physicians choice (alternatively known as UK SoC [standard-of-care]).

Figure 20: Distribution of ATO propensity scores by treatment; amivantamab vs. US RWE cohort

Abbreviations: ATT: average treatment effect for the overlap population; PC: physicians choice (alternatively known as UK SoC [standard-of-care]).

Figure 21: Standardised mean difference plot; unadjusted versus ATT weighted US RWE cohort

Abbreviations: ATT: average treatment effect among the treated.

Figure 22: Standardised mean difference plot; unadjusted versus ATO weighted US cohort

Abbreviations: ATO: average treatment effect for the overlap population.

Figure 23. Distribution of propensity scores by treatment for the unweighted populations; amivantamab vs. PHE RWE cohort

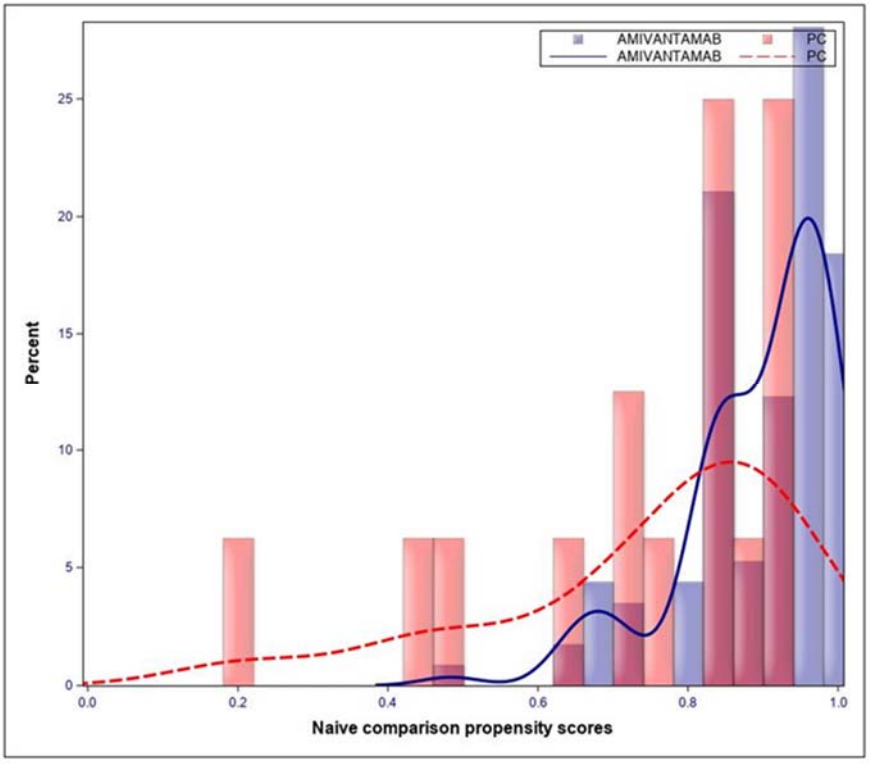
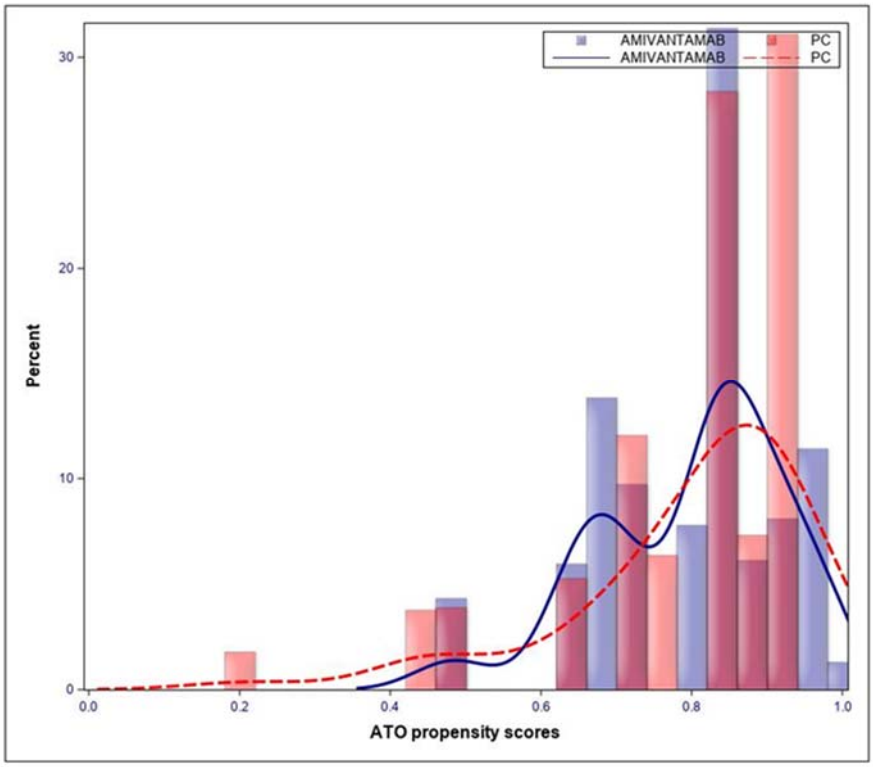


Figure 24. Distribution of ATO propensity scores by treatment; amivantamab vs. PHE RWE cohort



OS-ATO

US cohort (OS)

For the US pooled cohort, the median OS of amivantamab is [redacted] months (95% CI: [redacted]) versus [redacted] months (95% CI: [redacted]) for the ATO-weighted SoC cohort. The adjusted HR for amivantamab versus SoC is [redacted]3 (95% CI: [redacted]) demonstrating that amivantamab is statistically significantly favoured over SoC in terms of OS. The Kaplan-Meier plot of OS for amivantamab versus the ATO-weighted SoC cohort is presented in Figure 25.

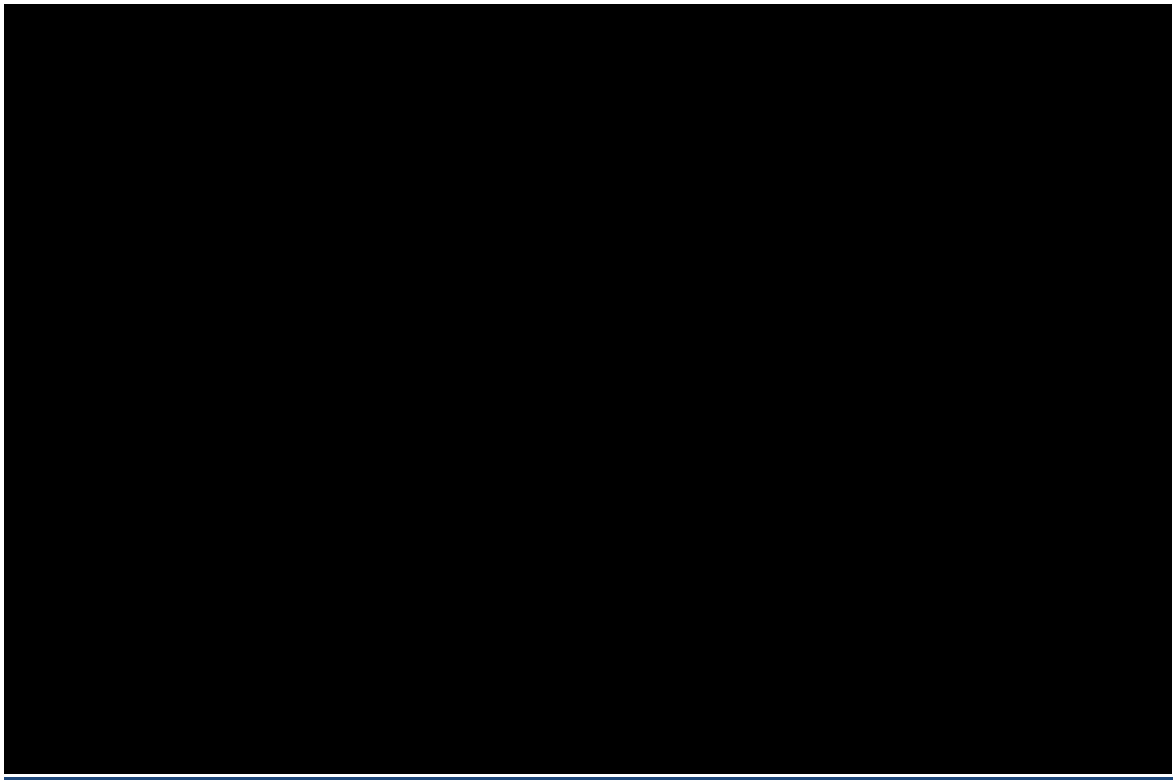
Figure 25: Kaplan-Meier curve for OS for CHRYSALIS versus US RWE cohort (amivantamab vs SoC) – IPW (ATO)

Abbreviations: ATO: average treatment effect for the overlap population; CI: confidence interval OS: overall survival; HR: hazard ratio; IPW: inverse probability weighting; PS: propensity score; RW: real world; SoC: standard of care.

PHE cohort (OS)

For the PHE pooled cohort, the median OS of amivantamab was non evaluable (95% CI:) versus months (95% CI:) for the ATO-weighted SoC cohort. The adjusted HR for amivantamab versus SoC is (95% CI:) demonstrating consistency with the base case results using covariate adjustment. The Kaplan-Meier plot of OS for amivantamab versus the ATO-weighted SoC cohort is presented in Figure 26.

Figure 26: Kaplan-Meier curve for OS for CHRYSALIS versus PHE RWE cohort (amivantamab vs SoC) – IPW (ATO)



Abbreviations: ATO: average treatment effect for the overlap population; CI: confidence interval OS: overall survival; HR: hazard ratio; IPW: inverse probability weighting; PS: propensity score; RW: real world; SoC: standard of care.

PFS – ATO

US cohort (PFS)

The median PFS for amivantamab is [redacted] months (95% CI: [redacted]) versus [redacted] months (95% CI: [redacted]) for the ATO-weighted US RWE cohort. The adjusted HR for amivantamab versus US RWE cohort is [redacted] (95% CI: [redacted]), which is consistent with ATT -based results from the base case. The Kaplan-Meier plot of PFS for amivantamab versus the ATO-weighted SoC cohort is presented in in Figure 27.

Figure 27: Kaplan-Meier curve for PFS for CHRYSALIS versus US RWE cohort (amivantamab vs SoC) – IPW (ATO)

Abbreviations: ATO: average treatment effect for the overlap population; CI: confidence interval; HR: hazard ratio; PC: physician's choice; PFS: progression-free survival; PS: propensity score; RW: real world; SoC: standard of care.

TTNT-ATO

US cohort (TTNT)

The median TTNT of amivantamab is [redacted] months (95% CI: [redacted]) versus [redacted] months (95% CI: [redacted]) for the ATO-weighted SoC cohort. The adjusted HR for amivantamab versus SoC is [redacted] (95% CI: [redacted]) demonstrating that amivantamab is statistically significantly favoured over SoC in terms of TTNT. The Kaplan-Meier plot of TTNT for amivantamab versus the ATO-weighted SoC cohort is presented in Figure 28.

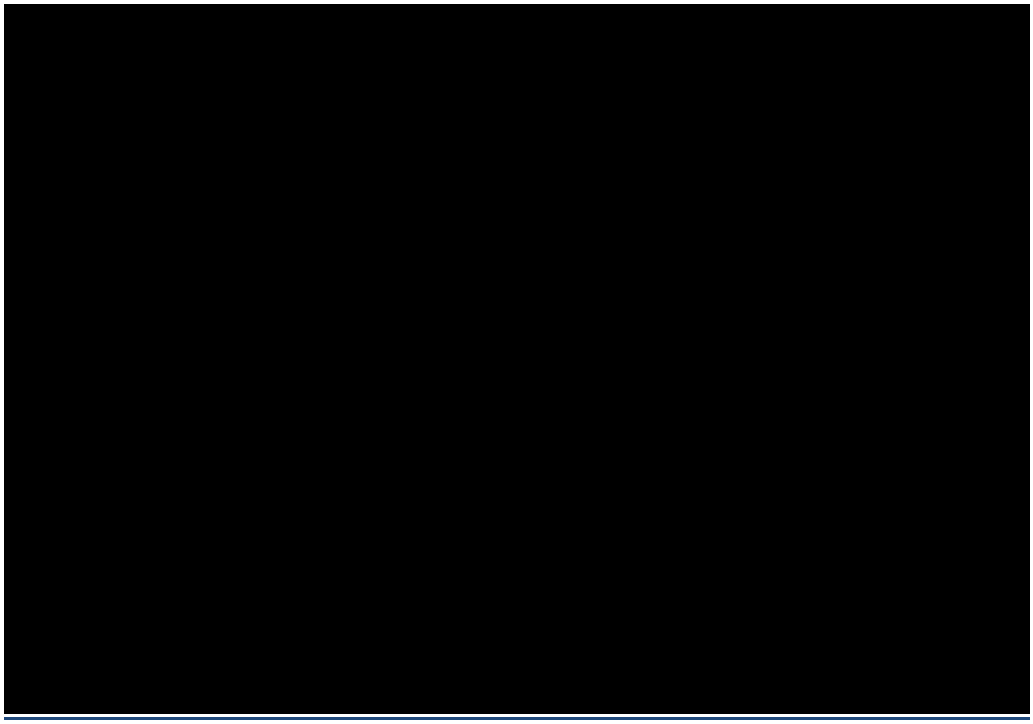
Figure 28: Kaplan-Meier curve for TTNT for CHRYSALIS versus US RWE cohort (amivantamab vs SoC) – IPW (ATO)

Abbreviations: ATO: average treatment effect for the overlap population; CI: confidence interval; HR: hazard ratio; IPW: inverse probability weighting; PS: propensity score; RW: real world; TTNT: time-to-next treatment; SoC: standard of care.

PHE cohort (TTNT)

The median TTNT of amivantamab is [redacted] months (95% CI: [redacted]) versus [redacted] months (95% CI: [redacted]) for the ATO-weighted SoC cohort. The adjusted HR for amivantamab versus SoC is [redacted]8 (95% CI: [redacted]) demonstrating that amivantamab is statistically significantly favoured over SoC in terms of TTNT. The Kaplan-Meier plot of TTNT for amivantamab versus the ATO-weighted SoC cohort is presented in Figure 29.

Figure 29: Kaplan-Meier curve for TTNT for CHRYSALIS versus PHE RWE cohort (amivantamab vs SoC) – IPW (ATO)



Abbreviations: ATO: average treatment effect for the overlap population; CI: confidence interval; HR: hazard ratio; IPW: inverse probability weighting; PS: propensity score; RW: real world; TTNT: time-to-next treatment; SoC: standard of care.

d. The CS states that multivariable regression was used as the main adjustment approach for the PHE database due to the small sample size and that the ATT approach did not achieve good covariate balance. Please provide the results of this analysis.

The reason that the ATT-results were not presented before, is that the sample size for the PHE cohort limits the validity of the approach: ATT weighting requires that the comparator cohort is reweighted in such a way that it reflects (is balanced with) the CHRYSALIS trial population. However, due to the small sample size, some patients in the PHE cohort need to be reweighted to try to obtain such balance versus the CHRYSALIS population.

Results of the ATT approach applied to the PHE database RWE cohort presented below illustrate this. The SMD plot in Figure 30 shows that covariate balance could not be achieved, and the balance even worsens for variables such as liver metastasis, brain metastasis, prior lines of therapy and ECOG.

The ATT-weighted KMs further illustrate the limitations of the ATT-weighting approach here: due to small sample size large weights are assigned to some of the observations, which induces big jumps in the survival curves as illustrated in Figure 31 (OS) to Figure 32 (TTNT). Counterfactual curves can technically be generated but become too unstable and lack clinical face validity.

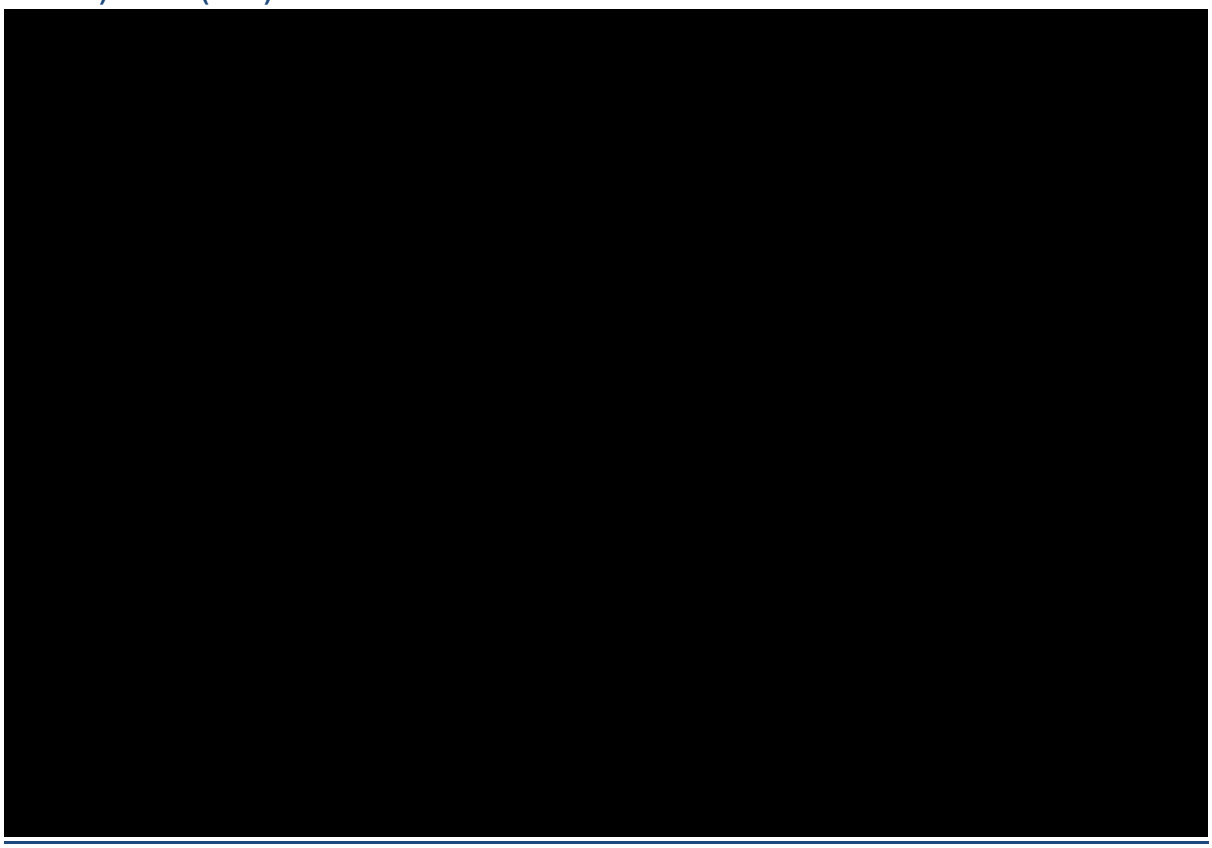
Figure 30: Standardised mean difference plot for the unadjusted versus ATT-weighted PHE cohort

Abbreviations: ATT: average treatment effect among the treated; ECOG: eastern cooperative oncology group; PC: physician's choice.

Figure 31: Kaplan-Meier curve for OS for CHRYSALIS versus PHE cohort (amivantamab vs SoC) – IPW (ATT)

Abbreviations: ATT: average treatment effect among the treated; CI: confidence interval OS: overall survival; HR: hazard ratio; IPW: inverse probability weighting; PC: physician's choice; PS: propensity score; RW: real world.

Figure 32: Kaplan-Meier curve for TTNT for CHRYSALIS versus PHE cohort (amivantamab vs SoC) – IPW (ATT)



Abbreviations: ATT: average treatment effect among the treated; CI: confidence interval; HR: hazard ratio; IPW: inverse probability weighting; PC: physician's choice; PS: propensity score; RW: real world; TTNT: time-to-next treatment.

e. Please explain why matching was not considered as an approach and implement it if deemed feasible.

The IPW ATT method keeps the CHRYSALIS data unchanged, effectively providing a counterfactual control arm for the CHRYSALIS population. The two arms show good overlap of their PS distribution (before weighting; including all variables in the base case in PS model) as well as an improved overlap and good balance between covariates after the ATT-weighting.

As a sensitivity analysis, optimal matching results are presented below (see section B4 for more detailed information and references on the algorithm used).

PS matching estimates the relative treatment effect based on a population restricted to the matched pairs between active and control arms. Pairwise optimal matching of both cohorts allowed only n=84 treatment lines from cohorts to be paired, even with less strict requirement on allowed difference between patients excluding all other patients from the cohort leading to loss of information. Additionally, this matching approach does not improve the balance between covariates compared to the IPW ATT method. Estimates of the relative treatment effect on the matched population are generally consistent with ATT estimates. in Figure 33 to Figure 35

Figure 33: Kaplan-Meier curve for OS for CHRYSALIS versus matched US cohort (amivantamab vs PC)

Abbreviations: ATT: average treatment effect among the treated; CI: confidence interval OS: overall survival; HR: hazard ratio; IPW: inverse probability weighting; PC: physician's choice; PS: propensity score; RW: real world.

Figure 34: Kaplan-Meier curve for PFS for CHRYSALIS versus matched US cohort (amivantamab vs PC)

Abbreviations: ATT: average treatment effect among the treated; CI: confidence interval; HR: hazard ratio; INV: investigator assessed; PC: physician's choice; PFS: progression-free survival; PS: propensity score; RW: real world.

Figure 35: Kaplan-Meier curve for TTNT for CHRYSALIS versus matched US cohort (amivantamab vs PC)

Abbreviations: ATT: average treatment effect among the treated; CI: confidence interval; HR: hazard ratio; IPW: inverse probability weighting; PC: physician's choice; PS: propensity score; RW: real world; TTNT: time-to-next treatment.

A23. In describing the approach to the indirect treatment comparisons, the CS states "Given the larger sample size of the data from the US RWE sources, and clinical expert feedback confirming that the US population and outcomes are generalisable to UK practice, the comparison of amivantamab versus SoC using US RWE was selected as the main analysis to inform the base case of the cost-effectiveness model."

Please provide the information and documentation along with any data that confirms that the US population and outcomes are generalisable to UK practice.

First, findings from literature state that the clinical characteristics of patients with NSCLC and EGFR Exon20ins are similar to patients with common EGFR mutations and are commonly seen in women.[16] This is reflected in the US RWE cohort, where [redacted]% of identified patients were women.

Second, the patient characteristics from the US RWE cohort are comparable to those from the PHE RWE cohort. The unadjusted baseline characteristics for patients in the US RWE cohort are presented in Table 23. These are broadly similar to the baseline characteristics for patients in the PHE cohort, presented in Table 24, which is a patient population directly generalisable to the UK as the data was derived from NCRAS and linked datasets that collect data on all cases of cancer that occur in people living in England.

Third, clinical experts who were consulted in the advisory board whose methodology is described in Janssen's response to Question B21 stated that the presented baseline characteristics were broadly representative of what would be expected in typical UK clinical practice. Additionally, clinicians at the advisory board validated that the outcomes from the US RWE cohort were generalisable to UK clinical practice.[17]

Table 23: Unadjusted baseline characteristics of treatment lines for patients in the US RWE cohort

Characteristic, n (%)	US RWE (N=206)
Prior lines of treatment	
1	
2	
3	
4+	
Age	
<60	
60-70	
>=70	
Brain metastasis	
No	
Yes	
ECOG	
0	
1	
Number of metastatic locations	
1	
2	
3	
4+	
Missing	
Haemoglobin	
Normal/High	
Low	
Gender	
Male	
Female	
Cancer stage at initial diagnosis	
I	
II	
IIIA	
IIIB/IV	

Abbreviations: ECOG PS: Eastern Cooperative Oncology Group performance score.

Table 24: Baseline characteristics of treatment lines for patients in the PHE RWE cohort

Characteristic, n (%)	PHE cohort (N=16)
Prior lines of treatment	
1	
2	
3+	
Brain metastasis	
No	
Yes	
Age	
<=55	
55- <=60	
>60	

ECOG PS			
0		[redacted]	
1			
Liver metastasis			
No		[redacted]	
Yes			
Sex			
Male		[redacted]	
Female			
BMI			
Underweight (<18.5)		[redacted]	
Normal (18.5- <25)			
Overweight (25- <30)			
Obese (>30)			

Abbreviations: BMI: body mass index; ECOG PS: Eastern Cooperative Oncology Group performance score; PHE: Public Health England.

A24. In describing the relevant covariate adjustments that were made (table 23 of the company submission), the company notes that "*Overall, clinical experts agreed that key prognostic factors had been considered in the adjustment*." Further information is pointed to in appendix M where it also states "*potential confounders identified by the SLR were considered irrelevant by the clinical experts so were not included in confounder adjustment. These included neutrophil-lymphocyte ratio, platelet-lymphocyte ratio and leukocyte relevant telomere length. A list of confounders identified as relevant by the SLR, after exclusion based on clinical expert opinion and data availability is presented in Table 57.*"

a. Please provide the documentation along with relevant data which provides the evidence basis for the clinical opinion on included and excluded covariates.

Expert opinion on the identified determinants for OS in patients with metastatic or locally advanced NSCLC with EGFR Exon20ins after failure of platinum-based chemotherapy was obtained by semi-structured single expert interviews. The interview structure was pre-specified in an interview guide, which contained specifically formulated questions while still allowing for optional and narrative elements. The interview guide was developed based on the results from the SLR and designed for one-hour interviews.

As Janssen conducted the validation at the European regional level, five medical experts in the field of EGFR Exon20ins NSCLC in Germany accepted the invitation for the interviews. They were identified via relevant treatment guidelines, scientific publications, and organizations such as the German Respiratory Society. The semi-structured single expert interviews were conducted via teleconference meetings. Each expert was interviewed individually to avoid group dynamics and mutual influencing. The interviews were recorded and transcribed for quality assurance and analysis purposes only if the experts provided their written consent.

Experts were interviewed individually to avoid group dynamics and mutual influencing. Interviews were structured in three differentiated parts. First, at the start of the interview and prior to the

semi-structured interview, experts were asked to compile a list, based on their expertise, of determinants that could act as potential confounders of treatment effects for OS and HRQoL independently in the target population. If applicable, listed potential confounders were added during the semi-structured interview to those already identified by the SLR. Experts were asked to estimate the effect direction, certainty (ordinal scale), and size (ordinal scale) for each listed variable. Categories for the effect certainty and size were prespecified in the interview guide based on the SLR findings. If applicable, experts defined whether, in their opinion, potential confounders should be used as continuous or categorical variables (and in the latter case, to advise reasonable categories) if introduced in statistical adjusting models. Second, any potential confounders identified in the SLR but not listed in the first part of the interviews were shown to the experts and evaluated the same way. Third, experts were asked to indicate relationships between the potential confounders rated as relevant.

After completion of the interviews, potential confounders were assigned a ranking score. Additionally, for each potential confounder, the number of experts who listed it on their own in the first part of the interview and the categories recommended by the experts were analysed. The statements of the experts regarding the relationships among the potential confounders were summarized qualitatively.

b. Please provide the documentation along with data which details the provision of that advice as evidence based expert clinical opinion.

A detailed description of the methods and results for the SLR and clinical expert validation of identified prognostic determinants of OS is presented in the reference document entitled Janssen DoF prognostic SLR (2022).[18]

Section B: Section B: Clarification on cost-effectiveness data

Model structure

B1. The company applied a cycle length of four weeks in its economic model without half-cycle correction to account for the fact that events and transitions can occur at any point during the cycle, not necessarily at the start or end of each cycle.

a. Please provide justification for not applying a half-cycle correction to the economic model.

b. Please provide an updated economic model including a half-cycle correction.

A half-cycle correction has already been applied to the economic model; please see the “Model Calcs” sheet, Columns AH to AS. As such, no updates to the model are required.

B2. The NICE Decision Support Unit (DSU) technical support document (TSD) 19 recommended the use of state transition models (STMs) alongside partitioned survival models (PSMs) to verify the plausibility of PSM extrapolations and to explore key clinical uncertainties in the extrapolation period.

a. Please justify the use of a partitioned survival approach given the issues highlighted in NICE DSU TSD 19, particularly regarding the extrapolation of PFS and OS while assuming structural independence between these endpoints.

Janssen acknowledge that strong justification of the chosen model structure is paramount. Therefore, both the partitioned survival model (PSM) and state transition model (STM; of which Markov is a common type) approaches have been compared and contrasted, considering previous NICE technology appraisals, the guidance from TSD19 and published literature.[19-21]

A potential limitation of a PSM is that they may over- or under-estimate long-term outcomes if the hazard rate changes over time such that the hazard rate calculated from the observed period does not accurately reflect the expected hazard ratio in the extrapolated period. However, estimates from a PSM and Markov models typically converge as the data mature and the data informing the PSM in this appraisal, which are derived from the CHRYSALIS trial, are relatively mature. As such, the risk of long-term over- or under-estimation of outcomes with a PSM, and thus the potential benefit of a STM versus a PSM in this regard, is limited. Another possible advantage of choosing a STM approach such as a Markov model would be to include additional health states either to capture the disease course in more detail, or to allow for more complex modelling of subsequent therapies. However, it is not clear that additional health states over and above the 3-state 'progression-free, post-progression, dead' PSM structure are required to capture the disease course of advanced NSCLC, or that subsequent therapies need to be captured in greater detail.

The findings of a review of prior literature on the use of a PSM approach versus a STM approach for oncology treatments supports that the choice of approach has a limited impact: the use of either model was observed to produce similar estimates for some outcomes and non-trivial differences for others, there was little evidence to support the use of one model over another. Similarly, an assessment of the impact of model structure (a PSM compared to two STMs) on long-term survival outcomes for nivolumab and everolimus in renal cell carcinoma found that all models provided a reasonable fit to observed OS data but estimates of difference in mean survival differed greatly, and a comparison of modelling approaches for the estimation and extrapolation of survival outcomes for nivolumab for the treatment of second-line advanced squamous NSCLC found no significant differences in estimates of expected costs, outcomes, and incremental cost-utility between a PSM and a Markov model.[22, 23] In contrast, an assessment of HTAs in SCLC found that both the PSM and Markov model approaches produced fairly accurate replications of observed survival outcomes, but the PSM approach produced marginally more accurate.[24]

The marginal preference for a PSM approach is reflected in prior NSCLC NICE submissions, where there is clear precedent for a PSM, and no strong criticisms from ERGs have been

received on this approach. This is expected as PSMs make for intuitively appealing models that replicate within-study data with relative ease given that there is direct correspondence between reported time-to-event endpoints (PFS and OS) and the survival functions. Of the two submissions utilising a STM approach in NSCLC, both utilised a Markov model: in TA402, no clear justification for the Markov approach was provided, but in TA181, the ERG had significant concerns with the implementation of the Markov structure, as it failed to accurately replicate the trial data within the period of follow-up. This may be a disadvantage of using an STM approach as there would be an increased risk that the model will not accurately represent outcomes within the period covered by the clinical evidence, partly due to additional strong assumptions that may be required (for example, a constant probability of death in the progressed disease health state). Additionally, prior submissions (such as TA531 and TA643) have used simple approaches to model subsequent therapies that are compatible with a PSM structure and that have not drawn criticism from the ERG.

Overall, based on the validity of the outcomes provided by a PSM, Janssen maintain that the PSM approach presented in the CS is the most appropriate approach for this submission. Therefore, an STM has not been presented.

b. If deemed necessary, please use state transition modelling to assist in verifying the plausibility of the PSM extrapolations and to address uncertainties in the extrapolation period (NICE DSU TSD 19, recommendation 11).

As discussed in answer to Part A of Question B2 above, Janssen do not consider that recommendation 11 of NICE DSU TSD 19, which discusses the use of a STM to verify the plausibility of an PSM or address uncertainties in the extrapolation period, to be relevant to this appraisal given that the PSM provides a robust reflection of clinical reality and is in alignment with prior NICE appraisals in NSCLC. As such, a STM has not been presented.

Intervention and comparator

B3. Priority question: The company stated in the CS that "due to considerable heterogeneity in treatments due to lack of specifically recommended treatments in the UK, evidence from real-world data sources of variability in treatments received and clinical expert feedback, amivantamab was compared to a basket of treatments termed UK SoC within the model". This basket of treatments includes immune-oncology agents, EGFR TKIs and platinum and non-platinum based chemotherapies.

a. Given that patients in the current submission progressed on or after platinum-based chemotherapy in an earlier line of treatment, please justify whether platinum-based chemotherapies should be considered as relevant comparators for amivantamab.

Despite all patients having progressed on or after platinum-based chemotherapy, RWE confirms that a small subset of these patients would be retreated with platinum-based chemotherapy: [redacted] of patients in the US cohort and [redacted] of patients in the PHE cohort were retreated with platinum-based chemotherapy. UK-based clinicians confirmed that these proportions are in alignment with their clinical expectations for patients receiving treatment in current UK clinical practice, further justifying the inclusion of platinum-based chemotherapy as of the relevant comparator for amivantamab.[17]

b. Please justify why EGFR TKIs osimertinib and afatinib were included in the comparator basket of treatments given that they are not explicitly listed as established clinical management without amivantamab by NICE in its final scope.

Janssen note that the final NICE scope defines the comparators as "established clinical management without amivantamab" and provides a non-exhaustive list of examples of treatments that may be included within this. Therefore, there is no contradiction between the scope and submission; the submission simply refines the scope.

Evidence from real world cohorts including the PHE data show that TKIs are used in this patient population as part of established clinical management without amivantamab, thus supporting their inclusion in the basket of treatments. Afatinib was included in the comparator basket of treatments following clinician feedback that this was the TKI most likely to be used in UK clinical practice.[17] To clarify, as per Section B.3.2.3 of the CS, in the base case, the cost of the TKI treatment class was based on afatinib; only in a scenario analysis was the impact on the ICER of basing the cost of TKIs on osimertinib assessed. This scenario analysis was conducted as osimertinib is recommended by NICE for patients with EGFR-mutated NSCLC (albeit not in the Exon20ins mutation population specifically).[25]

c. Please provide a justification for using the treatment mix as observed in the real-world data as comparator, i.e. does this reflect UK clinical practice in terms of:

a. Treatment mix of primary treatments

b. Treatment mix of subsequent treatments

c. Population

d. Effectiveness of usual care

Treatment mix of primary and subsequent treatments

As discussed in Section B.1.3.2.1 of the CS, the disease rarity coupled with the lack of UK-specific treatment guidelines means that there is no established SoC for patients with EGFR Exon20ins mutated NSCLC in the UK. In the absence of a SoC therapy or therapies for patients with EGFR Exon20ins mutated NSCLC in the UK, it is not possible to robustly identify which

specific treatments would be displaced at the margin upon the introduction of amivantamab and therefore assuming a basket comparator is the most appropriate approach. Clinical experts confirmed this, highlighting that clinical practice varies between centres and clinicians based on factors such as previous treatments received and patient or clinician preferences.[17] As such, deriving the SoC treatment mixes for primary and subsequent treatments from real-world data permits capture of the heterogeneity of treatment currently experienced by patients in typical UK clinical practice.

Primary treatment mix data are available from two RWE sources, PHE and US databases (Flatiron, COTA and ConcertAI), as presented in Table 5 of the CS. UK-based clinicians consulted by Janssen confirmed that the treatment class proportions derived from the US RWE data source are broadly reflective of typical UK clinical practice. Although the PHE data did not inform the base case analysis due to the limited sample size (based on [redacted] treatment lines), the broad alignment between the two datasets and the derivation of these data from patients in England specifically strongly supports the generalisibility of the US RWE data to the UK.

Data regarding subsequent treatments received by patients in the PHE cohort are not available. However, robust US RWE subsequent treatment data are available, and clinicians further confirmed that these proportions are in alignment with their expectations for patients in the UK, including that approximately [redacted]% of patients would switch to receiving no active treatment at this point. In addition, a scenario was presented in Section B.3.8.3 of the CS where subsequent treatments for amivantamab were based on data from the CHRYSALIS trial and this had a minimal impact on the ICER, showing that this is not a key driver of model results.

Overall, the use of the UK SoC basket comparator is also the most appropriate approach not only given the lack of clarity on the treatments that would be displaced at the margin, but also due to the fact that providing subgroup analyses by treatment received based on the RWE data available for SoC is not a robust approach due to the reductions in sample size associated with this. Therefore, comparing amivantamab to individual treatments as part of an incremental analysis would introduce a high degree of uncertainty in the relative efficacy estimates, and thus would not provide a solid basis for decision making.

Population

The RWE datasets are both derived from adult patients with EGFR mutated Exon20ins NSCLC at second-line and beyond and are thus in alignment with the population of interest in this appraisal. The naïve and adjusted baseline characteristics for the US RWE and PHE datasets presented in Section B.2.9 of the CS were validated by UK clinicians as being in alignment with patients in the UK who would be eligible to receive amivantamab.

Results for subgroup analyses of 2L and 3L+ patients have been presented in response to Question A5 above. Given the consistency of these results with the full population (albeit taking into account the limitations of comparing a restricted population to the full popualtion and that these subgroup analyses are based on smaller sample sizes), the full patient population considered for amivantamab presented within the CS (i.e. those patients at 2L+) is considered the most appropriate approach. This is because it is reflective of the positioning in UK practice, given the licensed indication is for the treatment of adult patients with locally advanced or metastatic NSCLC with activating EGFR Exon20ins mutations, whose disease progressed on or after platinum-based chemotherapy (rather than stating a particular treatment line).

Effectiveness of usual care

As discussed further in response to Part G of this question below, use of a mix of treatments derived from RWE to inform SoC means that SoC effectiveness is modelled as the average clinical efficacy of these treatments. Given that these treatment mixes are representative of the treatments that are received by patients in typical UK clinical practice, as outlined above, it follows that the effectiveness of SoC implemented within the model is reflective of the average clinical efficacy that can be expected by patients with EGFR Exon20ins mutated NSCLC in UK clinical practice.

Summary

In summary, the US RWE provides a highly valuable and robust source to inform SoC comparator efficacy. Clinician feedback and available data from a cohort of UK-based patients support that the US data are broadly generalisable to the UK in terms of treatments received and their efficacy. As such, Janssen maintain that the proposed approach is reflective of the outcomes expected in typical UK clinical practice and makes best use of the data available which are scarce given the rarity of the indication of interest.

d. Please provide a justification for not separately considering patients with PD-L1-positive tumours as nivolumab and pembrolizumab are only applicable for these patients.

Janssen acknowledge that nivolumab and pembrolizumab are only recommended for use in patients with PD-L1 positive tumours.[4, 26] However, as discussed further below in response to Part E of this question, the limitations of both the CHRYSALIS and RWE data mean that it is not possible for scenario analyses considering PD-L1 subgroups to be performed. In addition, the current approach, which considers a basket of several treatments for all patients regardless of PD-L1 tumour status, appropriately reflects clinical reality for the following reasons:

- The comparator basket comprises a mixture of treatments including nivolumab and pembrolizumab. As such, patients with PD-L1 positive tumours could receive nivolumab and pembrolizumab while patients with PD-L1 negative tumours could receive alternative options. Similarly, atezolizumab (an immune-oncology [IO] agent), would be a relevant comparator regardless of PD-L1 status.
- Feedback received from a UK clinical advisory board was that patients with tumours expressing high levels of PD-L1 would be likely to receive pembrolizumab with pemetrexed and platinum-based chemotherapy at first-line.[17] In line with their feedback that patients who failed on a treatment class would not typically receive the same treatment class as a subsequent therapy, patients with PD-L1 positive tumours would be unlikely to receive pembrolizumab at a later line. As such, the same comparators would apply for both PD-L1 positive and negative patients.

As such, Janssen maintain that the current approach is both necessary based on data limitations and appropriately reflective of the heterogeneity of treatments received by patients in the UK.

e. Please provide an updated economic model and scenario analyses specifically considering PD-L1-positive tumours also including nivolumab and pembrolizumab as comparators in the economic model.

At the request of the ERG, Janssen have investigated the plausibility of conducting subgroup analyses for patients with PD-L1 positive tumours only. Unfortunately, within the US RWE data sources, only [redacted] lines of therapy corresponded to patients who tested PD-L1 positive, and of these, only [redacted] consisted of nivolumab or pembrolizumab. Within the CHRYSALIS data set, only [redacted] patients in the trial had their PD-L1 status recorded. As such, it is not feasible to conduct scenario analyses considering this subgroup and therefore associated results cannot be incorporated into the economic model.

f. Please provide an updated economic model that enables a scenario analysis excluding platinum-based chemotherapies and EGFR TKIs (i.e., those that are not in the final scope) from the pooled basket of comparators and from any potential analysis looking at separate comparators (see questions B3i below).

Due to a combination of the lack of recommended treatments, the observed variability of the distribution of treatments used in clinical practice, and the fact that the decision on treatment selection is predicated on clinical judgement and made on a case-by-case basis, there is no robust way to define standard of care. In this situation there are no methods available to inform decision making at the margin, when the relevant comparator is a basket of treatments that reflects the observed, and clinical-expert-confirmed variability of treatments.

In addition, as described above, the US RWE cohort provides a robust source of information regarding the heterogenous mix of treatments received by patients with EGFR Exon20ins mutated NSCLC and their efficacy. Since these data evidence that platinum-based chemotherapies and EGFR TKIs are used for these patients in real-world clinical practice, and that UK-based clinicians have validated that the comparator basket treatment mix is representative of the treatment classes patients would typically receive in UK clinical practice, it is not appropriate to exclude these two treatment classes from the economic model. In addition, the rarity of the disease coupled with the heterogenous mix of treatments patients receive means that patient numbers would be reduced if these two treatment classes were removed from the comparator arm, thus introducing considerable uncertainty. As such, this scenario analysis has not been presented.

g. Please provide a justification for assuming equal effectiveness for the individual treatments in the comparator basket and elaborate on how this could potentially bias the results of the analyses.

Clinical efficacy of the UK SoC basket comparator is informed by data from pooled real-world evidence (RWE) data from US databases: Flatiron, COTA and ConcertAI. As such, these efficacy data reflect the average clinical efficacy across the treatments currently used, collectively referred to as the standard of care (SoC) comparator. Whilst there is a single efficacy assumed for SoC overall, this is based on the efficacy of the constituent treatments included in the basket, and therefore an assumption of equal efficacy for individual treatments is not made.

As described in Section B.3.2.3 of the CS, the use of a basket comparator was selected in order to reflect the considerable heterogeneity of treatments currently received by patients. Janssen acknowledge that this approach could introduce bias to the analyses if the basket of comparators

differed considerably to the treatment patients in current typical UK practice would receive. However, feedback received from UK-based clinicians at a Janssen-led advisory board was that the treatment classes received by patients in the pooled US RWE study, as well as the outcomes seen from the analyses, were broadly aligned with those which would be received by patients in the UK. This is supported by RWE data sourced from the UK (PHE dataset, presented in Table 5 of the CS), which show that the treatment class proportions received by patients with EGFR Exon20ins mutated NSCLC in the UK in 2016, 2018 and 2020 following failure of platinum-based chemotherapy are broadly aligned with the proportions observed in the US RWE.

Therefore, Janssen consider that the comparator basket reflects current UK clinical practice, and the average efficacy results patients can expect to receive from it, as closely as is possible given the paucity of data available in this very rare indication.

h. Even when assuming equal effectiveness for the treatments included within usual care, these treatments can be considered separately differentiating based on costs (which are likely not equal). Please provide a justification for not including all comparators mentioned in the final scope, as comparators in the economic model.

As described above, an assumption of equal efficacy for individual treatments in the comparator basket is not made since the efficacy data that inform the model reflect the average clinical efficacy across all of the currently used treatments. Similarly, the model implements the average cost of the treatments included in the comparator arm weighed by the treatment class distributions observed in the US RWE cohort. As such, cost differentiation between comparators is reflected in the current approach.

Regarding the treatments included within the basket comparator, the relevant comparator in this appraisal as per the final NICE scope is “established clinical management”. As outlined above and confirmed by UK clinicians, there is no established standard of care for EGFR Exon20ins mutated NSCLC patients, with country-specific guidelines lacking and a paucity of available data due to the rarity of the condition. The heterogenous nature of treatments received by patients in clinical practice, which is supported by data from RWE sources, supports the view that the basket of treatments is the relevant comparator. In this situation there are no methods available to inform decision making at the margin, when the relevant comparator is a basket of treatments that reflects the observed, and clinical-expert-confirmed variability of treatments.

i. Please provide the results of a fully incremental analysis (and updated economic model used for this analysis) with all comparators listed in the final scope as comparators modelled separately.

a. Including analyses assuming equal effectiveness but treatment specific costs.

b. Including analyses assuming both treatment specific effectiveness and costs.

It is not possible to conduct a full incremental analysis given the lack of methodological basis when the relevant comparator can only be accurately reflected as a basket of treatments. Due to a combination of the lack of recommended treatments, the observed variability of the distribution of treatments used in clinical practice, and the fact that the decision on treatment selection is predicated on clinical judgement and made on a case-by-case basis, there is no robust way to define standard of care. It is thus not feasible to identify any single treatment that would be displaced by amivantamab at the margin.

As described in Part H above, comparison between amivantamab and individual treatments is inappropriate and would not provide estimates suitable for decision-making given that the lack of definition of SoC. In addition, the small sample sizes of patients receiving individual treatments in the RWE sources informing the efficacy of UK SoC. It is also not relevant to compare to individual treatments given the heterogeneous nature of treatment patterns in UK practice, as a basket of therapies is a true representation of what would be displaced should amivantamab be recommended by NICE.

Therefore, a fully incremental analysis with all individual components of "established clinical management without amivantamab" listed in the final scope modelled separately has not been included in the economic model.

Treatment effectiveness

B4. Priority question. Clinical inputs informing OS and PFS for intervention and comparator were derived from the following RWE sources: Flatiron, COTA, and ConcertAI. The comparative effectiveness of amivantamab vs SoC was explored via covariate adjustment and inverse probability weighting (IPW). Alternative approaches to address confounding in the indirect treatment comparison are possible, and the ERG would like to examine the potential uncertainty introduced by different methodological choices. In line with Question A.24:

a. **Please provide an updated economic model that enables a scenario analysis that uses matching instead of IPW.**

At the request of the ERG, Janssen have performed a propensity score matching analysis in which SoC patients from the US RWE and those from CHRYSALIS have been matched to estimate the relative efficacy of AMI versus UK SoC. The results of a scenario analysis in which the output of this analysis has been included in the cost-effectiveness model is presented in Table 25. These results indicate that the use of matching, rather than IPW, increases the base case ICER marginally but it remains under the willingness-to-pay (WTP) threshold of £50,000.

However, in this analysis, patients in the US RWE cohort whose logit(propensity score) value were within a distance of 0.2 standard deviations of all pooled logit(propensity scores) to the logit(propensity score) of the patients in CHRYSALIS trial were matched. An optimal matching algorithm, which selected all matches simultaneously and without replacement to minimise the total absolute difference in propensity score across all matches, was used.[27-29] As such, Janssen

wish to highlight that the presented analyses utilise only 84 patients from CHRYSALIS, as only 84 patients could be matched to the US RWE cohort. This is in comparison to the larger and more robust sample size of N=114 amivantamab-treated patients and the N=206 patients from the US RWE cohort in the presented base case, which induces additional uncertainty. Given this, the matching analysis can be considered to provide estimates of a relative treatment effect for only a subset of the CHRYSALIS cohort. Furthermore, as presented in Table 26, which shows the uncertainty in incremental costs and incremental benefits as estimated by coefficient of variation (ratio of standard deviation to average) in the base case and matched PSAs, the approach of using results from matched cohorts increases the uncertainty associated with this analysis.

Therefore, the matching approach is associated with a higher degree of uncertainty as compared with the submitted base case approach and is consequently less suitable for decision-making.

Table 25: Scenario analysis results – matched data (deterministic)

#	Scenario analysis	LIST PRICE			WITH PAS		
		Incr. costs (£)	Incr. QALYs	ICER (£/QALY)	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)
Base case		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£39,764
1	**Matched data (rather than IPW)**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£45,092

Abbreviations: ICER: incremental cost-effectiveness ratio; LY: life years; Incr: incremental; IPW: inverse probability weighting; PAS: patient access scheme; QALYs: quality-adjusted life years; SoC: standard of care.

Table 26: Incremental costs and QALYs in the base case and matched PSA

	Incremental costs		Incremental QALYs	
	Base case PSA	Matched PSA	Base case PSA	Matched PSA
Average	[redacted]	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]	[redacted]
Coefficient of variation	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: PSA: probabilistic sensitivity analysis; QALY: quality-adjusted life year; SD: standard deviation.

b. Please provide an updated economic model that enables a scenario analysis with another alternative method (e.g. regression adjustment).

As discussed above, an updated economic model is provided in which the matching approach can be implemented, but it increases uncertainty in the analysis as compared with the base case approach. Given that Janssen consider the submitted base case approach to be the most robust and suitable for use, the model has not been updated to include another alternative method.

B5. Priority question. It is unclear whether the estimation of parametric survival models is fully consistent with reported guidance from NICE DSU TSD 14 and 21 on (flexible methods for) survival analyses. Please provide, for OS and PFS separately for the intervention and comparator:

a. Tables with the numbers of patients at risk, per 3 months.

The number of patients at risk for amivantamab and UK SoC are presented in Table 27 and Table 28 for OS and PFS, respectively, as per Section B.2.9 of the CS.

Table 27: Number of patients at risk over time for OS

Timepoint	Amivantamab	Unadjusted UK SoC (US RWE cohort)	IPW (ATT) adjusted UK SoC (US RWE cohort)
Month 0	[redacted]	[redacted]	[redacted]
Month 3	[redacted]	[redacted]	[redacted]
Month 6	[redacted]	[redacted]	[redacted]
Month 9	[redacted]	[redacted]	[redacted]
Month 12	[redacted]	[redacted]	[redacted]
Month 15	[redacted]	[redacted]	[redacted]
Month 18	[redacted]	[redacted]	[redacted]
Month 21	[redacted]	[redacted]	[redacted]
Month 24	[redacted]	[redacted]	[redacted]
Month 27	[redacted]	[redacted]	[redacted]
Month 30	[redacted]	[redacted]	[redacted]
Month 33	[redacted]	[redacted]	[redacted]
Month 36	-	[redacted]	[redacted]
Month 39	-	[redacted]	[redacted]
Month 42	-	[redacted]	[redacted]
Month 45	-	[redacted]	[redacted]
Month 48	-	[redacted]	[redacted]
Month 51	-	[redacted]	[redacted]
Month 54	-	[redacted]	[redacted]

Abbreviations: ATT: average treatment effect among the treated; IPW: inverse probability weighting; OS: overall survival; RWE: real-world evidence; SoC: standard of care.

Table 28: Number of patients at risk over time for PFS

Timepoint	Amivantamab	Observed UK SoC (US RWE cohort)	UK SoC (US RWE cohort)
Month 0	[redacted]	[redacted]	[redacted]
Month 3	[redacted]	[redacted]	[redacted]
Month 6	[redacted]	[redacted]	[redacted]
Month 9	[redacted]	[redacted]	[redacted]
Month 12	[redacted]	[redacted]	[redacted]
Month 15	[redacted]	[redacted]	[redacted]
Month 18	[redacted]	[redacted]	[redacted]
Month 21	[redacted]	[redacted]	[redacted]
Month 24	[redacted]	[redacted]	[redacted]
Month 27	-	[redacted]	[redacted]
Month 30	-	[redacted]	[redacted]
Month 33	-	[redacted]	[redacted]
Month 36	-	[redacted]	[redacted]
Month 39	-	[redacted]	[redacted]

Month 42	-	[redacted]	[redacted]
Month 45	-	[redacted]	[redacted]
Month 48	-	[redacted]	[redacted]
Month 51	-	[redacted]	[redacted]
Month 54	-	[redacted]	[redacted]

Abbreviations: PFS: progression-free survival; RWE: real-world evidence; SoC: standard of care.

b. To examine the proportional hazard assumption:

a. Plot the scaled Schoenfeld residuals versus time (all survival curves)

The Schoenfeld residual plot over time for OS is presented in Figure 36, with SoC data informed by the ATT-weighted US RWE cohort. As presented in the figure, the Schoenfeld test for OS is not significant (p=0.7183), which suggests that the assumption of proportional hazards (PH) holds. However, the estimate of hazard ratio over time (represented by the solid blue line) varies over time, decreasing and increasing twice before remaining stable after Month 20. As such, there is considerable uncertainty regarding the assumption of proportional hazards.

For PFS BICR, the Schoenfeld residual plot is presented in Figure 37. The Schoenfeld test is statistically significant (p=0.0028), indicating that there is a correlation between the estimate of the hazard ratio and time, and an upward trend in the estimate of HR is observed in the early follow up, before remaining stable after around Month 10. As such, the proportional hazards assumption does not hold.

Overall, these plots indicate that an assumption of proportional hazards for OS would be associated with considerable uncertainty and would be inappropriate for PFS. Please note that the cost effectiveness analysis base case compares CHRYSALIS OS and PFS outcomes to an ATT-weighted US RWE cohort and does not rely on an assumption of proportional hazards.

Figure 36: Schoenfeld residual plot over time (OS, amivantamab versus US RWE cohort)

Abbreviations: OS: overall survival; RWE: real-world evidence.

Figure 37: Schoenfeld residual plot over time (PFS [BICR], amivantamab versus US RWE cohort)

Abbreviations: BICR: blinded independent committee review; PFS: progression-free survival; RWE: real-world evidence.

Plot the log cumulative hazard versus log time

The log cumulative hazard plot for OS and PFS (BICR) are presented in Figure 38 and Figure 39, respectively. UK SoC is informed by the ATT-weighted US RWE cohort.

For OS, the hazards associated with amivantamab and UK SoC cross, indicating a violation of the proportional hazard assumption in the early stages of follow up. For the PFS BICR endpoint, the log of cumulative hazards are not parallel, particularly in the beginning of follow up, similarly indicating that the proportional hazard assumption does not hold. As discussed further in response to Parts G and H of this question below, this evidence that proportional hazards does not hold supports the base case approach of using different parametric models for the different treatment arms as per the methodology laid out in NICE Technical Support Document 14.[30]

Figure 38: Log cumulative hazard plot (OS, amivantamab versus US RWE cohort)

Abbreviations; OS: overall survival; RWE: real-world evidence.

Figure 39: Log cumulative hazard plot (PFS [BICR], amivantamab versus US RWE cohort)

Abbreviations: BICR: blinded independent committee review; PFS: progression-free survival; RWE: real-world evidence.

To examine the heuristics of the hazard function over time:

a. Plot the smoothed hazards over time

OS

For amivantamab (see Figure 40 and Figure 42), the smoothed hazard curve suggests that the hazard is first increasing then slightly decreasing. Towards the end of the follow up there is an increase in the unsmoothed hazard, though by this time there are only five patients at risk and the results should be interpreted with caution due to increased uncertainty. Weibull has lowest AIC and long-term extrapolations with loglogistic and lognormal have long tails. Weibull can be considered as a conservative choice.

For UK SoC informed by US cohort data (see Figure 41 and Figure 43), the smoothed hazard curve is increasing. Towards the end of the follow up there is an increase in the unsmoothed hazard, though by this time there are only five patients at risk, and results should be interpreted with caution due to increased uncertainty. These data are mature, with the Weibull having the lowest Akaike's Information Criteria (AIC) and the best fit to the observed data. This fit is consistent with the smoothed hazard curve, which suggests that hazard increase over time.

Hazards for both arms increase initially, then starts to decrease from month 10 onwards for the active arm and from month 20 for the comparator arm.

Figure 40: CHRYSALIS OS – parametric models and smoothed hazard

Abbreviations: OS: overall survival.

Figure 41: ATT-weighted US RWE OS – parametric models and smoothed hazard

Abbreviations: ATT: average treatment effect among the treated; OS: overall survival; RWE: real-world evidence.

Figure 42: CHRYSALIS OS – smoothed and unsmoothed hazards

Abbreviations: OS: overall survival.

Figure 43: ATT-weighted US RWE OS – smoothed and unsmoothed hazards

Abbreviations: ATT: average treatment effect among the treated; OS: overall survival; RWE: real-world evidence.

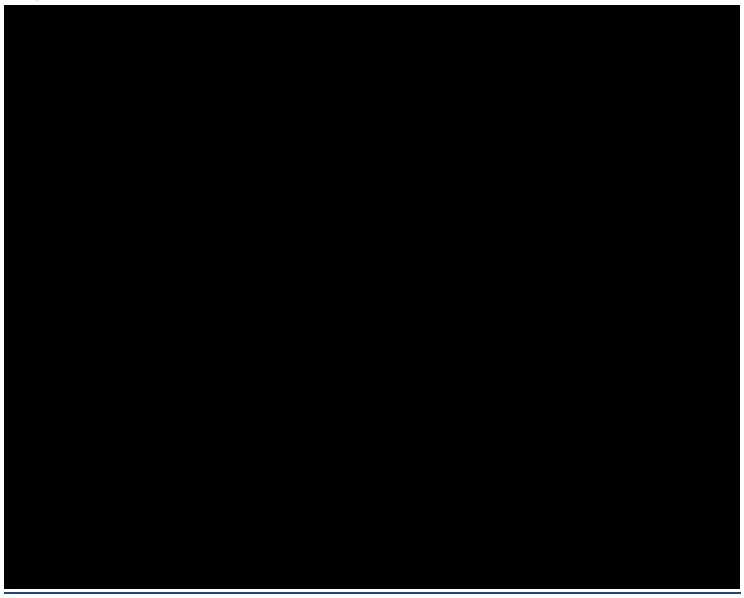
PFS

For amivantamab (see Figure 44 and Figure 46), the smoothed hazard increases then decreases, before increasing again, though the increase at the end of follow up is based on a small number of patients at risk (nine patients are at risk at Month 15), increasing the uncertainty in estimates towards the end of follow up. Even though lognormal and loglogistic have the best fit to observed data (lowest AICs), and loglogistic is consistent with increasing then decreasing hazard, these parametric models have long tails that lead to an optimistic estimate of percentage of progression-free patients beyond the observed time period. Generalised gamma, which has the lowest AIC after lognormal and loglogistic, was therefore selected as the parametric model for amivantamab PFS.

For UK SoC informed by US cohort data (see Figure 45 and Figure 47), the unsmoothed hazard suggests that the hazard is slightly increasing at the very beginning of follow up, then decreasing with time, before increasing again, although the spike at the end is based partly on only one patient at risk beyond Month 20, and should be interpreted with caution. US RWE data is mature and the loglogistic model has the lowest AIC, and is consistent with increasing then decreasing hazard.

Comparing the smoothed hazard of the active arm and the comparator, the active arm hazard increases until about Month 8, starting from a lower hazard value, whereas the comparator hazard starts from a higher base and after an initial increase, decreases until about Month 10. The log cumulative hazard curves are not parallel; therefore, the hazard changes differently in the two arms with time.

Figure 44: CHRYSALIS PFS (BICR) – parametric models and smoothed hazard



Abbreviations: BICR: blinded independent committee review; PFS: progression-free survival.

Figure 45: ATT-weighted US RWE PFS (BICR) – parametric models and smoothed hazard

Abbreviations: ATT: average treatment effect among the treated BICR: blinded independent committee review; PFS: progression-free survival; RWE: real-world evidence.

Figure 46: CHRYSALIS PFS (BICR) – smoothed and unsmoothed hazards

Abbreviations: BICR: blinded independent committee review; PFS: progression-free survival.

Figure 47: ATT-weighted US RWE PFS (BICR) – smoothed and unsmoothed hazards

Abbreviations: ATT: average treatment effect among the treated BICR: blinded independent committee review; PFS: progression-free survival; RWE: real-world evidence.

c. To examine diagnostics of parametric survival models (using the observed data):

a. Plot the cumulative hazard versus time

b. Plot the log smoothed hazard versus time

c. Plot the standard normal quartiles versus log time

d. Plot the log survival odds versus log time

OS (see Figure 48 to Figure 52 below)

For amivantamab OS, the loglogistic, lognormal and Gompertz diagnostic curves deviate from a linear trend. Weibull and exponential diagnostic curves conform better with linear trend compared with the other three parametric curves.

As described in Section B.3.3.2 of the CS, extrapolation of the US RWE data informing efficacy for UK SoC was not deemed necessary in the base case due to the maturity of the available data. However, at the request of the ERG, diagnostic curves are presented for SoC OS (informed by the US RWE cohort). Greater deviation from a linear trend is observed for the loglogistic, lognormal and Gompertz diagnostic curves, than there is for Weibull and exponential curves.

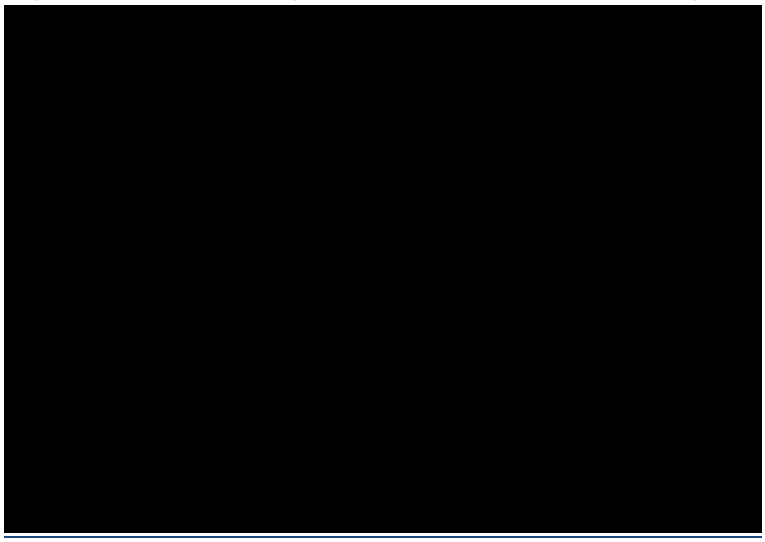
Figure 48: Exponential (cumulative hazard versus time) – OS

Abbreviations: OS: overall survival.

Figure 49: Loglogistic (negative log survival odds versus log time) – OS

Abbreviations: OS: overall survival.

Figure 50: Weibull (log cumulative hazard versus log time) – OS



Abbreviations: OS: overall survival.

Figure 51: Gompertz (log hazard versus time) – OS

Abbreviations: OS: overall survival.

Figure 52: Lognormal (inverse cumulative standard normal probability versus log time) – OS

Abbreviations: OS: overall survival.

PFS (see Figure 53 to Figure 57)

For amivantamab PFS (BICR), there is substantial deviation from a linear trend for Gompertz. For other curves, there is deviation from a linear trend especially at the beginning of follow up, for lognormal, loglogistic, and Weibull, and at the end for exponential.

For SoC PFS (informed by the US RWE cohort), diagnostic plots follow a similar pattern as the amivantamab diagnostic curves.

Figure 53: Exponential (cumulative hazard versus time) – PFS (BICR)

Abbreviations: BICR: blinded independent committee review; PFS: progression-free survival.

Figure 54: Loglogistic (negative log survival odds versus log time) – PFS (BICR)

Abbreviations: BICR: blinded independent committee review; PFS: progression-free survival.

Figure 55: Weibull (log cumulative hazard versus log time) – PFS (BICR)

Abbreviations: BICR: blinded independent committee review; PFS: progression-free survival.

Figure 56: Gompertz (log hazard versus time) – PFS (BICR)

Abbreviations: BICR: blinded independent committee review; PFS: progression-free survival.

Figure 57: Lognormal (inverse cumulative standard normal probability versus log time) – PFS (BICR)

Abbreviations: BICR: blinded independent committee review; PFS: progression-free survival.

e. To examine the validity of the extrapolation beyond the data, please provide supporting evidence that the extrapolations are consistent with relevant external data and/or expert opinion. In case of expert opinion, please provide a full description of the methods and results of the expert consultation conducted.

Due to the rarity of EGFR Exon20ins mutated NSCLC, external data regarding the long-term clinical outcomes of these patients against which the current extrapolations could be validated is lacking. However, as discussed in Section B.3.3.2 of the CS, UK clinicians were consulted in order to validate the long-term extrapolations used. As described in the submitted minutes from the meeting, clinicians were presented with both Kaplan-Meier data and curve extrapolation options for OS and PFS for both amivantamab and UK SoC (as informed by US RWE or PHE cohort data). The clinicians were then asked whether the Kaplan-Meier curves and the available extrapolations broadly aligned with their clinical expectations for EGFR Exon20ins mutated NSCLC patients in UK clinical practice receiving either amivantamab or UK SoC after the failure of platinum-based chemotherapy. A summary of their estimations for the proportion of patients alive (OS) and progression-free (PFS) at the two- and five-year timepoints is provided in Table 29.

The proportion of patients estimated by the model to be alive at the five-year timepoint and progression-free at the two- and five-year timepoints is presented in Table 30; a strong alignment between the clinician-estimated proportions and the outputs of the model can be observed, supporting that the curve choices are in alignment with clinical validation of the long-term outcomes.

In addition, these modelled outcomes are broadly in alignment with previous NICE appraisals in NSCLC. In TA713, the model estimates for nivolumab and docetaxel at Year 4 were 1–2% and 7–15%, respectively, and in TA520, the mixed cure model estimated 12% and 2% of atezolizumab-treated and docetaxel-treated patients to be alive at Year 5, respectively. The

consistency of the presented estimates with previous models accepted in the NSCLC space provides further support that they are clinically valid and appropriate for use.

Table 29: Summary of clinician estimations of long-term OS and PFS rates

	OS (5-year)	PFS	
		2-year	5-year
UK SoC	[redacted]	[redacted]	[redacted]
Amivantamab	[redacted]	[redacted]	[redacted]

Abbreviations: OS: overall survival; PFS: progression-free survival; SoC: standard-of-care.

Table 30: Long-term OS and PFS rates assumed in the base case economic analysis

	OS (5-year)	PFS	
		2-year	5-year
UK SoC	[redacted]	[redacted]	[redacted]
Amivantamab	[redacted]	[redacted]	[redacted]

Abbreviations: OS: overall survival; PFS: progression-free survival; SoC: standard-of-care.

f. Please provide for all parametric models for OS and PFS the rate of survival gain in the pre-extrapolation period (defined as the difference in survival between intervention and comparator at data cut-off divided by the number of months in the pre-extrapolation period) and the post extrapolation period (defined as the marginal relative difference in the extrapolated period (post cut-off) divided by the number of months post-cut-off).

An Excel file entitled "*Rate of survival gain_B5f*" has been provided alongside this response document. Within this file, the rate of survival gain of patients in the amivantamab arm, as compared with UK SoC as informed by ATT-weighted data from the US RWE cohort, has been calculated as the ERG request. The rate of survival gain can be interpreted as the relative difference between the amivantamab and UK SoC arms in the section of the model in which efficacy is informed by direct available data (the pre-extrapolation period) and the section in which extrapolated data must be employed (the post cut-off period). Within the Excel file, the impact of using all of the parametric models for OS and PFS on the survival gain can be explored; for brevity, the results in which the base case inputs, as presented in the CS, are implemented are discussed.

In the base case, amivantamab OS is informed by the Weibull distribution and UK SoC is informed by US RWE Kaplan-Meier (KM) data. Using these inputs, amivantamab has a [redacted]% rate of survival gain in the pre-extrapolation period, and [redacted]% in the post-cut off period. For PFS, the base case inputs are a generalised gamma distribution for amivantamab and KM data for UK SoC. With these inputs, amivantamab has a [redacted]% rate of survival gain in the pre-extrapolation period, and [redacted]% in the post-cut off period.

g. Please justify the selection of the approaches to estimate and extrapolate OS and PFS, considering the responses to the preceding

questions as well as the "Survival Model Selection Process Algorithm" provided in NICE DSU TSD 14.

NICE Technical Support Document 14 outlines four steps to the fitting of survival models to patient-level data. As outlined below, Janssen consider that these steps have been addressed sufficiently to justify the selection of the approach taken to the extrapolation of OS and PFS in the base case.

1. Log-cumulative hazard plots should be assessed to determine the type of hazards observed and whether proportional hazards can be assumed. As presented in response to Part A of this question above, an assumption of proportional hazards is not supported by the available data. This further supports the approach to model OS and PFS for the active arm and the comparator arm separately.

2. If the log-cumulative hazard plots produce approximately straight lines for any of the parametric models then those models should be fitted to the data and assessed further. As presented in Part B of this question, the log-cumulative plots are approximately straight for both amivantamab and UK SoC, indicating that fitting of separate parametric distributions to the data is plausible. The crossing of the log-cumulative hazard plots further supports that an assumption of proportional hazards cannot be made.

3. The statistical fit of curves to the data should be considered, e.g., in terms of AIC/BIC. As presented in the CS, statistical fit to the data has been considered in each parametric model, with the base case inputs representing the best or second-best fitted option. In addition, visual inspection of the parametric model extrapolations ensured that the curves did not cross at any point, as better clinical outcomes for UK SoC than amivantamab does not hold face validity, and extensive clinical validation of the curve options was sought from UK-based experts to ensure that the selected options maintained clinical plausibility.

4. Where more than one plausible option exists, scenario sensitivity analyses should be presented with uncertainty around the parameter estimates for each scenario inputs included in the probabilistic sensitivity analyses (PSA). In the CS, scenario analyses are presented for alternative curve options, and these alternative curve options are included in the PSA.

h. As suggested in NICE DSU TSD 14, please provide "substantial justification" in case different types of parametric models are used for different treatment arms.

As discussed above, in the base case, Kaplan–Meier data from the US RWE cohort were used to inform efficacy in the UK SoC arm due to their maturity, reducing uncertainty as compared with implementing extrapolation methods. As such, different types of parametric models are not utilised in the base case. However, when considering a scenario in which extrapolation of these data is implemented, an assumption of proportional hazards between the amivantamab and UK SoC treatment arms within the model is not justified; as such, fitting separate parametric models to each arm is suitable. The distributions implemented in the base case have been selected in

alignment with feedback from UK-based clinicians regarding the proportion of patients they would expect to be progression-free and/or alive in the long-term.

This approach of fitting separate parametric models to each arm is in alignment with the final approach taken in TA713, in which joint modelling was considered not to be suitable given that an assumption of proportional hazards did not hold, and the independent fitting of data was considered by the NICE Committee to be reasonable and clinically plausible.[4]

i. Please enable joint modelling in the cost-effectiveness model.

As discussed in depth above, the application of independent parametric models to amivantamab and UK SoC is considered to be in alignment with NICE DSU TSD and to represent the most appropriate approach. However, at the request of the ERG, a scenario has been performed in which joint modelling is implemented. In this scenario, the parametric distributions have been aligned with the base case selections for amivantamab: Weibull for OS, and generalised gamma for PFS.

The results for this scenario are presented in Table 31 and indicate that joint modelling has a minimal impact on the overall cost-effectiveness results and the ICER remains under the WTP threshold of £50,000. However, for the reasons outlined above, Janssen maintain that use of different parametric distributions for the two treatment arms is the most appropriate approach.

Table 31: Scenario analysis results – joint modelling (deterministic)

#	Scenario analysis	LIST PRICE			WITH PAS		
		Incr. costs (£)	Incr. QALYs	ICER (£/QALY)	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)
Base case		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£39,764**
1	**Joint modelling**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£47,929**

Abbreviations: AMI: amivantamab; ICER: incremental cost-effectiveness ratio; LY: life years; PAS: patient access scheme; QALYs: quality-adjusted life years; SoC: standard of care.

B6. It is unclear from the CS whether the treatment effect of amivantamab could wane over time.

a. Please clarify whether waning of the amivantamab treatment effect was incorporated in the economic model.

Janssen can confirm that treatment waning is not explicitly included in the model, above and beyond the observed trial data and its extrapolations.

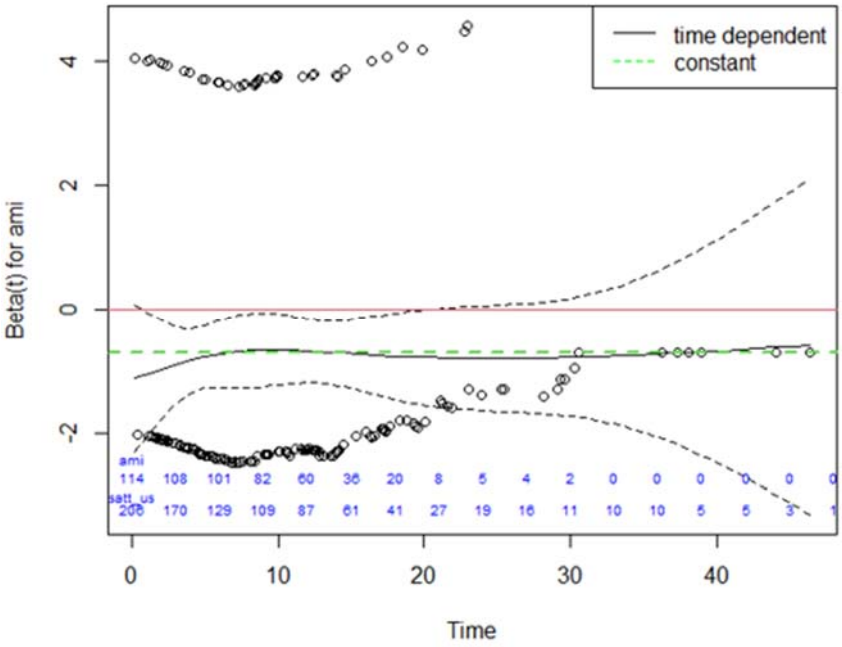
b. Please provide hazard ratio plots for OS and PFS with numbers of patients at risk over time.

The economic model base case comparison against the ATT-weighted US RWE does not rely on a relative treatment effect and does not assume proportional hazards. For the purposes of answering query B6, we have estimated time dependent (solid black lines) and the time invariant

(dashed green line) log(HR) of amivantamab vs. ATT-weighted US cohort for OS and PFS endpoints (Figure 58 and

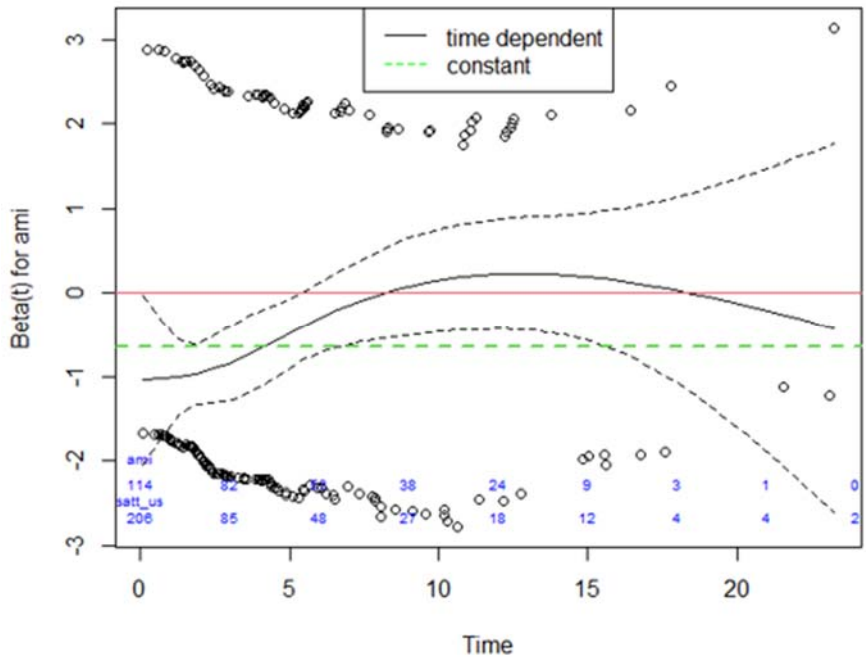
Figure 59). The OS estimate of log HR is generally stable over time. For PFS, the estimate of log HR shows greater variation over time.

Figure 58. OS estimate of log HR for amivantamab vs ATT weighted US RWE



Abbreviations: ATT: average treatment effect among the treated; HR: hazard ratio; OS: overall survival; RWE: Real world evidence

Figure 59. PFS estimate of log HR for amivantamab vs. ATT weighted US RWE



Abbreviations: ATT: average treatment effect among the treated; HR: hazard ratio; PFS: Progression-free survival; RWE: Real world evidence

c. Please provide an updated economic model and scenario analyses exploring treatment waning at different time points.

Treatment waning has not been incorporated in the model, and Janssen maintain this to be a suitable approach for the following reasons:

- **Any treatment effect waning would be implicitly captured in the selected curves.** As described in Section B.3.3.2 of the CS, UK clinicians consulted by Janssen validated the long-term clinical plausibility of the selected amivantamab OS and PFS curve extrapolations. For example, the clinicians indicated that an overall survival probability of 7–8% at the Year 5 timepoint for patients receiving amivantamab aligned with their clinical expectations for this treatment. Based on this feedback and statistical fit data, the Weibull and generalised gamma extrapolations were selected for use in the base case and scenario analysis, respectively, since they have Year 5 survival probabilities of 8.7% and 7.3%, respectively. Given that the long-term outcomes implemented within the model were confirmed by UK clinicians as clinically plausible, Janssen consider that should any treatment effect waning be observed, it would be captured implicitly in the selected curves. As such, explicit application of treatment effect waning for amivantamab is not appropriate.
- **Patients with EGFR Exon20ins mutated NSCLC have a poor prognosis.** Although survival improves following amivantamab treatment, patients remain progression free for relatively short periods of time given this is a severe disease: from CHRYSALIS, amivantamab-treated patients had a median PFS and OS of [redacted] months and [redacted] months, respectively, at the latest data cut, whereas data from the US RWE indicate a median PFS and OS of [redacted] months and [redacted] months, respectively, following receipt of SoC. As such, patients in receipt of amivantamab are unlikely to experience treatment effect waning within their lifespan, and if they did, it would be highly unlikely to have a clinically meaningful impact due to the short time periods over which it could apply.
- **Amivantamab is a continuous, treat to progression treatment.** Amivantamab is administered until patients experience a progression event rather than for a prespecified period of time. In addition, subsequent lines of therapy are included in the model. Therefore, patients are continuously receiving treatment throughout the model time horizon and thus the inclusion of treatment waning is not considered to be necessary.

For these reasons, Janssen maintain that the current approach of modelling no explicit treatment effect waning for amivantamab is appropriate and suitably reflective of clinical reality. As such, an updated economic model has not been presented.

B7. Priority question. For survival analyses of OS and PFS in the SoC arm, the company argued that due to the maturity of the data and all patients reaching the specified end point or being censored within the timeframe of data collection, KM data could be directly implemented rather than fitting a parametric model. Hence, the company's base case PSA did not include fitted parametric models for the extrapolation of OS and PFS in the SoC arm. Please

select the most appropriate parametric models for OS and PFS in the SoC arm and rerun the PSA (preferably 5,000 iterations) including these.

Janssen note that the base case probabilistic and deterministic sensitivity analyses presented in the CS do account for the uncertainty in comparator OS and PFS by sampling the Kaplan–Meier curve for the comparator, using the standard error of the Kaplan–Meier survival estimates at each model cycle.

When scenario analyses are considered in which extrapolation is implemented rather than use of Kaplan-Meier data directly, the model is set up such that the selected curves will automatically be included in the PSA. As described in Section B.3.3.2 of Document B of the CS, the Weibull curve provided the best statistical fit to the UK SoC OS data, and was the second choice of UK clinical experts consulted during feedback elicitation (the preferred method to model UK SoC OS and PFS in the base case was to use the KM estimates directly). For PFS, the log-logistic curve showed the best statistical fit to the UK SoC data. As such, these curves have been selected and the PSA re-run using 5,000 iterations as requested. The results are presented below.

The updated probabilistic base case results are presented in Table 32 (list price) and Table 33 (PAS price). Cost-effectiveness planes and cost-effectiveness acceptability curves are presented in Figure 60 and Figure 61, respectively, for list price and Figure 62 and Figure 63, respectively, for PAS price. The probabilistic base case results remain in close alignment with the deterministic base case results.

Table 32: Updated results at amivantamab list price (probabilistic)

	Total			Incremental			ICER (£/QALY)
	Costs	QALYs	LYs	Costs	QALYs	LYs	
UK SoC	[redacted]	[redacted]	1.33	-	-	-	-
AMI	[redacted]	[redacted]	2.21	[redacted]	[redacted]	0.87	[redacted]

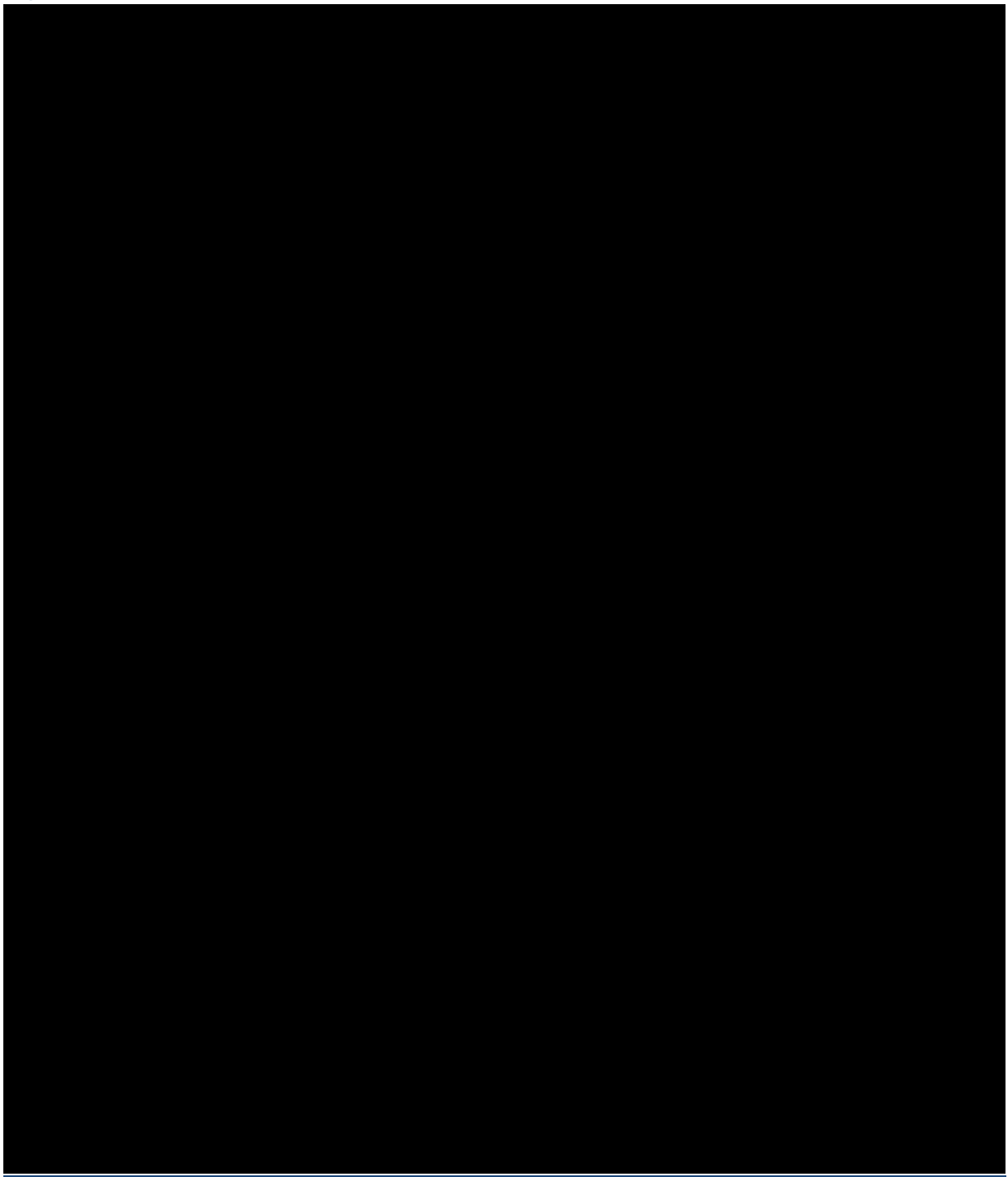
Abbreviations: AMI: amivantamab; ICER: incremental cost-effectiveness ratio; LY: life years; QALYs: quality-adjusted life years; SoC: standard of care.

Table 33: Updated results at amivantamab PAS price (probabilistic)

	Total			Incremental			ICER (£/QALY)
	Costs	QALYs	LYs	Costs	QALYs	LYs	
UK SoC	[redacted]	[redacted]	1.33	-	-	-	-
AMI	[redacted]	[redacted]	2.20	[redacted]	[redacted]	0.87	£40,353

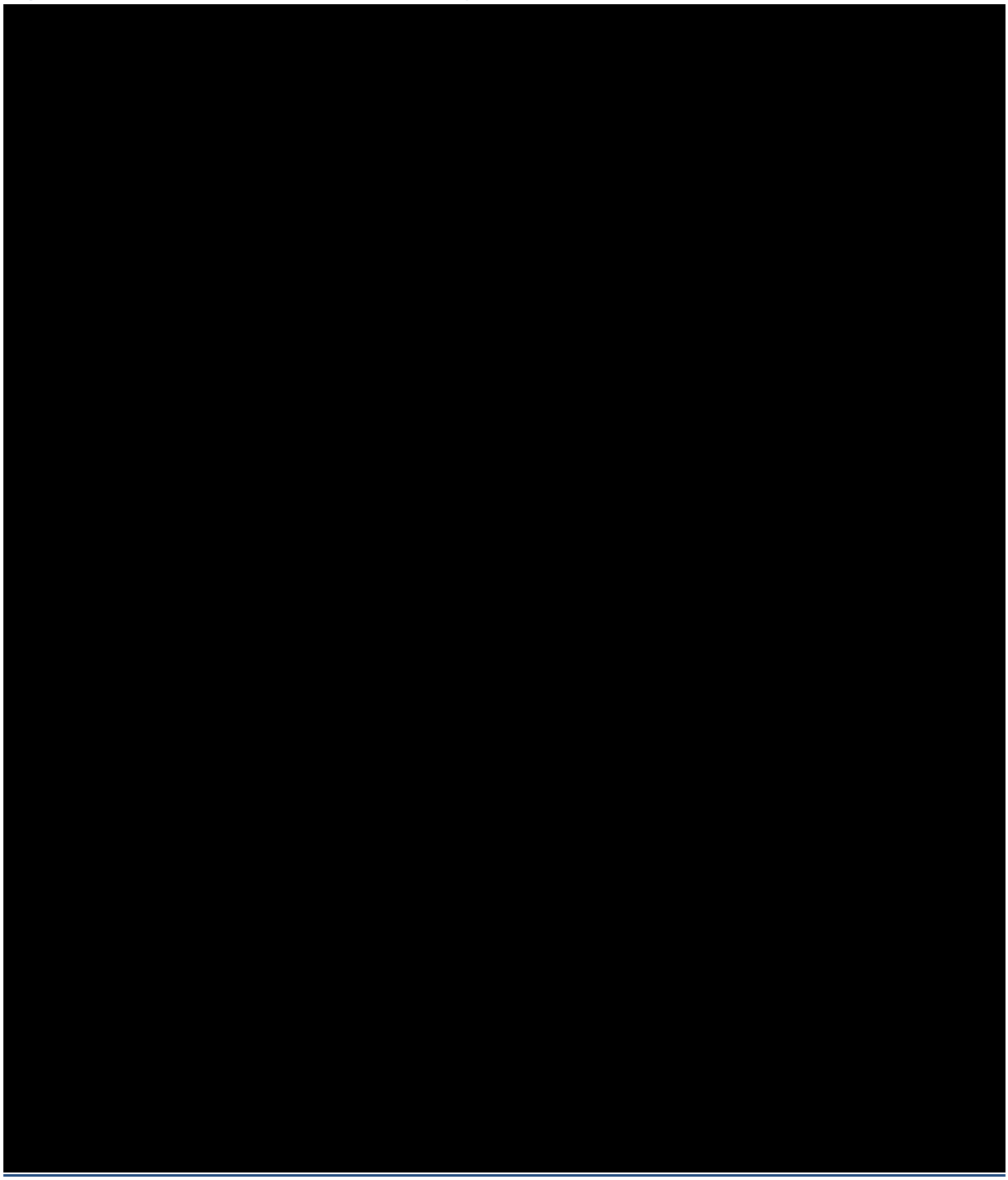
Abbreviations: AMI: amivantamab; ICER: incremental cost-effectiveness ratio; LY: life years; PAS: patient access scheme; QALYs: quality-adjusted life years; SoC: standard of care.

Figure 60: Cost effectiveness plane scatterplot at amivantamab list price



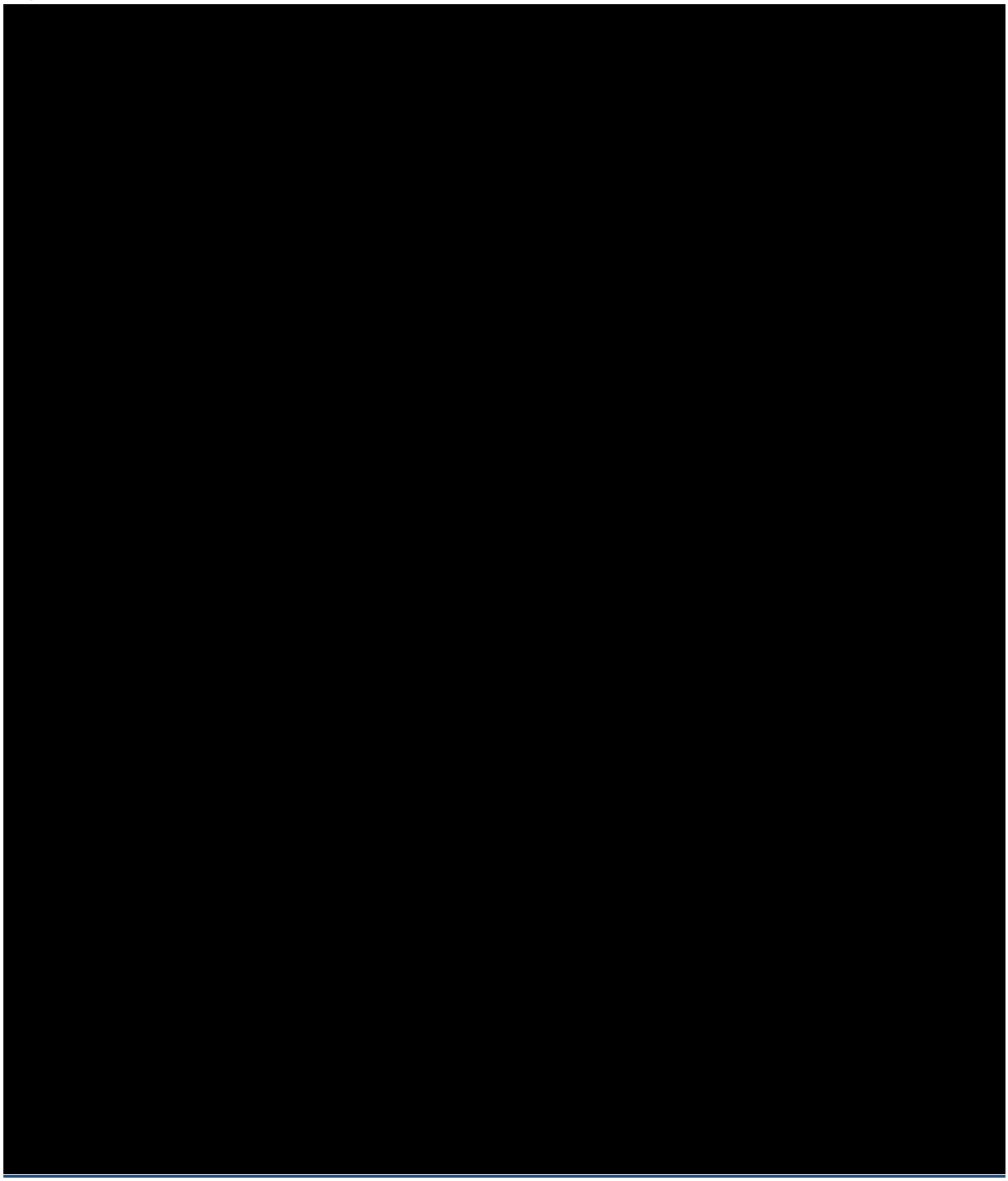
Abbreviations: ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; SoC: standard of care.

Figure 61: Cost-effectiveness acceptability curve at amivantamab list price



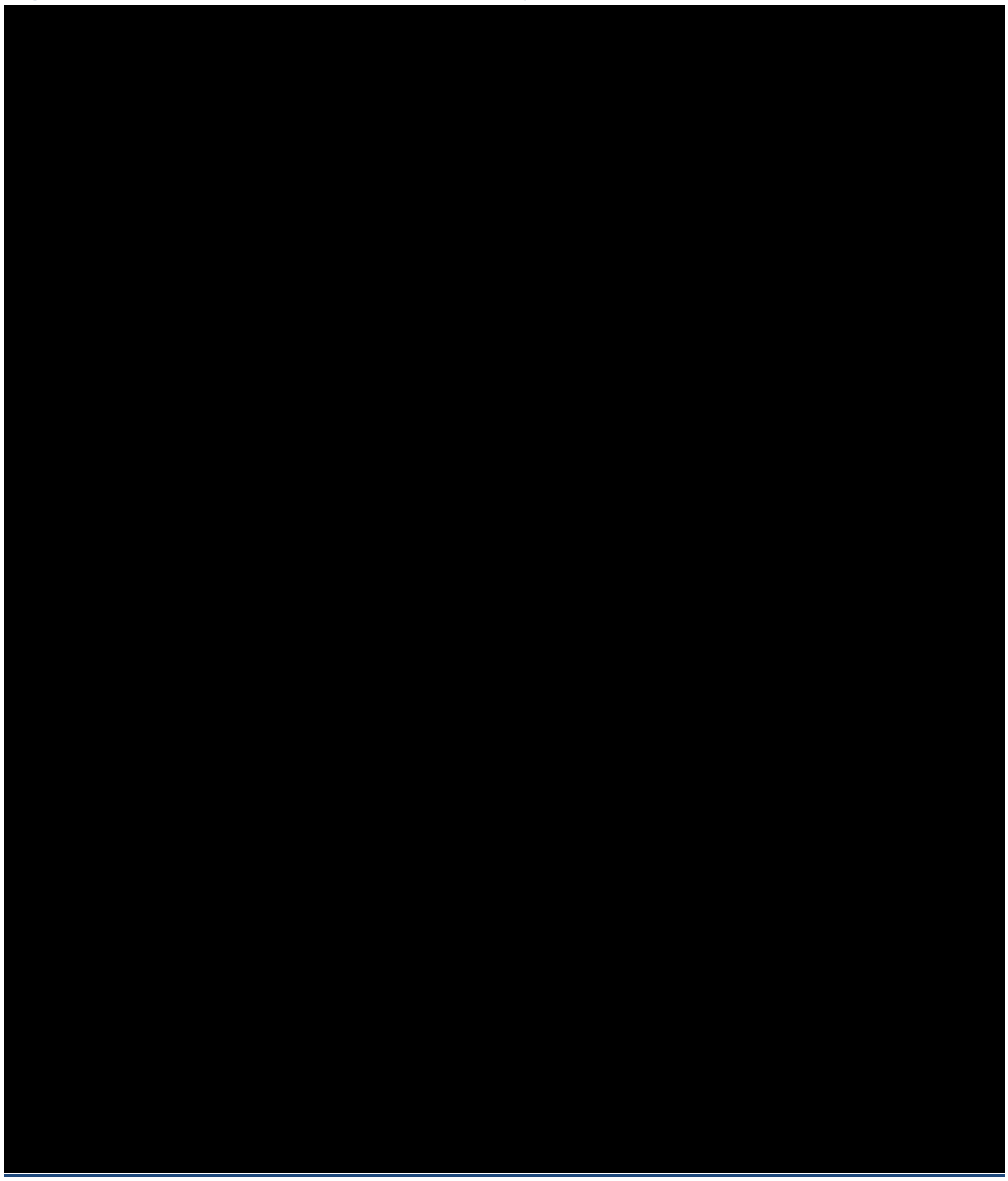
Abbreviations: CE: cost-effectiveness; SoC: standard of care.

Figure 62: Cost effectiveness plane scatterplot at amivantamab PAS price



Abbreviations: ICER: incremental cost-effectiveness ratio; PAS: patient access scheme; QALY: quality-adjusted life year; SoC: standard of care.

Figure 63: Cost-effectiveness acceptability curve at amivantamab PAS price



Abbreviations: CE: cost-effectiveness; PAS: patient access scheme; SoC: standard of care.

B8. As per the protocol of the CHRYSALIS clinical trial, patients could continue to receive treatment following disease progression. However, UK clinical experts stated that this does not reflect expected clinical practice, where patients would stop current treatment upon progression and time on treatment was assumed equal to PFS in the model.

a. Please clarify whether patients in the economic model could also discontinue before disease progression, for example as a consequence of a serious adverse event?

Within the model, patients are assumed to be on treatment until they progress; in other words, it is assumed that time to treatment discontinuation (TTD) is equal to PFS. As such, any reasons for treatment discontinuation are those captured in the CHRYSALIS PFS definition.

b. Please clarify whether treatment discontinuation in the economic model involves cost reductions only.

See Part A above.

c. Please provide an updated economic model and scenario analysis assuming patients could continue to receive treatment (and accounting for associated costs and health effects) following disease progression as per the CHRYSALIS trial protocol.

As described in Section B.3.3.2.3 of the CS, feedback received from UK clinical experts at a Janssen-led advisory board was that patients receiving treatment following disease progression does not reflect expected clinical practice, where patients would stop current treatment upon progression. As such, an assumption was made that time on treatment is equal to PFS and Janssen maintain this to be the most appropriate approach for the economic analysis.

Whilst Janssen maintain that the approach taken in the base case analysis is the most appropriate and reflective of UK practice, at the request of the ERG, the following scenario analyses have been performed for the comparison of amivantamab (as informed by CHRYSALIS trial data) and UK SoC (as informed by US RWE data):

- Amivantamab time on treatment is informed by time to treatment discontinuation data from CHRYSALIS (TTD) (Gompertz distribution)
- Amivantamab time on treatment is informed by TTD and UK SoC time on treatment is informed by TTNT (Kaplan–Meier data from US RWE)
    - TTD data are not available from the US RWE cohort. As such, TTNT data are used as a proxy
    - Of the two presented scenarios, this latter scenario is considered more appropriate for the following reasons:
        - In the absence of TTD data for SoC, TTNT is used as a proxy over PFS because if you assume, that as per the CHRYSALIS protocol, that patients were permitted to remain on treatment beyond progression, time on treatment is greater than PFS. Therefore, in order to utilise a similar assumption for SoC, TTNT data are more appropriate than maintaining PFS data for SoC, as time on treatment is then assumed to be greater than PFS in both arms. In addition, when comparing median PFS to TTD for amivantamab (PFS: [redacted] months and TTD: [redacted] months [difference: [redacted] months]) and median TTNT and median PFS for SoC (PFS: [redacted] months and TTNT: [redacted] months [difference: [redacted] months]), the differences in duration are broadly similar, implying that TTNT is a reasonable proxy

The results of this scenario analyses are presented in Table 34. Consideration of treatment beyond progression for amivantamab only resulted in an ICER of £50,549 at PAS price for

amivantamab, whereas consideration of TTD and TTNT for amivantamab and UK SoC, respectively, resulted in an ICER of £33,708 at PAS price for amivantamab.

Table 34: Scenario analysis results – treatment past progression (deterministic)

#	Scenario analysis	LIST PRICE			WITH PAS		
		Incr. costs (£)	Incr. QALYs	ICER (£/QALY)	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)
Base case		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£39,764
1	Amivantamab TTD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£50,549
2	Amivantamab TTD and UK SoC TTNT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£33,708

Abbreviations: ICER: incremental cost-effectiveness ratio; Incr.: incremental; LY: life years; PAS: patient access scheme; QALYs: quality-adjusted life years; SoC: standard of care; TTD: time to treatment discontinuation; TTNT: time to next treatment.

B9. OS and PFS were secondary outcomes in the CHRYSALIS trial. Please elaborate on the potential implications of this on the analyses given that these outcomes are the primary input for treatment effectiveness in the economic model.

In the CHRYSALIS trial, PFS was defined as the time from first infusion of study drug to progressive disease (PD) or death due to any cause. PD in turn, was assessed according to RECIST v1.1. OS was defined as the time from first infusion of study drug to death due to any cause. PFS and OS were summarised using Kaplan-Meier estimates.

These are standard definitions for PFS and OS in oncology clinical trials. In CHRYSALIS, these endpoints measured the absolute treatment effects for amivantamab given the single arm nature of the trial. Thus, Janssen see no potential implications of using PFS and OS as the primary input for treatment effectiveness in the economic model.

Adverse events

B10. As stated in the CS, disutilities associated with AEs were applied in the model in the first cycle.

a. Please elaborate on the clinical plausibility of incorporating AEs in the first cycle only (e.g., is it realistic to assume that all AEs would last for 4 weeks) and compare this to the implementation of AE disutilities in other STAs (i.e., TA520 and TA484/TA713).

Incorporation of AEs in the first cycle was implemented as a simplified approach because it is not anticipated that this would have a material impact on the ICER given the small contribution AEs have to total costs and QALYs across the model horizon. That this approach is minimally impactful is supported by the conclusion of the ERG in TA484, in which a similar approach of applying AE disutilities only to the first model cycle was implemented, which summarised that although event rates could have been considered instead of the incidence rate, it was unlikely that the approach to the modelling of AE disutilities would have a major impact on the ICER.[31]

b. Please explain whether the AE disutilities were corrected for the cycle length (e.g., the cycle length in TA520 is one week).

AE disutilities were applied per event rather than per duration and as such do not need to be corrected for cycle length.

c. The model includes treatment-specific AE disutilities. Considering that SoC is a basket of treatments including immune-oncology agents, EGFR TKIs and platinum and non-platinum based chemotherapies, please elaborate on the clinical plausibility that amivantamab has a more favourable AEs distribution.

The disutilities associated with Grade ≥3 AEs considered in the model are presented in Section 3.4.4 (Table 50) of the CS. These disutilities were applied to each patient modelled to experience the specified AE regardless of which treatment they are receiving; as such, treatment-specific disutilities are not implemented within the model. However, as presented in Section 3.4.1 (Table 49) of the CS, the incidence of these AEs was modelled in a treatment-specific manner given that treatments of different treatment classes are expected to have different safety profiles. This approach is in alignment with previous HTA appraisals in NSCLC, such as TA520.[3] The safety profile of UK SoC was informed by a weighted average based on the treatment class proportions in the US RWE database, thus reflecting the average AE profile of current treatment options in the UK. UK clinicians validated that the AE profiles associated with each of the comparator treatment classes included in the UK SoC comparator were in line with their clinical expectations.

UK clinicians further validated that the safety profile for amivantamab, which was sourced directly from the CHRYSALIS trial, was reflective of their clinical expectations. As a first-in-human, multicentre, two-part trial designed to investigate that efficacy and safety of amivantamab in patients with EGFR Exon20ins mutated NSCLC, the CHRYSALIS trial represents the most robust data source available to inform the modelled safety profile of amivantamab.

d. Please include a scenario that does not assume treatment-specific AE disutilities.

As described above, the economic model presented in the CS does not assume treatment-specific AE disutilities. As such, there is no need for a scenario to be presented.

e. Given that some comparators in SoC are not mentioned as established clinical management without amivantamab in the final scope (see question B3) and hence should not be included in the model (partly dependent on justifications provided in response to question A6b), update the AE disutility values accordingly.

As discussed in response to Question B3, Janssen maintain that the economic approach presented in the CS compares amivantamab to established clinical practice as per the scope. However, at the request of the ERG and in response to Part F of Question B3, scenario analyses in which EGFR TKIs, EGFR TKIs and platinum-based chemotherapies or EGFR TKIs and 'other'

treatments have been removed from the UK SoC comparator arm have been provided. In these scenarios, AE disutilities are not applied for the excluded treatment classes, thus satisfying this request of the ERG to align AE disutility values applied in the model with a UK SoC comparator that excludes some treatment classes. As presented in response to Question B3, the results of these scenario analyses show that amivantamab has an improved cost-effectiveness versus UK SoC as compared with the submitted base case approach.

Health-related quality of life

B11. Priority question. Although EQ-5D-5L data were collected in CHRYSALIS, health state utilities in the economic model were sourced from TA484/TA713 as the number of EQ-5D-5L responses from the CHYRSALIS trial was low at the time of data cut-off.

a. Please provide an updated economic model and scenario analysis informing health state utilities based on the collected HRQoL data in CHYRSALIS and elaborate on how these values compare to the ones currently used in the economic model.

EQ-5D-3L data were collected in CHRYSALIS at Day 1 of each cycle, at the end of treatment and during post-treatment follow-up.[9] However, patient reported outcome (PRO) assessments were not introduced until Amendment 7 (August 2019) and as a result, the number of responses to the EQ-5D-5L questionnaire was very low at the time of data cut-off (n=27) and thus do not represent a robust basis for generating health state utilities. Further, the missing data is not missing at random and thus requires more complex utility analysis methods (than that implemented to generate the results in the next paragraph) to account for this.

However, at the request of the ERG, a scenario analysis has been conducted in which a pre-progression (PFS) health state utility value of 0.617 derived from the CHRYSALIS data is implemented within the model. The results for this scenario analysis are presented in Table 35 and indicate that use of a CHRYSALIS-derived utility value to inform the PFS health state has a minimal impact on the overall cost-effectiveness results and the ICER remains under the WTP threshold of £50,000. However, given the considerable uncertainty associated with a value derived from only 27 patients, these results should not be considered suitable for decision-making.

Table 35: Scenario analysis results – alternative PFS health state utility value derived from CHRYSALIS (deterministic)

#	Scenario analysis	LIST PRICE			WITH PAS		
		Incr. costs (£)	Incr. QALYs	ICER (£/QALY)	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)
Base case		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£39,764
1	CHRYSALIS PFS utility value	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£42,117

Abbreviations: ICER: incremental cost-effectiveness ratio; Incr.: incremental; LY: life years; PFS: progression-free survival; PAS: patient access scheme; QALYs: quality-adjusted life years; SoC: standard of care.

b. Please provide an updated economic model and scenario analysis informing health state utilities from all other TAs that were identified in the SLR and elaborate on how these values compare to the ones currently used in the economic model.

As described in the CS, the health state utility values used in the base case are derived from TA484/TA713 given that they were accepted as part of a previous NICE appraisal in NSCLC, are in a similarly advanced population with non-squamous NSCLC, and were considered by UK clinical experts to be the utility values most appropriate for the relevant population for this appraisal.[17] At the request of the ERG, scenario analyses have been conducted investigating the effect of using health state utilities from TA428 and TA347 in line with the NICE appraisals mentioned in the final scope for this appraisal for which pre- and post-progression utility values were available. The utility values utilised in TA520 could not be implemented in a scenario analysis given that they were based on time to death rather than progression state.[3, 6, 26]

The results of these analyses are presented in Table 36. These results show that the health state utilities used in the company's base case are a conservative estimate. Scenarios were not presented for all TAs identified in the SLR for pragmatism; those from the final scope were considered the most relevant for inclusion here.

Table 36: Scenario analysis results – alternative health state utility values derived from previous NICE appraisals (deterministic)

#	Scenario analysis	LIST PRICE			WITH PAS		
		Incr. costs (£)	Incr. QALYs	ICER (£/QALY)	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)
Base case		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£39,764
1	TA428 utility values	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£35,617
2	TA347 utility values	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£38,086

Abbreviations: ICER: incremental cost-effectiveness ratio; Incr.: incremental; LY: life years; PAS: patient access scheme; QALYs: quality-adjusted life years; SoC: standard of care.

B12. The company stated that given the relatively short time horizon of the model, the impact of age-adjustment on results is likely to be marginal and as such, utilities are not age-adjusted. Please provide an updated model and scenario analysis including age-adjustments to the health state utilities.

To investigate the impact of age adjustment on the ICER a scenario analysis was conducted in which age-adjustments were applied to the health-state utilities. As presented in Table 37, the results of this analysis show that of age-adjustment has minimal impact on the overall cost-effectiveness results and the ICER remains under the WTP threshold of £50,000.

Table 37: Scenario analysis results – inclusion of age-adjusted utilities (deterministic)

#	Scenario analysis	LIST PRICE			WITH PAS		
		Incr. costs (£)	Incr. QALYs	ICER (£/QALY)	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)

Base case		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£39,764
1	Inclusion of age adjusted utilities	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£40,293

Abbreviations: ICER: incremental cost-effectiveness ratio; Incr.: incremental; LY: life years; PAS: patient access scheme; QALYs: quality-adjusted life years; SoC: standard of care.

Cost and resource use

B13. The NICE scope stated "The use of amivantamab is conditional on the presence of an EGFR mutation. The economic modelling should therefore include the costs associated with diagnostic testing for EGFR in people with NSCLC who would not otherwise have been tested. A sensitivity analysis should be provided without the cost of the diagnostic test". The company argued: "EGFR Exon20ins mutations can be tested as part of the EGFR test conducted at diagnosis for all NSCLC patients. As such, Janssen, considers there are no additional costs likely to be incurred by the NHS over and above the current standard of care EGFR testing requirements for all NSCLC patients." Please provide a scenario analysis with the addition of these costs should implemented in the model.

Please provide a scenario (implemented also in the model), in which the costs for diagnostic testing for EGFR in people with NSCLC are included. In this scenario, please ensure that costs for all people tested are included, not only for those people that tested positive.

As discussed in the CS, it is mandatory for patients with NSCLC in UK clinical practice to undergo EGFR Exon20ins mutation testing at diagnosis to identify the presence of driver mutations that are amenable to targeted therapy. (this was confirmed by UK-based clinicians at an advisory board). As such, the introduction of amivantamab to UK clinical practice would not be associated with any marginal genetic testing costs beyond those already incurred by patients with NSCLC receiving UK SoC.

For this reason, Janssen do not consider that the inclusion of additional costs associated with EGFR Exon20ins mutation testing in the model would reflect clinical reality and thus would not be suitable for decision making, so a scenario analysis is not provided.

B14. In the company's base case, the composition of the basket for subsequent treatments received following amivantamab or UK SoC was sourced from the subsequent treatment distribution of patients receiving third-line or later therapy in the pooled US RWE database. A scenario analysis was conducted in which the subsequent treatment composition for patients

following amivantamab was sourced from the subsequent treatment distribution of patients receiving third-line or later therapy in the CHRYSALIS trial.

For both analyses, please justify the generalisability of the modelled subsequent treatment distributions to UK clinical practice.

As described in Question B3 above, data regarding subsequent treatments received by patients in the PHE cohort are not available. However, robust US RWE subsequent treatment data are available, and clinicians further confirmed that these proportions are in alignment with their expectations for patients in the UK. The subsequent treatment distributions from CHRYSALIS were also presented in the advisory board. Whilst a detailed discussion on the generalisability of these treatments did not feature as part of the meeting, the treatment classes included are aligned with those from the subsequent treatments from the US RWE, and the proportions of patients are also similar between sources.

In addition, a scenario was presented in Section B.3.8.3 of the CS where subsequent treatments for amivantamab were based on data from the CHRYSALIS trial and this had a minimal impact on the ICER, showing that this is not a key driver of model results.

B15. In table 55 of the company submission the frequencies of administration of therapies are described. The source of these frequencies is unclear.

Please provide the source of the frequencies for all therapies described in table 55.

The frequencies of all therapies included in the model and presented in Table 55 of the CS have been derived from the respective SmPC for each treatment as per its NSCLC indication or published NHS guidelines. Where treatment cycle lengths differ from the model cycle length of four weeks, the frequency has been adjusted accordingly as described below.

- **Amivantamab.** Administered as a monotherapy intravenously every in Weeks 1–4, totalling four doses in the first model cycle. From Week 5 onwards, administered intravenously every two weeks (i.e., twice in all subsequent model cycles) until disease progression or unacceptable toxicity.[1]
- **Atezolizumab or pembrolizumab.** Administered as a monotherapy intravenously once every three weeks (i.e., 1.33 times per four-week model cycle) until loss of clinical benefit or unmanageable toxicity.[32, 33]
- **Nivolumab.** Administered as a monotherapy intravenously once every two weeks (i.e., twice per four-week model cycle) until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression.[34]
- **Afatinib and osimertinib.** Administered orally; as described in Section B.3.5.1 of the CS, oral administration is assumed to be associated with a one-off oral administration cost applied at the start of treatment duration. As such, no treatment administration costs associated with afatinib (base case) or osimertinib (scenario analysis only) are applied in model cycle two and beyond.[35, 36]

- **Carboplatin + gemcitabine and carboplatin + vinorelbine.** Carboplatin is administered intravenously once every 21-day treatment cycle (i.e., 1.33 times per four-week model cycle). During combination therapy with carboplatin, gemcitabine or vinorelbine are administered twice as often as carboplatin: each is administered intravenously on Day 1 and Day 8 of the 21-day treatment cycle, equating to 2.33 administrations per four-week model cycle. Therefore, administration costs associated with complex chemotherapy (carboplatin in combination with gemcitabine or vinorelbine) and simple chemotherapy (gemcitabine or vinorelbine as monotherapies) are applied 1.33 times each per four-week model cycle. Platinum-based chemotherapies can be used for a maximum of 12 weeks (i.e., four three-week model cycles); as such, no administration costs associated with carboplatin + gemcitabine or carboplatin + vinorelbine are applied in model cycle four and beyond.[37, 38]
- **Carboplatin + pemetrexed.** Carboplatin and pemetrexed are administered together intravenously once every three weeks (i.e., 1.33 times per four-week model cycle). Platinum-based chemotherapies can be used for a maximum of 12 weeks (i.e., four three-week treatment cycles); as such, no administration costs associated with carboplatin + pemetrexed are applied in model cycle four and beyond.[39]
- **Docetaxel.** Administered as a monotherapy intravenously once every three weeks (i.e., 1.33 times per four-week model cycle).[40]
- **Docetaxel + nintedanib.** Docetaxel is administered as a monotherapy intravenously once every three weeks (i.e., 1.33 times per four-week model cycle). Nintedanib is administered orally, with the one-off oral administration cost applied to the first model cycle only. Nintedanib in combination with docetaxel is administered for a maximum of six three-week treatment cycles; as such, no administration costs associated with docetaxel + nintedanib are applied from model cycle five onwards.[41]

Cost effectiveness results, scenario and sensitivity analyses

B16. [redacted] of incremental QALY gain was accrued in the post-progression state, when presumably most patients had discontinued treatment.

Please justify why most incremental QALY gain occurs beyond treatment discontinuation.

As presented in Section J.1 of the CS appendices, the outcomes of the cost-effectiveness model for amivantamab are median PFS and median OS of [redacted] months and [redacted] months, respectively. For UK SoC, median PFS and median OS are [redacted] months and [redacted] months, respectively. These values are in close alignment with the outcomes observed in the source data: for amivantamab, the CHRYSALIS trial found median PFS and median OS to be [redacted] months and [redacted] months, respectively, and data from adjusted US RWE analysis showed these to be [redacted] months and [redacted] months, respectively, for patients receiving SoC. This alignment with the source data coupled with confirmation from UK-based clinical experts that the PFS and OS outcomes for both amivantamab and UK SoC were in line with their clinical expectations provide considerable support to the clinical validity of the modelled outcomes. Based on these modelled outcomes, patients are in the post-progression survival (PPS) state, i.e., between PFS and OS, for a median of [redacted] months for amivantamab and [redacted] months for UK SoC, which is at least twice as long as the period for which they are pre-progression. Given this, a marginally

greater accrual of QALYs in the PPS state holds face validity despite the lower health state utility value associated with the PPS state as compared with the PFS state.

An additional consideration for amivantamab is that feedback received from UK clinicians supported that amivantamab would be expected to continue providing patients with a clinical benefit even following a progression event.[17] The clinicians stated that in current clinical practice, approximately half of patients would be expected to have exhausted all available treatment options by the third line. However, if amivantamab were to be introduced to clinical practice, they observed that patients would have more treatment options reserved for use following progression at second line (i.e., after amivantamab treatment), thus likely leading to improved clinical outcomes due to the greater availability of treatment options.

As such, Janssen consider that the accrual of slightly more incremental QALYs in the post-progression state, at which point patients would have discontinued from amivantamab treatment, is clinically plausible and in line with feedback received from UK-based clinicians.

Validation and transparency

B17. Please provide detailed minutes, notes and results supporting modelling assumptions and input parameters, from the different expert advisory boards.

The reports detailing the discussions for each of the expert advisory boards are included in the reference pack accompanying this submission.[17, 42, 43]

B18. The results of the validity assessments are not described nor are detailed validation exercises (i.e., specific black-box tests) described (in CS section B.3.10).

a. Please provide a detailed description of the validity assessment performed as well as the results.

The stress test checklist used to validate the model and the results of this test are presented in Table 38. The results indicate that the model behaved as expected and passed all of the stress tests implemented. All changes to the model were made by a health economist, and each change made after the performance of the stress test checklist was fully quality controlled by a second health economist.

Table 38: Stress test checklist used for cost-effectiveness model validation

#	Test	Expected effect	Observed effect equivalent to expected effect?
1	Set all efficacy data equal across treatments, and set disutility associated with adverse events to 0.	QALYs across all treatments should be equal.	Yes
2	Set mortality rate to 0% at all ages (and any other mortality in the model)	There are no deaths in the model.	Yes
3	Set mortality rate to 100% at all ages	All patients are dead in the first cycle.	Yes

4	Increase mortality rate	Costs are reduced.	Yes
5	Set the health state utilities the same for all states	Life years to QALY ratio should be the same across all treatments	Yes
6	Set the utilities for all health states to 0 and adverse events to 0	All QALYS = 0.	Yes
7	Set the cost and utility consequences for adverse events and discontinuation to 0, then undo these changes and set all adverse event rates to 0	Results in both cases are the same	Yes
8	Set adverse event and discontinuation rates to 0, then undo these changes and set adverse and discontinuation rates to a high level	The first scenario should result in lower costs, higher life years and greater QALYs than the second	Yes
9	Decrease the utilities for all health states simultaneously whilst keeping event-based utility decrements constant	QALYs are reduced	Yes
10	Set equal the effectiveness, utility and safety-related model inputs for all treatment options	No difference between LYs and QALYs for each treatment arm, at any given time	Yes
11	Set the costs of treatments to 0	All treatments costs = 0	Yes
12	Double the costs of treatments	Treatment costs doubled	Yes
13	Increase body weight and/or body surface area (only relevant for weight/BSA dependent dosing)	Treatment costs (for weight/BSA dependent treatments) are increased	Yes
14	Set all administration costs to 0	All administration costs = 0	Yes
15	Double all administration costs	Administration costs doubled	Yes
16	Turn off/on vial sharing	Costs should increase without vial sharing	Yes
17	Set all monitoring/follow-up costs to 0	Monitoring/follow-up costs = 0	Yes
18	Double all monitoring/follow-up costs	Monitoring/follow-up costs doubled	Yes
19	Alter the time horizon	Total costs and QALYS increase/decrease in accordance with longer/shorter horizons	Yes
20	Set discount rates to 0%	Undiscounted results = discounted results	Yes
21	Set discount rates to 100%	Costs and QALYs reduce significantly.	Yes
22	Run the DSA/OWSA and check all input parameters affect results when values are changed	Any input parameters should affect the incremental QALYS, costs or both (unless it has an exactly equal effect on all arms in the model)	Yes

Abbreviations: BSA: body surface area; DSA: deterministic sensitivity analysis; OWSA: one-way sensitivity analysis; QALY: quality-adjusted life years.

b. Please provide complete the TECH-VER checklist (Büyükkaramikli et al. 2019, https://pubmed.ncbi.nlm.nih.gov/31705406/) and provide the results.

The checklist described in Part A above was derived based on the TECH-VER checklist and thus provides the same verification of validity as the TECH-VER checklist. As such, a completed TECH-VER checklist has not been provided.

B19. Please provide cross validations, i.e., comparisons with other relevant NICE TAs focused on similar, potentially relevant, diseases (e.g., related NICE recommendations and NICE Pathways listed in the final scope) and elaborate on the identified differences regarding:

a. Model structure and assumptions

b. Input parameters related to:

    a. Clinical effectiveness

    b. Health state utility values

    c. Resource use and costs

c. Estimated (disaggregated) outcomes per comparator/ intervention

    a. Life years

    b. QALYs

    c. Costs

A summary of key previous appraisals as per the NICE final scope and NG122 (TA347, TA428, TA484/TA713, TA520 and TA653) is presented in Table 39 below, summarising the model structure and assumptions, as well as the input parameters related to clinical effectiveness, health state utility values and resource use.[3-5, 31, 44]

In Table 40, Part C of Question B19 has been addressed by presenting the estimated outcomes per comparator and intervention for the same appraisals, plus the current appraisal, as presented in their respective ingoing company submissions. List price results are presented given that results considering the confidential PAS price are redacted in the published materials. Disaggregated results are not available for TA484, TA713 and TA347, so total costs, LYG and QALYs have been presented; where total results are not available, incremental results have been presented. The disaggregated results that are available can be found in the following:

- TA520: Section 5.7.3, Tables 89–92 of the ingoing company submission, published in the Committee Papers[3]

- TA428: Section 5.7.6, Tables 100 and 101 of the ingoing company submission, published in the Committee Papers[5]

- Current appraisal: Appendix J of the CS

The results presented in Table 40 indicate that incremental costs, LYG and QALYs of [redacted], 0.84 and [redacted], respectively, in the current appraisal are broadly in line with the results of previous appraisals in the NSCLC disease area, supporting their clinical validity. However, the other appraisals presented did not consider an EGFR Exon20ins-mutated NSCLC population specifically, likely contributing to any differences observed.

Table 39: Features of the economic analysis

Factor	Previous appraisals				Current appraisal	Identified differences/ justification for the current submission
	TA520[3]	TA484[31] and TA713[4]	TA428[5]	TA347[44]		
Model structure	Partitioned survival model					Captures the clinical benefits of amivantamab, utilises the outcome data available from the adjusted treatment comparison and aligned with previous similar submissions
Time horizon	25 years	20 years	30 years	15 years	15 years	Expected to sufficiently capture the lifetime of targeted population given their poor prognosis
Cycle length	1 week	1 week	1 week	3 weeks	4 weeks	A 4-week cycle length is in line with the dosing regimens for amivantamab and expected to be sufficiently short to capture time-to-event outcomes
Discount	3.5%					NICE reference case[45]
Health effects measure	QALYs					NICE reference case[45]
Perspective	NHS/PSS					NICE reference case[45]
Clinical effectiveness inputs informing the cost-	The OAK trial was the primary data source. The clinical efficacy outcomes derived from this trial and	The CheckMate 057 trial was the primary data source. The clinical efficacy outcomes derived from this	The KEYNOTE-010 trial was the primary data source. The clinical efficacy outcomes derived	The LUME-Lung 1 trial was the primary data source. The clinical efficacy outcomes derived	The CHRYSALIS trial was the primary data source. The clinical efficacy outcomes derived from this trial and informing the model	The SLR identified 278 interventional studies. Of the 88 studies considered for full extraction, only one (CHRYSALIS) provides

effective model	informing the model were OS, PFS, AEs.	trial and informing the model were OS, TTD and AEs.	from this trial and informing the model were OS, PFS and AEs.	from this trial and informing the model were OS, PFS and QoL data.	were OS, PFS and AEs. For the SoC arm, PFS and OS were derived from adjusted RWE, and AEs were derived from published sources.	evidence for the clinical efficacy and safety of amivantamab in the patient population of interest for this appraisal (patients with EGFR Exon20ins mutated NSCLC).
Source of health state utilities	EQ-5D results collected in OAK trial	*TA484:* EQ-5D results collected in CheckMate 057 *TA713:* Combination of EQ-5D values from CheckMate 057 with a Dutch lung cancer study (van den Hout *et al*. 2006)[46]	EQ-5D results collected in KEYNOTE-010 trial	EQ-5D results collected in LUME-Lung 1 trial	TA484/TA713	Due to low sample size in the EQ-5D-3L data collected in the CHRYSALIS trial (data are available for only [redacted]% of the population due to the late introduction of the QoL questionnaire), published sources were required to estimate the utility values in patients with advanced EGFR Exon20ins mutated NSCLC. However, in response to Question B11 above, a scenario in which a pre-progression utility value derived from the CHRYSALIS data is presented
Source of costs	• NHS National Reference costs • PSSRU • eMIT • BNF					NICE reference case[45]
Key assumptions	See Table 82, Pages 196–198 of the TA	See Table 73, Pages 198–199 of the TA	See Table 95, Pages 216–218 of the TA	See Section 7.3.8, Pages 209–211 of the TA	See Table 61, Pages 128–131 in Section B.3.6.2 of Document B	N/A

Abbreviations: AE: adverse event; BNF: British National Formulary; eMIT: electronic market information tool; EGFR: epidermal growth factor receptor; EQ-5D: EuroQol five-dimensions instrument; Exon20ins: Exon 20 insertion mutations; NHS: National Health Service; NICE: National Institute for Health and Care Excellence; NSCLC: non-small-cell lung cancer; OS: overall survival; PFS: progression-free survival; PSS: personal social services; QALYs: quality-adjusted life years; QoL: quality of life; RWE: real-world evidence; SLR: systematic literature review; SoC: standard of care; TA: technology appraisal.

Table 40: Base case results for key previous appraisals as per the final NICE scope (list price)

Technologies	Total costs	Total LYG	Total QALYs
TA520[3] (discounted, deterministic)			
Docetaxel	£19,941	1.19	0.73
Nintedanib plus docetaxel	£37,702	1.31	0.83
Atezolizumab	£73,911	2.22	1.47
TA484[31] (costs and QALYs discounted, LYs undiscounted, deterministic)			
Nivolumab	£93,306	2.24	1.42
Docetaxel	£17,854	1.09	0.70
Nintedanib plus docetaxel	£30,708	1.44	0.93
TA713[4] (discounting not stated, deterministic)			
Nivolumab	£28,360 (incremental costs)	1.23 (incremental LYG)	0.73 (incremental QALYs)
Docetaxel			
TA428[5] (discounted, deterministic)			
Pembrolizumab	Base case 1: £41,509 Base case 2: £11,267	Base case 1: 1.90 Base case 2: 0.87	Base case 1: 1.30 Base case 2: 0.60
Docetaxel	Base case 1: £41,283 Base case 2: £11,267	Base case 1: 1.77 Base case 2: 0.87	Base case 1: 1.22 Base case 2: 0.60
TA347[44] (deterministic or probabilistic not stated, discounted)			
Nintedanib plus docetaxel	£11,051 (incremental costs)	0.33 (incremental LYG)	0.22 (incremental QALYs)
Docetaxel			
Current appraisal (discounted, deterministic)			
UK SoC	[redacted]	0.80	[redacted]
Amivantamab	[redacted]	1.34	[redacted]

Abbreviations: LYG: life years gained; NICE: National Institute for Health and Care Excellence; QALY: quality adjusted life year; SoC: standard of care; TA: technology appraisal.

B20. Priority question. Further external validation of modelled effectiveness would be desirable.

a. Please report on the face validity of the model structure, model assumptions, model inputs, intermediate outcomes as well as final outcomes in more detail (including what aspects were assessed and what were the considerations as well as conclusions).

As described in Section B.3.10.1 of the CS, expert clinical input was sought during the development of the cost-effectiveness model to ensure that the inputs and assumptions used in the analysis were relevant to UK clinical practice and to validate the clinical plausibility of the outcomes predicted by the model. Feedback was obtained in two advisory boards and in total, input was gathered from seven UK clinical experts. As part of validation, the following aspects of the cost-effectiveness model were included:

- Testing algorithms
    - Considerations: feedback was sought on whether testing was routinely conducted in UK practice to ensure generalisability of the inclusion of testing costs (or not) in the cost-effectiveness model
    - Conclusions: it was considered a valid assumption to exclude testing costs
- The treatment pathway for NSCLC and relevant comparators
    - Considerations: whether the treatment pathways and comparator treatments within the SoC comparator considered within the cost-effectiveness model represent UK practice i.e. that we are making valid comparisons and accurately representing UK clinical practice with the modelled treatment pathway
    - Conclusions: clinicians were presented with a treatment pathway diagram summarising the NICE guidelines for people with non-squamous (adenocarcinoma, large cell undifferentiated) carcinoma and non-small-cell carcinoma (non-otherwise specified) as per NG122. The clinicians agreed that, in the absence of treatment guidelines for Exon20ins mutations specifically, patients with Exon20ins in the UK would likely be treated in a manner broadly similar to patients without EGFR or ALK mutations (i.e. no gene mutation or fusion protein) as per the presented pathway. The clinicians acknowledged that clinical practice would be highly variable country-wide and agreed that using a basket comparator approach would be suitable in this situation, particularly noting the heterogeneity of treatments received in the RWE sources. Overall, the clinicians agreed that the proportions patients receiving different treatment classes from RWE sources are broadly representative of what would be expected in UK clinical practice. With regards to subsequent therapies, the experts agreed that RWE was in reasonable alignment with UK clinical practice
- Appropriate estimates of PFS and OS for amivantamab and UK SoC
    - Considerations: whether predicted outcomes from the model make sense at a superficial level based on expert opinion
    - Conclusions: for both PFS and OS, the experts agreed that predicted outcomes for the US RWE and CHRYSALIS were in line with clinical expectations for UK practice

based on a presentation of mean and median survival at relevant timepoints and different curve choices for extrapolation. The clinicians also had experience in treating patients with amivantamab; therefore, they were well-placed to assess outcomes for this treatment as well as SoC therapies. The definition of progression in CHRYSALIS was also validated, with experts stating that the specific criteria were not used directly in clinical practice to the same stringency, but confirmed that they are broadly in alignment with progression assessment conducted. Further, experts concluded that the assumption that patients would switch treatments upon progression would be reasonable and clinically plausible, demonstrating the validity of this assumption in the model

- Generalisability of CHRYSALIS and RWE sources
    - Considerations: whether CHRYSALIS and RWE sources are representative of a UK population
    - Conclusions: the clinicians agreed that the presented baseline characteristics were broadly representative of what would be expected in typical UK clinical practice and, as above, that the predicted outcomes from the model were in line with clinical expectations for the modelled population
- AE rates
    - Considerations: to consider whether the model assesses the key AEs relevant for the indication in question
    - Conclusions: clinicians agreed that the observed safety profile was broadly aligned with their clinical expectations for amivantamab. It was highlighted that there may be some difficulties in comparing the safety profile different treatment classes within SoC; for example, patients receiving chemotherapies are likely to experience common but relatively mild AEs, whereas IO agents are more likely to be associated with rare but severe AEs. Some considerations were raised with regards to AE incidences for individual treatment classes, which were subsequently amended in the final model for submission in line with this feedback to best reflect UK practice
- Utility values
    - Considerations: the suitability of the chosen base case utility values for use as representative of a UK patient population
    - Conclusions: clinicians agreed that the utility values derived from NICE TA484 (TA713) were the most appropriate for use in the current appraisal given that the population from which they were derived is most similar to the EGFR Exon20ins mutated NSCLC population, demonstrating the validity of this approach
- Monitoring and follow-up resource use assumptions
    - Considerations: the appropriateness of monitoring and resource use assumptions from a previous NICE appraisal for the present submission
    - Conclusions: based on clinical feedback, a number of monitoring appointments and associated frequencies were amended to best reflect UK practice

Further, the model was subject to stress testing and responded as expected to all applied tests (see Question B18). In addition, there are no anomalous results e.g. crossing of predicted survival curves between treatments or for PFS and OS curves, with no adjusted required to achieve this outcome.

As part of model development (and as detailed in Question B19) previous NICE appraisals were also consulted to ensure alignment of the current model to existing precedent and to ensure that previous feedback regarding the most appropriate assumptions was taken into account.

Overall, the model can be considered to be highly face valid based on the extensive seeking of expert input and comparison to previous models in relevant disease areas.

b. Please assess the external validity of model inputs, intermediate outcomes as well as final outcomes using

a. evidence used to develop the economic model.

External validity of the model inputs and outputs can be demonstrated via comparison of the results to the clinical data feeding into the model. When comparing the clinical outcomes of the model to the clinical data from CHRYSALIS for amivantamab and the US RWE for UK SoC (Table 41), the data are also consistent, highlighting the validity of the model.

Table 41: Comparison of clinical inputs and outputs in the cost-effectiveness model

Endpoint	Amivantamab (CHRYSALIS)	UK SoC (US RWE; adjusted)	Amivantamab (modelled survival)	UK SoC (modelled survival)
Median PFS	[redacted]	[redacted]	[redacted]	[redacted]
Median OS	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: OS: overall survival; PFS: progression-free survival; SoC: standard of care.

In addition, when comparing the output of the adjusted comparison with the US data to the analysis utilising data from PHE, there is consistency of results from both sources, supporting the robustness of the analyses and that amivantamab is a valuable treatment option in a population relevant to UK clinical practice.

b. evidence not used to develop the economic model.

Due to the rare nature of EGFR Exon20ins mutations, there are extremely limited external data to the model with which to validate outcomes. However, some comparisons can be made to support external validity of the model. For example, when comparing the LYs presented in the base case for this appraisal versus previous NICE appraisals, they are similar in magnitude, supporting the validity of the final outcomes presented in this submission (see Table 42). However, as noted in response to Question B19 above, these prior appraisals did not consider the specific population of interest for this appraisal (EGFR Exon20ins-mutated NSCLC), likely contributing to the differences in LYs reported.

Table 42: Comparison of LYs in relevant previous NICE appraisals

Technologies	Total LY
TA520[3]	
Nivolumab	1.19
Docetaxel	1.31
Nintedanib plus docetaxel	2.22
TA484[31]	

Nivolumab	2.24
Docetaxel	1.09
Nintedanib plus docetaxel	1.44
TA713[4]	
Nivolumab	1.23 (incremental)
Docetaxel	
TA428[5]	
Pembrolizumab	Base case 1: 1.90; base case 2: 0.87
Docetaxel	Base case 1: 1.77; base case 2: 0.87
Current appraisal	
UK SoC	0.80
Amivantamab	1.34

Abbreviations: LYs: life years; SoC: standard of care.

In addition, Dersarkissian *et al.* (2019) reported on outcomes for patients with relapsed/refractory NSCLC with EGFR Exon20ins mutations receiving chemotherapy, EGFR TKIs only or IO in any combination, and reported a median OS (interquartile range [IQR]) of 12.5 (5.0–21.1) months, which aligns well with the predicted outcomes of the model for UK SoC ([redacted] months) as well as the raw output of the adjusted comparison ([redacted] months).[47]

B21. Throughout the submission reference is frequently made to a clinical advisory board (reference 12 in the submission). The reference contains the minutes of the clinical advisory board. The NICE health technology evaluations manual (https://www.nice.org.uk/process/pmg36/resources/nice-health-technology-evaluations-the-manual-pdf-72286779244741) states that the reporting of expert opinion should contain information about "*the identification and selection of experts, and the reporting of results including the consensus of opinions or data aggregation*."

Please provide these details where experts were used.

Janssen conducted an advisory board comprising of two consultant oncologists selected for their extensive and ongoing experience of treating patients with NSCLC as well as their expertise as investigators in clinical trials involving targeted therapies. The aim of this advisory board was to understand the treatment pathway, including unmet need and clinical outcomes for patients with EGFR Exon20ins mutation positive NSCLC, and to validate clinical assumptions informing economic model, including parametric extrapolations, HRQoL and medical resource use.

The opinions of the clinical experts on the various topics were captured and summarised in the report which was submitted alongside the company submission.

B22. The company performed a scenario analysis to explore the impact of using investigator-assessed (INV) PFS from the CHRYSALIS trial to inform amivantamab PFS.

Please provide a detailed description of the methodology used for the investigator-assessment.

Beginning with Amendment 3 (May 2017), disease assessments were performed every 6 (±1) weeks during Parts 1 (dose escalation phase) and 2 (dose expansion phase), according to the Time and Events Schedule presented in Section 7.2 (Table 25) of the CHRYSALIS trial protocol, and as clinically indicated. The investigator evaluated sites of disease by radiological imaging, physical examination, and other procedures as necessary, and all results including the tumour response, were recorded in the CRF. At all visits, consistent methodology was to be used for the evaluation of each lesion. Full details of the assessments performed can be found in the CHRYSALIS trial protocol. Disease assessments were required to follow the original schedule until disease progression or death, regardless of discontinuation of study treatment. Disease assessments were to occur prior to initiation of any new anti-cancer therapy for subjects who discontinued study treatment prior to disease progression.[9]

B23. The CS frequently mentions the use of a blinded independent central review (BICR) for the survival analyses. Two references are provided for the BICR. Neither of the two specifies the methodology used for the conduct of the BICR.

Please provide a detailed description of the methodology used for the conduct of the BICR.

In addition to the investigator assessment, scans were centrally collected for potential assessment of response by BICR using RECIST v1.1 criteria. Efficacy for the respective efficacy populations were independently determined by the central vendor, Bioclinica, Inc. (Princeton, NJ US), utilising a 2-reader with adjudication paradigm. Each imaging timepoint for a subject was reviewed in chronological order independently by 2 different radiologists. Cases for which the best response (adjudication variable number 1) or date for first response (adjudication variable number 2) were discordant between the two independent readers were adjudicated to a third independent radiologist, who reviewed both reader evaluations (blinded to the identities of the two primary readers) and chose the evaluation that the third independent radiologist believed most accurate, according to the higher priority variable of best response. Following the radiographic review (and adjudication, if necessary), an independent oncologist incorporated applicable clinical data to determine an overall response assessment.[48]

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Appendix A

Table 43: Concomitant medications in CHRYSALIS, EGFR exon20ins RP2D expanded efficacy analysis set (N=114). 31 March 2021 Data cut-off

Indication	Class 1	Class 2	CMDECOD (treatment)	N patients		
				Between start-end treatment	Pre-	Post-
ADVERSE EVENT	ALIMENTARY TRACT AND METABOLISM	ANTACIDS WITH ANTIFLATULENTS	ALUMINIUM W/MAGNESIUM HYDROXIDE/SIMETICONE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	ALIMENTARY TRACT AND METABOLISM	ANTIBIOTICS	NEOMYCIN	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	ALIMENTARY TRACT AND METABOLISM	ANTIBIOTICS	NYSTATIN	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	ALIMENTARY TRACT AND METABOLISM	ANTIDIARRHEAL MICROORGANISMS	BIO-THREE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	ALIMENTARY TRACT AND METABOLISM	ANTIDIARRHEAL MICROORGANISMS	MEDILAC-S	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	ALIMENTARY TRACT AND METABOLISM	ANTIDIARRHEAL MICROORGANISMS	NATURES WAY PRIMADOPHILUS ORIGINAL	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	ALIMENTARY TRACT AND METABOLISM	ANTIINFECTIVES AND ANTISEPTICS FOR LOCAL ORAL TREATMENT	MAGIC MOUTHWASH	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	ALIMENTARY TRACT AND METABOLISM	ANTIINFECTIVES AND ANTISEPTICS FOR LOCAL ORAL TREATMENT	SM 33	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	ALIMENTARY TRACT AND METABOLISM	ANTIPROPULSIVES	LOPERAMIDE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	ALIMENTARY TRACT AND METABOLISM	ANTIPROPULSIVES	LOPERAMIDE HYDROCHLORIDE	[redacted]	[redacted]	[redacted]

ADVERSE EVENT	ALIMENTARY TRACT AND METABOLISM	APPETITE STIMULANTS	CARNITINE HYDROCHLORIDE W/CYANOCOBA/08463401/	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	ALIMENTARY TRACT AND METABOLISM	BELLADONNA ALKALOIDS, SEMISYNTHETIC, QUATERNARY AMMONIUM COMPOUNDS	CIMETROPIUM BROMIDE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	ALIMENTARY TRACT AND METABOLISM	BELLADONNA ALKALOIDS, SEMISYNTHETIC, QUATERNARY AMMONIUM COMPOUNDS	HYOSCINE BUTYLBROMIDE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	ALIMENTARY TRACT AND METABOLISM	BIGUANIDES	METFORMIN HYDROCHLORIDE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	ALIMENTARY TRACT AND METABOLISM	BILE ACID PREPARATIONS	URSODEOXYCHOLIC ACID	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	ALIMENTARY TRACT AND METABOLISM	BULK-FORMING LAXATIVES	POLYCARBOPHIL CALCIUM	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	ALIMENTARY TRACT AND METABOLISM	BULK-FORMING LAXATIVES	PSYLLIUM HYDROPHILIC MUCILLOID	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	ALIMENTARY TRACT AND METABOLISM	CALCIUM	CALCIUM CHLORIDE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	ALIMENTARY TRACT AND METABOLISM	CALCIUM	CALCIUM GLUCONATE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	ALIMENTARY TRACT AND METABOLISM	CALCIUM COMPOUNDS	CALCIUM CARBONATE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	ALIMENTARY TRACT AND METABOLISM	CALCIUM, COMBINATIONS WITH VITAMIN D AND/OR OTHER DRUGS	CALCIDO	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	ALIMENTARY TRACT AND METABOLISM	CALCIUM, COMBINATIONS WITH VITAMIN D AND/OR OTHER DRUGS	LEKOVIT CA	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	ALIMENTARY TRACT AND METABOLISM	COMBINATIONS AND COMPLEXES OF	ALUDROX /00082501/	[redacted]	[redacted]	[redacted]

		ALUMINIUM, CALCIUM AND MAGNESIUM COMPOUNDS				
ADVERSE EVENT	ALIMENTARY TRACT AND METABOLISM	CONTACT LAXATIVES	BISACODYL	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	ALIMENTARY TRACT AND METABOLISM	CONTACT LAXATIVES	COLOXYL WITH SENNA	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	ALIMENTARY TRACT AND METABOLISM	CONTACT LAXATIVES	DULCODOS	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	ALIMENTARY TRACT AND METABOLISM	CONTACT LAXATIVES	SENNOSIDE A+B	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	ALIMENTARY TRACT AND METABOLISM	CORTICOSTEROIDS ACTING LOCALLY	HYDROCORTISONE VALERATE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	ALIMENTARY TRACT AND METABOLISM	DRUGS FOR BILE THERAPY AND LIPOTROPICS IN COMBINATION	UDB /07159101/	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	ALIMENTARY TRACT AND METABOLISM	DRUGS FOR PEPTIC ULCER AND GASTRO-OESOPHAGEAL REFLUX DISEASE (GORD)	TEPRENONE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	ALIMENTARY TRACT AND METABOLISM	ENEMAS	ENEMAS	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	ALIMENTARY TRACT AND METABOLISM	ENZYME PREPARATIONS	PANCREATIN	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	ALIMENTARY TRACT AND METABOLISM	H2-RECEPTOR ANTAGONISTS	FAMOTIDINE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	ALIMENTARY TRACT AND METABOLISM	H2-RECEPTOR ANTAGONISTS	RANITIDINE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	ALIMENTARY TRACT AND METABOLISM	H2-RECEPTOR ANTAGONISTS	RANITIDINE HYDROCHLORIDE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	ALIMENTARY TRACT AND METABOLISM	INSULINS AND ANALOGUES FOR INJECTION, FAST-ACTING	INSULIN	[redacted]	[redacted]	[redacted]

ADVERSE EVENT	ALIMENTARY TRACT AND METABOLISM	INSULINS AND ANALOGUES FOR INJECTION, FAST-ACTING	INSULIN HUMAN	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	ALIMENTARY TRACT AND METABOLISM	LIVER THERAPY	GODEX	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	ALIMENTARY TRACT AND METABOLISM	MAGNESIUM	DYNAMAG	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	ALIMENTARY TRACT AND METABOLISM	MAGNESIUM	MAG64	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	ALIMENTARY TRACT AND METABOLISM	MAGNESIUM	MAGNESIUM	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	ALIMENTARY TRACT AND METABOLISM	MAGNESIUM	MAGNESIUM ASPARTATE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	ALIMENTARY TRACT AND METABOLISM	MAGNESIUM	MAGNESIUM CHLORIDE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	ALIMENTARY TRACT AND METABOLISM	MAGNESIUM	MAGNESIUM SULFATE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	ALIMENTARY TRACT AND METABOLISM	MAGNESIUM COMPOUNDS	MAGNESIUM OXIDE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	ALIMENTARY TRACT AND METABOLISM	MULTIVITAMINS, OTHER COMBINATIONS	ASCORBIC ACID W/BIOTIN/CALCIUM CHLORIDE/CALCI	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	ALIMENTARY TRACT AND METABOLISM	ORAL REHYDRATION SALT FORMULATIONS	GASTROLIT /05812201/	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	ALIMENTARY TRACT AND METABOLISM	OSMOTICALLY ACTING LAXATIVES	ELECTROLYTES NOS W/MACROGOL 3350	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	ALIMENTARY TRACT AND METABOLISM	OSMOTICALLY ACTING LAXATIVES	LACTULOSE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	ALIMENTARY TRACT AND METABOLISM	OSMOTICALLY ACTING LAXATIVES	MACROGOL	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	ALIMENTARY TRACT AND METABOLISM	OSMOTICALLY ACTING LAXATIVES	MACROGOL 3350	[redacted]	[redacted]	[redacted]

ADVERSE EVENT	ALIMENTARY TRACT AND METABOLISM	OSMOTICALLY ACTING LAXATIVES	MOVICOL	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	ALIMENTARY TRACT AND METABOLISM	OTHER AGENTS FOR LOCAL ORAL TREATMENT	ALOCLAIR /06503801/	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	ALIMENTARY TRACT AND METABOLISM	OTHER AGENTS FOR LOCAL ORAL TREATMENT	FIRST BLM	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	ALIMENTARY TRACT AND METABOLISM	OTHER AGENTS FOR LOCAL ORAL TREATMENT	MENTHA X PIPERITA OIL W/METHYL SALICYLATE/SOD	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	ALIMENTARY TRACT AND METABOLISM	OTHER AGENTS FOR LOCAL ORAL TREATMENT	OTHER AGENTS FOR LOCAL ORAL TREATMENT	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	ALIMENTARY TRACT AND METABOLISM	OTHER AGENTS FOR LOCAL ORAL TREATMENT	SODIUM GUALENATE HYDRATE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	ALIMENTARY TRACT AND METABOLISM	OTHER DRUGS FOR CONSTIPATION	GLYCEROL	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	ALIMENTARY TRACT AND METABOLISM	OTHER DRUGS FOR FUNCTIONAL GASTROINTESTINAL DISORDERS	SPASFON /00765801/	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	ALIMENTARY TRACT AND METABOLISM	OTHER DRUGS FOR PEPTIC ULCER AND GASTRO-OESOPHAGEAL REFLUX DISEASE (GORD)	ECABET MONOSODIUM	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	ALIMENTARY TRACT AND METABOLISM	OTHER INTESTINAL ADSORBENTS	DIOSMECTITE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	ALIMENTARY TRACT AND METABOLISM	OTHER MINERAL PRODUCTS	PHOS-NAK	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	ALIMENTARY TRACT AND METABOLISM	OTHER PLAIN VITAMIN PREPARATIONS	DEXPANTHENOL	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	ALIMENTARY TRACT AND METABOLISM	OTHER PLAIN VITAMIN PREPARATIONS	FLAVINE ADENINE DINUCLEOTIDE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	ALIMENTARY TRACT AND METABOLISM	PERIPHERAL OPIOID RECEPTOR ANTAGONISTS	NALOXEGOL OXALATE	[redacted]	[redacted]	[redacted]

ADVERSE EVENT	ALIMENTARY TRACT AND METABOLISM	POTASSIUM	POTASSIUM	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	ALIMENTARY TRACT AND METABOLISM	POTASSIUM	POTASSIUM CHLORIDE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	ALIMENTARY TRACT AND METABOLISM	PROPULSIVES	ITOPRIDE HYDROCHLORIDE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	ALIMENTARY TRACT AND METABOLISM	PROPULSIVES	METOCLOPRAMIDE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	ALIMENTARY TRACT AND METABOLISM	PROPULSIVES	METOCLOPRAMIDE HYDROCHLORIDE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	ALIMENTARY TRACT AND METABOLISM	PROPULSIVES	MOSAPRIDE CITRATE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	ALIMENTARY TRACT AND METABOLISM	PROTON PUMP INHIBITORS	ESOMEPRAZOLE MAGNESIUM	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	ALIMENTARY TRACT AND METABOLISM	PROTON PUMP INHIBITORS	OMEPRAZOLE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	ALIMENTARY TRACT AND METABOLISM	PROTON PUMP INHIBITORS	PANTOPRAZOLE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	ALIMENTARY TRACT AND METABOLISM	PROTON PUMP INHIBITORS	PANTOPRAZOLE MAGNESIUM	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	ALIMENTARY TRACT AND METABOLISM	PROTON PUMP INHIBITORS	PANTOPRAZOLE SODIUM SESQUIHYDRATE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	ALIMENTARY TRACT AND METABOLISM	PROTON PUMP INHIBITORS	RABEPRAZOLE SODIUM	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	ALIMENTARY TRACT AND METABOLISM	PROTON PUMP INHIBITORS	VONOPRAZAN FUMARATE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	ALIMENTARY TRACT AND METABOLISM	SEROTONIN (5HT3) ANTAGONISTS	GRANISETRON	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	ALIMENTARY TRACT AND METABOLISM	SEROTONIN (5HT3) ANTAGONISTS	GRANISETRON HYDROCHLORIDE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	ALIMENTARY TRACT AND METABOLISM	SEROTONIN (5HT3) ANTAGONISTS	ONDANSETRON	[redacted]	[redacted]	[redacted]

ADVERSE EVENT	ALIMENTARY TRACT AND METABOLISM	SEROTONIN (5HT3) ANTAGONISTS	ONDANSETRON HYDROCHLORIDE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	ALIMENTARY TRACT AND METABOLISM	SEROTONIN (5HT3) ANTAGONISTS	RAMOSETRON HYDROCHLORIDE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	ALIMENTARY TRACT AND METABOLISM	SODIUM-GLUCOSE CO-TRANSPORTER 2 (SGLT2) INHIBITORS	DAPAGLIFLOZIN PROPANEDIOL MONOHYDRATE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	ALIMENTARY TRACT AND METABOLISM	SOFTENERS, EMOLLIENTS	DOCUSATE SODIUM	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	ALIMENTARY TRACT AND METABOLISM	SYNTHETIC ANTICHOLINERGICS, ESTERS WITH TERTIARY AMINO GROUP	TRIMEBUTINE MALEATE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	ALIMENTARY TRACT AND METABOLISM	SYNTHETIC ANTISPASMODICS, AMIDES WITH TERTIARY AMINES	TIROPRAMIDE HYDROCHLORIDE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	ALIMENTARY TRACT AND METABOLISM	VARIOUS ALIMENTARY TRACT AND METABOLISM PRODUCTS	PHOSPHORUS	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	ALIMENTARY TRACT AND METABOLISM	VARIOUS ALIMENTARY TRACT AND METABOLISM PRODUCTS	UBIDECARENONE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	ALIMENTARY TRACT AND METABOLISM	VITAMIN B1, PLAIN	THIAMINE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	ALIMENTARY TRACT AND METABOLISM	VITAMIN D AND ANALOGUES	VITAMIN D NOS	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	ALIMENTARY TRACT AND METABOLISM	VITAMINS, OTHER COMBINATIONS	FORCAPIL	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	ANTIINFECTIVES FOR SYSTEMIC USE	AMPHENICOLS	CHLORAMPHENICOL	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	ANTIINFECTIVES FOR SYSTEMIC USE	ANTIBACTERIALS FOR SYSTEMIC USE	ANTIBIOTICS	[redacted]	[redacted]	[redacted]

ADVERSE EVENT	ANTIINFECTIVES FOR SYSTEMIC USE	ANTIBACTERIALS FOR SYSTEMIC USE	BROAD SPECTRUM ANTIBIOTICS	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	ANTIINFECTIVES FOR SYSTEMIC USE	ANTIBIOTICS	AMPHOTERICIN B	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	ANTIINFECTIVES FOR SYSTEMIC USE	BETA-LACTAMASE INHIBITORS	CLAVULANIC ACID	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	ANTIINFECTIVES FOR SYSTEMIC USE	BETA-LACTAMASE RESISTANT PENICILLINS	CLOXACILLIN SODIUM	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	ANTIINFECTIVES FOR SYSTEMIC USE	BETA-LACTAMASE RESISTANT PENICILLINS	DICLOXACILLIN	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	ANTIINFECTIVES FOR SYSTEMIC USE	BETA-LACTAMASE RESISTANT PENICILLINS	FLUCLOXACILLIN	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	ANTIINFECTIVES FOR SYSTEMIC USE	CARBAPENEMS	ERTAPENEM	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	ANTIINFECTIVES FOR SYSTEMIC USE	CARBAPENEMS	MEROPENEM	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	ANTIINFECTIVES FOR SYSTEMIC USE	COMBINATIONS OF PENICILLINS, INCL. BETA-LACTAMASE INHIBITORS	AMOXICILLIN W/CLAVULANATE POTASSIUM	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	ANTIINFECTIVES FOR SYSTEMIC USE	COMBINATIONS OF PENICILLINS, INCL. BETA-LACTAMASE INHIBITORS	AUGMENTIN /00756801/	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	ANTIINFECTIVES FOR SYSTEMIC USE	COMBINATIONS OF PENICILLINS, INCL. BETA-LACTAMASE INHIBITORS	PIP/TAZO	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	ANTIINFECTIVES FOR SYSTEMIC USE	COMBINATIONS OF PENICILLINS, INCL. BETA-LACTAMASE INHIBITORS	PIPERACILLIN SODIUM W/TAZOBACTAM	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	ANTIINFECTIVES FOR SYSTEMIC USE	COMBINATIONS OF PENICILLINS, INCL. BETA-LACTAMASE INHIBITORS	PIPERACILLIN W/TAZOBACTAM /01606301/	[redacted]	[redacted]	[redacted]

ADVERSE EVENT	ANTIINFECTIVES FOR SYSTEMIC USE	COMBINATIONS OF PENICILLINS, INCL. BETA-LACTAMASE INHIBITORS	SPEKTRAMOX	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	ANTIINFECTIVES FOR SYSTEMIC USE	COMBINATIONS OF SULFONAMIDES AND TRIMETHOPRIM, INCL. DERIVATIVES	BACTRIM	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	ANTIINFECTIVES FOR SYSTEMIC USE	FIRST-GENERATION CEPHALOSPORINS	CEFADROXIL	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	ANTIINFECTIVES FOR SYSTEMIC USE	FIRST-GENERATION CEPHALOSPORINS	CEFALEXIN	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	ANTIINFECTIVES FOR SYSTEMIC USE	FIRST-GENERATION CEPHALOSPORINS	CEFAZOLIN	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	ANTIINFECTIVES FOR SYSTEMIC USE	FIRST-GENERATION CEPHALOSPORINS	CEFAZOLIN SODIUM	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	ANTIINFECTIVES FOR SYSTEMIC USE	FIRST-GENERATION CEPHALOSPORINS	CEFRADINE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	ANTIINFECTIVES FOR SYSTEMIC USE	FLUOROQUINOLONES	CIPROFLOXACIN	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	ANTIINFECTIVES FOR SYSTEMIC USE	FLUOROQUINOLONES	LEVOFLOXACIN	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	ANTIINFECTIVES FOR SYSTEMIC USE	FLUOROQUINOLONES	MOXIFLOXACIN	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	ANTIINFECTIVES FOR SYSTEMIC USE	FLUOROQUINOLONES	OFLOXACIN	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	ANTIINFECTIVES FOR SYSTEMIC USE	FOURTH-GENERATION CEPHALOSPORINS	CEFEPIME	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	ANTIINFECTIVES FOR SYSTEMIC USE	GLYCOPEPTIDE ANTIBACTERIALS	TEICOPLANIN	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	ANTIINFECTIVES FOR SYSTEMIC USE	GLYCOPEPTIDE ANTIBACTERIALS	VANCOMYCIN	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	ANTIINFECTIVES FOR SYSTEMIC USE	IMIDAZOLE DERIVATIVES	KETOCONAZOLE	[redacted]	[redacted]	[redacted]

ADVERSE EVENT	ANTIINFECTIVES FOR SYSTEMIC USE	LINCOSAMIDES	CLINDAMYCIN	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	ANTIINFECTIVES FOR SYSTEMIC USE	LINCOSAMIDES	CLINDAMYCIN HYDROCHLORIDE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	ANTIINFECTIVES FOR SYSTEMIC USE	LINCOSAMIDES	CLINDAMYCIN PHOSPHATE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	ANTIINFECTIVES FOR SYSTEMIC USE	MACROLIDES	AZITHROMYCIN	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	ANTIINFECTIVES FOR SYSTEMIC USE	MACROLIDES	CLARITHROMYCIN	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	ANTIINFECTIVES FOR SYSTEMIC USE	MACROLIDES	ERYTHROMYCIN	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	ANTIINFECTIVES FOR SYSTEMIC USE	MACROLIDES	ROXITHROMYCIN	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	ANTIINFECTIVES FOR SYSTEMIC USE	MONOBACTAMS	AZTREONAM	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	ANTIINFECTIVES FOR SYSTEMIC USE	NEURAMINIDASE INHIBITORS	OSELTAMIVIR PHOSPHATE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	ANTIINFECTIVES FOR SYSTEMIC USE	NUCLEOSIDES AND NUCLEOTIDES EXCL. REVERSE TRANSCRIPTASE INHIBITORS	ACICLOVIR	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	ANTIINFECTIVES FOR SYSTEMIC USE	NUCLEOSIDES AND NUCLEOTIDES EXCL. REVERSE TRANSCRIPTASE INHIBITORS	FAMCICLOVIR	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	ANTIINFECTIVES FOR SYSTEMIC USE	NUCLEOSIDES AND NUCLEOTIDES EXCL. REVERSE TRANSCRIPTASE INHIBITORS	VALACICLOVIR HYDROCHLORIDE	[redacted]	[redacted]	[redacted]

ADVERSE EVENT	ANTIINFECTIVES FOR SYSTEMIC USE	OTHER AMINOGLYCOSIDES	GENTAMICIN	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	ANTIINFECTIVES FOR SYSTEMIC USE	OTHER AMINOGLYCOSIDES	GENTAMICIN SULFATE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	ANTIINFECTIVES FOR SYSTEMIC USE	OTHER ANTIBACTERIALS	FOSFOMYCIN	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	ANTIINFECTIVES FOR SYSTEMIC USE	OTHER ANTIBACTERIALS	METHENAMINE HIPPURATE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	ANTIINFECTIVES FOR SYSTEMIC USE	PENICILLINS WITH EXTENDED SPECTRUM	AMOXICILLIN	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	ANTIINFECTIVES FOR SYSTEMIC USE	PENICILLINS WITH EXTENDED SPECTRUM	AMPICILLIN	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	ANTIINFECTIVES FOR SYSTEMIC USE	PENICILLINS WITH EXTENDED SPECTRUM	PIPERACILLIN SODIUM	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	ANTIINFECTIVES FOR SYSTEMIC USE	SECOND-GENERATION CEPHALOSPORINS	CEFACLOR	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	ANTIINFECTIVES FOR SYSTEMIC USE	STREPTOGRAMINS	PRISTINAMYCIN	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	ANTIINFECTIVES FOR SYSTEMIC USE	TETRACYCLINES	DOXYCYCLINE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	ANTIINFECTIVES FOR SYSTEMIC USE	TETRACYCLINES	DOXYCYCLINE HYCLATE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	ANTIINFECTIVES FOR SYSTEMIC USE	TETRACYCLINES	MINOCYCLINE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	ANTIINFECTIVES FOR SYSTEMIC USE	TETRACYCLINES	MINOCYCLINE HYDROCHLORIDE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	ANTIINFECTIVES FOR SYSTEMIC USE	TETRACYCLINES	OXYTETRACYCLINE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	ANTIINFECTIVES FOR SYSTEMIC USE	TETRACYCLINES	TETRACYCLINE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	ANTIINFECTIVES FOR SYSTEMIC USE	THIRD-GENERATION CEPHALOSPORINS	CEFCAPENE PIVOXIL HYDROCHLORIDE	[redacted]	[redacted]	[redacted]

ADVERSE EVENT	ANTIINFECTIVES FOR SYSTEMIC USE	THIRD-GENERATION CEPHALOSPORINS	CEFPODOXIME	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	ANTIINFECTIVES FOR SYSTEMIC USE	THIRD-GENERATION CEPHALOSPORINS	CEFPODOXIME PROXETIL	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	ANTIINFECTIVES FOR SYSTEMIC USE	THIRD-GENERATION CEPHALOSPORINS	CEFTRIAXONE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	ANTIINFECTIVES FOR SYSTEMIC USE	THIRD-GENERATION CEPHALOSPORINS	CEFTRIAXONE SODIUM	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	ANTIINFECTIVES FOR SYSTEMIC USE	TRIAZOLE DERIVATIVES	ITRACONAZOLE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	ANTIINFECTIVES FOR SYSTEMIC USE	TRIAZOLE DERIVATIVES	VORICONAZOLE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS	CALCINEURIN INHIBITORS	CICLOSPORIN	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS	CALCINEURIN INHIBITORS	TACROLIMUS	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS	COLONY STIMULATING FACTORS	FILGRASTIM	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	ANTIPARASITIC PRODUCTS, INSECTICIDES AND REPELLENTS	AMINOQUINOLINES	HYDROXYCHLOROQUINE PHOSPHATE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	BLOOD AND BLOOD FORMING ORGANS	AMINO ACIDS	TRANEXAMIC ACID	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	BLOOD AND BLOOD FORMING ORGANS	BLOOD COAGULATION FACTORS	FACTOR VIII (ANTIHAEMOPHILIC FACTOR)	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	BLOOD AND BLOOD FORMING ORGANS	BLOOD SUBSTITUTES AND PLASMA PROTEIN FRACTIONS	ALBUMIN HUMAN	[redacted]	[redacted]	[redacted]

ADVERSE EVENT	BLOOD AND BLOOD FORMING ORGANS	BLOOD SUBSTITUTES AND PLASMA PROTEIN FRACTIONS	POVIDONE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	BLOOD AND BLOOD FORMING ORGANS	DIRECT FACTOR XA INHIBITORS	APIXABAN	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	BLOOD AND BLOOD FORMING ORGANS	DIRECT FACTOR XA INHIBITORS	EDOXABAN	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	BLOOD AND BLOOD FORMING ORGANS	DIRECT FACTOR XA INHIBITORS	RIVAROXABAN	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	BLOOD AND BLOOD FORMING ORGANS	ELECTROLYTE SOLUTIONS	POTASSIUM W/SODIUM CHLORIDE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	BLOOD AND BLOOD FORMING ORGANS	FOLIC ACID AND DERIVATIVES	FOLIC ACID	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	BLOOD AND BLOOD FORMING ORGANS	HEPARIN GROUP	DALTEPARIN	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	BLOOD AND BLOOD FORMING ORGANS	HEPARIN GROUP	ENOXAPARIN	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	BLOOD AND BLOOD FORMING ORGANS	HEPARIN GROUP	ENOXAPARIN SODIUM	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	BLOOD AND BLOOD FORMING ORGANS	HEPARIN GROUP	HEPARIN	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	BLOOD AND BLOOD FORMING ORGANS	HEPARIN GROUP	HEPARINOID	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	BLOOD AND BLOOD FORMING ORGANS	HEPARIN GROUP	MUCOPOLYSACCHARIDE POLYSULFURIC ACID ESTER	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	BLOOD AND BLOOD FORMING ORGANS	HEPARIN GROUP	TINZAPARIN	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	BLOOD AND BLOOD FORMING ORGANS	HEPARIN GROUP	TINZAPARIN SODIUM	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	BLOOD AND BLOOD FORMING ORGANS	IRON BIVALENT, ORAL PREPARATIONS	FERROUS FUMARATE	[redacted]	[redacted]	[redacted]

ADVERSE EVENT	BLOOD AND BLOOD FORMING ORGANS	IRON BIVALENT, ORAL PREPARATIONS	FERROUS SULFATE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	BLOOD AND BLOOD FORMING ORGANS	IRON PREPARATIONS	IRON	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	BLOOD AND BLOOD FORMING ORGANS	IRON, PARENTERAL PREPARATIONS	FERRIC CARBOXYMALTOSE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	BLOOD AND BLOOD FORMING ORGANS	LOCAL HEMOSTATICS	FERRIC SUBSULFATE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	BLOOD AND BLOOD FORMING ORGANS	OTHER ANTIANEMIC PREPARATIONS	DARBEPOETIN ALFA	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	BLOOD AND BLOOD FORMING ORGANS	OTHER BLOOD PRODUCTS	RED BLOOD CELLS, CONCENTRATED	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	BLOOD AND BLOOD FORMING ORGANS	SALT SOLUTIONS	SODIUM BICARBONATE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	BLOOD AND BLOOD FORMING ORGANS	SALT SOLUTIONS	SODIUM CHLORIDE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	BLOOD AND BLOOD FORMING ORGANS	SOLUTIONS AFFECTING THE ELECTROLYTE BALANCE	FLEBOBAG RING LACT	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	BLOOD AND BLOOD FORMING ORGANS	SOLUTIONS AFFECTING THE ELECTROLYTE BALANCE	RINGER-LACTATE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	BLOOD AND BLOOD FORMING ORGANS	SOLUTIONS PRODUCING OSMOTIC DIURESIS	MANNITOL	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	BLOOD AND BLOOD FORMING ORGANS	VITAMIN K	PHYTOMENADIONE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	CARDIOVASCULAR SYSTEM	ADRENERGIC AND DOPAMINERGIC AGENTS	NOREPINEPHRINE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	CARDIOVASCULAR SYSTEM	ALDOSTERONE ANTAGONISTS	SPIRONOLACTONE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	CARDIOVASCULAR SYSTEM	ALPHA-ADRENORECEPTOR ANTAGONISTS	DOXAZOSIN	[redacted]	[redacted]	[redacted]

ADVERSE EVENT	CARDIOVASCULAR SYSTEM	ALPHA-ADRENORECEPTOR ANTAGONISTS	DOXAZOSIN MESILATE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	CARDIOVASCULAR SYSTEM	ANGIOTENSIN II ANTAGONISTS, PLAIN	TELMISARTAN	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	CARDIOVASCULAR SYSTEM	ANTIARRHYTHMICS, CLASS III	AMIODARONE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	CARDIOVASCULAR SYSTEM	ANTIVARICOSE THERAPY	HEMOAL	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	CARDIOVASCULAR SYSTEM	BENZOTHIAZEPINE DERIVATIVES	DILTIAZEM HYDROCHLORIDE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	CARDIOVASCULAR SYSTEM	BETA BLOCKING AGENTS, NON-SELECTIVE	PROPRANOLOL HYDROCHLORIDE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	CARDIOVASCULAR SYSTEM	BETA BLOCKING AGENTS, SELECTIVE	BISOPROLOL	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	CARDIOVASCULAR SYSTEM	BETA BLOCKING AGENTS, SELECTIVE	METOPROLOL	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	CARDIOVASCULAR SYSTEM	BIOFLAVONOIDS	CAPIVEN	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	CARDIOVASCULAR SYSTEM	CORTICOSTEROIDS	FLUOCINONIDE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	CARDIOVASCULAR SYSTEM	CORTICOSTEROIDS	JAMPZINC HC	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	CARDIOVASCULAR SYSTEM	CORTICOSTEROIDS	LEVAN H	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	CARDIOVASCULAR SYSTEM	CORTICOSTEROIDS	NERIPROCT	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	CARDIOVASCULAR SYSTEM	CORTICOSTEROIDS	PREDNISOLONE METASULFOBENZOATE SODIUM	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	CARDIOVASCULAR SYSTEM	DIHYDROPYRIDINE DERIVATIVES	NICARDIPINE	[redacted]	[redacted]	[redacted]

ADVERSE EVENT	CARDIOVASCULAR SYSTEM	HMG COA REDUCTASE INHIBITORS	ATORVASTATIN	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	CARDIOVASCULAR SYSTEM	ORGANIC NITRATES	GLYCERYL TRINITRATE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	CARDIOVASCULAR SYSTEM	SULFONAMIDES, PLAIN	FUROSEMIDE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	DERMATOLOGICALS	AGENTS FOR DERMATITIS, EXCLUDING CORTICOSTEROIDS	ALITRETINOIN	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	DERMATOLOGICALS	ANESTHETICS FOR TOPICAL USE	BENZOCAINE W/CHLORPHENAMINE MALEATE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	DERMATOLOGICALS	ANTIFUNGALS FOR SYSTEMIC USE	TERBINAFINE HYDROCHLORIDE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	DERMATOLOGICALS	ANTIINFECTIVES FOR TREATMENT OF ACNE	BENZACLIN TOPICAL	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	DERMATOLOGICALS	ANTIINFECTIVES FOR TREATMENT OF ACNE	BENZOYL PEROXIDE W/CLINDAMYCIN	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	DERMATOLOGICALS	ANTIINFECTIVES FOR TREATMENT OF ACNE	NADIFLOXACIN	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	DERMATOLOGICALS	ANTIVIRALS	DOCOSANOL	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	DERMATOLOGICALS	CARBAMIDE PRODUCTS	OPTIDERM /01148801/	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	DERMATOLOGICALS	CARBAMIDE PRODUCTS	UREA	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	DERMATOLOGICALS	CICATRIZANTS	NEPIDERMIN	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	DERMATOLOGICALS	CORTICOSTEROIDS, MODERATELY POTENT (GROUP II)	ALCLOMETASONE DIPROPIONATE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	DERMATOLOGICALS	CORTICOSTEROIDS, MODERATELY POTENT (GROUP II)	CLOBETASONE BUTYRATE	[redacted]	[redacted]	[redacted]

ADVERSE EVENT	DERMATOLOGICALS	CORTICOSTEROIDS, MODERATELY POTENT (GROUP II)	DESONIDE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	DERMATOLOGICALS	CORTICOSTEROIDS, MODERATELY POTENT (GROUP II)	FLUOROMETHOLONE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	DERMATOLOGICALS	CORTICOSTEROIDS, MODERATELY POTENT (GROUP II)	FLUOROMETHOLONE ACETATE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	DERMATOLOGICALS	CORTICOSTEROIDS, MODERATELY POTENT (GROUP II)	TRIAMCINOLONE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	DERMATOLOGICALS	CORTICOSTEROIDS, MODERATELY POTENT, COMBINATIONS WITH ANTIBIOTICS	MYCOLOG	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	DERMATOLOGICALS	CORTICOSTEROIDS, MODERATELY POTENT, COMBINATIONS WITH ANTIBIOTICS	POSITON /06400001/	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	DERMATOLOGICALS	CORTICOSTEROIDS, POTENT (GROUP III)	BETAMETHASONE BUTYRATE PROPIONATE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	DERMATOLOGICALS	CORTICOSTEROIDS, POTENT (GROUP III)	BUDESONIDE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	DERMATOLOGICALS	CORTICOSTEROIDS, POTENT (GROUP III)	DESOXIMETASONE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	DERMATOLOGICALS	CORTICOSTEROIDS, POTENT (GROUP III)	DIFLORASONE DIACETATE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	DERMATOLOGICALS	CORTICOSTEROIDS, POTENT (GROUP III)	DIFLUCORTOLONE VALERATE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	DERMATOLOGICALS	CORTICOSTEROIDS, POTENT (GROUP III)	DIFLUPREDNATE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	DERMATOLOGICALS	CORTICOSTEROIDS, POTENT (GROUP III)	FLUOCINOLONE ACETONIDE	[redacted]	[redacted]	[redacted]

ADVERSE EVENT	DERMATOLOGICALS	CORTICOSTEROIDS, POTENT (GROUP III)	FLUTICASONE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	DERMATOLOGICALS	CORTICOSTEROIDS, POTENT (GROUP III)	METHYLPREDNISOLONE ACEPONATE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	DERMATOLOGICALS	CORTICOSTEROIDS, POTENT (GROUP III)	MOMETASONE FUROATE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	DERMATOLOGICALS	CORTICOSTEROIDS, POTENT (GROUP III)	PREDNICARBATE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	DERMATOLOGICALS	CORTICOSTEROIDS, POTENT (GROUP III)	ULOBETASOL PROPIONATE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	DERMATOLOGICALS	CORTICOSTEROIDS, POTENT, COMBINATIONS WITH ANTIBIOTICS	DIPROGENT /00541301/	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	DERMATOLOGICALS	CORTICOSTEROIDS, POTENT, COMBINATIONS WITH ANTIBIOTICS	DIPROGENTA	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	DERMATOLOGICALS	CORTICOSTEROIDS, POTENT, COMBINATIONS WITH ANTIBIOTICS	FUCICORT	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	DERMATOLOGICALS	CORTICOSTEROIDS, POTENT, COMBINATIONS WITH ANTIBIOTICS	VALISONE-G	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	DERMATOLOGICALS	CORTICOSTEROIDS, POTENT, OTHER COMBINATIONS	BETADERMIC	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	DERMATOLOGICALS	CORTICOSTEROIDS, VERY POTENT (GROUP IV)	CLOBETASOL	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	DERMATOLOGICALS	CORTICOSTEROIDS, VERY POTENT (GROUP IV)	CLOBETASOL PROPIONATE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	DERMATOLOGICALS	CORTICOSTEROIDS, WEAK (GROUP I)	HYDROCORTISONE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	DERMATOLOGICALS	CORTICOSTEROIDS, WEAK (GROUP I)	HYDROCORTISONE VALERATE	[redacted]	[redacted]	[redacted]

ADVERSE EVENT	DERMATOLOGICALS	CORTICOSTEROIDS, WEAK (GROUP I)	METHYLPREDNISOLONE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	DERMATOLOGICALS	CORTICOSTEROIDS, WEAK, COMBINATIONS WITH ANTIBIOTICS	HYDROCORTISON MED TERRAMYCIN	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	DERMATOLOGICALS	EMOLLIENTS AND PROTECTIVES	EMOLLIENTS AND PROTECTIVES	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	DERMATOLOGICALS	IMIDAZOLE AND TRIAZOLE DERIVATIVES	CLOTRIMAZOLE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	DERMATOLOGICALS	IMIDAZOLE AND TRIAZOLE DERIVATIVES	EFINACONAZOLE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	DERMATOLOGICALS	IMIDAZOLE AND TRIAZOLE DERIVATIVES	FLUCONAZOLE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	DERMATOLOGICALS	IMIDAZOLE AND TRIAZOLE DERIVATIVES	LOTRISONE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	DERMATOLOGICALS	IMIDAZOLE AND TRIAZOLE DERIVATIVES	SERTACONAZOLE NITRATE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	DERMATOLOGICALS	IMIDAZOLE AND TRIAZOLE DERIVATIVES	TRAVOCORT	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	DERMATOLOGICALS	MEDICATED DRESSINGS WITH ANTIINFECTIVES	CHARCOAL, ACTIVATED W/SILVER SULFATE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	DERMATOLOGICALS	OTHER ANTIBIOTICS FOR TOPICAL USE	CENTELLA ASIATICA;NEOMYCIN	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	DERMATOLOGICALS	OTHER ANTIBIOTICS FOR TOPICAL USE	MUPIROCIN	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	DERMATOLOGICALS	OTHER ANTIBIOTICS FOR TOPICAL USE	MUPIROCIN CALCIUM	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	DERMATOLOGICALS	OTHER ANTIBIOTICS FOR TOPICAL USE	NEOSPORIN /00130801/	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	DERMATOLOGICALS	OTHER ANTIBIOTICS FOR TOPICAL USE	NEOTRACIN /00038301/	[redacted]	[redacted]	[redacted]

ADVERSE EVENT	DERMATOLOGICALS	OTHER ANTIFUNGALS FOR TOPICAL USE	CICLOPIROX	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	DERMATOLOGICALS	OTHER ANTIPSORIATICS FOR TOPICAL USE	DAIVOBET	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	DERMATOLOGICALS	OTHER ANTISEPTICS AND DISINFECTANTS	COPPER SULFATE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	DERMATOLOGICALS	OTHER ANTISEPTICS AND DISINFECTANTS	DERMO-CUIVRE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	DERMATOLOGICALS	OTHER ANTISEPTICS AND DISINFECTANTS	LACTICARE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	DERMATOLOGICALS	OTHER ANTISEPTICS AND DISINFECTANTS	POTASSIUM PERMANGANATE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	DERMATOLOGICALS	OTHER DERMATOLOGICALS	OTHER DERMATOLOGICALS	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	DERMATOLOGICALS	OTHER DERMATOLOGICALS	PYRITHIONE ZINC	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	DERMATOLOGICALS	OTHER EMOLLIENTS AND PROTECTIVES	CERAMIDE W/PALMITIC ACID/PARAFFIN, LIQUID/PHY	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	DERMATOLOGICALS	OTHER EMOLLIENTS AND PROTECTIVES	DEXERYL /01579901/	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	DERMATOLOGICALS	OTHER EMOLLIENTS AND PROTECTIVES	OTHER EMOLLIENTS AND PROTECTIVES	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	DERMATOLOGICALS	OTHER EMOLLIENTS AND PROTECTIVES	PARAFFIN SOFT	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	DERMATOLOGICALS	OTHER EMOLLIENTS AND PROTECTIVES	RECONVAL K1	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	DERMATOLOGICALS	OTHER EMOLLIENTS AND PROTECTIVES	SORBOLENE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	DERMATOLOGICALS	PEROXIDES	BENZOYL PEROXIDE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	DERMATOLOGICALS	PHENOL AND DERIVATIVES	TRICLOSAN	[redacted]	[redacted]	[redacted]

ADVERSE EVENT	DERMATOLOGICALS	PREPARATIONS CONTAINING SULFUR	SULFUR	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	DERMATOLOGICALS	QUINOLINE DERIVATIVES	HYDROXYQUINOLINE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	DERMATOLOGICALS	QUINOLINE DERIVATIVES	HYDROXYQUINOLINE SULFATE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	DERMATOLOGICALS	RETINOIDS FOR TOPICAL USE IN ACNE	ADAPALENE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	DERMATOLOGICALS	RETINOIDS FOR TOPICAL USE IN ACNE	EPIDUO	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	DERMATOLOGICALS	RETINOIDS FOR TOPICAL USE IN ACNE	TRETINOIN	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	DERMATOLOGICALS	RETINOIDS FOR TREATMENT OF ACNE	ISOTRETINOIN	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	DERMATOLOGICALS	SALICYLIC ACID PREPARATIONS	SALICYLIC ACID	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	DERMATOLOGICALS	SILICONE PRODUCTS	DIMETICONE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	DERMATOLOGICALS	SILICONE PRODUCTS	SILICON	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	DERMATOLOGICALS	SILVER COMPOUNDS	AQUACEL AG	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	DERMATOLOGICALS	SILVER COMPOUNDS	SILVER NITRATE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	DERMATOLOGICALS	SOFT PARAFFIN AND FAT PRODUCTS	DIPROBASE /01210201/	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	DERMATOLOGICALS	SOFT PARAFFIN AND FAT PRODUCTS	PARAFFIN	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	DERMATOLOGICALS	SOFT PARAFFIN AND FAT PRODUCTS	PETROLATUM	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	DERMATOLOGICALS	SOFT PARAFFIN AND FAT PRODUCTS	QV /02118801/	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	DERMATOLOGICALS	SOFT PARAFFIN AND FAT PRODUCTS	WHITE SOFT PARAFFIN	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	DERMATOLOGICALS	SULFONAMIDES	SULFADIAZINE SILVER	[redacted]	[redacted]	[redacted]

ADVERSE EVENT	DERMATOLOGICALS	TETRACYCLINE AND DERIVATIVES	DOXYCYCLINE HYDROCHLORIDE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	DERMATOLOGICALS	TETRACYCLINE AND DERIVATIVES	OXYTETRACYCLINE HYDROCHLORIDE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	DERMATOLOGICALS	ZINC BANDAGES	ALOPLASTINE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	DERMATOLOGICALS	ZINC PRODUCTS	AVENA SATIVA W/COPPER SULFATE/ZINC OXIDE/ZINC	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	DERMATOLOGICALS	ZINC PRODUCTS	CICALFATE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	DERMATOLOGICALS	ZINC PRODUCTS	DALIBOUR	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	DERMATOLOGICALS	ZINC PRODUCTS	ZINC OXIDE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	GENITO URINARY SYSTEM AND SEX HORMONES	ALPHA-ADRENORECEPTOR ANTAGONISTS	ALFUZOSIN HYDROCHLORIDE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	GENITO URINARY SYSTEM AND SEX HORMONES	ALPHA-ADRENORECEPTOR ANTAGONISTS	TAMSULOSIN	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	GENITO URINARY SYSTEM AND SEX HORMONES	ALPHA-ADRENORECEPTOR ANTAGONISTS	TAMSULOSIN HYDROCHLORIDE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	GENITO URINARY SYSTEM AND SEX HORMONES	DRUGS FOR URINARY FREQUENCY AND INCONTINENCE	MIRABEGRON	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	GENITO URINARY SYSTEM AND SEX HORMONES	DRUGS FOR URINARY FREQUENCY AND INCONTINENCE	VIBEGRON	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	GENITO URINARY SYSTEM AND SEX HORMONES	IMIDAZOLE DERIVATIVES	METRONIDAZOLE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	GENITO URINARY SYSTEM AND SEX HORMONES	IMIDAZOLE DERIVATIVES	SERTACONAZOLE NITRATE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	GENITO URINARY SYSTEM AND SEX HORMONES	OTHER ANTIINFECTIVES AND ANTISEPTICS	CICLOPIROX OLAMINE	[redacted]	[redacted]	[redacted]

ADVERSE EVENT	GENITO URINARY SYSTEM AND SEX HORMONES	OTHER UROLOGICALS	PHENAZOPYRIDINE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	GENITO URINARY SYSTEM AND SEX HORMONES	PROGESTOGENS	MEGESTROL	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	GENITO URINARY SYSTEM AND SEX HORMONES	PROGESTOGENS	MEGESTROL ACETATE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	MUSCULO-SKELETAL SYSTEM	ACETIC ACID DERIVATIVES AND RELATED SUBSTANCES	ACECLOFENAC	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	MUSCULO-SKELETAL SYSTEM	ACETIC ACID DERIVATIVES AND RELATED SUBSTANCES	DICLOFENAC	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	MUSCULO-SKELETAL SYSTEM	ACETIC ACID DERIVATIVES AND RELATED SUBSTANCES	DICLOFENAC SODIUM	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	MUSCULO-SKELETAL SYSTEM	ACETIC ACID DERIVATIVES AND RELATED SUBSTANCES	KETOROLAC	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	MUSCULO-SKELETAL SYSTEM	ACETIC ACID DERIVATIVES AND RELATED SUBSTANCES	KETOROLAC TROMETHAMINE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	MUSCULO-SKELETAL SYSTEM	COXIBS	CELECOXIB	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	MUSCULO-SKELETAL SYSTEM	OTHER ANTIINFLAMMATORY AND ANTIRHEUMATIC AGENTS, NON-STEROIDS	BENZYDAMINE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	MUSCULO-SKELETAL SYSTEM	OTHER ANTIINFLAMMATORY AND ANTIRHEUMATIC AGENTS, NON-STEROIDS	BENZYDAMINE HYDROCHLORIDE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	MUSCULO-SKELETAL SYSTEM	OTHER ANTIINFLAMMATORY AND	NIFLURIL /06114101/	[redacted]	[redacted]	[redacted]

		ANTIRHEUMATIC AGENTS, NON-STEROIDS				
ADVERSE EVENT	MUSCULO-SKELETAL SYSTEM	OTHER CENTRALLY ACTING AGENTS	BACLOFEN	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	MUSCULO-SKELETAL SYSTEM	OTHER TOPICAL PRODUCTS FOR JOINT AND MUSCULAR PAIN	ISOPROPANOL;SALICYLIC ACID	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	MUSCULO-SKELETAL SYSTEM	OXICAMS	MELOXICAM	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	MUSCULO-SKELETAL SYSTEM	PROPIONIC ACID DERIVATIVES	CAROL-F	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	MUSCULO-SKELETAL SYSTEM	PROPIONIC ACID DERIVATIVES	DEXKETOPROFEN TROMETAMOL	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	MUSCULO-SKELETAL SYSTEM	PROPIONIC ACID DERIVATIVES	IBUPROFEN	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	MUSCULO-SKELETAL SYSTEM	PROPIONIC ACID DERIVATIVES	KETOPROFEN	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	MUSCULO-SKELETAL SYSTEM	PROPIONIC ACID DERIVATIVES	LOXOPROFEN SODIUM	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	MUSCULO-SKELETAL SYSTEM	PROPIONIC ACID DERIVATIVES	NAPROXEN	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	MUSCULO-SKELETAL SYSTEM	PROPIONIC ACID DERIVATIVES	VIMOVO	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	NERVOUS SYSTEM	AMIDES	LIDOCAINE HYDROCHLORIDE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	NERVOUS SYSTEM	ANILIDES	PARACETAMOL	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	NERVOUS SYSTEM	ANILIDES	PROPACETAMOL	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	NERVOUS SYSTEM	ANILIDES	PROPACETAMOL HYDROCHLORIDE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	NERVOUS SYSTEM	BENZODIAZEPINE DERIVATIVES	DIAZEPAM	[redacted]	[redacted]	[redacted]

ADVERSE EVENT	NERVOUS SYSTEM	BENZODIAZEPINE DERIVATIVES	LORAZEPAM	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	NERVOUS SYSTEM	BENZODIAZEPINE DERIVATIVES	TEMAZEPAM	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	NERVOUS SYSTEM	BENZODIAZEPINE DERIVATIVES	TRIAZOLAM	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	NERVOUS SYSTEM	BENZODIAZEPINE RELATED DRUGS	ZOLPIDEM	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	NERVOUS SYSTEM	BENZODIAZEPINE RELATED DRUGS	ZOLPIDEM TARTRATE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	NERVOUS SYSTEM	BENZODIAZEPINE RELATED DRUGS	ZOPICLONE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	NERVOUS SYSTEM	BUTYROPHENONE DERIVATIVES	DROPERIDOL	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	NERVOUS SYSTEM	BUTYROPHENONE DERIVATIVES	HALOPERIDOL	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	NERVOUS SYSTEM	CHOLINE ESTERS	BETHANECHOL	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	NERVOUS SYSTEM	CHOLINE ESTERS	BETHANECHOL CHLORIDE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	NERVOUS SYSTEM	DIAZEPINES, OXAZEPINES, THIAZEPINES AND OXEPINES	OLANZAPINE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	NERVOUS SYSTEM	DIPHENYLMETHANE DERIVATIVES	HYDROXYZINE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	NERVOUS SYSTEM	DIPHENYLMETHANE DERIVATIVES	HYDROXYZINE HYDROCHLORIDE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	NERVOUS SYSTEM	DRUGS USED IN OPIOID DEPENDENCE	METHADONE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	NERVOUS SYSTEM	HALOGENATED HYDROCARBONS	SEVOFLURANE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	NERVOUS SYSTEM	NATURAL OPIUM ALKALOIDS	HYDROMORPHONE	[redacted]	[redacted]	[redacted]

ADVERSE EVENT	NERVOUS SYSTEM	NATURAL OPIUM ALKALOIDS	HYDROMORPHONE HYDROCHLORIDE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	NERVOUS SYSTEM	NATURAL OPIUM ALKALOIDS	MORPHINE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	NERVOUS SYSTEM	NATURAL OPIUM ALKALOIDS	MORPHINE HYDROCHLORIDE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	NERVOUS SYSTEM	NATURAL OPIUM ALKALOIDS	MORPHINE SULFATE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	NERVOUS SYSTEM	NATURAL OPIUM ALKALOIDS	OXYCODONE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	NERVOUS SYSTEM	NATURAL OPIUM ALKALOIDS	OXYCODONE HYDROCHLORIDE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	NERVOUS SYSTEM	NATURAL OPIUM ALKALOIDS	TARGIN	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	NERVOUS SYSTEM	NATURAL OPIUM ALKALOIDS	VICODIN	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	NERVOUS SYSTEM	NON-SELECTIVE MONOAMINE REUPTAKE INHIBITORS	DOXEPIN	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	NERVOUS SYSTEM	OPIOID ANESTHETICS	SUFENTANIL	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	NERVOUS SYSTEM	OPIOIDS IN COMBINATION WITH NON-OPIOID ANALGESICS	MYPRODOL	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	NERVOUS SYSTEM	OPIOIDS IN COMBINATION WITH NON-OPIOID ANALGESICS	OXYCOCET	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	NERVOUS SYSTEM	OPIOIDS IN COMBINATION WITH NON-OPIOID ANALGESICS	PANADEINE CO	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	NERVOUS SYSTEM	OPIOIDS IN COMBINATION WITH NON-OPIOID ANALGESICS	PARDALE	[redacted]	[redacted]	[redacted]

ADVERSE EVENT	NERVOUS SYSTEM	OPIOIDS IN COMBINATION WITH NON-OPIOID ANALGESICS	ULTRACET	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	NERVOUS SYSTEM	ORIPAVINE DERIVATIVES	BUPRENORPHINE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	NERVOUS SYSTEM	OTHER ANALGESICS AND ANTIPYRETICS	NEFOPAM	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	NERVOUS SYSTEM	OTHER ANALGESICS AND ANTIPYRETICS	NEFOPAM HYDROCHLORIDE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	NERVOUS SYSTEM	OTHER ANALGESICS AND ANTIPYRETICS	PREGABALIN	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	NERVOUS SYSTEM	OTHER ANTIDEPRESSANTS	DULOXETINE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	NERVOUS SYSTEM	OTHER ANTIDEPRESSANTS	DULOXETINE HYDROCHLORIDE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	NERVOUS SYSTEM	OTHER ANTIDEPRESSANTS	TRAZODONE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	NERVOUS SYSTEM	OTHER ANTIEPILEPTICS	GABAPENTIN	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	NERVOUS SYSTEM	OTHER ANTIEPILEPTICS	LEVETIRACETAM	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	NERVOUS SYSTEM	OTHER GENERAL ANESTHETICS	ETOMIDATE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	NERVOUS SYSTEM	OTHER GENERAL ANESTHETICS	KETAMINE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	NERVOUS SYSTEM	OTHER GENERAL ANESTHETICS	KETAMINE HYDROCHLORIDE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	NERVOUS SYSTEM	OTHER GENERAL ANESTHETICS	PROPOFOL	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	NERVOUS SYSTEM	OTHER OPIOIDS	TAPENTADOL HYDROCHLORIDE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	NERVOUS SYSTEM	OTHER OPIOIDS	TRAMADOL	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	NERVOUS SYSTEM	OTHER OPIOIDS	TRAMADOL HYDROCHLORIDE	[redacted]	[redacted]	[redacted]

ADVERSE EVENT	NERVOUS SYSTEM	PHENOTHIAZINES WITH ALIPHATIC SIDE-CHAIN	CHLORPROMAZINE HYDROCHLORIDE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	NERVOUS SYSTEM	PHENOTHIAZINES WITH PIPERAZINE STRUCTURE	PROCHLORPERAZINE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	NERVOUS SYSTEM	PHENOTHIAZINES WITH PIPERAZINE STRUCTURE	PROCHLORPERAZINE EDISYLATE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	NERVOUS SYSTEM	PHENYLPIPERIDINE DERIVATIVES	FENTANYL	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	NERVOUS SYSTEM	PHENYLPIPERIDINE DERIVATIVES	FENTANYL CITRATE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	NERVOUS SYSTEM	PHENYLPIPERIDINE DERIVATIVES	PETHIDINE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	NERVOUS SYSTEM	PHENYLPIPERIDINE DERIVATIVES	PETHIDINE HYDROCHLORIDE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	NERVOUS SYSTEM	PYRAZOLONES	METAMIZOLE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	NERVOUS SYSTEM	PYRAZOLONES	METAMIZOLE MAGNESIUM	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	NERVOUS SYSTEM	PYRAZOLONES	METAMIZOLE SODIUM	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	NERVOUS SYSTEM	SALICYLIC ACID AND DERIVATIVES	ACETYLSALICYLIC ACID	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	NERVOUS SYSTEM	SALICYLIC ACID AND DERIVATIVES	PANSORAL	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	NERVOUS SYSTEM	SELECTIVE SEROTONIN (5HT1) AGONISTS	ALMOTRIPTAN MALATE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	NERVOUS SYSTEM	SELECTIVE SEROTONIN REUPTAKE INHIBITORS	CITALOPRAM	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	NERVOUS SYSTEM	SELECTIVE SEROTONIN REUPTAKE INHIBITORS	ESCITALOPRAM	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	RESPIRATORY SYSTEM	ADRENERGICS IN COMBINATION WITH ANTICHOLINERGICS	COMBIVENT	[redacted]	[redacted]	[redacted]

ADVERSE EVENT	RESPIRATORY SYSTEM	ADRENERGICS IN COMBINATION WITH CORTICOSTEROIDS OR OTHER DRUGS, EXCL. ANTICHOLINERGICS	BUDESONIDE W/FORMOTEROL FUMARATE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	RESPIRATORY SYSTEM	ADRENERGICS, INHALANTS	ADRENERGICS, INHALANTS	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	RESPIRATORY SYSTEM	ALPHA- AND BETA-ADRENORECEPTOR AGONISTS	EPINEPHRINE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	RESPIRATORY SYSTEM	AMINOALKYL ETHERS	DIMENHYDRINATE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	RESPIRATORY SYSTEM	AMINOALKYL ETHERS	DIPHENHYDRAMINE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	RESPIRATORY SYSTEM	AMINOALKYL ETHERS	DIPHENHYDRAMINE HYDROCHLORIDE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	RESPIRATORY SYSTEM	AMINOALKYL ETHERS	PIPRINHYDRINATE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	RESPIRATORY SYSTEM	ANESTHETICS, LOCAL	LIDOCAINE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	RESPIRATORY SYSTEM	ANTIALLERGIC AGENTS, EXCL. CORTICOSTEROIDS	AZELASTINE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	RESPIRATORY SYSTEM	ANTICHOLINERGICS	IPRATROPIUM BROMIDE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	RESPIRATORY SYSTEM	ANTISEPTICS	CHLORHEXIDINE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	RESPIRATORY SYSTEM	ANTISEPTICS	CHLORHEXIDINE GLUCONATE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	RESPIRATORY SYSTEM	ANTISEPTICS	POVIDONE-IODINE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	RESPIRATORY SYSTEM	EXPECTORANTS	GUAIFENESIN	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	RESPIRATORY SYSTEM	GLUCOCORTICOIDS	FLUTICASONE PROPIONATE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	RESPIRATORY SYSTEM	LEUKOTRIENE RECEPTOR ANTAGONISTS	MONTELUKAST SODIUM	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	RESPIRATORY SYSTEM	MUCOLYTICS	ACETYLCYSTEINE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	RESPIRATORY SYSTEM	MUCOLYTICS	AMBROXOL	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	RESPIRATORY SYSTEM	MUCOLYTICS	BROMHEXINE	[redacted]	[redacted]	[redacted]

ADVERSE EVENT	RESPIRATORY SYSTEM	MUCOLYTICS	ERDOSTEINE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	RESPIRATORY SYSTEM	OPIUM ALKALOIDS AND DERIVATIVES	CODEINE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	RESPIRATORY SYSTEM	OPIUM ALKALOIDS AND DERIVATIVES	CODEINE LINCTUS	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	RESPIRATORY SYSTEM	OPIUM ALKALOIDS AND DERIVATIVES	CODEINE PHOSPHATE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	RESPIRATORY SYSTEM	OPIUM ALKALOIDS AND DERIVATIVES	CODENA-S	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	RESPIRATORY SYSTEM	OPIUM ALKALOIDS AND DERIVATIVES	DEXTROMETHORPHAN	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	RESPIRATORY SYSTEM	OPIUM DERIVATIVES AND EXPECTORANTS	CHERACOL /00693301/	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	RESPIRATORY SYSTEM	OPIUM DERIVATIVES AND EXPECTORANTS	TUSSIN DM	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	RESPIRATORY SYSTEM	OTHER ANTIHISTAMINES FOR SYSTEMIC USE	BEPOTASTINE BESILATE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	RESPIRATORY SYSTEM	OTHER ANTIHISTAMINES FOR SYSTEMIC USE	BEPOTASTINE SALICYLATE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	RESPIRATORY SYSTEM	OTHER ANTIHISTAMINES FOR SYSTEMIC USE	DESLORATADINE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	RESPIRATORY SYSTEM	OTHER ANTIHISTAMINES FOR SYSTEMIC USE	EBASTINE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	RESPIRATORY SYSTEM	OTHER ANTIHISTAMINES FOR SYSTEMIC USE	FEXOFENADINE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	RESPIRATORY SYSTEM	OTHER ANTIHISTAMINES FOR SYSTEMIC USE	FEXOFENADINE HYDROCHLORIDE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	RESPIRATORY SYSTEM	OTHER ANTIHISTAMINES FOR SYSTEMIC USE	LORATADINE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	RESPIRATORY SYSTEM	OTHER COUGH SUPPRESSANTS	BENPROPERINE EMBONATE	[redacted]	[redacted]	[redacted]

ADVERSE EVENT	RESPIRATORY SYSTEM	OTHER COUGH SUPPRESSANTS	BENZONATATE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	RESPIRATORY SYSTEM	OTHER COUGH SUPPRESSANTS	LEVODROPROPIZINE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	RESPIRATORY SYSTEM	PHENOTHIAZINE DERIVATIVES	PROMETHAZINE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	RESPIRATORY SYSTEM	PHENOTHIAZINE DERIVATIVES	PROMETHAZINE HYDROCHLORIDE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	RESPIRATORY SYSTEM	PIPERAZINE DERIVATIVES	CETIRIZINE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	RESPIRATORY SYSTEM	PIPERAZINE DERIVATIVES	CETIRIZINE HYDROCHLORIDE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	RESPIRATORY SYSTEM	PIPERAZINE DERIVATIVES	LEVOCETIRIZINE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	RESPIRATORY SYSTEM	PIPERAZINE DERIVATIVES	LEVOCETIRIZINE DIHYDROCHLORIDE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	RESPIRATORY SYSTEM	PIPERAZINE DERIVATIVES	OXATOMIDE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	RESPIRATORY SYSTEM	SELECTIVE BETA-2-ADRENORECEPTOR AGONISTS	PROCATEROL HYDROCHLORIDE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	RESPIRATORY SYSTEM	SELECTIVE BETA-2-ADRENORECEPTOR AGONISTS	SALBUTAMOL	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	RESPIRATORY SYSTEM	SELECTIVE BETA-2-ADRENORECEPTOR AGONISTS	SALBUTAMOL SULFATE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	RESPIRATORY SYSTEM	SUBSTITUTED ALKYLAMINES	CHLORPHENAMINE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	RESPIRATORY SYSTEM	SUBSTITUTED ALKYLAMINES	CHLORPHENAMINE MALEATE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	RESPIRATORY SYSTEM	SUBSTITUTED ALKYLAMINES	DEXCHLORPHENIRAMINE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	RESPIRATORY SYSTEM	SUBSTITUTED ALKYLAMINES	DEXCHLORPHENIRAMINE MALEATE	[redacted]	[redacted]	[redacted]

ADVERSE EVENT	RESPIRATORY SYSTEM	SYMPATHOMIMETICS	ACTIFED /00005601/	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	RESPIRATORY SYSTEM	SYMPATHOMIMETICS	RINO EBASTEL	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	SENSORY ORGANS	ANTIBIOTICS	FUSIDATE SODIUM	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	SENSORY ORGANS	ANTIBIOTICS	FUSIDIC ACID	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	SENSORY ORGANS	ANTICHOLINERGICS	ATROPINE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	SENSORY ORGANS	ANTICHOLINERGICS	HYOSCINE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	SENSORY ORGANS	ANTICHOLINERGICS	MYDRIN P	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	SENSORY ORGANS	ANTICHOLINERGICS	TROPICAMIDE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	SENSORY ORGANS	ANTIINFECTIVES	HEXAMIDINE ISETIONATE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	SENSORY ORGANS	ANTIINFLAMMATORY AGENTS, NON-STEROIDS	DICLOFENAC	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	SENSORY ORGANS	BETA BLOCKING AGENTS	COSOPT	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	SENSORY ORGANS	BETA BLOCKING AGENTS	TIMOLOL	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	SENSORY ORGANS	BETA BLOCKING AGENTS	TIMOLOL MALEATE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	SENSORY ORGANS	CORTICOSTEROIDS AND MYDRIATICS IN COMBINATION	PHENYLEPHRINE;PREDNISOLONE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	SENSORY ORGANS	CORTICOSTEROIDS, PLAIN	LOTEPREDNOL ETABONATE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	SENSORY ORGANS	INDIFFERENT PREPARATIONS	SEA WATER	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	SENSORY ORGANS	OTHER OPHTHALMOLOGICALS	CARBOMER	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	SENSORY ORGANS	OTHER OPHTHALMOLOGICALS	CARMELLOSE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	SENSORY ORGANS	OTHER OPHTHALMOLOGICALS	POLYVINYL ALCOHOL	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	SENSORY ORGANS	OTHER OPHTHALMOLOGICALS	SYSTANE LUBRICANT	[redacted]	[redacted]	[redacted]

ADVERSE EVENT	SENSORY ORGANS	OTHER OPHTHALMOLOGICALS	TEARS NATURAL II	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	SENSORY ORGANS	VISCOELASTIC SUBSTANCES	HYALURONATE SODIUM	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	SENSORY ORGANS	VISCOELASTIC SUBSTANCES	HYALURONIC ACID	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	SYSTEMIC HORMONAL PREPARATIONS, EXCL. SEX HORMONES AND INSULINS	GLUCOCORTICOIDS	BETAMETHASONE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	SYSTEMIC HORMONAL PREPARATIONS, EXCL. SEX HORMONES AND INSULINS	GLUCOCORTICOIDS	BETAMETHASONE DIPROPIONATE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	SYSTEMIC HORMONAL PREPARATIONS, EXCL. SEX HORMONES AND INSULINS	GLUCOCORTICOIDS	BETAMETHASONE SODIUM PHOSPHATE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	SYSTEMIC HORMONAL PREPARATIONS, EXCL. SEX HORMONES AND INSULINS	GLUCOCORTICOIDS	BETAMETHASONE VALERATE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	SYSTEMIC HORMONAL PREPARATIONS, EXCL. SEX HORMONES AND INSULINS	GLUCOCORTICOIDS	CORTISONE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	SYSTEMIC HORMONAL PREPARATIONS, EXCL. SEX HORMONES AND INSULINS	GLUCOCORTICOIDS	DEXAMETHASONE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	SYSTEMIC HORMONAL PREPARATIONS, EXCL. SEX HORMONES AND INSULINS	GLUCOCORTICOIDS	DEXAMETHASONE PHOSPHATE	[redacted]	[redacted]	[redacted]

ADVERSE EVENT	SYSTEMIC HORMONAL PREPARATIONS, EXCL. SEX HORMONES AND INSULINS	GLUCOCORTICOIDS	HYDROCORTISONE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	SYSTEMIC HORMONAL PREPARATIONS, EXCL. SEX HORMONES AND INSULINS	GLUCOCORTICOIDS	HYDROCORTISONE ACETATE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	SYSTEMIC HORMONAL PREPARATIONS, EXCL. SEX HORMONES AND INSULINS	GLUCOCORTICOIDS	HYDROCORTISONE BUTYRATE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	SYSTEMIC HORMONAL PREPARATIONS, EXCL. SEX HORMONES AND INSULINS	GLUCOCORTICOIDS	HYDROCORTISONE SODIUM PHOSPHATE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	SYSTEMIC HORMONAL PREPARATIONS, EXCL. SEX HORMONES AND INSULINS	GLUCOCORTICOIDS	HYDROCORTISONE SODIUM SUCCINATE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	SYSTEMIC HORMONAL PREPARATIONS, EXCL. SEX HORMONES AND INSULINS	GLUCOCORTICOIDS	METHYLPREDNISOLONE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	SYSTEMIC HORMONAL PREPARATIONS, EXCL. SEX HORMONES AND INSULINS	GLUCOCORTICOIDS	METHYLPREDNISOLONE SODIUM SUCCINATE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	SYSTEMIC HORMONAL PREPARATIONS, EXCL. SEX HORMONES AND INSULINS	GLUCOCORTICOIDS	PREDNISOLONE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	SYSTEMIC HORMONAL PREPARATIONS, EXCL.	GLUCOCORTICOIDS	PREDNISOLONE ACETATE	[redacted]	[redacted]	[redacted]

	SEX HORMONES AND INSULINS					
ADVERSE EVENT	SYSTEMIC HORMONAL PREPARATIONS, EXCL. SEX HORMONES AND INSULINS	GLUCOCORTICOIDS	PREDNISOLONE VALEROACETATE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	SYSTEMIC HORMONAL PREPARATIONS, EXCL. SEX HORMONES AND INSULINS	GLUCOCORTICOIDS	PREDNISONE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	SYSTEMIC HORMONAL PREPARATIONS, EXCL. SEX HORMONES AND INSULINS	GLUCOCORTICOIDS	TRIAMCINOLONE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	SYSTEMIC HORMONAL PREPARATIONS, EXCL. SEX HORMONES AND INSULINS	GLUCOCORTICOIDS	TRIAMCINOLONE ACETONIDE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	SYSTEMIC HORMONAL PREPARATIONS, EXCL. SEX HORMONES AND INSULINS	SULFUR-CONTAINING IMIDAZOLE DERIVATIVES	THIAMAZOLE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	SYSTEMIC HORMONAL PREPARATIONS, EXCL. SEX HORMONES AND INSULINS	VASOPRESSIN AND ANALOGUES	VASOPRESSIN	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	VARIOUS	ALL OTHER THERAPEUTIC PRODUCTS	ALL OTHER THERAPEUTIC PRODUCTS	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	VARIOUS	ANTIDOTES	NALOXONE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	VARIOUS	CARBOHYDRATES	GLUCOSE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	VARIOUS	DRUGS FOR TREATMENT OF HYPERKALEMIA AND HYPERPHOSPHATEMIA	CALCIUM POLYSTYRENE SULFONATE	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	VARIOUS	GENERAL NUTRIENTS	GENERAL NUTRIENTS	[redacted]	[redacted]	[redacted]

ADVERSE EVENT	VARIOUS	GENERAL NUTRIENTS	NUTRIENTS NOS	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	VARIOUS	INVESTIGATIONAL DRUG	INVESTIGATIONAL DRUG	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	VARIOUS	MEDICAL GASES	OXYGEN	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	VARIOUS	OTHER COMBINATIONS OF NUTRIENTS	ALANINE W/ARGININE/CALCIUM CHLORIDE/08566301/	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	VARIOUS	PROTEIN SUPPLEMENTS	PROTEIN	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	VARIOUS	UNSPECIFIED HERBAL AND TRADITIONAL MEDICINE	CANNABIS SATIVA	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	VARIOUS	UNSPECIFIED HERBAL AND TRADITIONAL MEDICINE	CENTELLA ASIATICA EXTRACT	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	VARIOUS	UNSPECIFIED HERBAL AND TRADITIONAL MEDICINE	HERBAL PREPARATION	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	VARIOUS	UNSPECIFIED HERBAL AND TRADITIONAL MEDICINE	PLANTAGO OVATA	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	VARIOUS	UNSPECIFIED HERBAL AND TRADITIONAL MEDICINE	SILYBUM MARIANUM	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	VARIOUS	UNSPECIFIED HERBAL AND TRADITIONAL MEDICINE	THYMUS VULGARIS	[redacted]	[redacted]	[redacted]
ADVERSE EVENT	VARIOUS	UNSPECIFIED HERBAL AND TRADITIONAL MEDICINE	UNSPECIFIED HERBAL AND TRADITIONAL MEDICINE	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	ALIMENTARY TRACT AND METABOLISM	ALPHA GLUCOSIDASE INHIBITORS	VOGLIBOSE	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	ALIMENTARY TRACT AND METABOLISM	AMINO ACIDS AND DERIVATIVES	LEVOGLUTAMIDE	[redacted]	[redacted]	[redacted]

MEDICAL HISTORY	ALIMENTARY TRACT AND METABOLISM	AMINOSALICYLIC ACID AND SIMILAR AGENTS	MESALAZINE	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	ALIMENTARY TRACT AND METABOLISM	ANTIBIOTICS	NEOMYCIN;NYSTATIN;POLYMYXIN B	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	ALIMENTARY TRACT AND METABOLISM	ANTIBIOTICS	NYSTATIN	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	ALIMENTARY TRACT AND METABOLISM	ANTIDIARRHEAL MICROORGANISMS	MEDILAC-S	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	ALIMENTARY TRACT AND METABOLISM	BELLADONNA ALKALOIDS, SEMISYNTHETIC, QUATERNARY AMMONIUM COMPOUNDS	HYOSCINE BUTYLBROMIDE	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	ALIMENTARY TRACT AND METABOLISM	BIGUANIDES	METFORMIN	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	ALIMENTARY TRACT AND METABOLISM	BIGUANIDES	METFORMIN HYDROCHLORIDE	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	ALIMENTARY TRACT AND METABOLISM	BILE ACID PREPARATIONS	URSODEOXYCHOLIC ACID	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	ALIMENTARY TRACT AND METABOLISM	BULK-FORMING LAXATIVES	POLYCARBOPHIL CALCIUM	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	ALIMENTARY TRACT AND METABOLISM	CALCIUM COMPOUNDS	CALCIUM CARBONATE	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	ALIMENTARY TRACT AND METABOLISM	CALCIUM, COMBINATIONS WITH VITAMIN D AND/OR OTHER DRUGS	LEKOVIT CA	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	ALIMENTARY TRACT AND METABOLISM	CENTRALLY ACTING ANTIOBESITY PRODUCTS	PHENTERMINE	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	ALIMENTARY TRACT AND METABOLISM	COMBINATIONS AND COMPLEXES OF ALUMINIUM, CALCIUM AND MAGNESIUM COMPOUNDS	ALMAGATE	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	ALIMENTARY TRACT AND METABOLISM	COMBINATIONS AND COMPLEXES OF	ALMAGEL /00909601/	[redacted]	[redacted]	[redacted]

		ALUMINIUM, CALCIUM AND MAGNESIUM COMPOUNDS				
MEDICAL HISTORY	ALIMENTARY TRACT AND METABOLISM	COMBINATIONS OF ORAL BLOOD GLUCOSE LOWERING DRUGS	EUCREAS	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	ALIMENTARY TRACT AND METABOLISM	COMBINATIONS OF ORAL BLOOD GLUCOSE LOWERING DRUGS	METFORMIN HYDROCHLORIDE W/TENELIGLIPTIN HYDRO	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	ALIMENTARY TRACT AND METABOLISM	CONTACT LAXATIVES	SENNOSIDE A+B	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	ALIMENTARY TRACT AND METABOLISM	DIPEPTIDYL PEPTIDASE 4 (DPP-4) INHIBITORS	EVOGLIPTIN	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	ALIMENTARY TRACT AND METABOLISM	DIPEPTIDYL PEPTIDASE 4 (DPP-4) INHIBITORS	GEMIGLIPTIN TARTRATE	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	ALIMENTARY TRACT AND METABOLISM	DIPEPTIDYL PEPTIDASE 4 (DPP-4) INHIBITORS	LINAGLIPTIN	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	ALIMENTARY TRACT AND METABOLISM	DIPEPTIDYL PEPTIDASE 4 (DPP-4) INHIBITORS	SITAGLIPTIN PHOSPHATE	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	ALIMENTARY TRACT AND METABOLISM	ENEMAS	MICROLAX /03136201/	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	ALIMENTARY TRACT AND METABOLISM	ENZYME PREPARATIONS	PANCREATIN	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	ALIMENTARY TRACT AND METABOLISM	ENZYME PREPARATIONS	PANGEST F	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	ALIMENTARY TRACT AND METABOLISM	ENZYME PREPARATIONS	PHAZYME /00164001/	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	ALIMENTARY TRACT AND METABOLISM	H2-RECEPTOR ANTAGONISTS	FAMOTIDINE	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	ALIMENTARY TRACT AND METABOLISM	H2-RECEPTOR ANTAGONISTS	RANITIDINE HYDROCHLORIDE	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	ALIMENTARY TRACT AND METABOLISM	INSULINS AND ANALOGUES FOR INJECTION, FAST-ACTING	INSULIN	[redacted]	[redacted]	[redacted]

MEDICAL HISTORY	ALIMENTARY TRACT AND METABOLISM	INSULINS AND ANALOGUES FOR INJECTION, FAST-ACTING	INSULIN ASPART	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	ALIMENTARY TRACT AND METABOLISM	INSULINS AND ANALOGUES FOR INJECTION, FAST-ACTING	INSULIN HUMAN	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	ALIMENTARY TRACT AND METABOLISM	INSULINS AND ANALOGUES FOR INJECTION, LONG-ACTING	INSULIN GLARGINE	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	ALIMENTARY TRACT AND METABOLISM	LIVER THERAPY	GODEX	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	ALIMENTARY TRACT AND METABOLISM	LIVER THERAPY	NEO NICHIPHAGEN C	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	ALIMENTARY TRACT AND METABOLISM	MAGNESIUM	MAGNESIUM	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	ALIMENTARY TRACT AND METABOLISM	MAGNESIUM	MAGNESIUM OXIDE	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	ALIMENTARY TRACT AND METABOLISM	MAGNESIUM COMPOUNDS	MAGNESIUM HYDROXIDE	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	ALIMENTARY TRACT AND METABOLISM	MAGNESIUM COMPOUNDS	MAGNESIUM OXIDE	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	ALIMENTARY TRACT AND METABOLISM	MULTIVITAMINS, PLAIN	VITAMINS NOS	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	ALIMENTARY TRACT AND METABOLISM	OSMOTICALLY ACTING LAXATIVES	LACTULOSE	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	ALIMENTARY TRACT AND METABOLISM	OSMOTICALLY ACTING LAXATIVES	MACROGOL	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	ALIMENTARY TRACT AND METABOLISM	OSMOTICALLY ACTING LAXATIVES	MOVICOL	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	ALIMENTARY TRACT AND METABOLISM	OTHER ANTIEMETICS	DRONABINOL	[redacted]	[redacted]	[redacted]

MEDICAL HISTORY	ALIMENTARY TRACT AND METABOLISM	OTHER BLOOD GLUCOSE LOWERING DRUGS, EXCL. INSULINS	MITIGLINIDE CALCIUM	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	ALIMENTARY TRACT AND METABOLISM	OTHER BLOOD GLUCOSE LOWERING DRUGS, EXCL. INSULINS	REPAGLINIDE	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	ALIMENTARY TRACT AND METABOLISM	OTHER DRUGS FOR CONSTIPATION	GLYCEROL	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	ALIMENTARY TRACT AND METABOLISM	OTHER DRUGS FOR CONSTIPATION	LINACLOTIDE	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	ALIMENTARY TRACT AND METABOLISM	OTHER DRUGS FOR CONSTIPATION	NEW LECICARBON	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	ALIMENTARY TRACT AND METABOLISM	OTHER DRUGS FOR PEPTIC ULCER AND GASTRO-OESOPHAGEAL REFLUX DISEASE (GORD)	SODIUM GUALENATE	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	ALIMENTARY TRACT AND METABOLISM	OTHER MINERAL PRODUCTS	MULTITRACE-4	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	ALIMENTARY TRACT AND METABOLISM	PERIPHERAL OPIOID RECEPTOR ANTAGONISTS	NALDEMEDINE TOSILATE	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	ALIMENTARY TRACT AND METABOLISM	POTASSIUM	POTASSIUM CHLORIDE	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	ALIMENTARY TRACT AND METABOLISM	PROPULSIVES	DOMPERIDONE	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	ALIMENTARY TRACT AND METABOLISM	PROPULSIVES	METOCLOPRAMIDE	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	ALIMENTARY TRACT AND METABOLISM	PROPULSIVES	METOCLOPRAMIDE HYDROCHLORIDE	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	ALIMENTARY TRACT AND METABOLISM	PROPULSIVES	MOSAPRIDE	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	ALIMENTARY TRACT AND METABOLISM	PROPULSIVES	MOSAPRIDE CITRATE	[redacted]	[redacted]	[redacted]

MEDICAL HISTORY	ALIMENTARY TRACT AND METABOLISM	PROTON PUMP INHIBITORS	ESOMEPRAZOLE	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	ALIMENTARY TRACT AND METABOLISM	PROTON PUMP INHIBITORS	ESOMEPRAZOLE MAGNESIUM	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	ALIMENTARY TRACT AND METABOLISM	PROTON PUMP INHIBITORS	LANSOPRAZOLE	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	ALIMENTARY TRACT AND METABOLISM	PROTON PUMP INHIBITORS	OMEPRAZOLE	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	ALIMENTARY TRACT AND METABOLISM	PROTON PUMP INHIBITORS	PANTOPRAZOLE SODIUM SESQUIHYDRATE	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	ALIMENTARY TRACT AND METABOLISM	PROTON PUMP INHIBITORS	RABEPRAZOLE	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	ALIMENTARY TRACT AND METABOLISM	PROTON PUMP INHIBITORS	VONOPRAZAN FUMARATE	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	ALIMENTARY TRACT AND METABOLISM	SEROTONIN (5HT3) ANTAGONISTS	GRANISETRON	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	ALIMENTARY TRACT AND METABOLISM	SEROTONIN (5HT3) ANTAGONISTS	ONDANSETRON	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	ALIMENTARY TRACT AND METABOLISM	SEROTONIN (5HT3) ANTAGONISTS	RAMOSETRON	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	ALIMENTARY TRACT AND METABOLISM	SOFTENERS, EMOLLIENTS	DOCUSATE SODIUM	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	ALIMENTARY TRACT AND METABOLISM	SULFONYLUREAS	GLICLAZIDE	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	ALIMENTARY TRACT AND METABOLISM	SULFONYLUREAS	GLIMEPIRIDE	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	ALIMENTARY TRACT AND METABOLISM	SYNTHETIC ANTICHOLINERGIC AGENTS IN COMBINATION WITH PSYCHOLEPTICS	CHLORDIAZEPOXIDE W/CLIDINIUM	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	ALIMENTARY TRACT AND METABOLISM	SYNTHETIC ANTICHOLINERGICS,	DICYCLOVERINE HYDROCHLORIDE	[redacted]	[redacted]	[redacted]

		ESTERS WITH TERTIARY AMINO GROUP				
MEDICAL HISTORY	ALIMENTARY TRACT AND METABOLISM	THIAZOLIDINEDIONES	PIOGLITAZONE	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	ALIMENTARY TRACT AND METABOLISM	TONICS	DIETARY SUPPLEMENT	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	ALIMENTARY TRACT AND METABOLISM	VARIOUS ALIMENTARY TRACT AND METABOLISM PRODUCTS	PROBIOTICS NOS	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	ALIMENTARY TRACT AND METABOLISM	VARIOUS ALIMENTARY TRACT AND METABOLISM PRODUCTS	THIOCTIC ACID	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	ALIMENTARY TRACT AND METABOLISM	VITAMIN D AND ANALOGUES	COLECALCIFEROL	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	ANTIINFECTIVES FOR SYSTEMIC USE	CARBAPENEMS	ERTAPENEM	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	ANTIINFECTIVES FOR SYSTEMIC USE	COMBINATIONS OF PENICILLINS, INCL. BETA-LACTAMASE INHIBITORS	AMOXICILLIN W/CLAVULANATE POTASSIUM	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	ANTIINFECTIVES FOR SYSTEMIC USE	COMBINATIONS OF PENICILLINS, INCL. BETA-LACTAMASE INHIBITORS	PIPERACILLIN W/TAZOBACTAM /01606301/	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	ANTIINFECTIVES FOR SYSTEMIC USE	COMBINATIONS OF SULFONAMIDES AND TRIMETHOPRIM, INCL. DERIVATIVES	BACTRIM	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	ANTIINFECTIVES FOR SYSTEMIC USE	FIRST-GENERATION CEPHALOSPORINS	CEFADROXIL	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	ANTIINFECTIVES FOR SYSTEMIC USE	FLUOROQUINOLONES	LEVOFLOXACIN	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	ANTIINFECTIVES FOR SYSTEMIC USE	FLUOROQUINOLONES	OFLOXACIN	[redacted]	[redacted]	[redacted]

MEDICAL HISTORY	ANTIINFECTIVES FOR SYSTEMIC USE	LINCOSAMIDES	CLINDAMYCIN PHOSPHATE	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	ANTIINFECTIVES FOR SYSTEMIC USE	MACROLIDES	AZITHROMYCIN	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	ANTIINFECTIVES FOR SYSTEMIC USE	NUCLEOSIDES AND NUCLEOTIDES EXCL. REVERSE TRANSCRIPTASE INHIBITORS	ACICLOVIR	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	ANTIINFECTIVES FOR SYSTEMIC USE	NUCLEOSIDES AND NUCLEOTIDES EXCL. REVERSE TRANSCRIPTASE INHIBITORS	VALACICLOVIR HYDROCHLORIDE	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	ANTIINFECTIVES FOR SYSTEMIC USE	PENICILLINS WITH EXTENDED SPECTRUM	PIPERACILLIN SODIUM	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	ANTIINFECTIVES FOR SYSTEMIC USE	SECOND-GENERATION CEPHALOSPORINS	CEFACLOR	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	ANTIINFECTIVES FOR SYSTEMIC USE	TETRACYCLINES	DOXYCYCLINE	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	ANTIINFECTIVES FOR SYSTEMIC USE	TETRACYCLINES	DOXYCYCLINE HYCLATE	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	ANTIINFECTIVES FOR SYSTEMIC USE	TETRACYCLINES	MINOCYCLINE	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	ANTIINFECTIVES FOR SYSTEMIC USE	TETRACYCLINES	MINOCYCLINE HYDROCHLORIDE	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	ANTIINFECTIVES FOR SYSTEMIC USE	THIRD-GENERATION CEPHALOSPORINS	CEFIXIME	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	ANTIINFECTIVES FOR SYSTEMIC USE	THIRD-GENERATION CEPHALOSPORINS	CEFTRIAXONE	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	ANTIINFECTIVES FOR SYSTEMIC USE	THIRD-GENERATION CEPHALOSPORINS	CEFTRIAXONE SODIUM	[redacted]	[redacted]	[redacted]

MEDICAL HISTORY	ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS	CALCINEURIN INHIBITORS	TACROLIMUS	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS	COLONY STIMULATING FACTORS	FILGRASTIM	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS	ESTROGENS	ESTRADIOL	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS	SELECTIVE IMMUNOSUPPRESSANTS	VEDOLIZUMAB	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	BLOOD AND BLOOD FORMING ORGANS	AMINO ACIDS	TRANEXAMIC ACID	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	BLOOD AND BLOOD FORMING ORGANS	DIRECT FACTOR XA INHIBITORS	APIXABAN	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	BLOOD AND BLOOD FORMING ORGANS	DIRECT FACTOR XA INHIBITORS	EDOXABAN	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	BLOOD AND BLOOD FORMING ORGANS	DIRECT FACTOR XA INHIBITORS	EDOXABAN TOSILATE	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	BLOOD AND BLOOD FORMING ORGANS	DIRECT FACTOR XA INHIBITORS	RIVAROXABAN	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	BLOOD AND BLOOD FORMING ORGANS	ENZYMES	BROEN-C	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	BLOOD AND BLOOD FORMING ORGANS	ENZYMES	HYALURONIDASE	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	BLOOD AND BLOOD FORMING ORGANS	FOLIC ACID AND DERIVATIVES	FOLIC ACID	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	BLOOD AND BLOOD FORMING ORGANS	HEPARIN GROUP	DALTEPARIN SODIUM	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	BLOOD AND BLOOD FORMING ORGANS	HEPARIN GROUP	ENOXAPARIN SODIUM	[redacted]	[redacted]	[redacted]

MEDICAL HISTORY	BLOOD AND BLOOD FORMING ORGANS	HEPARIN GROUP	TINZAPARIN SODIUM	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	BLOOD AND BLOOD FORMING ORGANS	IRON BIVALENT, ORAL PREPARATIONS	FERROUS SULFATE	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	BLOOD AND BLOOD FORMING ORGANS	OTHER BLOOD PRODUCTS	RED BLOOD CELLS, CONCENTRATED	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	BLOOD AND BLOOD FORMING ORGANS	PLATELET AGGREGATION INHIBITORS EXCL. HEPARIN	CLOPIDOGREL	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	BLOOD AND BLOOD FORMING ORGANS	SALT SOLUTIONS	SODIUM BICARBONATE	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	BLOOD AND BLOOD FORMING ORGANS	SALT SOLUTIONS	SODIUM CHLORIDE	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	BLOOD AND BLOOD FORMING ORGANS	SOLUTIONS FOR PARENTERAL NUTRITION	AMINIC /01983901/	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	BLOOD AND BLOOD FORMING ORGANS	SOLUTIONS FOR PARENTERAL NUTRITION	CLINIMIX N14G30E	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	BLOOD AND BLOOD FORMING ORGANS	SOLUTIONS FOR PARENTERAL NUTRITION	FREAMINE	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	BLOOD AND BLOOD FORMING ORGANS	VITAMIN B12 (CYANOCOBALAMIN AND ANALOGUES)	CYANOCOBALAMIN	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	BLOOD AND BLOOD FORMING ORGANS	VITAMIN B12 (CYANOCOBALAMIN AND ANALOGUES)	MECOBALAMIN	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	CARDIOVASCULAR SYSTEM	ACE INHIBITORS, PLAIN	ENALAPRIL	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	CARDIOVASCULAR SYSTEM	ACE INHIBITORS, PLAIN	LISINOPRIL	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	CARDIOVASCULAR SYSTEM	ACE INHIBITORS, PLAIN	RAMIPRIL	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	CARDIOVASCULAR SYSTEM	ALDOSTERONE ANTAGONISTS	SPIRONOLACTONE	[redacted]	[redacted]	[redacted]

MEDICAL HISTORY	CARDIOVASCULAR SYSTEM	ALPHA-ADRENORECEPTOR ANTAGONISTS	DOXAZOSIN MESILATE	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	CARDIOVASCULAR SYSTEM	ANGIOTENSIN II ANTAGONISTS AND CALCIUM CHANNEL BLOCKERS	AZOR /06230801/	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	CARDIOVASCULAR SYSTEM	ANGIOTENSIN II ANTAGONISTS AND CALCIUM CHANNEL BLOCKERS	DIOVAN AMLO	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	CARDIOVASCULAR SYSTEM	ANGIOTENSIN II ANTAGONISTS AND CALCIUM CHANNEL BLOCKERS	TWYNSTA	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	CARDIOVASCULAR SYSTEM	ANGIOTENSIN II ANTAGONISTS AND DIURETICS	BLOPRESS PLUS	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	CARDIOVASCULAR SYSTEM	ANGIOTENSIN II ANTAGONISTS AND DIURETICS	HYDROCHLOROTHIAZIDE W/LOSARTAN	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	CARDIOVASCULAR SYSTEM	ANGIOTENSIN II ANTAGONISTS, PLAIN	CANDESARTAN	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	CARDIOVASCULAR SYSTEM	ANGIOTENSIN II ANTAGONISTS, PLAIN	IRBESARTAN	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	CARDIOVASCULAR SYSTEM	ANGIOTENSIN II ANTAGONISTS, PLAIN	LOSARTAN POTASSIUM	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	CARDIOVASCULAR SYSTEM	ANGIOTENSIN II ANTAGONISTS, PLAIN	TELMISARTAN	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	CARDIOVASCULAR SYSTEM	ANGIOTENSIN II ANTAGONISTS, PLAIN	VALSARTAN	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	CARDIOVASCULAR SYSTEM	ANTIARRHYTHMICS, CLASS III	AMIODARONE HYDROCHLORIDE	[redacted]	[redacted]	[redacted]

MEDICAL HISTORY	CARDIOVASCULAR SYSTEM	ANTIHYPERTENSIVES FOR PULMONARY ARTERIAL HYPERTENSION	TADALAFIL	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	CARDIOVASCULAR SYSTEM	BENZOTHIAZEPINE DERIVATIVES	DILTIAZEM	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	CARDIOVASCULAR SYSTEM	BETA BLOCKING AGENTS, NON-SELECTIVE	PROPRANOLOL HYDROCHLORIDE	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	CARDIOVASCULAR SYSTEM	BETA BLOCKING AGENTS, SELECTIVE	BISOPROLOL	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	CARDIOVASCULAR SYSTEM	BETA BLOCKING AGENTS, SELECTIVE	METOPROLOL SUCCINATE	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	CARDIOVASCULAR SYSTEM	BETA BLOCKING AGENTS, SELECTIVE, AND THIAZIDES	BISELECT /01166101/	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	CARDIOVASCULAR SYSTEM	BIOFLAVONOIDS	CAPIVEN	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	CARDIOVASCULAR SYSTEM	CORTICOSTEROIDS	CINCHOCAINE;ESCULOSIDE;HYDROCORTISONE;NEOMYCI	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	CARDIOVASCULAR SYSTEM	CORTICOSTEROIDS	CORTICOSTEROID NOS	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	CARDIOVASCULAR SYSTEM	CORTICOSTEROIDS	LEVAN H	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	CARDIOVASCULAR SYSTEM	DIGITALIS GLYCOSIDES	DIGOXIN	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	CARDIOVASCULAR SYSTEM	DIHYDROPYRIDINE DERIVATIVES	AMLODIPINE	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	CARDIOVASCULAR SYSTEM	DIHYDROPYRIDINE DERIVATIVES	AMLODIPINE BESILATE	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	CARDIOVASCULAR SYSTEM	DIHYDROPYRIDINE DERIVATIVES	AMLODIPINE OROTATE	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	CARDIOVASCULAR SYSTEM	DIHYDROPYRIDINE DERIVATIVES	LERCANIDIPINE HYDROCHLORIDE	[redacted]	[redacted]	[redacted]

MEDICAL HISTORY	CARDIOVASCULAR SYSTEM	DIHYDROPYRIDINE DERIVATIVES	S AMLODIPINE NICOTINATE	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	CARDIOVASCULAR SYSTEM	HMG COA REDUCTASE INHIBITORS	ATORVASTATIN	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	CARDIOVASCULAR SYSTEM	HMG COA REDUCTASE INHIBITORS	PITAVASTATIN CALCIUM	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	CARDIOVASCULAR SYSTEM	HMG COA REDUCTASE INHIBITORS	PRAVASTATIN	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	CARDIOVASCULAR SYSTEM	HMG COA REDUCTASE INHIBITORS	ROSUVASTATIN	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	CARDIOVASCULAR SYSTEM	HMG COA REDUCTASE INHIBITORS	ROSUVASTATIN CALCIUM	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	CARDIOVASCULAR SYSTEM	HMG COA REDUCTASE INHIBITORS	SIMVASTATIN	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	CARDIOVASCULAR SYSTEM	HMG COA REDUCTASE INHIBITORS IN COMBINATION WITH OTHER LIPID MODIFYING AGENTS	ROSUVAST EZ	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	CARDIOVASCULAR SYSTEM	HMG COA REDUCTASE INHIBITORS IN COMBINATION WITH OTHER LIPID MODIFYING AGENTS	ZETITOR	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	CARDIOVASCULAR SYSTEM	HMG COA REDUCTASE INHIBITORS, OTHER COMBINATIONS	CADUET	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	CARDIOVASCULAR SYSTEM	LOW-CEILING DIURETICS AND POTASSIUM-SPARING AGENTS	DYAZIDE	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	CARDIOVASCULAR SYSTEM	ORGANIC NITRATES	GLYCERYL TRINITRATE	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	CARDIOVASCULAR SYSTEM	OTHER LIPID MODIFYING AGENTS	EZETIMIBE	[redacted]	[redacted]	[redacted]

MEDICAL HISTORY	CARDIOVASCULAR SYSTEM	PROSTAGLANDINS	LIMAPROST ALFADEX	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	CARDIOVASCULAR SYSTEM	SULFONAMIDES, PLAIN	FUROSEMIDE	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	CARDIOVASCULAR SYSTEM	THIAZIDES, PLAIN	HYDROCHLOROTHIAZIDE	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	DERMATOLOGICALS	CORTICOSTEROIDS, MODERATELY POTENT (GROUP II)	CLOBETASONE BUTYRATE	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	DERMATOLOGICALS	CORTICOSTEROIDS, MODERATELY POTENT (GROUP II)	FLUOROMETHOLONE	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	DERMATOLOGICALS	CORTICOSTEROIDS, POTENT (GROUP III)	BUDESONIDE	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	DERMATOLOGICALS	CORTICOSTEROIDS, POTENT (GROUP III)	DIFLUCORTOLONE VALERATE	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	DERMATOLOGICALS	CORTICOSTEROIDS, POTENT (GROUP III)	DIFLUPREDNATE	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	DERMATOLOGICALS	CORTICOSTEROIDS, POTENT (GROUP III)	FLUTICASONE	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	DERMATOLOGICALS	CORTICOSTEROIDS, POTENT (GROUP III)	METHYLPREDNISOLONE ACEPONATE	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	DERMATOLOGICALS	CORTICOSTEROIDS, POTENT, COMBINATIONS WITH ANTISEPTICS	PROPADERM-C	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	DERMATOLOGICALS	IMIDAZOLE AND TRIAZOLE DERIVATIVES	FLUCONAZOLE	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	DERMATOLOGICALS	RETINOIDS FOR TOPICAL USE IN ACNE	EPIDUO	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	DERMATOLOGICALS	SOFT PARAFFIN AND FAT PRODUCTS	PETROLATUM	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	GENITO URINARY SYSTEM AND SEX HORMONES	3-OXOANDROSTEN (4) DERIVATIVES	TESTOSTERONE	[redacted]	[redacted]	[redacted]

MEDICAL HISTORY	GENITO URINARY SYSTEM AND SEX HORMONES	ALPHA-ADRENORECEPTOR ANTAGONISTS	SILODOSIN	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	GENITO URINARY SYSTEM AND SEX HORMONES	ALPHA-ADRENORECEPTOR ANTAGONISTS	TAMSULOSIN	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	GENITO URINARY SYSTEM AND SEX HORMONES	ALPHA-ADRENORECEPTOR ANTAGONISTS	TAMSULOSIN HYDROCHLORIDE	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	GENITO URINARY SYSTEM AND SEX HORMONES	DRUGS FOR URINARY FREQUENCY AND INCONTINENCE	SOLIFENACIN SUCCINATE	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	GENITO URINARY SYSTEM AND SEX HORMONES	DRUGS USED IN ERECTILE DYSFUNCTION	SILDENAFIL	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	GENITO URINARY SYSTEM AND SEX HORMONES	PREGNEN (4) DERIVATIVES	PROGESTERONE	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	GENITO URINARY SYSTEM AND SEX HORMONES	PROGESTOGENS	MEGESTROL	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	GENITO URINARY SYSTEM AND SEX HORMONES	PROGESTOGENS	MEGESTROL ACETATE	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	GENITO URINARY SYSTEM AND SEX HORMONES	TESTOSTERONE-5-ALPHA REDUCTASE INHIBITORS	FINASTERIDE	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	MUSCULO-SKELETAL SYSTEM	ACETIC ACID DERIVATIVES AND RELATED SUBSTANCES	ACECLOFENAC	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	MUSCULO-SKELETAL SYSTEM	ACETIC ACID DERIVATIVES AND RELATED SUBSTANCES	DICLOFENAC SODIUM	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	MUSCULO-SKELETAL SYSTEM	ACETIC ACID DERIVATIVES AND RELATED SUBSTANCES	ETODOLAC	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	MUSCULO-SKELETAL SYSTEM	ACETIC ACID DERIVATIVES AND RELATED SUBSTANCES	INDOMETACIN	[redacted]	[redacted]	[redacted]

MEDICAL HISTORY	MUSCULO-SKELETAL SYSTEM	BISPHOSPHONATES	PAMIDRONATE DISODIUM	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	MUSCULO-SKELETAL SYSTEM	COXIBS	CELECOXIB	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	MUSCULO-SKELETAL SYSTEM	OTHER CENTRALLY ACTING AGENTS	EPERISONE HYDROCHLORIDE	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	MUSCULO-SKELETAL SYSTEM	OTHER DRUGS AFFECTING BONE STRUCTURE AND MINERALIZATION	DENOSUMAB	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	MUSCULO-SKELETAL SYSTEM	PREPARATIONS INHIBITING URIC ACID PRODUCTION	FEBUXOSTAT	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	MUSCULO-SKELETAL SYSTEM	PROPIONIC ACID DERIVATIVES	CAROL-F	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	MUSCULO-SKELETAL SYSTEM	PROPIONIC ACID DERIVATIVES	DEXIBUPROFEN	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	MUSCULO-SKELETAL SYSTEM	PROPIONIC ACID DERIVATIVES	DEXKETOPROFEN	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	MUSCULO-SKELETAL SYSTEM	PROPIONIC ACID DERIVATIVES	DEXKETOPROFEN TROMETAMOL	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	MUSCULO-SKELETAL SYSTEM	PROPIONIC ACID DERIVATIVES	IBUPROFEN	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	MUSCULO-SKELETAL SYSTEM	PROPIONIC ACID DERIVATIVES	KETOPROFEN	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	MUSCULO-SKELETAL SYSTEM	PROPIONIC ACID DERIVATIVES	LOXOPROFEN	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	MUSCULO-SKELETAL SYSTEM	PROPIONIC ACID DERIVATIVES	LOXOPROFEN SODIUM DIHYDRATE	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	MUSCULO-SKELETAL SYSTEM	PROPIONIC ACID DERIVATIVES	NAPROXEN	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	MUSCULO-SKELETAL SYSTEM	PROPIONIC ACID DERIVATIVES	NAPROXEN SODIUM	[redacted]	[redacted]	[redacted]

MEDICAL HISTORY	MUSCULO-SKELETAL SYSTEM	PROPIONIC ACID DERIVATIVES	VIMOVO	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	NERVOUS SYSTEM	ANILIDES	PARACETAMOL	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	NERVOUS SYSTEM	ANILIDES	PROPACETAMOL	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	NERVOUS SYSTEM	BENZODIAZEPINE DERIVATIVES	ALPRAZOLAM	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	NERVOUS SYSTEM	BENZODIAZEPINE DERIVATIVES	BROMAZEPAM	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	NERVOUS SYSTEM	BENZODIAZEPINE DERIVATIVES	BROTIZOLAM	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	NERVOUS SYSTEM	BENZODIAZEPINE DERIVATIVES	CLONAZEPAM	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	NERVOUS SYSTEM	BENZODIAZEPINE DERIVATIVES	ETIZOLAM	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	NERVOUS SYSTEM	BENZODIAZEPINE DERIVATIVES	LORAZEPAM	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	NERVOUS SYSTEM	BENZODIAZEPINE DERIVATIVES	LORMETAZEPAM	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	NERVOUS SYSTEM	BENZODIAZEPINE DERIVATIVES	TEMAZEPAM	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	NERVOUS SYSTEM	BENZODIAZEPINE RELATED DRUGS	ESZOPICLONE	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	NERVOUS SYSTEM	BENZODIAZEPINE RELATED DRUGS	ZOLPIDEM	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	NERVOUS SYSTEM	BENZODIAZEPINE RELATED DRUGS	ZOLPIDEM TARTRATE	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	NERVOUS SYSTEM	DIAZEPINES, OXAZEPINES, THIAZEPINES AND OXEPINES	OLANZAPINE	[redacted]	[redacted]	[redacted]

MEDICAL HISTORY	NERVOUS SYSTEM	DIPHENYLMETHANE DERIVATIVES	HYDROXYZINE HYDROCHLORIDE	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	NERVOUS SYSTEM	DOPA AND DOPA DERIVATIVES	MADOPAR	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	NERVOUS SYSTEM	DOPAMINE AGONISTS	ROTIGOTINE	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	NERVOUS SYSTEM	DRUGS USED IN OPIOID DEPENDENCE	NALOXONE HYDROCHLORIDE	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	NERVOUS SYSTEM	MELATONIN RECEPTOR AGONISTS	MELATONIN	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	NERVOUS SYSTEM	MONOAMINE OXIDASE B INHIBITORS	RASAGILINE MESYLATE	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	NERVOUS SYSTEM	NATURAL OPIUM ALKALOIDS	HYDROMORPHONE	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	NERVOUS SYSTEM	NATURAL OPIUM ALKALOIDS	HYDROMORPHONE HYDROCHLORIDE	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	NERVOUS SYSTEM	NATURAL OPIUM ALKALOIDS	MORPHINE	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	NERVOUS SYSTEM	NATURAL OPIUM ALKALOIDS	MORPHINE HYDROCHLORIDE	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	NERVOUS SYSTEM	NATURAL OPIUM ALKALOIDS	MORPHINE SULFATE	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	NERVOUS SYSTEM	NATURAL OPIUM ALKALOIDS	MORPHINE SULFATE PENTAHYDRATE	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	NERVOUS SYSTEM	NATURAL OPIUM ALKALOIDS	OXYCODONE	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	NERVOUS SYSTEM	NATURAL OPIUM ALKALOIDS	OXYCODONE HYDROCHLORIDE	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	NERVOUS SYSTEM	NATURAL OPIUM ALKALOIDS	TARGIN	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	NERVOUS SYSTEM	NATURAL OPIUM ALKALOIDS	VICODIN	[redacted]	[redacted]	[redacted]

MEDICAL HISTORY	NERVOUS SYSTEM	NON-SELECTIVE MONOAMINE REUPTAKE INHIBITORS	AMITRIPTYLINE	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	NERVOUS SYSTEM	NON-SELECTIVE MONOAMINE REUPTAKE INHIBITORS	CLOMIPRAMINE HYDROCHLORIDE	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	NERVOUS SYSTEM	NON-SELECTIVE MONOAMINE REUPTAKE INHIBITORS	DOXEPIN HYDROCHLORIDE	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	NERVOUS SYSTEM	NON-SELECTIVE MONOAMINE REUPTAKE INHIBITORS	NORTRIPTYLINE	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	NERVOUS SYSTEM	OPIOIDS IN COMBINATION WITH NON-OPIOID ANALGESICS	IBUPAIN	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	NERVOUS SYSTEM	OPIOIDS IN COMBINATION WITH NON-OPIOID ANALGESICS	LENOLTEC WITH CODEINE NO 1	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	NERVOUS SYSTEM	OPIOIDS IN COMBINATION WITH NON-OPIOID ANALGESICS	MYPRODOL	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	NERVOUS SYSTEM	OPIOIDS IN COMBINATION WITH NON-OPIOID ANALGESICS	ULTRACET	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	NERVOUS SYSTEM	OTHER ANALGESICS AND ANTIPYRETICS	CANNABIDIOL	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	NERVOUS SYSTEM	OTHER ANALGESICS AND ANTIPYRETICS	OTHER ANALGESICS AND ANTIPYRETICS	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	NERVOUS SYSTEM	OTHER ANALGESICS AND ANTIPYRETICS	PREGABALIN	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	NERVOUS SYSTEM	OTHER ANTIDEPRESSANTS	BUPROPION	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	NERVOUS SYSTEM	OTHER ANTIDEPRESSANTS	DULOXETINE HYDROCHLORIDE	[redacted]	[redacted]	[redacted]

MEDICAL HISTORY	NERVOUS SYSTEM	OTHER ANTIDEPRESSANTS	MIRTAZAPINE	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	NERVOUS SYSTEM	OTHER ANTIDEPRESSANTS	TRAZODONE	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	NERVOUS SYSTEM	OTHER ANTIDEPRESSANTS	TRAZODONE HYDROCHLORIDE	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	NERVOUS SYSTEM	OTHER ANTIEPILEPTICS	GABAPENTIN	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	NERVOUS SYSTEM	OTHER ANTIEPILEPTICS	LAMOTRIGINE	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	NERVOUS SYSTEM	OTHER ANTIEPILEPTICS	LEVETIRACETAM	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	NERVOUS SYSTEM	OTHER DOPAMINERGIC AGENTS	ENTACAPONE	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	NERVOUS SYSTEM	OTHER OPIOIDS	TRAMADOL	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	NERVOUS SYSTEM	OTHER OPIOIDS	TRAMADOL HYDROCHLORIDE	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	NERVOUS SYSTEM	PHENOTHIAZINES WITH ALIPHATIC SIDE-CHAIN	LEVOMEPROMAZINE	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	NERVOUS SYSTEM	PHENYLPIPERIDINE DERIVATIVES	FENTANYL	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	NERVOUS SYSTEM	PHENYLPIPERIDINE DERIVATIVES	FENTANYL CITRATE	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	NERVOUS SYSTEM	PHENYLPIPERIDINE DERIVATIVES	PETHIDINE	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	NERVOUS SYSTEM	PHENYLPIPERIDINE DERIVATIVES	PETHIDINE HYDROCHLORIDE	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	NERVOUS SYSTEM	PYRAZOLONES	METAMIZOLE	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	NERVOUS SYSTEM	PYRAZOLONES	METAMIZOLE MAGNESIUM	[redacted]	[redacted]	[redacted]

MEDICAL HISTORY	NERVOUS SYSTEM	SALICYLIC ACID AND DERIVATIVES	ACETYLSALICYLIC ACID	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	NERVOUS SYSTEM	SELECTIVE SEROTONIN REUPTAKE INHIBITORS	ESCITALOPRAM	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	NERVOUS SYSTEM	SELECTIVE SEROTONIN REUPTAKE INHIBITORS	ESCITALOPRAM OXALATE	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	NERVOUS SYSTEM	SELECTIVE SEROTONIN REUPTAKE INHIBITORS	SERTRALINE HYDROCHLORIDE	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	RESPIRATORY SYSTEM	ADRENERGICS IN COMBINATION WITH ANTICHOLINERGICS	ADRENERGICS IN COMBINATION WITH ANTICHOLINERG	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	RESPIRATORY SYSTEM	ADRENERGICS IN COMBINATION WITH ANTICHOLINERGICS	GLYCOPYRRONIUM BROMIDE W/INDACATEROL MALEATE	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	RESPIRATORY SYSTEM	ADRENERGICS IN COMBINATION WITH ANTICHOLINERGICS	UMECLIDINIUM BROMIDE W/VILANTEROL TRIFENATATE	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	RESPIRATORY SYSTEM	ADRENERGICS IN COMBINATION WITH CORTICOSTEROIDS OR OTHER DRUGS, EXCL. ANTICHOLINERGICS	BEKFORM	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	RESPIRATORY SYSTEM	ADRENERGICS IN COMBINATION WITH CORTICOSTEROIDS OR OTHER DRUGS, EXCL. ANTICHOLINERGICS	BUDESONIDE W/FORMOTEROL FUMARATE	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	RESPIRATORY SYSTEM	ADRENERGICS IN COMBINATION WITH CORTICOSTEROIDS OR OTHER DRUGS, EXCL. ANTICHOLINERGICS	SERETIDE	[redacted]	[redacted]	[redacted]

MEDICAL HISTORY	RESPIRATORY SYSTEM	AMINOALKYL ETHERS	DIMENHYDRINATE	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	RESPIRATORY SYSTEM	ANESTHETICS, LOCAL	LIDOCAINE	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	RESPIRATORY SYSTEM	ANTIALLERGIC AGENTS, EXCL. CORTICOSTEROIDS	OLOPATADINE	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	RESPIRATORY SYSTEM	ANTICHOLINERGICS	IPRATROPIUM BROMIDE	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	RESPIRATORY SYSTEM	CORTICOSTEROIDS	FLUTICASONE FUROATE	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	RESPIRATORY SYSTEM	EXPECTORANTS	GUAIFENESIN	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	RESPIRATORY SYSTEM	GLUCOCORTICOIDS	FLUTICASONE PROPIONATE	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	RESPIRATORY SYSTEM	MUCOLYTICS	ACETYLCYSTEINE	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	RESPIRATORY SYSTEM	MUCOLYTICS	AMBROXOL	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	RESPIRATORY SYSTEM	MUCOLYTICS	BROMHEXINE	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	RESPIRATORY SYSTEM	MUCOLYTICS	BROMHEXINE HYDROCHLORIDE	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	RESPIRATORY SYSTEM	MUCOLYTICS	CARBOCISTEINE	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	RESPIRATORY SYSTEM	MUCOLYTICS	ERDOSTEINE	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	RESPIRATORY SYSTEM	MUCOLYTICS	SPASMO-MUCOSOLVAN	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	RESPIRATORY SYSTEM	OPIUM ALKALOIDS AND DERIVATIVES	CODEINE	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	RESPIRATORY SYSTEM	OPIUM ALKALOIDS AND DERIVATIVES	CODEINE PHOSPHATE	[redacted]	[redacted]	[redacted]

MEDICAL HISTORY	RESPIRATORY SYSTEM	OPIUM ALKALOIDS AND DERIVATIVES	CODEINE PHOSPHATE HEMIHYDRATE	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	RESPIRATORY SYSTEM	OPIUM ALKALOIDS AND DERIVATIVES	CODENA-S	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	RESPIRATORY SYSTEM	OPIUM ALKALOIDS AND DERIVATIVES	DEXTROMETHORPHAN	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	RESPIRATORY SYSTEM	OPIUM ALKALOIDS AND DERIVATIVES	DEXTROMETHORPHAN HYDROBROMIDE	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	RESPIRATORY SYSTEM	OPIUM ALKALOIDS AND DERIVATIVES	HYDROCODONE	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	RESPIRATORY SYSTEM	OPIUM ALKALOIDS AND DERIVATIVES	MEDICON A	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	RESPIRATORY SYSTEM	OPIUM ALKALOIDS AND DERIVATIVES	PHOLCODINE	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	RESPIRATORY SYSTEM	OPIUM DERIVATIVES AND EXPECTORANTS	BROWN MIXTURE /01682301/	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	RESPIRATORY SYSTEM	OPIUM DERIVATIVES AND EXPECTORANTS	CODEINE W/GUAIFENESIN /08428801/	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	RESPIRATORY SYSTEM	OPIUM DERIVATIVES AND EXPECTORANTS	TUSSIN DM	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	RESPIRATORY SYSTEM	OTHER ANTIHISTAMINES FOR SYSTEMIC USE	BILASTINE	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	RESPIRATORY SYSTEM	OTHER ANTIHISTAMINES FOR SYSTEMIC USE	FEXOFENADINE	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	RESPIRATORY SYSTEM	OTHER ANTIHISTAMINES FOR SYSTEMIC USE	FEXOFENADINE HYDROCHLORIDE	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	RESPIRATORY SYSTEM	OTHER ANTIHISTAMINES FOR SYSTEMIC USE	OLOPATADINE HYDROCHLORIDE	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	RESPIRATORY SYSTEM	OTHER COUGH SUPPRESSANTS	BENPROPERINE EMBONATE	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	RESPIRATORY SYSTEM	OTHER COUGH SUPPRESSANTS	BENZONATATE	[redacted]	[redacted]	[redacted]

MEDICAL HISTORY	RESPIRATORY SYSTEM	OTHER COUGH SUPPRESSANTS	LEVODROPROPIZINE	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	RESPIRATORY SYSTEM	PIPERAZINE DERIVATIVES	BUCLIZINE HYDROCHLORIDE	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	RESPIRATORY SYSTEM	PIPERAZINE DERIVATIVES	CETIRIZINE	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	RESPIRATORY SYSTEM	PIPERAZINE DERIVATIVES	CETIRIZINE HYDROCHLORIDE	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	RESPIRATORY SYSTEM	SELECTIVE BETA-2-ADRENORECEPTOR AGONISTS	FORMOTEROL	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	RESPIRATORY SYSTEM	SELECTIVE BETA-2-ADRENORECEPTOR AGONISTS	FORMOTEROL FUMARATE	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	RESPIRATORY SYSTEM	SELECTIVE BETA-2-ADRENORECEPTOR AGONISTS	INDACATEROL MALEATE	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	RESPIRATORY SYSTEM	SELECTIVE BETA-2-ADRENORECEPTOR AGONISTS	SALBUTAMOL	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	RESPIRATORY SYSTEM	SELECTIVE BETA-2-ADRENORECEPTOR AGONISTS	SALBUTAMOL SULFATE	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	RESPIRATORY SYSTEM	SUBSTITUTED ALKYLAMINES	CHLORPHENAMINE MALEATE	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	RESPIRATORY SYSTEM	SYMPATHOMIMETICS	ACTIFED /00005601/	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	RESPIRATORY SYSTEM	SYMPATHOMIMETICS	CONTAC 600	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	RESPIRATORY SYSTEM	SYMPATHOMIMETICS	PSEUDOEPHEDRINE	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	RESPIRATORY SYSTEM	SYMPATHOMIMETICS	PSEUDOEPHEDRINE HYDROCHLORIDE	[redacted]	[redacted]	[redacted]

MEDICAL HISTORY	RESPIRATORY SYSTEM	XANTHINES	THEOBROMINE	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	RESPIRATORY SYSTEM	XANTHINES	THEOPHYLLINE	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	SENSORY ORGANS	OTHER OPHTHALMOLOGICALS	OTHER OPHTHALMOLOGICALS	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	SENSORY ORGANS	PROSTAGLANDIN ANALOGUES	LATANOPROST	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	SENSORY ORGANS	VISCOELASTIC SUBSTANCES	HYALURONATE SODIUM	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	SYSTEMIC HORMONAL PREPARATIONS, EXCL. SEX HORMONES AND INSULINS	GLUCOCORTICOIDS	DEXAMETHASONE	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	SYSTEMIC HORMONAL PREPARATIONS, EXCL. SEX HORMONES AND INSULINS	GLUCOCORTICOIDS	HYDROCORTISONE SODIUM SUCCINATE	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	SYSTEMIC HORMONAL PREPARATIONS, EXCL. SEX HORMONES AND INSULINS	GLUCOCORTICOIDS	METHYLPREDNISOLONE	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	SYSTEMIC HORMONAL PREPARATIONS, EXCL. SEX HORMONES AND INSULINS	GLUCOCORTICOIDS	METHYLPREDNISOLONE SODIUM SUCCINATE	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	SYSTEMIC HORMONAL PREPARATIONS, EXCL. SEX HORMONES AND INSULINS	GLUCOCORTICOIDS	PREDNISOLONE	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	SYSTEMIC HORMONAL PREPARATIONS, EXCL. SEX HORMONES AND INSULINS	GLUCOCORTICOIDS	PREDNISONE	[redacted]	[redacted]	[redacted]

MEDICAL HISTORY	SYSTEMIC HORMONAL PREPARATIONS, EXCL. SEX HORMONES AND INSULINS	GLUCOCORTICOIDS	TRIAMCINOLONE ACETONIDE	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	SYSTEMIC HORMONAL PREPARATIONS, EXCL. SEX HORMONES AND INSULINS	THYROID HORMONES	LEVOTHYROXINE	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	SYSTEMIC HORMONAL PREPARATIONS, EXCL. SEX HORMONES AND INSULINS	THYROID HORMONES	LEVOTHYROXINE SODIUM	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	SYSTEMIC HORMONAL PREPARATIONS, EXCL. SEX HORMONES AND INSULINS	THYROID HORMONES	THYROID	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	VARIOUS	DRUGS FOR TREATMENT OF HYPERKALEMIA AND HYPERPHOSPHATEMIA	CALCIUM POLYSTYRENE SULFONATE	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	VARIOUS	MEDICAL GASES	OXYGEN	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	VARIOUS	OTHER COMBINATIONS OF NUTRIENTS	ALANINE W/ARGININE/CALCIUM CHLORIDE/08566301/	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	VARIOUS	PROTEIN SUPPLEMENTS	PROTEINS NOS	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	VARIOUS	UNSPECIFIED HERBAL AND TRADITIONAL MEDICINE	GOSHAJINKIGAN	[redacted]	[redacted]	[redacted]
MEDICAL HISTORY	VARIOUS	UNSPECIFIED HERBAL AND TRADITIONAL MEDICINE	HERBAL PREPARATION	[redacted]	[redacted]	[redacted]
OTHER	ALIMENTARY TRACT AND METABOLISM	ASCORBIC ACID (VITAMIN C), PLAIN	ASCORBIC ACID	[redacted]	[redacted]	[redacted]

OTHER	ALIMENTARY TRACT AND METABOLISM	BELLADONNA ALKALOIDS, SEMISYNTHETIC, QUATERNARY AMMONIUM COMPOUNDS	CIMETROPIUM BROMIDE	[redacted]	[redacted]	[redacted]
OTHER	ALIMENTARY TRACT AND METABOLISM	CALCIUM	CALCIUM	[redacted]	[redacted]	[redacted]
OTHER	ALIMENTARY TRACT AND METABOLISM	CALCIUM, COMBINATIONS WITH VITAMIN D AND/OR OTHER DRUGS	A D VIT	[redacted]	[redacted]	[redacted]
OTHER	ALIMENTARY TRACT AND METABOLISM	CALCIUM, COMBINATIONS WITH VITAMIN D AND/OR OTHER DRUGS	CALCIUM W/VITAMIN D NOS	[redacted]	[redacted]	[redacted]
OTHER	ALIMENTARY TRACT AND METABOLISM	CALCIUM, COMBINATIONS WITH VITAMIN D AND/OR OTHER DRUGS	LEKOVIT CA	[redacted]	[redacted]	[redacted]
OTHER	ALIMENTARY TRACT AND METABOLISM	COMBINATIONS OF VITAMINS	FOLIC ACID;PYRIDOXINE;VITAMIN B12 NOS	[redacted]	[redacted]	[redacted]
OTHER	ALIMENTARY TRACT AND METABOLISM	CONTACT LAXATIVES	PICO-SALAX	[redacted]	[redacted]	[redacted]
OTHER	ALIMENTARY TRACT AND METABOLISM	CONTACT LAXATIVES	SENNOSIDE A+B	[redacted]	[redacted]	[redacted]
OTHER	ALIMENTARY TRACT AND METABOLISM	H2-RECEPTOR ANTAGONISTS	FAMOTIDINE	[redacted]	[redacted]	[redacted]
OTHER	ALIMENTARY TRACT AND METABOLISM	H2-RECEPTOR ANTAGONISTS	NIZATIDINE	[redacted]	[redacted]	[redacted]
OTHER	ALIMENTARY TRACT AND METABOLISM	LIVER THERAPY	ARCTIUM LAPPA ROOT W/CYNARA CARDUNC/08512201/	[redacted]	[redacted]	[redacted]
OTHER	ALIMENTARY TRACT AND METABOLISM	MAGNESIUM	MAGNESIUM	[redacted]	[redacted]	[redacted]
OTHER	ALIMENTARY TRACT AND METABOLISM	MAGNESIUM	MAGNESIUM SULFATE	[redacted]	[redacted]	[redacted]

OTHER	ALIMENTARY TRACT AND METABOLISM	MAGNESIUM COMPOUNDS	MAGNESIUM CARBONATE	[redacted]	[redacted]	[redacted]
OTHER	ALIMENTARY TRACT AND METABOLISM	MAGNESIUM COMPOUNDS	MAGNESIUM HYDROXIDE	[redacted]	[redacted]	[redacted]
OTHER	ALIMENTARY TRACT AND METABOLISM	MULTIVITAMINS, PLAIN	VITAMINS NOS	[redacted]	[redacted]	[redacted]
OTHER	ALIMENTARY TRACT AND METABOLISM	OSMOTICALLY ACTING LAXATIVES	MOVPREP	[redacted]	[redacted]	[redacted]
OTHER	ALIMENTARY TRACT AND METABOLISM	OTHER ANTIEMETICS	APREPITANT	[redacted]	[redacted]	[redacted]
OTHER	ALIMENTARY TRACT AND METABOLISM	OTHER PLAIN VITAMIN PREPARATIONS	PYRIDOXINE	[redacted]	[redacted]	[redacted]
OTHER	ALIMENTARY TRACT AND METABOLISM	POTASSIUM	POTASSIUM CHLORIDE	[redacted]	[redacted]	[redacted]
OTHER	ALIMENTARY TRACT AND METABOLISM	POTASSIUM	POTASSIUM GLUCONATE	[redacted]	[redacted]	[redacted]
OTHER	ALIMENTARY TRACT AND METABOLISM	PROPULSIVES	METOCLOPRAMIDE HYDROCHLORIDE	[redacted]	[redacted]	[redacted]
OTHER	ALIMENTARY TRACT AND METABOLISM	PROTON PUMP INHIBITORS	PANTOPRAZOLE	[redacted]	[redacted]	[redacted]
OTHER	ALIMENTARY TRACT AND METABOLISM	SELENIUM	SELENIUM	[redacted]	[redacted]	[redacted]
OTHER	ALIMENTARY TRACT AND METABOLISM	SEROTONIN (5HT3) ANTAGONISTS	PALONOSETRON	[redacted]	[redacted]	[redacted]
OTHER	ALIMENTARY TRACT AND METABOLISM	SEROTONIN (5HT3) ANTAGONISTS	PALONOSETRON HYDROCHLORIDE	[redacted]	[redacted]	[redacted]
OTHER	ALIMENTARY TRACT AND METABOLISM	SEROTONIN (5HT3) ANTAGONISTS	RAMOSETRON	[redacted]	[redacted]	[redacted]
OTHER	ALIMENTARY TRACT AND METABOLISM	SYNTHETIC ANTICHOLINERGICS, QUATERNARY AMMONIUM COMPOUNDS	GLYCOPYRRONIUM	[redacted]	[redacted]	[redacted]

OTHER	ALIMENTARY TRACT AND METABOLISM	TONICS	CURCUMIN	[redacted]	[redacted]	[redacted]
OTHER	ALIMENTARY TRACT AND METABOLISM	TONICS	DIETARY SUPPLEMENT	[redacted]	[redacted]	[redacted]
OTHER	ALIMENTARY TRACT AND METABOLISM	VARIOUS ALIMENTARY TRACT AND METABOLISM PRODUCTS	UBIDECARENONE	[redacted]	[redacted]	[redacted]
OTHER	ALIMENTARY TRACT AND METABOLISM	VITAMIN A, PLAIN	RETINOL	[redacted]	[redacted]	[redacted]
OTHER	ALIMENTARY TRACT AND METABOLISM	VITAMIN B-COMPLEX, PLAIN	BETALIN COMPLEX	[redacted]	[redacted]	[redacted]
OTHER	ALIMENTARY TRACT AND METABOLISM	VITAMIN B-COMPLEX, PLAIN	VITAMIN B COMPLEX	[redacted]	[redacted]	[redacted]
OTHER	ALIMENTARY TRACT AND METABOLISM	VITAMIN B1 IN COMBINATION WITH VITAMIN B6 AND/OR VITAMIN B12	NEOLAMIN 3B /05665201/	[redacted]	[redacted]	[redacted]
OTHER	ALIMENTARY TRACT AND METABOLISM	VITAMIN B1 IN COMBINATION WITH VITAMIN B6 AND/OR VITAMIN B12	NEUROBION /00176001/	[redacted]	[redacted]	[redacted]
OTHER	ALIMENTARY TRACT AND METABOLISM	VITAMIN B1, PLAIN	THIAMINE	[redacted]	[redacted]	[redacted]
OTHER	ALIMENTARY TRACT AND METABOLISM	VITAMIN D AND ANALOGUES	COLECALCIFEROL	[redacted]	[redacted]	[redacted]
OTHER	ALIMENTARY TRACT AND METABOLISM	VITAMIN D AND ANALOGUES	VITAMIN D NOS	[redacted]	[redacted]	[redacted]
OTHER	ANTIINFECTIVES FOR SYSTEMIC USE	COMBINATIONS OF SULFONAMIDES AND TRIMETHOPRIM, INCL. DERIVATIVES	BACTRIM	[redacted]	[redacted]	[redacted]
OTHER	ANTIINFECTIVES FOR SYSTEMIC USE	FIRST-GENERATION CEPHALOSPORINS	CEFAZOLIN	[redacted]	[redacted]	[redacted]

OTHER	ANTIINFECTIVES FOR SYSTEMIC USE	FLUOROQUINOLONES	CIPROFLOXACIN	[redacted]	[redacted]	[redacted]
OTHER	ANTIINFECTIVES FOR SYSTEMIC USE	FLUOROQUINOLONES	CIPROFLOXACIN HYDROCHLORIDE	[redacted]	[redacted]	[redacted]
OTHER	ANTIINFECTIVES FOR SYSTEMIC USE	FLUOROQUINOLONES	LEVOFLOXACIN	[redacted]	[redacted]	[redacted]
OTHER	ANTIINFECTIVES FOR SYSTEMIC USE	INFLUENZA VACCINES	INFLUENZA VACCINE	[redacted]	[redacted]	[redacted]
OTHER	ANTIINFECTIVES FOR SYSTEMIC USE	INFLUENZA VACCINES	INFLUENZA VACCINE INACT SAG 3V	[redacted]	[redacted]	[redacted]
OTHER	ANTIINFECTIVES FOR SYSTEMIC USE	LINCOSAMIDES	CLINDAMYCIN	[redacted]	[redacted]	[redacted]
OTHER	ANTIINFECTIVES FOR SYSTEMIC USE	MACROLIDES	AZITHROMYCIN	[redacted]	[redacted]	[redacted]
OTHER	ANTIINFECTIVES FOR SYSTEMIC USE	OTHER VIRAL VACCINES	OTHER VIRAL VACCINES	[redacted]	[redacted]	[redacted]
OTHER	ANTIINFECTIVES FOR SYSTEMIC USE	TETRACYCLINES	DOXYCYCLINE	[redacted]	[redacted]	[redacted]
OTHER	ANTIINFECTIVES FOR SYSTEMIC USE	THIRD-GENERATION CEPHALOSPORINS	CEFTRIAXONE	[redacted]	[redacted]	[redacted]
OTHER	ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS	ESTROGENS	ESTROGENS CONJUGATED	[redacted]	[redacted]	[redacted]
OTHER	BLOOD AND BLOOD FORMING ORGANS	AMINO ACIDS	CAFSOL	[redacted]	[redacted]	[redacted]
OTHER	BLOOD AND BLOOD FORMING ORGANS	AMINO ACIDS	TRANEXAMIC ACID	[redacted]	[redacted]	[redacted]
OTHER	BLOOD AND BLOOD FORMING ORGANS	BLOOD COAGULATION FACTORS	THROMBIN	[redacted]	[redacted]	[redacted]
OTHER	BLOOD AND BLOOD FORMING ORGANS	BLOOD SUBSTITUTES AND PLASMA PROTEIN FRACTIONS	POVIDONE	[redacted]	[redacted]	[redacted]

OTHER	BLOOD AND BLOOD FORMING ORGANS	ELECTROLYTE SOLUTIONS	MULTITRACE-4	[redacted]	[redacted]	[redacted]
OTHER	BLOOD AND BLOOD FORMING ORGANS	ENZYMES	ALTEPLASE	[redacted]	[redacted]	[redacted]
OTHER	BLOOD AND BLOOD FORMING ORGANS	FOLIC ACID AND DERIVATIVES	FOLIC ACID	[redacted]	[redacted]	[redacted]
OTHER	BLOOD AND BLOOD FORMING ORGANS	HEMOFILTRATES	MULTIBIC	[redacted]	[redacted]	[redacted]
OTHER	BLOOD AND BLOOD FORMING ORGANS	HEPARIN GROUP	ANTITHROMBIN III	[redacted]	[redacted]	[redacted]
OTHER	BLOOD AND BLOOD FORMING ORGANS	HEPARIN GROUP	HEPARIN	[redacted]	[redacted]	[redacted]
OTHER	BLOOD AND BLOOD FORMING ORGANS	IRON BIVALENT, ORAL PREPARATIONS	FERROUS GLUCONATE	[redacted]	[redacted]	[redacted]
OTHER	BLOOD AND BLOOD FORMING ORGANS	IRON BIVALENT, ORAL PREPARATIONS	FERROUS SULFATE	[redacted]	[redacted]	[redacted]
OTHER	BLOOD AND BLOOD FORMING ORGANS	OTHER BLOOD PRODUCTS	PLASMA	[redacted]	[redacted]	[redacted]
OTHER	BLOOD AND BLOOD FORMING ORGANS	PLATELET AGGREGATION INHIBITORS EXCL. HEPARIN	CLOPIDOGREL RESINATE	[redacted]	[redacted]	[redacted]
OTHER	BLOOD AND BLOOD FORMING ORGANS	PROTEINASE INHIBITORS	NAFAMOSTAT MESILATE	[redacted]	[redacted]	[redacted]
OTHER	BLOOD AND BLOOD FORMING ORGANS	SALT SOLUTIONS	SODIUM BICARBONATE	[redacted]	[redacted]	[redacted]
OTHER	BLOOD AND BLOOD FORMING ORGANS	SALT SOLUTIONS	SODIUM CHLORIDE	[redacted]	[redacted]	[redacted]
OTHER	BLOOD AND BLOOD FORMING ORGANS	SOLUTIONS AFFECTING THE ELECTROLYTE BALANCE	OSMOTAN	[redacted]	[redacted]	[redacted]
OTHER	BLOOD AND BLOOD FORMING ORGANS	SOLUTIONS AFFECTING THE ELECTROLYTE BALANCE	PLASMALYTE A	[redacted]	[redacted]	[redacted]

OTHER	BLOOD AND BLOOD FORMING ORGANS	SOLUTIONS AFFECTING THE ELECTROLYTE BALANCE	RINGER-LACTATE	[redacted]	[redacted]	[redacted]
OTHER	BLOOD AND BLOOD FORMING ORGANS	SOLUTIONS FOR PARENTERAL NUTRITION	ALANINE W/ARGININE/CALCIUM CHLORIDE/08864301/	[redacted]	[redacted]	[redacted]
OTHER	BLOOD AND BLOOD FORMING ORGANS	SOLUTIONS FOR PARENTERAL NUTRITION	AMINIC /01983901/	[redacted]	[redacted]	[redacted]
OTHER	BLOOD AND BLOOD FORMING ORGANS	SOLUTIONS FOR PARENTERAL NUTRITION	SMOFKABIVEN PERIFER	[redacted]	[redacted]	[redacted]
OTHER	BLOOD AND BLOOD FORMING ORGANS	SOLUTIONS FOR PARENTERAL NUTRITION	SMOFLIPID	[redacted]	[redacted]	[redacted]
OTHER	BLOOD AND BLOOD FORMING ORGANS	VITAMIN B12 (CYANOCOBALAMIN AND ANALOGUES)	COBAMAMIDE	[redacted]	[redacted]	[redacted]
OTHER	BLOOD AND BLOOD FORMING ORGANS	VITAMIN B12 (CYANOCOBALAMIN AND ANALOGUES)	HEPAGRISEVIT FORTE-N /01079901/	[redacted]	[redacted]	[redacted]
OTHER	BLOOD AND BLOOD FORMING ORGANS	VITAMIN B12 (CYANOCOBALAMIN AND ANALOGUES)	VITAMIN B12 NOS	[redacted]	[redacted]	[redacted]
OTHER	CARDIOVASCULAR SYSTEM	BETA BLOCKING AGENTS, SELECTIVE	METOPROLOL	[redacted]	[redacted]	[redacted]
OTHER	CARDIOVASCULAR SYSTEM	CORTICOSTEROIDS	FLUOCINONIDE	[redacted]	[redacted]	[redacted]
OTHER	CARDIOVASCULAR SYSTEM	DIHYDROPYRIDINE DERIVATIVES	NICARDIPINE HYDROCHLORIDE	[redacted]	[redacted]	[redacted]
OTHER	CARDIOVASCULAR SYSTEM	OTHER LIPID MODIFYING AGENTS	FISH OIL	[redacted]	[redacted]	[redacted]
OTHER	CARDIOVASCULAR SYSTEM	SULFONAMIDES, PLAIN	FUROSEMIDE	[redacted]	[redacted]	[redacted]

OTHER	DERMATOLOGICALS	CORTICOSTEROIDS, MODERATELY POTENT (GROUP II)	DESONIDE	[redacted]	[redacted]	[redacted]
OTHER	DERMATOLOGICALS	ZINC PRODUCTS	ZINC SULFATE	[redacted]	[redacted]	[redacted]
OTHER	GENITO URINARY SYSTEM AND SEX HORMONES	DRUGS FOR URINARY FREQUENCY AND INCONTINENCE	OXYBUTYNIN	[redacted]	[redacted]	[redacted]
OTHER	GENITO URINARY SYSTEM AND SEX HORMONES	IMIDAZOLE DERIVATIVES	METRONIDAZOLE	[redacted]	[redacted]	[redacted]
OTHER	GENITO URINARY SYSTEM AND SEX HORMONES	PROGESTOGENS	MEGESTROL ACETATE	[redacted]	[redacted]	[redacted]
OTHER	GENITO URINARY SYSTEM AND SEX HORMONES	PROGESTOGENS AND ESTROGENS, FIXED COMBINATIONS	MARVELON	[redacted]	[redacted]	[redacted]
OTHER	MUSCULO-SKELETAL SYSTEM	ACETIC ACID DERIVATIVES AND RELATED SUBSTANCES	KETOROLAC TROMETHAMINE	[redacted]	[redacted]	[redacted]
OTHER	MUSCULO-SKELETAL SYSTEM	BISPHOSPHONATES	ZOLEDRONIC ACID	[redacted]	[redacted]	[redacted]
OTHER	MUSCULO-SKELETAL SYSTEM	FENAMATES	MEFENAMIC ACID	[redacted]	[redacted]	[redacted]
OTHER	MUSCULO-SKELETAL SYSTEM	OTHER ANTIINFLAMMATORY AND ANTIRHEUMATIC AGENTS, NON-STEROIDS	BENZYDAMINE HYDROCHLORIDE	[redacted]	[redacted]	[redacted]
OTHER	MUSCULO-SKELETAL SYSTEM	OTHER ANTIINFLAMMATORY AND ANTIRHEUMATIC AGENTS, NON-STEROIDS	GLUCOSAMINE	[redacted]	[redacted]	[redacted]
OTHER	MUSCULO-SKELETAL SYSTEM	OTHER DRUGS AFFECTING BONE STRUCTURE AND MINERALIZATION	DENOSUMAB	[redacted]	[redacted]	[redacted]

OTHER	MUSCULO-SKELETAL SYSTEM	OTHER QUATERNARY AMMONIUM COMPOUNDS	ROCURONIUM BROMIDE	[redacted]	[redacted]	[redacted]
OTHER	MUSCULO-SKELETAL SYSTEM	OTHER QUATERNARY AMMONIUM COMPOUNDS	VECURONIUM	[redacted]	[redacted]	[redacted]
OTHER	NERVOUS SYSTEM	AMIDES	EMLA /00675501/	[redacted]	[redacted]	[redacted]
OTHER	NERVOUS SYSTEM	AMIDES	LIDOCAINE HYDROCHLORIDE	[redacted]	[redacted]	[redacted]
OTHER	NERVOUS SYSTEM	ANILIDES	PARACETAMOL	[redacted]	[redacted]	[redacted]
OTHER	NERVOUS SYSTEM	ANILIDES	PROPACETAMOL	[redacted]	[redacted]	[redacted]
OTHER	NERVOUS SYSTEM	ANTICHOLINESTERASES	PYRIDOSTIGMINE	[redacted]	[redacted]	[redacted]
OTHER	NERVOUS SYSTEM	BARBITURATES, PLAIN	THIOPENTAL SODIUM	[redacted]	[redacted]	[redacted]
OTHER	NERVOUS SYSTEM	BENZODIAZEPINE DERIVATIVES	MIDAZOLAM	[redacted]	[redacted]	[redacted]
OTHER	NERVOUS SYSTEM	BENZODIAZEPINE DERIVATIVES	MIDAZOLAM HYDROCHLORIDE	[redacted]	[redacted]	[redacted]
OTHER	NERVOUS SYSTEM	BUTYROPHENONE DERIVATIVES	HALOPERIDOL	[redacted]	[redacted]	[redacted]
OTHER	NERVOUS SYSTEM	DIAZEPINES, OXAZEPINES, THIAZEPINES AND OXEPINES	QUETIAPINE FUMARATE	[redacted]	[redacted]	[redacted]
OTHER	NERVOUS SYSTEM	MELATONIN RECEPTOR AGONISTS	MELATONIN	[redacted]	[redacted]	[redacted]
OTHER	NERVOUS SYSTEM	NATURAL OPIUM ALKALOIDS	HYDROMORPHONE	[redacted]	[redacted]	[redacted]
OTHER	NERVOUS SYSTEM	NATURAL OPIUM ALKALOIDS	MORPHINE	[redacted]	[redacted]	[redacted]
OTHER	NERVOUS SYSTEM	NATURAL OPIUM ALKALOIDS	TARGIN	[redacted]	[redacted]	[redacted]
OTHER	NERVOUS SYSTEM	NATURAL OPIUM ALKALOIDS	VICODIN	[redacted]	[redacted]	[redacted]
OTHER	NERVOUS SYSTEM	OPIOID ANESTHETICS	REMIFENTANIL	[redacted]	[redacted]	[redacted]

OTHER	NERVOUS SYSTEM	OPIOID ANESTHETICS	REMIFENTANIL HYDROCHLORIDE	[redacted]	[redacted]	[redacted]
OTHER	NERVOUS SYSTEM	OPIOIDS IN COMBINATION WITH NON-OPIOID ANALGESICS	OXYCOCET	[redacted]	[redacted]	[redacted]
OTHER	NERVOUS SYSTEM	OPIOIDS IN COMBINATION WITH NON-OPIOID ANALGESICS	ULTRACET	[redacted]	[redacted]	[redacted]
OTHER	NERVOUS SYSTEM	OTHER ANTI-DEMENTIA DRUGS	MEMANTINE	[redacted]	[redacted]	[redacted]
OTHER	NERVOUS SYSTEM	OTHER ANTIDEPRESSANTS	BUPROPION	[redacted]	[redacted]	[redacted]
OTHER	NERVOUS SYSTEM	OTHER ANTIEPILEPTICS	LEVETIRACETAM	[redacted]	[redacted]	[redacted]
OTHER	NERVOUS SYSTEM	OTHER GENERAL ANESTHETICS	PROPOFOL	[redacted]	[redacted]	[redacted]
OTHER	NERVOUS SYSTEM	OTHER OPIOIDS	TRAMADOL HYDROCHLORIDE	[redacted]	[redacted]	[redacted]
OTHER	NERVOUS SYSTEM	PHENYLPIPERIDINE DERIVATIVES	FENTANYL	[redacted]	[redacted]	[redacted]
OTHER	NERVOUS SYSTEM	PHENYLPIPERIDINE DERIVATIVES	PETHIDINE	[redacted]	[redacted]	[redacted]
OTHER	NERVOUS SYSTEM	PHENYLPIPERIDINE DERIVATIVES	PETHIDINE HYDROCHLORIDE	[redacted]	[redacted]	[redacted]
OTHER	NERVOUS SYSTEM	SALICYLIC ACID AND DERIVATIVES	ACETYLSALICYLIC ACID	[redacted]	[redacted]	[redacted]
OTHER	RESPIRATORY SYSTEM	ADRENERGICS IN COMBINATION WITH CORTICOSTEROIDS OR OTHER DRUGS, EXCL. ANTICHOLINERGICS	BUDESONIDE W/FORMOTEROL FUMARATE	[redacted]	[redacted]	[redacted]
OTHER	RESPIRATORY SYSTEM	ALPHA- AND BETA-ADRENORECEPTOR AGONISTS	EPINEPHRINE	[redacted]	[redacted]	[redacted]

OTHER	RESPIRATORY SYSTEM	AMINOALKYL ETHERS	DIPHENHYDRAMINE HYDROCHLORIDE	[redacted]	[redacted]	[redacted]
OTHER	RESPIRATORY SYSTEM	ANESTHETICS, LOCAL	LIDOCAINE	[redacted]	[redacted]	[redacted]
OTHER	RESPIRATORY SYSTEM	MUCOLYTICS	ACETYLCYSTEINE	[redacted]	[redacted]	[redacted]
OTHER	RESPIRATORY SYSTEM	MUCOLYTICS	AMBROXOL	[redacted]	[redacted]	[redacted]
OTHER	RESPIRATORY SYSTEM	OTHER ANTIHISTAMINES FOR SYSTEMIC USE	BEPOTASTINE BESILATE	[redacted]	[redacted]	[redacted]
OTHER	RESPIRATORY SYSTEM	PIPERAZINE DERIVATIVES	CETIRIZINE	[redacted]	[redacted]	[redacted]
OTHER	RESPIRATORY SYSTEM	PIPERAZINE DERIVATIVES	LEVOCETIRIZINE DIHYDROCHLORIDE	[redacted]	[redacted]	[redacted]
OTHER	RESPIRATORY SYSTEM	SELECTIVE BETA-2-ADRENORECEPTOR AGONISTS	SALBUTAMOL	[redacted]	[redacted]	[redacted]
OTHER	RESPIRATORY SYSTEM	SUBSTITUTED ALKYLAMINES	CHLORPHENAMINE	[redacted]	[redacted]	[redacted]
OTHER	RESPIRATORY SYSTEM	SUBSTITUTED ALKYLAMINES	CHLORPHENAMINE MALEATE	[redacted]	[redacted]	[redacted]
OTHER	SENSORY ORGANS	ANTIBIOTICS	FUSIDATE SODIUM	[redacted]	[redacted]	[redacted]
OTHER	SENSORY ORGANS	ANTICHOLINERGICS	ATROPINE SULFATE	[redacted]	[redacted]	[redacted]
OTHER	SYSTEMIC HORMONAL PREPARATIONS, EXCL. SEX HORMONES AND INSULINS	ACTH	TETRACOSACTIDE	[redacted]	[redacted]	[redacted]
OTHER	SYSTEMIC HORMONAL PREPARATIONS, EXCL. SEX HORMONES AND INSULINS	GLUCOCORTICOIDS	DEXAMETHASONE	[redacted]	[redacted]	[redacted]
OTHER	SYSTEMIC HORMONAL PREPARATIONS, EXCL. SEX HORMONES AND INSULINS	GLUCOCORTICOIDS	HYDROCORTISONE SODIUM SUCCINATE	[redacted]	[redacted]	[redacted]
OTHER	SYSTEMIC HORMONAL PREPARATIONS, EXCL.	GLUCOCORTICOIDS	PREDNISOLONE	[redacted]	[redacted]	[redacted]

	SEX HORMONES AND INSULINS					
OTHER	SYSTEMIC HORMONAL PREPARATIONS, EXCL. SEX HORMONES AND INSULINS	GLUCOCORTICOIDS	PREDNISONE	[redacted]	[redacted]	[redacted]
OTHER	VARIOUS	ALL OTHER NON-THERAPEUTIC PRODUCTS	ALL OTHER NON-THERAPEUTIC PRODUCTS	[redacted]	[redacted]	[redacted]
OTHER	VARIOUS	ANTIDOTES	FLUMAZENIL	[redacted]	[redacted]	[redacted]
OTHER	VARIOUS	CARBOHYDRATES	GLUCOSE	[redacted]	[redacted]	[redacted]
OTHER	VARIOUS	FAT/CARBOHYDRATES/PROTEINS/MINERALS/VITAMINS, COMBINATIONS	ASCORBIC ACID W/BIOTIN/CALCIUM CITR/08868901/	[redacted]	[redacted]	[redacted]
OTHER	VARIOUS	FAT/CARBOHYDRATES/PROTEINS/MINERALS/VITAMINS, COMBINATIONS	ASCORBIC ACID W/BIOTIN/CALCIUM/CARB/ 08371201/	[redacted]	[redacted]	[redacted]
OTHER	VARIOUS	MEDICAL GASES	OXYGEN	[redacted]	[redacted]	[redacted]
OTHER	VARIOUS	OTHER COMBINATIONS OF NUTRIENTS	ALANINE W/ARGININE/CALCIUM CHLORIDE/08566301/	[redacted]	[redacted]	[redacted]
OTHER	VARIOUS	UNSPECIFIED HERBAL AND TRADITIONAL MEDICINE	CURCUMA LONGA RHIZOME	[redacted]	[redacted]	[redacted]
OTHER	VARIOUS	UNSPECIFIED HERBAL AND TRADITIONAL MEDICINE	HERBAL PREPARATION	[redacted]	[redacted]	[redacted]
OTHER	VARIOUS	UNSPECIFIED HERBAL AND TRADITIONAL MEDICINE	LINUM USITATISSIMUM SEED OIL	[redacted]	[redacted]	[redacted]
OTHER	VARIOUS	UNSPECIFIED HERBAL AND TRADITIONAL MEDICINE	UNSPECIFIED HERBAL AND TRADITIONAL MEDICINE	[redacted]	[redacted]	[redacted]

PROPHYLAXIS	ALIMENTARY TRACT AND METABOLISM	ALUMINIUM COMPOUNDS	ALUMINIUM HYDROXIDE	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	ALIMENTARY TRACT AND METABOLISM	ANTIBIOTICS	NEOMYCIN	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	ALIMENTARY TRACT AND METABOLISM	ANTIDIARRHEAL MICROORGANISMS	MEDILAC-S	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	ALIMENTARY TRACT AND METABOLISM	ANTIDIARRHEAL MICROORGANISMS	SACCHAROMYCES BOULARDII	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	ALIMENTARY TRACT AND METABOLISM	ANTIPROPULSIVES	LOPERAMIDE	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	ALIMENTARY TRACT AND METABOLISM	BILE ACID PREPARATIONS	URSODEOXYCHOLIC ACID	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	ALIMENTARY TRACT AND METABOLISM	CALCIUM	CALCIUM	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	ALIMENTARY TRACT AND METABOLISM	CALCIUM	CALCIUM CHLORIDE	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	ALIMENTARY TRACT AND METABOLISM	CALCIUM	CALCIUM GLUCONATE	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	ALIMENTARY TRACT AND METABOLISM	CALCIUM COMPOUNDS	CALCIUM CARBONATE	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	ALIMENTARY TRACT AND METABOLISM	CALCIUM, COMBINATIONS WITH VITAMIN D AND/OR OTHER DRUGS	CALCIUM W/MAGNESIUM	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	ALIMENTARY TRACT AND METABOLISM	CALCIUM, COMBINATIONS WITH VITAMIN D AND/OR OTHER DRUGS	LEKOVIT CA	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	ALIMENTARY TRACT AND METABOLISM	CALCIUM, COMBINATIONS WITH VITAMIN D AND/OR OTHER DRUGS	SUPER CAL600-MG300	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	ALIMENTARY TRACT AND METABOLISM	COMBINATIONS AND COMPLEXES OF ALUMINIUM, CALCIUM AND MAGNESIUM COMPOUNDS	ALMAGATE	[redacted]	[redacted]	[redacted]

PROPHYLAXIS	ALIMENTARY TRACT AND METABOLISM	CONTACT LAXATIVES	COLOXYL WITH SENNA	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	ALIMENTARY TRACT AND METABOLISM	CONTACT LAXATIVES	DOCUSATE W/SENNA	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	ALIMENTARY TRACT AND METABOLISM	CONTACT LAXATIVES	DULCODOS	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	ALIMENTARY TRACT AND METABOLISM	CONTACT LAXATIVES	SENNOSIDE A+B	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	ALIMENTARY TRACT AND METABOLISM	ENZYME PREPARATIONS	PANCREATIN	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	ALIMENTARY TRACT AND METABOLISM	H2-RECEPTOR ANTAGONISTS	CIMETIDINE	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	ALIMENTARY TRACT AND METABOLISM	H2-RECEPTOR ANTAGONISTS	FAMOTIDINE	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	ALIMENTARY TRACT AND METABOLISM	H2-RECEPTOR ANTAGONISTS	LAFUTIDINE	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	ALIMENTARY TRACT AND METABOLISM	H2-RECEPTOR ANTAGONISTS	RANITIDINE	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	ALIMENTARY TRACT AND METABOLISM	LIVER THERAPY	GODEX	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	ALIMENTARY TRACT AND METABOLISM	MAGNESIUM	MAGNESIUM	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	ALIMENTARY TRACT AND METABOLISM	MAGNESIUM	MAGNESIUM SULFATE	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	ALIMENTARY TRACT AND METABOLISM	MAGNESIUM COMPOUNDS	MAGNESIUM OXIDE	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	ALIMENTARY TRACT AND METABOLISM	MULTIVITAMINS WITH MINERALS	MINERALS NOS W/VITAMINS NOS	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	ALIMENTARY TRACT AND METABOLISM	MULTIVITAMINS, PLAIN	VITAMINS NOS	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	ALIMENTARY TRACT AND METABOLISM	OSMOTICALLY ACTING LAXATIVES	LACTULOSE	[redacted]	[redacted]	[redacted]

PROPHYLAXIS	ALIMENTARY TRACT AND METABOLISM	OSMOTICALLY ACTING LAXATIVES	MACROGOL	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	ALIMENTARY TRACT AND METABOLISM	OTHER AGENTS FOR LOCAL ORAL TREATMENT	PROPOLIS	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	ALIMENTARY TRACT AND METABOLISM	OTHER AGENTS FOR LOCAL ORAL TREATMENT	SODIUM GUALENATE HYDRATE	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	ALIMENTARY TRACT AND METABOLISM	OTHER ANTIEMETICS	DRONABINOL	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	ALIMENTARY TRACT AND METABOLISM	OTHER DRUGS FOR CONSTIPATION	PRUCALOPRIDE	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	ALIMENTARY TRACT AND METABOLISM	OTHER DRUGS FOR FUNCTIONAL GASTROINTESTINAL DISORDERS	PEPSANE	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	ALIMENTARY TRACT AND METABOLISM	OTHER DRUGS FOR PEPTIC ULCER AND GASTRO-OESOPHAGEAL REFLUX DISEASE (GORD)	ALBIS	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	ALIMENTARY TRACT AND METABOLISM	OTHER DRUGS FOR PEPTIC ULCER AND GASTRO-OESOPHAGEAL REFLUX DISEASE (GORD)	ECABET MONOSODIUM	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	ALIMENTARY TRACT AND METABOLISM	OTHER DRUGS FOR PEPTIC ULCER AND GASTRO-OESOPHAGEAL REFLUX DISEASE (GORD)	POLAPREZINC	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	ALIMENTARY TRACT AND METABOLISM	OTHER DRUGS FOR PEPTIC ULCER AND GASTRO-OESOPHAGEAL REFLUX DISEASE (GORD)	REBAMIPIDE	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	ALIMENTARY TRACT AND METABOLISM	OTHER DRUGS FOR PEPTIC ULCER AND GASTRO-OESOPHAGEAL REFLUX DISEASE (GORD)	SODIUM ALGINATE	[redacted]	[redacted]	[redacted]

PROPHYLAXIS	ALIMENTARY TRACT AND METABOLISM	OTHER INTESTINAL ADSORBENTS	DIOSMECTITE	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	ALIMENTARY TRACT AND METABOLISM	OTHER PLAIN VITAMIN PREPARATIONS	FLAVINE ADENINE DINUCLEOTIDE	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	ALIMENTARY TRACT AND METABOLISM	PERIPHERAL OPIOID RECEPTOR ANTAGONISTS	NALDEMEDINE TOSILATE	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	ALIMENTARY TRACT AND METABOLISM	POTASSIUM	POTASSIUM CHLORIDE	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	ALIMENTARY TRACT AND METABOLISM	POTASSIUM	POTASSIUM PHOSPHATE MONOBASIC	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	ALIMENTARY TRACT AND METABOLISM	PROPULSIVES	ITOPRIDE	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	ALIMENTARY TRACT AND METABOLISM	PROPULSIVES	ITOPRIDE HYDROCHLORIDE	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	ALIMENTARY TRACT AND METABOLISM	PROPULSIVES	METOCLOPRAMIDE	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	ALIMENTARY TRACT AND METABOLISM	PROPULSIVES	METOCLOPRAMIDE HYDROCHLORIDE	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	ALIMENTARY TRACT AND METABOLISM	PROTON PUMP INHIBITORS	DEXLANSOPRAZOLE	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	ALIMENTARY TRACT AND METABOLISM	PROTON PUMP INHIBITORS	ESOMEPRAZOLE	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	ALIMENTARY TRACT AND METABOLISM	PROTON PUMP INHIBITORS	ESOMEPRAZOLE MAGNESIUM	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	ALIMENTARY TRACT AND METABOLISM	PROTON PUMP INHIBITORS	LANSOPRAZOLE	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	ALIMENTARY TRACT AND METABOLISM	PROTON PUMP INHIBITORS	OMEPRAZOLE	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	ALIMENTARY TRACT AND METABOLISM	PROTON PUMP INHIBITORS	PANTOPRAZOLE	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	ALIMENTARY TRACT AND METABOLISM	PROTON PUMP INHIBITORS	PANTOPRAZOLE SODIUM SESQUIHYDRATE	[redacted]	[redacted]	[redacted]

PROPHYLAXIS	ALIMENTARY TRACT AND METABOLISM	PROTON PUMP INHIBITORS	RABEPRAZOLE	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	ALIMENTARY TRACT AND METABOLISM	SEROTONIN (5HT3) ANTAGONISTS	ONDANSETRON	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	ALIMENTARY TRACT AND METABOLISM	SEROTONIN (5HT3) ANTAGONISTS	RAMOSETRON HYDROCHLORIDE	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	ALIMENTARY TRACT AND METABOLISM	SOFTENERS, EMOLLIENTS	DOCUSATE SODIUM	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	ALIMENTARY TRACT AND METABOLISM	VARIOUS ALIMENTARY TRACT AND METABOLISM PRODUCTS	THIOCTIC ACID TROMETHAMINE	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	ALIMENTARY TRACT AND METABOLISM	VARIOUS ALIMENTARY TRACT AND METABOLISM PRODUCTS	UBIDECARENONE	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	ALIMENTARY TRACT AND METABOLISM	VITAMIN B1 IN COMBINATION WITH VITAMIN B6 AND/OR VITAMIN B12	NEOLAMIN 3B /05665201/	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	ALIMENTARY TRACT AND METABOLISM	VITAMIN D AND ANALOGUES	CALCIFEDIOL	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	ALIMENTARY TRACT AND METABOLISM	VITAMIN D AND ANALOGUES	COLECALCIFEROL	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	ALIMENTARY TRACT AND METABOLISM	VITAMIN D AND ANALOGUES	ELDECALCITOL	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	ALIMENTARY TRACT AND METABOLISM	VITAMIN D AND ANALOGUES	ERGOCALCIFEROL	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	ANTIINFECTIVES FOR SYSTEMIC USE	CARBAPENEMS	ERTAPENEM	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	ANTIINFECTIVES FOR SYSTEMIC USE	COMBINATIONS OF PENICILLINS, INCL. BETA-LACTAMASE INHIBITORS	AUGMENTIN /00756801/	[redacted]	[redacted]	[redacted]

PROPHYLAXIS	ANTIINFECTIVES FOR SYSTEMIC USE	COMBINATIONS OF PENICILLINS, INCL. BETA-LACTAMASE INHIBITORS	PIP/TAZO	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	ANTIINFECTIVES FOR SYSTEMIC USE	COMBINATIONS OF PENICILLINS, INCL. BETA-LACTAMASE INHIBITORS	PIPERACILLIN W/TAZOBACTAM /01606301/	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	ANTIINFECTIVES FOR SYSTEMIC USE	COMBINATIONS OF SULFONAMIDES AND TRIMETHOPRIM, INCL. DERIVATIVES	BACTRIM	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	ANTIINFECTIVES FOR SYSTEMIC USE	FIRST-GENERATION CEPHALOSPORINS	CEFADROXIL	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	ANTIINFECTIVES FOR SYSTEMIC USE	FIRST-GENERATION CEPHALOSPORINS	CEFAZOLIN	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	ANTIINFECTIVES FOR SYSTEMIC USE	FLUOROQUINOLONES	CIPROFLOXACIN HYDROCHLORIDE	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	ANTIINFECTIVES FOR SYSTEMIC USE	FLUOROQUINOLONES	LEVOFLOXACIN	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	ANTIINFECTIVES FOR SYSTEMIC USE	FLUOROQUINOLONES	OFLOXACIN	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	ANTIINFECTIVES FOR SYSTEMIC USE	FOURTH-GENERATION CEPHALOSPORINS	CEFEPIME	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	ANTIINFECTIVES FOR SYSTEMIC USE	GLYCOPEPTIDE ANTIBACTERIALS	VANCOMYCIN	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	ANTIINFECTIVES FOR SYSTEMIC USE	INFLUENZA VACCINES	INFLUENZA VACCINE	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	ANTIINFECTIVES FOR SYSTEMIC USE	INFLUENZA VACCINES	INFLUENZA VACCINE INACT SAG 4V	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	ANTIINFECTIVES FOR SYSTEMIC USE	INFLUENZA VACCINES	INFLUENZA VACCINE INACT SPLIT VIRION 3V	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	ANTIINFECTIVES FOR SYSTEMIC USE	INTERMEDIATE-ACTING SULFONAMIDES	SULFAMETHOXAZOLE	[redacted]	[redacted]	[redacted]

PROPHYLAXIS	ANTIINFECTIVES FOR SYSTEMIC USE	MACROLIDES	AZITHROMYCIN	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	ANTIINFECTIVES FOR SYSTEMIC USE	NUCLEOSIDES AND NUCLEOTIDES EXCL. REVERSE TRANSCRIPTASE INHIBITORS	PENCICLOVIR	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	ANTIINFECTIVES FOR SYSTEMIC USE	NUCLEOSIDES AND NUCLEOTIDES EXCL. REVERSE TRANSCRIPTASE INHIBITORS	VALACICLOVIR HYDROCHLORIDE	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	ANTIINFECTIVES FOR SYSTEMIC USE	OTHER VIRAL VACCINES	OTHER VIRAL VACCINES	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	ANTIINFECTIVES FOR SYSTEMIC USE	PENICILLINS WITH EXTENDED SPECTRUM	AMOXICILLIN	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	ANTIINFECTIVES FOR SYSTEMIC USE	PNEUMOCOCCAL VACCINES	PNEUMOCOCCAL VACCINE CONJ 13V (CRM197)	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	ANTIINFECTIVES FOR SYSTEMIC USE	SECOND-GENERATION CEPHALOSPORINS	CEFACLOR	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	ANTIINFECTIVES FOR SYSTEMIC USE	SECOND-GENERATION CEPHALOSPORINS	CEFOTETAN	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	ANTIINFECTIVES FOR SYSTEMIC USE	TETANUS VACCINES	TETANUS VACCINE	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	ANTIINFECTIVES FOR SYSTEMIC USE	TETRACYCLINES	DOXYCYCLINE	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	ANTIINFECTIVES FOR SYSTEMIC USE	THIRD-GENERATION CEPHALOSPORINS	CEFTRIAXONE	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	ANTIINFECTIVES FOR SYSTEMIC USE	TRIMETHOPRIM AND DERIVATIVES	TRIMETHOPRIM	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS	CALCINEURIN INHIBITORS	CICLOSPORIN	[redacted]	[redacted]	[redacted]

PROPHYLAXIS	BLOOD AND BLOOD FORMING ORGANS	AMINO ACIDS	TRANEXAMIC ACID	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	BLOOD AND BLOOD FORMING ORGANS	BLOOD SUBSTITUTES AND PLASMA PROTEIN FRACTIONS	ALBUMIN HUMAN	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	BLOOD AND BLOOD FORMING ORGANS	BLOOD SUBSTITUTES AND PLASMA PROTEIN FRACTIONS	VOLULYTE	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	BLOOD AND BLOOD FORMING ORGANS	DIRECT FACTOR XA INHIBITORS	APIXABAN	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	BLOOD AND BLOOD FORMING ORGANS	DIRECT FACTOR XA INHIBITORS	EDOXABAN TOSILATE	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	BLOOD AND BLOOD FORMING ORGANS	DIRECT FACTOR XA INHIBITORS	RIVAROXABAN	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	BLOOD AND BLOOD FORMING ORGANS	ELECTROLYTE SOLUTIONS	MULTITRACE-4	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	BLOOD AND BLOOD FORMING ORGANS	FOLIC ACID AND DERIVATIVES	FOLIC ACID	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	BLOOD AND BLOOD FORMING ORGANS	HEPARIN GROUP	BEMIPARIN	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	BLOOD AND BLOOD FORMING ORGANS	HEPARIN GROUP	ENOXAPARIN	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	BLOOD AND BLOOD FORMING ORGANS	HEPARIN GROUP	ENOXAPARIN SODIUM	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	BLOOD AND BLOOD FORMING ORGANS	HEPARIN GROUP	HEPARINOID	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	BLOOD AND BLOOD FORMING ORGANS	HEPARIN GROUP	MUCOPOLYSACCHARIDE POLYSULFURIC ACID ESTER	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	BLOOD AND BLOOD FORMING ORGANS	HEPARIN GROUP	TINZAPARIN	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	BLOOD AND BLOOD FORMING ORGANS	HEPARIN GROUP	TINZAPARIN SODIUM	[redacted]	[redacted]	[redacted]

PROPHYLAXIS	BLOOD AND BLOOD FORMING ORGANS	IRON BIVALENT, ORAL PREPARATIONS	FERROUS FUMARATE	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	BLOOD AND BLOOD FORMING ORGANS	IRON BIVALENT, ORAL PREPARATIONS	FERROUS SULFATE	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	BLOOD AND BLOOD FORMING ORGANS	OTHER ANTIANEMIC PREPARATIONS	DARBEPOETIN ALFA	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	BLOOD AND BLOOD FORMING ORGANS	PLATELET AGGREGATION INHIBITORS EXCL. HEPARIN	CLOPIDOGREL	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	BLOOD AND BLOOD FORMING ORGANS	PLATELET AGGREGATION INHIBITORS EXCL. HEPARIN	CLOPIDOGREL CAMSILATE	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	BLOOD AND BLOOD FORMING ORGANS	PLATELET AGGREGATION INHIBITORS EXCL. HEPARIN	NEFAZAN COMPUESTO	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	BLOOD AND BLOOD FORMING ORGANS	SALT SOLUTIONS	SODIUM BICARBONATE	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	BLOOD AND BLOOD FORMING ORGANS	SALT SOLUTIONS	SODIUM CHLORIDE	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	BLOOD AND BLOOD FORMING ORGANS	SOLUTIONS AFFECTING THE ELECTROLYTE BALANCE	AMINO ACIDS NOS W/ELECTROLYTES NOS/GLUCOSE	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	BLOOD AND BLOOD FORMING ORGANS	SOLUTIONS AFFECTING THE ELECTROLYTE BALANCE	PLASMALYTE A	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	BLOOD AND BLOOD FORMING ORGANS	SOLUTIONS AFFECTING THE ELECTROLYTE BALANCE	RINGER-LACTATE	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	BLOOD AND BLOOD FORMING ORGANS	SOLUTIONS FOR PARENTERAL NUTRITION	AMINO ACIDS NOS W/ELECTROLYTES NOS/GLUCOSE	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	BLOOD AND BLOOD FORMING ORGANS	SOLUTIONS FOR PARENTERAL NUTRITION	CLINIMIX N14G30E	[redacted]	[redacted]	[redacted]

PROPHYLAXIS	BLOOD AND BLOOD FORMING ORGANS	SOLUTIONS FOR PARENTERAL NUTRITION	FREAMINE	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	BLOOD AND BLOOD FORMING ORGANS	VITAMIN B12 (CYANOCOBALAMIN AND ANALOGUES)	COBAMAMIDE	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	CARDIOVASCULAR SYSTEM	ACE INHIBITORS, PLAIN	RAMIPRIL	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	CARDIOVASCULAR SYSTEM	ADRENERGIC AND DOPAMINERGIC AGENTS	NOREPINEPHRINE	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	CARDIOVASCULAR SYSTEM	BENZOTHIAZEPINE DERIVATIVES	DILTIAZEM HYDROCHLORIDE	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	CARDIOVASCULAR SYSTEM	BETA BLOCKING AGENTS, SELECTIVE	BISOPROLOL	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	CARDIOVASCULAR SYSTEM	BETA BLOCKING AGENTS, SELECTIVE	BISOPROLOL FUMARATE	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	CARDIOVASCULAR SYSTEM	DIHYDROPYRIDINE DERIVATIVES	NIFEDIPINE	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	CARDIOVASCULAR SYSTEM	HMG COA REDUCTASE INHIBITORS	ATORVASTATIN	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	CARDIOVASCULAR SYSTEM	HMG COA REDUCTASE INHIBITORS	ATORVASTATIN CALCIUM	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	CARDIOVASCULAR SYSTEM	HMG COA REDUCTASE INHIBITORS	ROSUVASTATIN CALCIUM	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	CARDIOVASCULAR SYSTEM	HMG COA REDUCTASE INHIBITORS IN COMBINATION WITH OTHER LIPID MODIFYING AGENTS	ROSUVAST EZ	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	CARDIOVASCULAR SYSTEM	ORGANIC NITRATES	ISOSORBIDE MONONITRATE	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	CARDIOVASCULAR SYSTEM	OTHER LIPID MODIFYING AGENTS	DOCOSAHEXAENOIC ACID W/EICOSAPENTAE/09087201/	[redacted]	[redacted]	[redacted]

PROPHYLAXIS	CARDIOVASCULAR SYSTEM	OTHER VASODILATORS USED IN CARDIAC DISEASES	NICORANDIL	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	CARDIOVASCULAR SYSTEM	SULFONAMIDES, PLAIN	FUROSEMIDE	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	DERMATOLOGICALS	ANTIINFECTIVES FOR TREATMENT OF ACNE	BENZACLIN TOPICAL	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	DERMATOLOGICALS	CARBAMIDE PRODUCTS	UREA	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	DERMATOLOGICALS	CORTICOSTEROIDS, MODERATELY POTENT (GROUP II)	FLUOROMETHOLONE	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	DERMATOLOGICALS	CORTICOSTEROIDS, POTENT, COMBINATIONS WITH ANTIBIOTICS	VALISONE-G	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	DERMATOLOGICALS	IMIDAZOLE AND TRIAZOLE DERIVATIVES	FLUCONAZOLE	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	DERMATOLOGICALS	OTHER EMOLLIENTS AND PROTECTIVES	DEXERYL /01579901/	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	DERMATOLOGICALS	ZINC PRODUCTS	ZINC OXIDE	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	GENITO URINARY SYSTEM AND SEX HORMONES	ALPHA-ADRENORECEPTOR ANTAGONISTS	ALFUZOSIN HYDROCHLORIDE	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	GENITO URINARY SYSTEM AND SEX HORMONES	PROGESTOGENS	MEGESTROL	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	GENITO URINARY SYSTEM AND SEX HORMONES	PROGESTOGENS	MEGESTROL ACETATE	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	MUSCULO-SKELETAL SYSTEM	ACETIC ACID DERIVATIVES AND RELATED SUBSTANCES	ACECLOFENAC	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	MUSCULO-SKELETAL SYSTEM	BISPHOSPHONATES	ALENDRONATE SODIUM	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	MUSCULO-SKELETAL SYSTEM	BISPHOSPHONATES	PAMIDRONATE DISODIUM	[redacted]	[redacted]	[redacted]

PROPHYLAXIS	MUSCULO-SKELETAL SYSTEM	BISPHOSPHONATES	ZOLEDRONIC ACID	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	MUSCULO-SKELETAL SYSTEM	COXIBS	CELECOXIB	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	MUSCULO-SKELETAL SYSTEM	OTHER ANTIINFLAMMATORY AND ANTIRHEUMATIC AGENTS, NON-STEROIDS	BENZYDAMINE	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	MUSCULO-SKELETAL SYSTEM	OTHER ANTIINFLAMMATORY AND ANTIRHEUMATIC AGENTS, NON-STEROIDS	BENZYDAMINE HYDROCHLORIDE	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	MUSCULO-SKELETAL SYSTEM	OTHER DRUGS AFFECTING BONE STRUCTURE AND MINERALIZATION	DENOSUMAB	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	MUSCULO-SKELETAL SYSTEM	PREPARATIONS INHIBITING URIC ACID PRODUCTION	ALLOPURINOL	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	MUSCULO-SKELETAL SYSTEM	PROPIONIC ACID DERIVATIVES	DEXKETOPROFEN	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	MUSCULO-SKELETAL SYSTEM	PROPIONIC ACID DERIVATIVES	DEXKETOPROFEN TROMETAMOL	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	MUSCULO-SKELETAL SYSTEM	PROPIONIC ACID DERIVATIVES	IBUPROFEN	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	NERVOUS SYSTEM	AMIDES	EMLA /00675501/	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	NERVOUS SYSTEM	ANILIDES	PARACETAMOL	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	NERVOUS SYSTEM	ANTIVERTIGO PREPARATIONS	FLUNARIZINE	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	NERVOUS SYSTEM	BENZODIAZEPINE DERIVATIVES	ALPRAZOLAM	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	NERVOUS SYSTEM	BENZODIAZEPINE DERIVATIVES	BENZODIAZEPINE DERIVATIVES	[redacted]	[redacted]	[redacted]

PROPHYLAXIS	NERVOUS SYSTEM	BENZODIAZEPINE DERIVATIVES	BROMAZEPAM	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	NERVOUS SYSTEM	BENZODIAZEPINE DERIVATIVES	CLOBAZAM	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	NERVOUS SYSTEM	BENZODIAZEPINE DERIVATIVES	DIAZEPAM	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	NERVOUS SYSTEM	BENZODIAZEPINE DERIVATIVES	LORAZEPAM	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	NERVOUS SYSTEM	BENZODIAZEPINE RELATED DRUGS	ZOLPIDEM	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	NERVOUS SYSTEM	BENZODIAZEPINE RELATED DRUGS	ZOLPIDEM TARTRATE	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	NERVOUS SYSTEM	DIAZEPINES, OXAZEPINES, THIAZEPINES AND OXEPINES	OLANZAPINE	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	NERVOUS SYSTEM	NATURAL OPIUM ALKALOIDS	MORPHINE SULFATE	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	NERVOUS SYSTEM	NATURAL OPIUM ALKALOIDS	OXYCODONE HYDROCHLORIDE	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	NERVOUS SYSTEM	NATURAL OPIUM ALKALOIDS	TARGIN	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	NERVOUS SYSTEM	NATURAL OPIUM ALKALOIDS	VICODIN	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	NERVOUS SYSTEM	OPIOIDS IN COMBINATION WITH NON-OPIOID ANALGESICS	ULTRACET	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	NERVOUS SYSTEM	OTHER ANALGESICS AND ANTIPYRETICS	PREGABALIN	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	NERVOUS SYSTEM	OTHER ANTI-DEMENTIA DRUGS	MEMANTINE	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	NERVOUS SYSTEM	OTHER ANTIEPILEPTICS	LACOSAMIDE	[redacted]	[redacted]	[redacted]

PROPHYLAXIS	NERVOUS SYSTEM	OTHER ANTIEPILEPTICS	LEVETIRACETAM	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	NERVOUS SYSTEM	OTHER OPIOIDS	TAPENTADOL HYDROCHLORIDE	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	NERVOUS SYSTEM	OTHER OPIOIDS	TRAMADOL	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	NERVOUS SYSTEM	OTHER PARASYMPATHOMIMETICS	CHOLINE ALFOSCERATE	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	NERVOUS SYSTEM	PHENOTHIAZINES WITH PIPERAZINE STRUCTURE	PROCHLORPERAZINE	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	NERVOUS SYSTEM	PHENOTHIAZINES WITH PIPERAZINE STRUCTURE	PROCHLORPERAZINE MALEATE	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	NERVOUS SYSTEM	PHENYLPIPERIDINE DERIVATIVES	FENTANYL	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	NERVOUS SYSTEM	PHENYLPIPERIDINE DERIVATIVES	PETHIDINE	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	NERVOUS SYSTEM	PYRAZOLONES	METAMIZOLE MAGNESIUM	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	NERVOUS SYSTEM	SALICYLIC ACID AND DERIVATIVES	ACETYLSALICYLATE LYSINE	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	NERVOUS SYSTEM	SALICYLIC ACID AND DERIVATIVES	ACETYLSALICYLIC ACID	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	NERVOUS SYSTEM	SELECTIVE SEROTONIN REUPTAKE INHIBITORS	ESCITALOPRAM	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	NERVOUS SYSTEM	SELECTIVE SEROTONIN REUPTAKE INHIBITORS	FLUOXETINE HYDROCHLORIDE	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	RESPIRATORY SYSTEM	ANESTHETICS, LOCAL	LIDOCAINE	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	RESPIRATORY SYSTEM	ANTISEPTICS	CHLORHEXIDINE	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	RESPIRATORY SYSTEM	ANTISEPTICS	CHLORHEXIDINE GLUCONATE	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	RESPIRATORY SYSTEM	ANTISEPTICS	POVIDONE-IODINE	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	RESPIRATORY SYSTEM	MUCOLYTICS	CARBOCISTEINE	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	RESPIRATORY SYSTEM	MUCOLYTICS	ERDOSTEINE	[redacted]	[redacted]	[redacted]

PROPHYLAXIS	RESPIRATORY SYSTEM	OTHER ANTIHISTAMINES FOR SYSTEMIC USE	LORATADINE	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	RESPIRATORY SYSTEM	PIPERAZINE DERIVATIVES	CETIRIZINE HYDROCHLORIDE	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	RESPIRATORY SYSTEM	SELECTIVE BETA-2-ADRENORECEPTOR AGONISTS	SALBUTAMOL	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	RESPIRATORY SYSTEM	SUBSTITUTED ALKYLAMINES	CHLORPHENAMINE	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	RESPIRATORY SYSTEM	SUBSTITUTED ALKYLAMINES	CHLORPHENAMINE MALEATE	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	RESPIRATORY SYSTEM	SUBSTITUTED ALKYLAMINES	DEXCHLORPHENIRAMINE MALEATE	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	SENSORY ORGANS	CORTICOSTEROIDS AND ANTIINFECTIVES IN COMBINATION	MAXITROL	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	SENSORY ORGANS	OTHER OPHTHALMOLOGICALS	CARBOMER	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	SENSORY ORGANS	OTHER OPHTHALMOLOGICALS	CARMELLOSE SODIUM	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	SYSTEMIC HORMONAL PREPARATIONS, EXCL. SEX HORMONES AND INSULINS	CALCITONIN PREPARATIONS	CALCITONIN, SALMON	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	SYSTEMIC HORMONAL PREPARATIONS, EXCL. SEX HORMONES AND INSULINS	GLUCOCORTICOIDS	DEXAMETHASONE	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	SYSTEMIC HORMONAL PREPARATIONS, EXCL. SEX HORMONES AND INSULINS	GLUCOCORTICOIDS	HYDROCORTISONE	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	SYSTEMIC HORMONAL PREPARATIONS, EXCL.	GLUCOCORTICOIDS	PREDNISOLONE	[redacted]	[redacted]	[redacted]

	SEX HORMONES AND INSULINS					
PROPHYLAXIS	SYSTEMIC HORMONAL PREPARATIONS, EXCL. SEX HORMONES AND INSULINS	GLUCOCORTICOIDS	PREDNISONE	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	SYSTEMIC HORMONAL PREPARATIONS, EXCL. SEX HORMONES AND INSULINS	GLUCOCORTICOIDS	TRIAMCINOLONE ACETONIDE	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	SYSTEMIC HORMONAL PREPARATIONS, EXCL. SEX HORMONES AND INSULINS	SULFUR-CONTAINING IMIDAZOLE DERIVATIVES	CARBIMAZOLE	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	VARIOUS	CARBOHYDRATES	GLUCOSE	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	VARIOUS	DRUGS FOR TREATMENT OF HYPERKALEMIA AND HYPERPHOSPHATEMIA	CALCIUM POLYSTYRENE SULFONATE	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	VARIOUS	FAT/CARBOHYDRATES/PROTEINS/MINERALS/VITAMINS, COMBINATIONS	ASCORBIC ACID W/BIOTIN/CALCIUM/CARB/ 08371201/	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	VARIOUS	OTHER COMBINATIONS OF NUTRIENTS	ALANINE W/ARGININE/CALCIUM CHLORIDE/08566301/	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	VARIOUS	UNSPECIFIED HERBAL AND TRADITIONAL MEDICINE	ALOE VERA	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	VARIOUS	UNSPECIFIED HERBAL AND TRADITIONAL MEDICINE	ECHINACEA PURPUREA	[redacted]	[redacted]	[redacted]
PROPHYLAXIS	VARIOUS	UNSPECIFIED HERBAL AND TRADITIONAL MEDICINE	HERBAL PREPARATION	[redacted]	[redacted]	[redacted]

PROPHYLAXIS	VARIOUS	UNSPECIFIED HERBAL AND TRADITIONAL MEDICINE	ZINGIBER OFFICINALE RHIZOME	[redacted]	[redacted]	[redacted]
TRIAL INDICATION	ALIMENTARY TRACT AND METABOLISM	CONTACT LAXATIVES	COMPOUND GLYCYRRHIZA	[redacted]	[redacted]	[redacted]
TRIAL INDICATION	ALIMENTARY TRACT AND METABOLISM	MAGNESIUM COMPOUNDS	MAGNESIUM OXIDE	[redacted]	[redacted]	[redacted]
TRIAL INDICATION	CARDIOVASCULAR SYSTEM	SULFONAMIDES, PLAIN	FUROSEMIDE	[redacted]	[redacted]	[redacted]
TRIAL INDICATION	GENITO URINARY SYSTEM AND SEX HORMONES	PROGESTOGENS	MEGESTROL ACETATE	[redacted]	[redacted]	[redacted]
TRIAL INDICATION	MUSCULO-SKELETAL SYSTEM	BISPHOSPHONATES	ZOLEDRONIC ACID	[redacted]	[redacted]	[redacted]
TRIAL INDICATION	MUSCULO-SKELETAL SYSTEM	COXIBS	CELECOXIB	[redacted]	[redacted]	[redacted]
TRIAL INDICATION	MUSCULO-SKELETAL SYSTEM	OTHER DRUGS AFFECTING BONE STRUCTURE AND MINERALIZATION	DENOSUMAB	[redacted]	[redacted]	[redacted]
TRIAL INDICATION	NERVOUS SYSTEM	ANILIDES	PARACETAMOL	[redacted]	[redacted]	[redacted]
TRIAL INDICATION	NERVOUS SYSTEM	NATURAL OPIUM ALKALOIDS	MORPHINE	[redacted]	[redacted]	[redacted]
TRIAL INDICATION	NERVOUS SYSTEM	NATURAL OPIUM ALKALOIDS	MORPHINE SULFATE	[redacted]	[redacted]	[redacted]
TRIAL INDICATION	NERVOUS SYSTEM	NATURAL OPIUM ALKALOIDS	OXYCODONE	[redacted]	[redacted]	[redacted]
TRIAL INDICATION	NERVOUS SYSTEM	NATURAL OPIUM ALKALOIDS	OXYCODONE HYDROCHLORIDE	[redacted]	[redacted]	[redacted]
TRIAL INDICATION	NERVOUS SYSTEM	NATURAL OPIUM ALKALOIDS	VICODIN	[redacted]	[redacted]	[redacted]

TRIAL INDICATION	NERVOUS SYSTEM	OPIOIDS IN COMBINATION WITH NON-OPIOID ANALGESICS	ULTRACET	[redacted]	[redacted]	[redacted]
TRIAL INDICATION	NERVOUS SYSTEM	PHENYLPIPERIDINE DERIVATIVES	FENTANYL	[redacted]	[redacted]	[redacted]
TRIAL INDICATION	RESPIRATORY SYSTEM	ANTICHOLINERGICS	IPRATROPIUM BROMIDE	[redacted]	[redacted]	[redacted]
TRIAL INDICATION	RESPIRATORY SYSTEM	MUCOLYTICS	ACETYLCYSTEINE	[redacted]	[redacted]	[redacted]
TRIAL INDICATION	RESPIRATORY SYSTEM	MUCOLYTICS	AMBROXOL HYDROCHLORIDE	[redacted]	[redacted]	[redacted]
TRIAL INDICATION	RESPIRATORY SYSTEM	OPIUM ALKALOIDS AND DERIVATIVES	CODEINE	[redacted]	[redacted]	[redacted]
TRIAL INDICATION	RESPIRATORY SYSTEM	OPIUM ALKALOIDS AND DERIVATIVES	DEXTROMETHORPHAN HYDROBROMIDE	[redacted]	[redacted]	[redacted]
TRIAL INDICATION	VARIOUS	MEDICAL GASES	OXYGEN	[redacted]	[redacted]	[redacted]

NICE National Institute for Health and Care Excellence

Patient organisation submission

Amivantamab for treating EGFR Exon 20 insertion-positive non-small-cell lung cancer after platinum-based chemotherapy [ID3836]

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

NICE National Institute for Health and Care Excellence

1.Your name	[redacted]
2. Name of organisation	EGFR Positive UK
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	EGFR Positive UK is a patient driven charity established to provide information and support for UK based EGFR-mutated lung cancer patients and their families. We are funded by donations. To date all of our donations have been from members, their families and friends or as a result of fundraising events organised either by the charity or it's members. We have 302 members
4b. 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.]	No

If so, please state the name of manufacturer, 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?	The submission was prepared by Angela Terry with the input of members of EGFR Positive UK and the Exon 20 Group. Members of EGFR Positive UK share their experiences of treatment pathways and drug toleration on our private Facebook group which is the main forum for the exchange of information. We have over 300 members and are therefore able to present a representative view of the experience of living with EGFR mutation positive lung cancer. We have canvassed opinion from UK Exon 20 patients on their disease and treatment experience and held a zoom meeting with 7 Exon 20 Group members based in the USA. UK members were invited to submit comments on their experiences via email.
Living with the condition	
6. What is it like to live with the condition? What do carers	Non-small cell lung cancer with an EGFR mutation is an aggressive disease that has a considerable physical, psychological, economic and social impact on patients and their families.

experience when caring for someone with the condition?	Like most EGFR positive NSCLC patients, 85% of our members were diagnosed at stage IV when their treatment options are limited. They also carry a significant risk of symptomatic central nervous system metastases. The diagnosis is devastating. PxC: who is forty two and a mother of 4 comments: 'My life, the life of my kids, my wonderful husband's life - these lives have been completely turned on their heads, and access to a treatment which helps us feel we could see another birthday or Christmas together as a family is so important' EGFR Exon 20 insertion is a distinct population. Patients with EGFR Exon 20 insertion have a worse prognosis and a propensity for brain and bone metastases. It is recommended that patients are offered platinum-based chemotherapy 1st line and there are no specific treatment recommendations beyond this. There are currently no approved targeted therapies available for EGFR Exon 20 insertion patients and EGFR Exon 20 insertion mutations are known to be associated with resistance/insensitivity to the currently available TKIs. The frequency of the EGFR Exon 20 insertion mutation ranges from 0.1%–4.0% among all patients with NSCLC and 1%–12% among those with EGFR mutations. The frequency of EGFR Exon 20 insertion may however have been significantly underestimated. Detection rates are currently increasing with the advent of more sensitive NGS testing. In essence they are an underdiagnosed and underserved population. The poor prognosis coupled with knowing that there are fewer treatments than those available to other EGFR patients, has a devastating impact. PxE: 'I was very frightened initially. The young doctor showed me a chart of targeted therapies available for treating EGFR and then told me that none of them would work for Exon 20. He gave me 6 months to live.' PxJ: 'I know from other patients that their targeted therapies are less toxic and more effective. I am angry and disappointed knowing they are available to others in the group but not to me.' PxP: 'I feel very isolated, I don't know anyone else who has this type of EGFR and I am not sure my Oncologist does either. My treatment feels like trial and error.'

	Late diagnosis perhaps reflects that EGFR patients are generally younger than typical lung cancer patients, non-smokers, more likely to be female, often still working and with dependent children. The diagnosis therefore is particularly devastating and affects all aspects of life. Lung Cancer patients carry the additional stigma of contracting a disease that is thought to be linked to smoking. Of our EGFR positive UK members (85%) have never smoked (59%) or gave up over 10 years ago (26%). PxS: 'I was diagnosed age 44 and felt very frightened, very alone and completely overwhelmed. As a never-smoker it was the last thing on my mind and the shock and disbelief is very hard to cope with'. Living with stage IV disease is extremely difficult. Many of our members are still working, in the prime of their lives, and have dependent children. For families, facing the loss of a parent and breadwinner, causes immense strain and many of our members suffer from anxiety and depression. This coupled with the burden of disease and treatment, impacts enormously on their quality of life and that of their families. The causes of poor quality of life were frequently treatment and disease related symptoms such as diarrhoea, fatigue, pain, shortness of breath and cough. Together these have a negative impact on daily activities including household chores and self-care, social activities, work, and family life. PxE:'the fatigue and diarrhoea has meant that I have given up so many things. I no longer drive, nor work and my family are not close by. My world is very small.' Psychologically, socially and economically life can be extremely challenging. Progression free survival and quality of life are key to patients - the ability to take part fully in family life and to support the family for as long as possible is vital. Recent members who have joined our group include a thirty seven year old father with 3 children under the age of 5 and a forty-three year old mother with a 10 and an 8 year old. PxM: 'I feel robbed of my future. All those memories I may never have a chance to make. My kids leaving school, going to university, getting married, starting a family…' EGFR positive patients have a very high probability of developing brain metastases. Evidence suggests that patients in whom brain metastases are treated early have improved overall survival. Only 42% of our

	members have regular routine brain scans. This impacts directly on treatment options, particularly if patients become symptomatic before brain metastases are discovered. Additionally once brain metastases are identified the patient must stop driving, this has implications for both the patient and their families. PxA: 'not being able to drive has affected my whole family and put the burden of 'taxi' to our three teenage children on my husband. For myself, I feel that my freedom has been stripped from me and my life is much smaller than it was.' Family and carers for patients may have a considerable burden providing care and assistance with the activities of daily living. This could affect the ability of family members to continue employment, have a detrimental effect on household income, and cause financial strain. This may add to the stress and anxiety of caring for a loved one with significant disease burden. For younger family members, educational choices may be affected which could have an impact for years to come. Patients deserve the chance of treatments which will give them as much time as possible with their families and the ability to continue their working lives as long as possible. PxG: 'I am driven by hope. I am trying to see it as a chronic disease but I need to know what is coming next for me and there doesn't seem to be much.' .
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	The population of patients with EGFR Exon 20 insertion is not well recognized and underserved. It is recommended that patients are offered platinum-based chemotherapy 1st line and there are no specific treatment recommendations beyond this.

	There are currently no approved targeted therapies available for EGFR Exon 20 insertion patients and EGFR Exon 20 insertion mutations are known to be associated with resistance/insensitivity to the currently available TKIs. PxE: 'I was very frightened initially. The young doctor showed me a chart of targeted therapies available for treating EGFR and then told me that none of them would work for Exon 20. He gave me 6 months to live.' We have found that following initial chemotherapy, there is little conformity in the treatment offered in the 2nd line setting. Patients were offered a range of treatments: TKI's approved for other EGFR mutations, chemotherapy and immunotherapy. This is surprising as it is known that these therapies offer limited clinical benefit to EGFR Exon 20 insertion patients. Patients however have a strong preference for targeted therapies and upon progression patients are pressing for another treatment so perhaps trying one that is available but not optimal, is preferable to nothing. PxP: 'I feel very isolated, I don't know anyone else who has this type of EGFR and I am not sure my Oncologist does either. My treatment feels like trial and error.' PxL: 'I am really positive about targeted therapies. I don't like this one size fits all approach (Chemo). We are becoming much better educated about our disease and I really dislike chemo, there must be other treatment available to us' PxJ: I know from other patients that their targeted therapies are less toxic and more effective. I am angry and disappointed knowing they are available to others in the group but not to me.' EGFR positive patients have a very high probability of developing brain metastases. No treatment currently offered to EGFR Exon 20 insertion patients offers protection to the brain and patients fear the inevitable CNS progression. When brain metastases develop the patient must relinquish their driving licence. This greatly affects the quality and logistics of life. Evidence suggests that patients in whom brain metastases are treated early have improved overall survival. Only 42% of our members report as having regular MRI brain scans after

	diagnosis. Their risk of developing brain metastases that go undiscovered until they become symptomatic is heightened and this impacts directly on treatment options. PxA: 'not being able to drive has affected my whole family and put the burden of 'taxi' to our three teenage children on my husband. For myself, I feel that my freedom has been stripped from me and my life is much smaller than it was.' Patients deserve the chance of treatments that will give them as much time as possible with their families and the ability to enjoy their life and continue their working lives as long as possible.
8. Is there an unmet need for patients with this condition?	EGFR Exon 20 insertion patients are a small population with a significant unmet need. They are outliers in the EGFR group. A very niche market who are often under or mis-diagnosed and have an urgent need for targeted, more effective and well tolerated therapies to prolong survival and improve quality of life. In terms of prognostic impact and clinical burden, there is a high unmet need for novel, effective therapies for patients with EGFR Exon 20 insertion. These patients have poorer treatment outcomes compared with patients with other EGFR mutations across different currently available therapy options and treatment lines. PxB: I have already had chemotherapy earlier on and I believe an Exon 20 targeted therapy would be another level of treatment to slow the progression of the disease.' PxL: 'I am really positive about targeted therapies. I don't like this one size fits approach (Chemo). We are becoming much better educated about our disease and I really dislike chemo, there must be other treatments available to us' PxN:'I am a fighter, I can't believe this (Chemo) is all there is for me!' Without approved targeted therapies in the 2nd line setting, EGFR Exon 20 insertion patients are offered treatments that seem to be 'what is available' and 'will give hope'. Sadly these treatments are unlikely to give patients longer progression free survival. Meanwhile the treatment they are living with has significant side effects that impact every aspect of their lives.

	PxK: ‘‘It had all been doom and gloom until we found out that I was EGFR positive Exon 20 insertion. I was prescribed Afatinib. The side effects are horrible, constant diarrhoea meant I can’t go out, my skin is like a pizza and I am so tired all the time but I have to keep going on this but I don’t know what will be next for me.’ Amivantamab is expected to be used after failure of platinum-based chemotherapy. Whilst being treated with it, patients could be expected to have a better quality of life for longer, be able to live independently, continue to work and drive and participate fully in family life and social activities. This is of crucial concern for patients as this type of NSCLC typically affects younger people. Many have young and adolescent children, are working and carry financial responsibilities. An unacceptable additional emotional pressure for EGFR Exon 20 insertion patients would be knowing that there are more effective treatment options available and that without being able to access Amivantamab they are enduring a suboptimal treatment regime. PxG: ‘I am driven by hope. I am trying to see it as a chronic disease but I need to know what is coming next for me and there doesn’t seem to be much.’ PxL: ‘We are becoming much better educated about our disease and I really dislike chemo, there must be other treatments available to us’
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	Amivantamab is proposed for use after the failure of platinum-based chemotherapy. It is well tolerated and has a low toxicity burden. It is an IV therapy that is delivered in a hospital or Clinic. There are few side effects with Amivantamab and those there are, are mainly linked to an infusion related reaction which often happens on the 1st infusion only. PxG: ‘I started reacting when I was given my first dose but I wasn’t frightened as the team had talked us through what might happen. They weren’t alarmed and knew exactly what to do and that calmed me down. I ended up having the first dose over 2 days.’

	It is crucial to have alternative treatments available for patients. Amivantamab is not just important for post-chemo treatment but potentially important when used in sequence with the other new drugs that target EGFR Exon 20 patients. In addition, some patients may be better candidates for Amivantamab rather than the other targeted drugs and vice versa. PxL: 'I am really positive about targeted therapies. I don't like this one size fits approach (chemo). We are becoming much better educated about our disease and I really dislike chemo, there must be other treatment available to us' This new treatment would change the clinical, mental and emotional state of the EGFR Exon 20 patients and give them hope. Treatment with Amivantamab would allow patients to live progression free for longer. This would likely result in more independence with day-to-day life and selfcare, which would reduce dependence on family and support services. This drug offers a lifeline of hope for the first time for these patients.
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	As a charity we see no disadvantages for patients in Amivantamib being available as a 2nd line treatment but there are some issues. Patients have a fear of Chemotherapy and may need to be persuaded that this IV therapy is the best option for them. Taking time to help the patient fully understand what the treatment is, how it will be administered and predicable reactions is key. PxQ: 'The 1st infusion is scaring a lot of people. I was told that the body is seeing the antibody as something it will reject. Patients need to know that this will happen and it should not be a deterrent to having the treatment. It is a 100% expected side effect.' PxG: 'I started reacting when I was given my first dose but I wasn't frightened as the team had talked us through what might happen. They weren't alarmed and knew exactly what to do and that calmed me down. I ended up having the first dose over 2 days.'

	IV therapy is delivered in a hospital or Clinic. The time required for the treatment and travelling to and from the hospital, will present challenges especially for those patients who have mobility issues or live a long distance from their hospital/clinic. Amivantamib does not offer CNS penetration. Brain metastases are common with this disease and patients who are on this drug will fear the inevitable progression to the brain.
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.	All EGFR positive Exon 20 insertion patients would benefit from Amivantamab being approved for use in the 2nd line setting. Amivantamab would give Clinicians more choice and flexibility in the treatment of their EGFR positive Exon 20 insertion patients. Amivantamab would, for the first time, offer EGFR Exon 20 positive patients access to a targeted therapy. This would bring them emotionally and clinically in line with their fellow EGFR patients who have had access to targeted treatments for some time.
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	A major equality issue for patients is often one of equal access to the best treatment available. Amivantamab would, for the first time, offer EGFR Exon 20 positive patients access to a targeted therapy. This would bring them emotionally and clinically in line with their fellow EGFR patients who have had access to targeted treatments for some time.

Other issues	
13. Are there any other issues that you would like the committee to consider?	The success of a targeted approach is dependent on understanding the genomic state of the tumour cells. It is imperative to identify EGFR patients with Exon 20 insertion so that they can be matched up with the right treatment. Patients who are EGFR Exon 20 insertion positive are a small and distinct group whose number may have been significantly underestimated. It is hoped detection rates will increase with the advent of more sensitive NGS testing. Disappointingly only 51% of our members were aware of NGS and the implications it has for their treatment. Amivantamab is an excellent addition to the EGFR Exon 20 insertion patient's treatment options however there is still a need for new drugs with intracranial activity and resistance mechanisms.
14. For people with EGFR Exon 20 insertion-positive non-small-cell lung cancer, what treatments are usually offered?	We found that there was little conformity in the treatments offered. Patients were given a range of treatments: TKI's approved for other EGFR mutations, chemotherapy and immunotherapy. This is surprising as it is known that these therapies offer limited clinical benefit to EGFR Exon 20 insertion patients. These treatments give them hope but are unlikely to give them longer progression free survival. Meanwhile they are living with significant side effects that impact every aspect of their lives. PxK: ''It had all been doom and gloom until we found out that I was EGFR positive Exon 20 insertion. I was prescribed Afatinib. The side effects are horrible, constant diarrhoea meant I can't go out, my skin is like a pizza and I am so tired all the time. My oncologist says the only treatment left is Chemo. I have to keep going on this but I don't know what will be next for me.' Upon progression patients are pressing for another treatment so perhaps trying one that is available but not optimal, is preferable to nothing. PxP: 'I feel very isolated, I don't know anyone else who has this type of EGFR and I am not sure my Oncologist does either. My treatment feels like trial and error.'

Key messages

15. In up to 5 bullet points, please summarise the key messages of your submission:

- Amivantamab would begin to meet a significant unmet need. For the first time, EGFR Exon 20 positive patients would have access to a targeted therapy. This would bring them emotionally and clinically in line with some of the treatment options their fellow EGFR patients have had access to for some time.
- Amivantamab offers Progression Free Survival and Quality of Life Benefits
- Amivantamab has a low toxicity profile and infusion related reactions are manageable
- Amivantamab has the potential to be used in sequence or in combination with other new treatments for EGFR Exon 20 insertion positive patients
- Whilst taking Amivantamab patients can be expected to have a good quality of life for longer, be able to live independently, continue to work and drive and participate fully in family life and social activities.

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

Patient organisation submission

Amivantamab for treating EGFR Exon 20 insertion-positive non-small-cell lung cancer after platinum-based chemotherapy [ID3836]

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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
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- Your response should not be longer than 10 pages.

About you

1.Your name	[redacted]
2. Name of organisation	Roy Castle Lung Cancer Foundation
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Roy Castle Lung Cancer Foundation is a UK wide lung cancer charity. We fund lung cancer research, tobacco control initiatives and work in lung cancer patient care (information, support and advocacy activity). Our funding base is a broad mixture including community, retail, corporate, legacies and charitable trusts. Clearly, our patient group members and contacts are a self-selected group, who have taken the step to seek out information or have accessed specialist support services. As most lung cancer sufferers tend to be older, from lower social class groups and with the five year survival being around 15%, less physically well, we acknowledge that our patients are perhaps not representative of the vast majority of lung cancer patients, who are not so well informed. It is, however, important that the opinions expressed to us, be passed on to NICE, as it considers the place of this product in the management of lung cancer
4b. 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.	
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?	As a result of the COVID pandemic, our contact with patients and carers has become virtual. The Foundation has contact with patients/carers through its UK wide network of Lung Cancer Patient Support Groups, patient/carer panel, online forums, Keep in Touch' service and its nurse-led Lung Cancer Information Helpline
Living with the condition	
6. What is it like to live with the condition? What do carers	According to the National Lung Cancer Audit, the one year survival for lung cancer is 37%. Thus, this group of lung cancer patients have a particularly poor outlook. with an obvious impact on family and carers. Symptoms such as breathlessness, cough and weight loss are difficult to treat, without active anti-cancer therapy. Furthermore, these are symptoms which can be distressing for loved ones to observe.

experience when caring for someone with the condition?	Approximately 10-15% of non small cell lung cancer (nsclc) patients in Europe and the US and 30-40% of those in Asia, have epidermal growth factor receptor (EGFR) mutated nsclc. These patients are particularly sensitive to treatment with EGFR-tyrosine kinase inhibitors (TKIs), which block the cell signaling pathways that drive the growth of EGFR expressing lung cancer cells – NICE has approved a number of these medicines. EGFR exon 20 insertion mutations occur in 1% to 2% of nsclcs. Patients with these mutations do not respond well to treatment with available TKIs and as such, these patients have a worse prognosis than those with other EGFR mutations.
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	In recent years, we have seen new therapy options for some patients with nsclc – Target Therapies (including EGFR mutation positive) and Immunotherapies. As above, this has, so far, not been the case for those with EGFR Exon 20 insertions. There are currently no NICE recommended treatments, specifically for Exon 20 insertion positive lung cancer patients. Current systemic treatment (first and second line treatment) would be with standard NSCLC treatment – a combination of chemotherapy and immunotherapy.
8. Is there an unmet need for patients with this condition?	Yes
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	As above, this would be the first NICE approved therapy available specifically targeted at Exon 20 insertion positive lung cancer. Data from the Phase 1 CHRYSALIS clinical trial, presented at the World Lung Cancer Conference, assessed the effectiveness and safety of amivantamab in patients with nsclc and EGFR exon 20 insertions, who had progressed on prior platinum based chemotherapy. The overall response to treatment was 40% and 4% of patients achieved a complete response. The median duration of response was 11.1 months and 63% of patients had responses of at

	least six months or greater duration.
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	The side effects associated with the therapy. Although the majority of patients, in the study, experienced side effects, most events were grade 1 and 2. We note the most common side effects reported included rash, reactions at the infusion site, skin infections around the finger and toe nails (paronychia) and oedema.
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.	

Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	
Other issues	
13. Are there any other issues that you would like the committee to consider?	We understand that further studies of Amivantamab are ongoing in several clinical trials, including as first line therapy and in combination therapy. As data matures and as new data emerges, this is perhaps a therapy, at this time, which could be made available through the Cancer Drugs Fund.
14. For people with EGFR Exon 20 insertion-positive non-small-cell lung cancer, what treatments are usually offered?	Current systemic treatment (first and second line treatment) would be with standard nsclc treatment – a combination of chemotherapy and immunotherapy.
Key messages	
15. In up to 5 bullet points, please summarise the key messages of your submission:	

- With current treatments, patients with EGFR Exon 20 insertions have a poorer prognosis than those with other EGFR mutations
- First targeted therapy being assessed specifically for EGFR Exon 20 insertion positive nsclc.
- Consider availability through the Cancer Drugs Fund, reassessing after data matures and new data emerges.

Thank you for your time.

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in collaboration with:

Erasmus School of Health Policy & Management

Maastricht University

Amivantamab for treating EGFR Exon 20 insertion-positive non-small-cell lung cancer after platinum-based chemotherapy (review of TA10729) [ID3836]

Produced by

Kleijnen Systematic Reviews (KSR) Ltd, in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University Medical Centre+ (UMC+)

Authors

Jeremy Howick, Reviews Manager, KSR Ltd, United Kingdom (UK)
Willem Witlox, Health Economist, Maastricht UMC+, The Netherlands
Kevin McDermott, Systematic Reviewer, KSR Ltd, UK
Ben Wijnen, Health Economist, Maastricht UMC+, The Netherlands
Evangelos Danopoulos, Systematic Reviewer, KSR Ltd, UK
Thomas Otten, Health Economist, Maastricht UMC, The Netherlands
Charlotte Ahmadu, Health Economist, KSR Ltd, UK
Steven Duffy, Information Specialist, KSR Ltd, UK
Marie Westwood, Reviews Manager, KSR Ltd, UK
Nigel Armstrong, Health Economics Manager, KSR Ltd, UK
Mark Perry, Reviews Manager, KSR Ltd, UK
Robert Wolff, Managing Director, KSR Ltd, UK
Manuela Joore, Health Economist, Maastricht UMC+, The Netherlands
Jos Kleijnen, Founder and Owner, KSR Ltd

Correspondence to Jeremy Howick, Kleijnen Systematic Reviews Ltd
Unit 6, Escrick Business Park
Riccall Road, Escrick
York, YO19 6FD
United Kingdom

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Any de-personalised data are highlighted in pink throughout the report.

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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Jeremy Howick acted as project lead and systematic reviewer on this assessment, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Willem Witlox and Ben Wijnen acted as health economic project leads, critiqued the company's economic evaluation, and contributed to the writing of the report. Thomas Otten, Charlotte Ahmadu, and Nigel Armstrong acted as health economists on this assessment, critiqued the company's economic evaluation and contributed to the writing of the report. Kevin McDermott, Evan Danopoulos, Mark Perry, and Marie Westwood acted as systematic reviewers, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Steven Duffy critiqued the search methods in the submission and contributed to the writing of the report. Manuela Joore acted as health economist on this assessment, critiqued the company's economic evaluation, contributed to the writing of the report and provided general guidance. Robert Wolff and Jos Kleijnen critiqued the company's definition of the decision problem and their description of the underlying health problem and current service provision, contributed to the writing of the report and supervised the project.

Abbreviations

AACR	American Association for Cancer Research
AE	Adverse event
AEMPS	Agencia Española de Medicamentos y Productos Sanitarios
AIFA	Agenzia Italiana del Farmaco
AMI	Amivantamab
ASCO	American Society of Clinical Oncology
ATT	Average treatment effect among the treated
AWMSG	All Wales Medicines Strategy Group
BAG	Bundesamt für Gesundheit
BICR	Blinded independent committee review assessed
BMI	Body mass index
BNF	British National Formulary
BOR	Best overall response
BSC	Best supportive care
CADTH	Canadian Agency for drugs and Technologies in Health
CBR	Clinical benefit rate
CDSR	Cochrane Database of Systematic Reviews
CENTRAL	Cochrane Central Register of Controlled Clinical Trials
CI	Confidence interval
cm	Centimetre
CR	Complete response
CRD	Centre for Reviews and Dissemination
CS	Company submission
DARE	Database of Abstracts of Reviews of Effects
DFS	Disease free survival
DOR	Duration of response
DSA	Deterministic sensitivity analysis
DSU	Decision Support Unit
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal growth factor receptor
EMA	European Medicines Agency
EQ-5D-5L	EuroQoL 5-dimensions 5-levels
EQ-5D-5L VAS	EuroQol-5 dimensions 5-levels visual analogue score
ERG	Evidence Review Group
ESMO	European Society for Medical Oncology
Exon20ins	Exon 20 insertion mutations
FE	Fixing errors
FinCCHTA	Finnish Coordinating Center for Health Technology Assessment
FDA	Food and Drugs Administration
FV	Fixing violations
G-BA	Gemeinsamer Bundesausschuss
HAS	Haute Autorité de Santé
HER2	Human epidermal growth factor receptor 2
HIV	Human immunodeficiency virus
HR	Hazard ratio
HRQoL	Health-related quality of life

HTA	Health technology assessment
IASLC	International Association for the Study of Lung Cancer
ICER	Incremental cost-effectiveness ratio
iDFS	Invasive disease-free survival
ILD	Interstitial lung disease
INV	Investigator-assessed
IPD	Individual participant data
IPW	Inverse probability weighting
IRR	Infusion related reaction
IO	Immuno-oncology
ITC	Indirect treatment comparison
ITT	Intention to treat
IV	Intravenous
kg	Kilogram
KM	Kaplan-Meier
LOT	Line of therapy
LS	Least squares
LY	Life year
mg	Milligram
MET	Mesenchymal epithelial transition
MHRA	Medicines and Healthcare Products Regulatory Agency
MJ	Matters of judgement
MSCBS	Ministerio de Sanidad, Consumo y Bienestar Social
MTD	Maximum tolerated dose
NCI CTCAE	National Cancer Institute common terminology criteria for adverse events
NCPE	National Centre for Pharmacoeconomics
NCRAS	National Cancer Registration and Analysis Service
NE	Not evaluable
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIPH	Norwegian Institute of Public Health
NR	Not reported
NSCLC	Non-small-cell lung cancer
NSCLC-SAQ	Non-small-cell lung cancer Symptom Assessment Questionnaire
ORR	Overall response rate
OS	Overall survival
PAS	Patient Access Scheme
pCR	Pathological complete response
PD	Progressed disease
PFS	Progression-free survival
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
PHE	Public Health England
PPS	Post-progression survival
PR	Partial response
PRESS	Peer Review of Electronic Search Strategies
PRO	Patient-reported outcome

PSA	Probabilistic sensitivity analysis
PSM	Propensity score matching
PSSRU	Personal Social Services Research Unit
Pt	Platinum
QALY	Quality-adjusted life year
QoL	Quality of life
RCT	Randomised controlled trial
RECIST	Response Evaluation Criteria in Solid Tumours
RID	Residual invasive disease
RP2D	Recommended Phase 2 dose
RWD	Real world data
RWE	Real world evidence
SBU	Swedish Agency for Health Technology Assessment and Assessment of Social Services
SCLC	Small cell lung cancer
SD	Standard deviation
SLR	Systematic literature review
SMC	Scottish Medicines Consortium
SMD	Standardised mean difference
SoC	Standard of Care
SoD	Sum of diameters
STM	State transition model
STA	Single technology appraisal
TEAE	Treatment-emergent adverse event
TKI	Tyrosine kinase inhibitor
TSD	Technical Support Document
TTD	Time to treatment discontinuation
TTF	Time to treatment failure
TTNT	Time to next treatment
UK	United Kingdom
US	United States
VAS	Visual analogue scale

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1. EXECUTIVE SUMMARY

This summary provides a brief overview of the key issues identified by the Evidence Review Group (ERG) as being potentially important for decision making. If possible, it also includes the ERG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 presents the key model outcomes. Section 1.3 discusses the decision problem, Section 1.4 issues relate to the clinical effectiveness, and Section 1.5 issues relate to the cost effectiveness. A summary is presented in Section 1.6.

Background information on the condition, technology and evidence and information on key as well as non-key issues are in the main ERG report, see Sections 2 (decision problem), 3 (clinical effectiveness) and 4 (cost effectiveness) for more details.

All issues identified represent the ERG's view, not the opinion of the National Institute for Health and Care Excellence (NICE).

1.1 Overview of the ERG's key issues

Table 1.1: Summary of key issues

ID3836	Summary of issue	Report Sections
1	The narrower population considered by company may not be generalisable to the England and Wales National Health Service (NHS) population and may have led to an underestimate of adverse events (AEs).	2.1, 3.2
2	Patients in the intervention group received concomitant medications (including targeted radiotherapy) that could have exaggerated the benefits of amivantamab.	2.2, 3.2
3	Some of the comparators lack justification and could have obscured or exaggerated the benefits of amivantamab.	2.3, 3.2
4	The short follow-up time of the CHRYSALIS trial makes medium- and longer-term results uncertain.	3.2
5	The efficacy and safety populations differ in a way that is likely to exaggerate benefits and understate harms.	3.2
6	The real-world evidence (RWE) sources to identify comparators for the indirect treatment comparison were not comprehensive, leading to uncertainty in the benefits of amivantamab compared with relevant comparators.	3.3, 3.4
7	The company assumed [redacted] of the comparator basket to consist of epidermal growth factor receptor tyrosine kinase inhibitors (EGFR TKIs) which may not be consistent with UK clinical practice; the relative cost effectiveness of amivantamab is therefore unclear.	4.2.4
8	The company implemented Kaplan-Meier (KM) curves instead of parametric survival models for the survival analyses of overall survival (OS) and progression-free survival (PFS) in the standard of care (SoC) arm, leading to potential overfitting of modelled survival outcomes.	4.2.6
9	Time to treatment discontinuation (TTD) was assumed to be equal to the duration of PFS, while evidence from the CHRYSALIS trial showed that amivantamab treatment had a longer median duration	4.2.6

ID3836	Summary of issue	Report Sections
	than PFS, leading to a possible underestimate of amivantamab's relative cost.	
10	The company did not explore treatment waning in the model, whereas the Evidence Review Group (ERG) considered that the assumption of a lifelong treatment effect may not be warranted.	4.2.6
11	The company's failure to include an age-adjustment to the health state utilities in their company submission (CS) base case is not in line with good modelling practice and may have exaggerated the cost effectiveness of amivantamab.	4.2.8
12	Lack of a fully incremental analysis for all relevant comparators in the comparator basket, increasing the uncertainty of estimates of amivantamab's cost effectiveness.	5.1
13	Lack of a fixed random seed in model probabilistic sensitivity analysis (PSA) leads to fluctuations in probabilistic results and hence increased uncertainty of estimates of amivantamab's cost-effectiveness.	5.3

AEs = adverse events; CS = company submission; EGFR = epidermal growth factor receptor; ERG = Evidence Review Group; KM = Kaplan-Meier; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; OS = overall survival; PFS = progression-free survival; PSA = probabilistic sensitivity analysis; RWE = real world evidence; SoC = standard of care; TTD = time to treatment discontinuation; TKI = tyrosine kinase inhibitor; UK = United Kingdom

The key differences between the company's preferred assumptions and the ERG's preferred assumptions include assumptions related to the population, comparators, outcomes, and sources of evidence to inform the indirect treatment comparison.

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life (QoL) in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost per QALY gained.

Overall, the technology is modelled to affect QALYs by (deterministic):

- Increased post-progression survival (PPS), with an increment of 0.526 years (63% of total incremental life years (LYs)) in the amivantamab arm (1.349 years) compared with United Kingdom (UK) standard of care (SoC) (0.823 years)
- Increased progression-free survival (PFS), with an increment of 0.314 years (37% of total incremental LYs) in the amivantamab arm (0.818 years) compared with UK SoC (0.504 years).

Overall, the technology is modelled to affect costs by (deterministic):

- The higher drug costs (additional cost of [redacted], [redacted] of total incremental costs), administration costs (additional cost of [redacted], [redacted] of total incremental costs) and post-progression disease management costs (additional cost of [redacted], [redacted] of total incremental costs).

The company performed and presented the results of probabilistic sensitivity analysis (PSA), deterministic sensitivity analysis (DSA) as well as scenario analyses. The parameters that had the greatest effect on the ICER based on the company's DSA were:

- PFS Kaplan-Meier (KM) curve for the UK SoC arm

- Drug costs in subsequent cycles for the amivantamab arm
- Health state utilities for PFS and PPS

Company submission (CS) scenarios that have the greatest impact on the ICER (not including scenarios related to discount rates and time horizon) were:

- UK SoC efficacy based on Public Health England (PHE) data (decreased ICER to £25,865)
- Using osimertinib to represent epidermal growth factor receptor tyrosine kinase inhibitors (EGFR TKIs) (decreased ICER to £31,224)
- Using investigator-assessment (INV) as a measure of progression (increased ICER to £42,249)

1.3 The decision problem: summary of the ERG's key issues

The decision problem addressed by the company in their submission is broadly in line with the final scope issued by NICE. However, there were potentially relevant differences between the populations (Table 1.2), intervention (Table 1.3), and comparator (Table 1.4)..

Table 1.2: Key issue 1. Population considered by company narrower than population in final NICE scope

Report Section	**2.1, 3.2**
Description of issue and why the ERG has identified it as important	Population considered by company is narrower than the population defined in final National Institute for Health and Care Excellence (NICE) scope; the narrower population may not be generalisable to the England and Wales National Health Service (NHS) population; and (because the company's population was "fitter"), may have led to an underestimate of adverse events (AEs).
What alternative approach has the ERG suggested?	Other than a new trial with the population specified in the final NICE scope, no alternative approach is suggested by the Evidence Review Group (ERG) who wanted to bring this to the attention of the committee.
What is the expected effect on the cost effectiveness estimates?	Could have (a) under-estimated AEs, and (b) over-estimated effectiveness and cost effectiveness.
What additional evidence or analyses might help to resolve this key issue?	N/A
AEs = adverse events; ERG = Evidence Review Group; NHS = National Health Service; N/A = not applicable; NICE = National Institute for Health and Care Excellence; UK = United Kingdom	

Table 1.3: Key issue 2. Patients in intervention group received additional medications that could have exaggerated the effects of amivantamab

Report Section	**2.2, 3.2**
Description of issue and why the ERG has identified it as important	Patients in the intervention group received a variety of concomitant medications (including targeted radiotherapy) that could have exaggerated the benefits of amivantamab.
What alternative approach has the ERG suggested?	Given that it is known which concomitant medications were received, an unbiased estimate of effectiveness of amivantamab with and without the potentially problematic concomitant medications such as targeted radiotherapy is possible.

Report Section	2.2, 3.2
What is the expected effect on the cost effectiveness estimates?	Could have over-estimated cost effectiveness.
What additional evidence or analyses might help to resolve this key issue?	Separate effectiveness and safety analyses of amivantamab with and without the problematic concomitant medications. The results of these analyses could then be input into separate cost effectiveness analyses.
ERG = Evidence Review Group	

Table 1.4: Key issue 3. Some of the comparators lack justification and could have obscured or exaggerated the benefits of amivantamab

Report Section	2.1, 3.2
Description of issue and why the ERG has identified it as important	Some of the comparators (especially tyrosine kinase inhibitors (TKIs) other than nintedanib) lack justification and could have exaggerated the benefits of amivantamab.
What alternative approach has the ERG suggested?	An exploration of the relative effects of amivantamab with the comparators suggested by the Evidence Review Group (ERG).
What is the expected effect on the cost effectiveness estimates?	Uncertain.
What additional evidence or analyses might help to resolve this key issue?	Separate effectiveness and safety analyses of the comparators with and without the problematic comparators. The results of these analyses could then be input into separate cost effectiveness analyses.
ERG = Evidence Review Group; TKI = tyrosine kinase inhibitor	

1.4 The clinical effectiveness evidence: summary of the ERG's key issues

The ERG identified three major concerns with the evidence presented on the clinical effectiveness: the short follow-up of the included randomised controlled trials (RCTs) (see Table 1.5), the problematic choice of safety and efficacy populations (see Table 1.6), and incomplete sources of real-world evidence (see Table 1.7).

Table 1.5: Key issue 4. Short follow-up time of included randomised trials

Report Section	3.2
Description of issue and why the ERG has identified it as important	The short follow-up time of the CHRYSALIS trial makes medium- and longer-term results uncertain.
What alternative approach has the ERG suggested?	None suggested.
What is the expected effect on the cost effectiveness estimates?	Uncertainty of the medium and long-term effects of amivantamab.
What additional evidence or analyses might help to resolve this key issue?	Updated data with longer follow-up times.
ERG = Evidence Review Group	

Table 1.6: Key issue 5: Problematic choice of populations

Report Section	3.2
Description of issue and why the ERG has identified it as important	The efficacy and safety populations seem to differ substantially.
What alternative approach has the ERG suggested?	Safety and efficacy analyses with populations that are the same (or at the very least not so different).
What is the expected effect on the cost effectiveness estimates?	Exaggeration of cost effectiveness estimates.
What additional evidence or analyses might help to resolve this key issue?	At least in an exploratory basis, use the intention to treat (ITT) population for both safety and efficacy.
ERG = Evidence Review Group; ITT = intention to treat	

Table 1.7: Key issue 6. Incomplete real world evidence sources for the indirect treatment comparison

Report Section	3.3, 3.4
Description of issue and why the ERG has identified it as important	The real world evidence (RWE) sources to identify comparators for the indirect treatment comparison were not comprehensive, leading to uncertainty in the benefits of amivantamab compared with relevant comparators.
What alternative approach has the ERG suggested?	A full search for and incorporation of all relevant studies.
What is the expected effect on the cost effectiveness estimates?	Increased uncertainty regarding the cost effectiveness of amivantamab relative to relevant comparators.
What additional evidence or analyses might help to resolve this key issue?	An updated intention to treat (ITT), conducted after a full search for and incorporation of all relevant studies.
ERG = Evidence Review Group; ITC = intention to treat; RWE = real world evidence	

1.5 The cost effectiveness evidence : summary of the ERG's key issues

A full summary of the cost effectiveness evidence review conclusions can be found in Section 6.4 of this report. The company's cost effectiveness results are presented in Section 5, the ERG's summary and detailed critique in Section 4, and the ERG's amendments to the company's model and results are presented in Section 6. The ERG identified seven major issues with the cost effectiveness evidence are discussed in the Tables 1.8 to 1.14 below.

Table 1.8: Key issue 7: Representativeness of the comparator basket effectiveness to UK clinical practice is unclear, leading to uncertainty in relative cost effectiveness of amivantamab

Report Section	4.2.4
Description of issue and why the ERG has identified it as important	The company assumed 19% of the comparator basket to consist of epidermal growth factor receptor tyrosine kinase inhibitors (EGFR TKIs) which may not be consistent with United Kingdom (UK) clinical practice; the relative cost effectiveness of amivantamab is therefore unclear.

Report Section	4.2.4
What alternative approach has the ERG suggested?	An analysis where EGFR TKI therapies are excluded from the United States (US) real world data (RWD) informing the comparator basket.
What is the expected effect on the cost effectiveness estimates?	Increased uncertainty regarding amivantamab cost effectiveness.
What additional evidence or analyses might help to resolve this key issue?	1. Updated economic model excluding the costs and effects of EGFR TKIs. 2. Updated assessment of the NICE DSU TSD 14 criteria for survival analyses without EGFR TKIs in the standard of care (SoC) basket to support curve selection.
ERG = Evidence Review Group; EGFR = epidermal growth factor receptor; NICE DSU TSD 14 = National Institute for Health and Care Excellence Decision Support Unit Technical Support Document 14; RWD = real world data; SoC = standard of care; TKI = tyrosine kinase inhibitors; UK = United Kingdom; US = United States	

Table 1.9: Key issue 8: Implementation of parametric survival curves instead of KM curves for SoC

Report Section	4.2.6
Description of issue and why the ERG has identified it as important	The company implemented Kaplan-Meier (KM) curves instead of parametric survival models for the survival analyses of overall survival (OS) and progression-free survival (PFS) in the standard of care (SoC) arm, leading to potential overfitting of modelled survival outcomes.
What alternative approach has the ERG suggested?	Implement parametric models based on NICE DSU TSD 14 for survival analyses of OS and PFS in the SoC arm.
What is the expected effect on the cost effectiveness estimates?	Depends on selected curves. Using a Weibull model for OS and a log-logistic model for PFS, the incremental cost effectiveness ratio (ICER) slightly increased.
What additional evidence or analyses might help to resolve this key issue?	N/A
ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; KM = Kaplan Meier; N/A = not applicable; NICE DSU TSD 14 = National Institute for Health and Care Excellence Decision Support Unit Technical Support Document 14; OS = overall survival; PFS = progression-free survival; SoC = standard of care	

Table 1.10: Key issue 9: Time to treatment discontinuation

Report Section	4.2.6
Description of issue and why the ERG has identified it as important	Time to treatment discontinuation (TTD) was assumed to be equal to the duration of progression-free survival (PFS), while evidence from the CHRYSALIS trial showed that amivantamab treatment had a longer median duration than PFS, leading to a possible underestimate of amivantamab's relative cost.
What alternative approach has the ERG suggested?	The Evidence Review Group (ERG) suggested applying a parametric survival model to TTD based on CHRYSALIS evidence.

What is the expected effect on the cost effectiveness estimates?	Applying an exponential model to TTD based on CHRYSALIS evidence increased the ICER.
What additional evidence or analyses might help to resolve this key issue?	Details of NICE DSU TSD 14 criteria assessment to support TTD curve selection.
ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; NICE DSU TSD 14 = National Institute for Health and Care Excellence Decision Support Unit Technical Support Document 14; PFS = progression-free survival; TTD = time to treatment discontinuation	

Table 1.11; Key issue 10: Treatment waning

Report Section	**4.2.6**
Description of issue and why the ERG has identified it as important	The company did not explore treatment waning in the model, whereas the Evidence Review Group (ERG) considered that the assumption of a lifelong treatment effect may not be warranted.
What alternative approach has the ERG suggested?	An updated economic model including treatment waning scenarios.
What is the expected effect on the cost effectiveness estimates?	Unclear.
What additional evidence or analyses might help to resolve this key issue?	An updated economic model including treatment waning scenarios. Additional evidence to support the company's statement that treatment waning would be implicitly captured in the selected curves.
ERG = Evidence Review Group	

Table 1.12: Key issue 11: Exclusion of age-adjusted health state utilities in the CS base case

Report Section	**4.2.8**
Description of issue and why the ERG has identified it as important	In the company submission (CS) base case, the company did not include an age-adjustment to the health state utilities given the relatively short time horizon of the model, which is not in line with, good modelling practice, and exaggerated the cost effectiveness of amivantamab. This was subsequently provided as a scenario analysis by the company at clarification question stage.
What alternative approach has the ERG suggested?	Include age-adjusted health state utilities in the CS base case.
What is the expected effect on the cost effectiveness estimates?	Minor exaggeration of the incremental cost effectiveness ratio (ICER).
What additional evidence or analyses might help to resolve this key issue?	N/A
CS = company submission; ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; N/A = not applicable	

Table 1.13: Key issue 12: Lack of a fully incremental analysis for all relevant comparators in the comparator basket.

Report Section	5.1
Description of issue and why the ERG has identified it as important	Amivantamab was compared to a basket of treatments. The comparator effectiveness and costs are therefore based on the average clinical effectiveness and costs across all the treatments included in the comparator basket, rather than a fully incremental analysis of all relevant comparators in the comparator basket. This increased uncertainty of estimates of amivantamab's cost effectiveness.
What alternative approach has the ERG suggested?	A fully incremental analysis of all relevant comparators in the comparator basket.
What is the expected effect on the cost effectiveness estimates?	Unclear.
What additional evidence or analyses might help to resolve this key issue?	A fully incremental analysis of all relevant comparators in the comparator basket.
ERG = Evidence Review Group	

Table 1.14: Key issue 13: lack of a fixed random seed in model PSA

Report Section	5.3
Description of issue and why the ERG has identified it as important	The differences between the probabilistic results when running the same model multiple times (i.e., without changing model settings, likely due to the lack of a fixed random seed in the model, adds to slightly different random draws each time the model runs, and consequent added uncertainty of the cost effectiveness estimates of amivantamab.
What alternative approach has the ERG suggested?	Implement fixed random seed to model PSA.
What is the expected effect on the cost effectiveness estimates?	The implementation of a fixed random seed will make the results of the model PSA reproducible.
What additional evidence or analyses might help to resolve this key issue?	Implement a fixed random seed to the model PSA.
ERG = Evidence Review Group; PSA = probabilistic sensitivity analysis	

1.6 Summary of the ERG's view

The CS base case probabilistic and deterministic ICERs were £40,246 and £39,764 per QALY gained, respectively. According to the company's model amivantamab is set to influence cost effectiveness by: 1) increased PPS, with an increment of 0.526 years (63% of total incremental LYs) in the amivantamab arm (1.349 years) compared with UK SoC (0.823 years); 2) increased PFS, with an increment of 0.314 years (37% of total incremental LYs) in the amivantamab arm (0.818 years) compared with UK SoC (0.504 years); and 3) the higher drug costs, administration costs and post-progression disease management costs. The two (probabilistic) ERG base case analyses resulted in ICERs of £55,043 per

QALY gained (when assuming all ERG changes and the inverse probability weighting (IPW) approach to determine comparative effectiveness) and £49,273 per QALY gained (when assuming all ERG changes and the propensity score matching (PSM) approach to determine comparative effectiveness). Time to treatment discontinuation (TTD) informed by parametric curves based on the CHRYSALIS trial protocol had the biggest impact in the ICER compared to the CS base case. The ICER increased most in the scenario analysis in which health state utilities were based on CHRYSALIS health-related quality of life (HRQoL) data. The ICER decreased most when assuming time to next treatment (TTNT) as a proxy for treatment discontinuation in SoC. It should be noted that the latter scenario assumes that TTNT is a good approximation to TTD, which is questionable according to the ERG (as discussed in Section 4.2.6. of this report).

In conclusion, there remains uncertainty about the effectiveness and relative effectiveness of amivantamab, which can be at least partly resolved by the company by conducting further analyses (e.g., incorporate the results of the indirect treatment comparison excluding TKIs in the model, perform a fully incremental analysis, and explore treatment waning). Moreover, the current assessment does not provide an appropriate estimation of the comparators listed in the scope. Therefore, the ERG believes that the CS nor the ERG report contains an unbiased ICER of amivantamab compared with relevant comparators (see Table 1.15).

Table 1.15: Summary of ERG's preferred assumptions and ICER

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
CS deterministic base case					
Amivantamab	[redacted]	[redacted]	[redacted]	[redacted]	39,764
UK SoC	[redacted]	[redacted]			
Fixing violation (1-Exclusion of age-adjustment to the health state utilities)					
Amivantamab	[redacted]	[redacted]	[redacted]	[redacted]	40,293
UK SoC	[redacted]	[redacted]			
Matter of judgement (2-Use of PSM approach)					
Amivantamab	[redacted]	[redacted]	[redacted]	[redacted]	45,790
UK SoC	[redacted]	[redacted]			
Matter of judgement (3-Implementation of parametric survival curves in SoC arm)					
Amivantamab	[redacted]	[redacted]	[redacted]	[redacted]	41,401
UK SoC	[redacted]	[redacted]			
Matter of judgement (4-TTD informed by the CHRYSALIS trial protocol)					
Amivantamab	[redacted]	[redacted]	[redacted]	[redacted]	55,695
UK SoC	[redacted]	[redacted]			
Deterministic ERG base case 1 (IPW approach)					
Amivantamab	[redacted]	[redacted]	[redacted]	[redacted]	56,799
UK SoC	[redacted]	[redacted]			
Probabilistic ERG base case 1 (IPW approach)					
Amivantamab	[redacted]	[redacted]	[redacted]	[redacted]	54,418
UK SoC	[redacted]	[redacted]			
Deterministic ERG base case 2 (PSM approach)					

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
Amivantamab	[redacted]	[redacted]	[redacted]	[redacted]	52,185
UK SoC	[redacted]	[redacted]			
Probabilistic ERG base case 2 (PSM approach)					
Amivantamab	[redacted]	[redacted]	[redacted]	[redacted]	49,880
UK SoC	[redacted]	[redacted]			

CS = company submission; ERG = Evidence Review Group; ICER = incremental cost-effectiveness ratio; IPW = inverse probability weighting; PSM = propensity score matching; QALY = quality-adjusted life year; SoC = standard of care; UK = United Kingdom

2. CRITIQUE OF COMPANY'S DEFINITION OF DECISION PROBLEM

Table 2.1: Statement of the decision problem (as presented by the company)

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG Comment
Population	Adults with EGFR Exon 20 insertion-positive NSCLC after previous platinum-based chemotherapy.	Adult patients with locally advanced or metastatic NSCLC with activating EGFR Exon20ins, whose disease has progressed on or after platinum-based chemotherapy.	Aligned with the licensed indication for amivantamab.	The population considered by the company is different than the population defined in the final NICE scope in a way that leads to potentially biased estimates of amivantamab efficacy, safety, and cost effectiveness.
Intervention	Amivantamab	Amivantamab monotherapy, administered via IV infusion 1,050 mg for patients with body weight <80 kg 1,400 mg for patients with body weight ≥80 kg	In line with the intervention received by patients falling within the licensed indication in the registrational CHRYSALIS trial.	No comment.
Comparator(s)	Established clinical management without amivantamab including: • Atezolizumab • Nivolumab (subject to an ongoing NICE appraisal)	UK SoC consisting of TKIs, IO agents, platinum-based chemotherapy and non-platinum-based chemotherapy.	Aligned with the final NICE scope. Further details can be found in Section B.1.3.2	There are differences between the comparators considered by the company and those listed in the final NICE scope (including the inclusion of TKIs other than nintedanib). These differences could have led to an exaggeration of the relative benefits of amivantamab.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG Comment
	• Pembrolizumab (for disease with PD-L1 >1%) • Chemotherapy such as docetaxel alone or with nintedanib, pemetrexed and carboplatin			Because the company used the term TKIs without qualification, the ERG had assumed that this included nintedanib. However, in the FAC the company stated: "Beginning at submission and at any timepoint afterwards, nintedanib was not treated as a TKI in the Company's classification of treatments." Therefore, it appears that when the company stated TKIs what was intended was EGFR TKIs.
Outcomes	The outcome measures to be considered include: • overall survival • progression-free or disease-free survival • response rate • TTD • adverse effects of treatment • HRQoL	Key outcomes from the CHRYSALIS trial include: • ORR • CBR • DOR • PFS • TTF • OS • AEs • HRQoL	Additional outcomes (CBR) and DOR were included to capture the most important health benefits for amivantamab.	The ERG is satisfied with this justification.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be	The cost effectiveness of the treatments evaluated in this appraisal is expressed in	The genetic test for the EGFR Exon20ins mutation, with a scope covering small variant detection, is included in the National Genomic Test Directory. The directory specifies which	The ERG is satisfied with this justification.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG Comment
	expressed in terms of incremental cost per QALY. 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. The use of amivantamab is conditional on the presence of an EGFR mutation. The economic modelling should include the costs associated with diagnostic testing for	terms of incremental cost per QALY. A lifetime time horizon was adopted to capture all relevant costs and health-related utilities. All costs and utilities were discounted at a rate of 3.5% per year in alignment with the NICE guide to the methods of technology appraisal. Costs were considered from an NHS and PSS perspective. The cost of diagnostic testing for EGFR Exon20ins mutations has not been included within the economic analysis.	genomic tests are commissioned by the NHS in England and is available at: https://www.england.nhs.uk/publication/national-genomic-test-directories/ EGFR Exon20ins mutations can be tested as part of the EGFR test conducted at diagnosis for all NSCLC patients. As such, Janssen, considers there are no additional costs likely to be incurred by the NHS over and above the current standard of care EGFR testing requirements for all NSCLC patients. Thus, the economic modelling excludes the costs associated with diagnostic testing for EGFR in people with NSCLC. This approach is aligned with that taken in previous appraisals in which testing for a specific mutation would be required (such as TA595, TA643 and TA670).[1-3] Some treatments comprising UK SoC (such as atezolizumab, pembrolizumab, nivolumab, afatinib and nintedanib) are subject to PASs. Due to their confidential nature, these discounts are not taken into account in the base case cost effectiveness analysis.	

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG Comment
	EGFR in people with NSCLC who would not otherwise have been tested. A sensitivity analysis should be provided without the cost of the diagnostic test. See Section 5.9 of the Guide to the Methods of Technology Appraisals.			
Subgroups to be considered				N/A
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.	None identified.	N/A – in line with the NICE final scope.	The sources cited by the company to support claims that there are special considerations related to equity or equality do not provide the support claimed by the company.

Based on Table 1 and pages 10 to 12 of the CS[4]

AE = adverse event; CBR = clinical benefit rate; CS = company submission; DCIS = ductal carcinoma in situ; DOR = duration of response; eBC = early breast cancer; EGFR = epidermal growth factor receptor; ERG = Evidence Review Group; Exon20ins = Exon 20 insertion mutations; HER2 = human epidermal growth factor receptor 2; IDFS = invasive disease-free survival; HRQoL = health-related quality of life; IO = immuno-oncology; IV = intravenous; mg = milligram; kg = kilogram; N/A = not applicable; NHS = National Health Service; NICE = National Institute of Health and Care Excellence; NSCLC = non-small-cell lung cancer; ORR = overall response rate; OS = overall survival

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG Comment
PAS = Patient Access Scheme; PD-L1 = progressed disease (level 1); PFS = progression free survival; pCR = pathological complete response; QALY = quality-adjusted life year; RID = residual invasive disease; SoC = standard of care; TKI = tyrosine kinase inhibitor; TTF = Time to treatment failure; UK = United Kingdom				

2.1 Population

The population defined in the scope is adults with EGFR Exon 20 insertion-positive non-small-cell lung cancer (NSCLC) after previous platinum-based chemotherapy.[5] The population in the CS is limited to *"Adult patients with locally advanced or metastatic NSCLC with activating EGFR Exon20ins, whose disease has progressed on or after platinum-based chemotherapy."*[4]

According to the company the decision problem addressed in the CS is slightly different from the population specified in the final NICE scope. The main difference between the population defined in the NICE scope listed below (CS, Table 1, page 10),[4] is that, whereas the final NICE scope includes all those with EGFR Exon 20 insertion-positive NSCLC, the company limits the population to those with locally advanced or metastatic NSCLC with activating EGFR Exon20ins.

The population in the clinical trial for amivantamab in this indication, the CHRYSALIS trial, is: "*Adult patients (aged ≥18 years) with confirmed metastatic or unresectable NSCLC who failed or were ineligible for SoC therapy. Patients in part two of the study had measurable disease, with qualifying EGFR mutations or MET mutations or amplifications. Previous treatment with investigational EGFR Exon 20 ins-targeted TKIs was prohibited in the EGFR Exon20ins expansion cohort*."[4] The company also notes that they present data for a subset of the population in the CHRYSALIS trial related to: "*patients with EGFR Exon20ins mutations who had received previous treatment with platinum-based chemotherapy.*"[4]

On May 2021, the US Food and Drug Administration (FDA) approved amivantamab for "*adult patients with non-small cell lung cancer whose tumors have specific types of genetic mutations: epidermal growth factor receptor (EGFR) exon 20 insertion mutations*."[6] The European Medicines Agency (EMA) granted conditional approval for amivantamab for: "*adult patients with advanced non-small cell lung cancer (NSCLC) with activating epidermal growth factor receptor (EGFR) Exon 20 insertion mutations, after failure of platinum-based therapy.*"[7] Amivantamab was granted an innovation passport by the Medicines & Healthcare Products Regulatory Agency (MHRA) on 8th April 2021. On 15th November 2021, the MHRA granted a marketing authorisation for amivantamab for adult patients with locally advanced or metastatic NSCLC with activating EGFR Exon 20 insertion mutations, whose disease has progressed on or after platinum-based chemotherapy.[8]

In their response to clarification, the company confirmed that "*the population in the submission is narrower than the NICE final scope population and is aligned with the licensed indication: adult patients with locally advanced or metastatic NSCLC with activating EGFR Exon20ins mutations, whose disease has progressed on or after platinum-based chemotherapy.*"[9]

In addition, the CHRYSALIS trial had several inclusion criteria that made the studied population narrower than the one in the final NICE scope. These include: (i) histologically- or cytologically-confirmed NSCLC that was metastatic or unresectable; and (ii) an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. In their response to clarification questions about this, the company stated: "*A situation in which the licensed indication is broader than the inclusion criteria of the pivotal clinical trial is not unusual as it permits equitable access to new therapies for patients who are not able to enrol in clinical trials. NICE appraise and make recommendations based on the licensed indication population. [10-13] The differences between the licensed indication and the CHRYSALIS trial population are common for oncology treatments (for example restricting to patients with ECOG status of 0 or 1), and mean that trial populations are generally, slightly fitter than the population in UK clinical practice for the reasons outlined in the bullets above*."[9]

The company consulted a clinical expert to inform their responses to clarification questions. The expert stated: "*Clinicians would consider amivantamab as a treatment option in some patients who are ECOG >1 if it was commissioned in such patients.*"[14]

ERG comment:

- The population specified in the decision problem appears to be different from the population defined in the final NICE scope. Although the specification of the mutation uses different wording, 'activating' can be regarded as implied because the insertion that is being referred to is one that is only relevant because it is activating i.e., causes activation of the EGFR pathway. However, only the experience of platinum-based chemotherapy is specified in the scope as opposed to having progressed to advanced, either locally advanced or metastatic disease, as expressed in the decision problem. Precisely which patients would be excluded is unclear, but presumably those who had not progressed. However, this should not be regarded as a key issue if NICE can only make a recommendation for the licensed population.
- With respect to the CHRYSALIS trial having a narrower population than the one defined in the final NICE scope (in the ways described above), the ERG notes that:
    - the results in the narrower trial population may not apply to patients in routine practice who may eventually receive amivantamab in the NHS setting; and
    - the company acknowledge that the patients in the trial might be "*fitter*"[9]
    - the clinical expert commissioned by the company stated that some patients in NHS clinical practice with an ECOG >1 (see above) would be considered for amivantamab. Therefore, the exclusion of patients with higher ECOGs may have led to an understatement of AEs, as these might have been more likely to arise in patients with worse performance statuses. It may also have impacted upon the effectiveness, as patients with the ECOG status required for admission to the CHRYSALIS trial may have been more likely to respond.

2.2 Intervention

The intervention (amivantamab) is broadly in line with the scope. In their submission, the company specifies that amivantamab is administered via IV (intravenous) infusion, and that the dose is 1,050 mg for patients with body weight <80 kg, and 1,400 mg for patients with body weight ≥80 kg.

The company also noted that patients receiving amivantamab also received *"any concomitant medications or treatments deemed necessary to provide adequate supportive care except for those listed as prohibited therapies.*"[4] The allowed concomitant medications included: symptomatic treatment, prophylactic medications. localised limited radiotherapy of short duration (e.g., 5 days) for palliative purposes only after discussion with approval by the sponsor's medical monitor.[4] The company provided a full list of concomitant medications in Table 43 of their responses to our clarification questions.[9]

The ERG asked the company whether the targeted radiotherapy could have been a confounder.[9] The company replied that "*the administration of these concomitant therapies would not have had an impact on ORR or DOR.*"[9] The company also consulted a clinical expert to inform their responses to clarification questions, and the clinical expert appeared to confirm that targeted radiotherapy could lead to a clinical benefit in a subset of patients: "*Palliative radiotherapy is part of supportive care and does not tend to cause any improvement in efficacy, except in patients who develop brain metastases treated by SRS. The latter population could derive clinical benefit from targeted radiotherapy (SRS).*"[14]

ERG comment: The ERG notes uncertainty regarding whether targeted radiotherapy confounded the results of the study. To confirm whether targeted radiotherapy confounded the study, the ERG would

need to see additional analyses that explored the effect of targeted radiotherapy on all outcomes (not just ORR or DOR).

2.3 Comparators

The description of the comparators in the NICE scope is as follows: *"Established clinical management without amivantamab including: atezolizumab, nivolumab (subject to an ongoing NICE appraisal), pembrolizumab (for disease with PD-L1>1%), or chemotherapy such as docetaxel alone or with nintedanib, pemetrexed and carboplatin."*[5]

The comparator chosen by the company is a pooled treatment basket in the form of real-world data to estimate clinical effectiveness and SoC in the cost effectiveness analysis: "*UK standard of care (SoC) consisting of TKIs, IO agents, platinum-based chemotherapy and non-platinum-based chemotherapy.*"[4] Table 52 (page 118) of the CS notes that immuno-oncology (IO) agents included atezolizumab, pembrolizumab and nivolumab, and the TKIs included afatinib and osimertinib.[4] Because the company used the term TKIs without qualification, the ERG had assumed that this included nintedanib. However, in the FAC the company stated: "Beginning at submission and at any timepoint afterwards, nintedanib was not treated as a TKI in the Company's classification of treatments." Therefore, it appears that when the company stated TKIs what was intended was EGFR TKIs.

The ERG asked the company to provide analyses in which TKIs other than nintedanib were excluded. In their response, the company provided hazard ratios (HRs) for PFS, OS, and TTNT for the base case, and a scenario excluding all TKIs (apart from nintedanib). The HRs were slightly higher in the scenario analysis with all EGFR TKIs excluded.

The company also claims that there is no SoC (CS, page 28), and notes a variety of treatments offered to this population (CS page 29, 30). The company therefore determined SoC with an advisory board with UK clinical experts who "*confirmed that patients with EGFR Exon20ins mutated NSCLC are treated in a manner broadly similar to patients without EGFR or anaplastic lymphoma kinase (ALK) mutations (i.e. no gene mutation or fusion protein), per NICE Guideline 122. Therefore, treatment options for patients in the UK may include the three pathways outlined in Table 4 below*."

The comparator chosen by the company is a pooled treatment basket in the form of real-world data. However, as specified in the scope, established clinical management depends upon line of therapy (first or later) and PD-L1 status. The ERG requested data from the company on the appropriateness of the comparator chosen by the company. More specifically, the company was asked to provide separate clinical effectiveness analyses (indirect treatment comparisons) by line of therapy and PD-L1 subgroup using only the comparators that would be standard care for the specific subgroup e.g., only pembrolizumab or nivolumab for PD-L1 positive patients. The response[9] from the company was as follows:

"Overall, Janssen maintain that a basket of comparators is the most appropriate comparator to amivantamab given expert feedback and the real-world evidence (RWE) indicating the heterogenous mix of treatments that patients receive in practice. Further, it is not considered appropriate to split the RWE data for SoC into subgroups given that this introduces additional uncertainty given the smaller sample sizes involved in such analyses, thus limiting their robustness. However, in order to provide some of the information requested in the ERGs question, subgroup analyses by line of therapy have been provided below. HRs are consistent with results from the base case;[9] however, these relative treatment effects are estimated for a restricted population and are therefore associated with greater uncertainty." In short, the company provided some, but not all, of the evidence requested by the ERG

The ERG also asked the company to further justify their definition of SoC.[9] The company responded by providing real world evidence (RWE) to "show that there is heterogeneity in the treatments used for this patient population with no definitive standard of care."[9]

ERG comment:

- There is evidence that EGFR TKIs (i.e., excluding nintedanib are unlikely to be effective against this EGFR Exon 20 insertion-positive NSCLC. In general *EGFR* Exon20ins mutations are known to be resistant to EGFR TKIs;[15-17] EGFR TKIs have shown limited to no activity in patients with Exon20ins mutations. Given the limited activity in this population, existing EGFR TKIs are rarely used in patients with *EGFR* Exon20ins mutation-positive NSCLC following platinum-based chemotherapy[18] (i.e., the position of the anticipated mobocertinib licence).
- EGFR TKIs are not included in the final scope for the ongoing appraisal of mobocertinib for treating *EGFR* Exon20ins mutation-positive NSCLC following platinum-based chemotherapy (ID3836). Given the amivantamab and mobocertinib appraisals target the same patient population, the comparators should be identical.
- Regarding the company's refusal to fully respond to the ERG's request to provide separate clinical effectiveness analyses by line of therapy and PD-L1 subgroup (to align with the final NICE scope):
    - The ERG understands that the smaller sample sizes in subgroups will lead to lower power. However, the extent to which the smaller subgroups would not be informative can only be verified after doing them. Comparison with the correct comparator in each subgroup is intended to address any potential bias notwithstanding the uncertainty.
    - Even if the estimates based on smaller subgroups are uncertain, they are appropriate to the decision problem defined in the final NICE scope.
    - Therefore, the ERG believes that the data should be presented according to different lines of therapy and PD-L1 status.
- With respect to the heterogeneity of SoC in standard practice, the ERG notes that heterogeneity in clinical practice does not imply that the company's determination is the correct one. The company might have explored a range of scenarios to explore whether a different choice of treatment basket would have made a difference to the main outcomes.

2.4 Outcomes

The NICE final scope lists the following outcome measures:[5]

- OS
- PFS or DFS
- Response rate
- TTD
- AEs of treatment
- HRQoL

The outcomes considered by the company were broadly in line with those listed in the final NICE scope, with two differences. Firstly, the company added two additional outcomes: clinical benefit rate, and duration of response. In addition, whereas the final NICE scope listed TTD as an outcome, the company listed time to treatment failure (TTF). In their response to clarification questions, the company states: "*TTF is identical to time to treatment discontinuation as it encompasses treatment discontinuation due to "any reason.*"

These were all assessed in the CHRYSALIS trial.

ERG comment:

- The ERG agrees that the company's definition of TTF (encompassing discontinuation for any reason) is the same as time to treatment discontinuation mentioned in the final NICE scope.
- With respect to the additional outcomes used by the company that go over and above those listed in the final NICE scope, the ERG recommends focusing on the outcomes listed in the final NICE scope.

2.5 Other relevant factors

2.5.1 Innovation

According to the company, amivantamab is innovative because it is the first targeted treatment for adult patients with EGFR Exon20ins mutated NSCLC.[4] The company claim that this is a population with a high unmet need and a poor prognosis.

An innovation passport was granted to amivantamab by the Medicines and Healthcare Products Regulatory Agency (MHRA) as part of the Innovative and Licensing and Access Pathway and enabled Janssen to apply for marketing authorisation under the MHRA accelerated regulatory pathway.[19]

ERG comment: The ERG agrees that amivantamab is innovative in that it meets the needs of an underserved population.

2.5.2 Equity and equality

The company states that the introduction of amivantamab to UK clinical practice has the potential to improve health inequity related to the stigma that can be associated with a lung cancer diagnosis, the relevance of cultural differences on treatment-seeking behaviours, and the impact of the COVID-19 pandemic on time to diagnosis.[4] The company emphasises that people of Asian heritage are more likely to receive a positive diagnosis for EGFR Exon20ins is also supported by the references they cite (including reference 3).[20] In their submission (Section B.1.4) The company claims that people who are diagnosed with lung cancer can be stigmatised due to its association with smoking.

The company also notes in their submission (Section B.1.4) that the stigma associated with a lung cancer diagnosis may be disproportionately high in Asian populations, and that this could be exacerbated by the COVID-19 pandemic. They state: "*Since many symptoms of lung cancer mimic those of COVID-19 (especially the persistent cough), people of Asian heritage who display lung cancer symptoms in public may face race-based prejudice and even outright racism as a result of public misunderstanding about the origins of the virus*."[4] On the basis of this background, in their submission on page 16, the company states that *"[t]his raises the prospect of patients being disproportionately disadvantaged on the basis of race*."[4]

The company concludes that these equity considerations are not inherently captured within the cost per QALY or budget impact frameworks.

ERG comment:

- The company presents strong evidence that there is stigma associated with lung cancer diagnoses.
- The references they use to support the claim that people of Asian origin may experience additional prejudice since some lung cancer symptoms overlap with those of COVID-19 (17, 18)[REFS 17, 18] were published in 2017 and 2016 respectively (before the pandemic) so do not support the company's claim. Therefore, the ERG notes that the claim about disproportionate prejudice or stigma towards people of Asian origin is highly speculative.

3. CLINICAL EFFECTIVENESS

3.1 Critique of the methods of review(s)

The CS states that a de novo clinical systematic literature review (SLR) was conducted in January 2021, and updated September 2021, to identify relevant evidence on clinical efficacy and safety outcomes in patients with EGFR Exon20ins mutated NSCLC. The SLR was designed to capture data specifically in EGFR Exon20ins mutated NSCLC that was reported in both interventional and observational studies. Full details of the SLR search strategy, study selection process and results were reported in Appendix D.[21]

3.1.1 Searches

The following Section contains a summary and critique of all searches related to clinical effectiveness presented in the CS.[4, 21] The Canadian Agency for Drugs and Technologies in Health (CADTH) evidence-based checklist for the Peer Review of Electronic Search Strategies (PRESS), was used to inform this critique.[22, 23] The CS was checked against the single technology appraisal (STA) specification for company/sponsor submission of evidence.[24]

Appendix D of the CS provided details of the literature searches conducted for the SLR of clinical efficacy and safety outcomes.[21] Database searches were conducted in January 2021, then updated in September 2021. A summary of the resources searched is provided in Table 3.1.

Table 3.1: Resources searched for the clinical effectiveness systematic review (as reported in the CS)

Resource	Host/Source	Date Ranges	Dates searched
Electronic databases			
MEDLINE, MEDLINE In-Process, MEDLINE Daily, Epub Ahead of Print	Ovid	1946 to 19 January 2021 1946 to 24 September 2021	20/01/21 27/09/21
Embase	Ovid	1974 to 2021 January 19 1974 to 2021 September 24	20/01/21 27/09/21
CDSR	Cochrane Library, Wiley	Issue 1 of 12, January 2021 Issue 9 of 12, September 2021	20/01/21 27/09/21
CENTRAL	Cochrane Library, Wiley	Issue 1 of 12, January 2021 Issue 9 of 12, September 2021	20/01/21 27/09/21
DARE	University of York CRD platform	Issue 2 of 4, April 2015	20/01/21

Resource	Host/Source	Date Ranges	Dates searched
Additional resources			
ClinicalTrials.gov	Internet	06/05/20 05/10/21	06/05/20 05/10/21
AACR	Internet	2018 to 2021	January 2021 September 2021
ASCO			January 2021 September 2021
ESMO			January 2021 September 2021
ESMO ELCC			January 2021 September 2021
ESMO Asia			January 2021 September 2021
IASLC World Conference on Lung Cancer			January 2021 September 2021
IASLC European Conference on Lung Cancer			January 2021 September 2021

AACR = American Association for Cancer Research; ASCO = American Society of Clinical Oncology; CDSR = Cochrane Database of Systematic Reviews; CENTRAL = Cochrane Central Register of Controlled Clinical Trials; CRD = Centre for Reviews and Dissemination; DARE = Database of Abstracts of Reviews of Effects; ELCC = European Lung Cancer Congress; ESMO = European Society for Medical Oncology; IASLC = International Association for the Study of Lung Cancer

ERG comment:

- The CS provided full details of the literature searches for the ERG to appraise.[4, 21]
- A good range of databases, clinical trials registry, grey literature resources, and a comprehensive range of relevant conference proceedings were searched.
- Full details of the database searches, including the database name, host platform, date range and date searched, were provided.
- Full details of the conference proceeding searches were provided. The search terms used, URL links, date range, date of searches, and results, were reported.
- Full details of the ClinicalTrials.com search was provided, including the search terms used (with an explanation that automatic synonym searching occurs in ClinicalTrials.com), all fields selected, date searched, and results.
- The database search strategies were well structured, transparent, and reproducible. They included truncation, proximity operators, synonyms, and subject headings (MeSH in MEDLINE and the Cochrane Library, and EMTREE in Embase). There were no language or date limits.
- It would have been preferable for the database search strategies to be presented exactly as run, rather than copied into a tabular format, as item 8 of the PRISMA-S checklist recommends.[25] The Cochrane Handbook also recommends that *"...bibliographic database search strategies should be copied and pasted into an appendix exactly as run and in full, together with the search set numbers and the total number of records retrieved by each search strategy. The search strategies should not be re-typed, because this can introduce errors"*.[26]

- The CS reported in Appendix D that the searches "aimed to capture a broader evidence base of EGFR + NSCLC", when the search strategy population facet actually combined 'NSCLC + advanced/metastatic + EGFR + mutations/TKI resistant': a much more focused approach.[21] It is unclear what effect this may have had on recall. The suggested broader approach would have been better and might have identified additional useful references. The searches would certainly have been improved if the set of search terms for 'mutations' had been omitted or had at least included search terms for 'exon 20 insertions'. However, the search strategy did not include an intervention/comparator facet of search terms, which probably compensated for the narrow focus of the population facet.
- Study design search filters for RCTs and observational studies were included in the search strategies. The search filters used were not cited, as current practice recommends.[25]
- Separate searches for safety outcomes were not conducted. It is unlikely that efficacy searches that include study design filters for RCTs and observational studies will be sensitive enough to identify safety data. Ideally, searches for AEs should be carried out alongside the searches for efficacy.[27]
- Targeted searches were conducted, as described in D.1.1.6: "*Ovid (MEDLINE and Embase), Google Scholar, and Google were additionally searched using terms for "exon 20 insertions" and "non-small cell lung cancer" to identify any additional, relevant studies for inclusion not identified via the database searches or other supplementary sources*".[21] It was not clear why search terms for 'exon 20 insertions' were not included in the main search strategies in the first instance, negating the need to conduct targeted searches. Full details of the search strategies or search terms used, date range, date searched, and results were not provided. In response to the ERG clarification letter the company explained that "*as no search terms specific to Exon 20 insertions (Exon20ins) were included in the database search strategies, additional targeted searches were conducted to increase the comprehensiveness of the review*" and full details of the search strategies were provided.[9]
- As the SLR for clinical efficacy and safety did not identify relevant evidence, the company conducted an additional SLR of prognostic patient and disease characteristics to identify potential confounders for the adjusted treatment comparison.[28] Searches were conducted for clinical guidelines, SLRs, and real-world observational studies in Embase and MEDLINE. The searches were limited to English language studies published between 2018 and 2020 and were conducted on 31st August 2020. Full details of the search strategies were not reported. Details of the search terms used were provided in response to the ERG clarification letter.[9]

3.1.2 Inclusion criteria

The eligibility criteria used in the search strategy for RCTs and non-RCTs is presented in Table 3.2.

Table 3.2 Eligibility criteria used in search strategy for RCT and non-RCT evidence

	Inclusion criteria	Exclusion criteria
Population	Patients with metastatic or surgically unresectable EGFR mutation positive NSCLC harbouring exon 20 insertion mutations, specifically: • Patients with stage IIIB, IIIC or IV disease • Studies with patients only specified as "stage 3" will be eligible only if stage 4 patients	• Patients with lung cancer not otherwise specified • Patients with NSCLC not otherwise defined • Patients with locally advanced disease not otherwise specified • Patients with stage 3 disease not otherwise specified, with no stage 4 patients included in the same study

	Inclusion criteria	Exclusion criteria
	are also included within the study population • Studies wherein staging was unclear, but patients received targeted therapy (e.g., TKIs), and were confirmed to harbour EGFR Exon20ins, were considered relevant unless their use was clearly out-of-scope (e.g., adjuvant use, or a trial specifically investigating interventions in early-stage patients)	• Patients without an EGFR Exon20ins • Patients that include eligible and ineligible populations but where results for the eligible population are not presented separately
Interventions	Any therapeutic or palliative intervention administered within the healthcare system	In addition to the comparator stated in the scope (BSC), other interventions (both first and second-line) were searched in the systematic review. Studies where patients received a therapy as first-line treatment were later excluded for the purpose of this submission.
Comparators	Any comparator (or none)	N/A
Outcomes	• Baseline characteristics of eligible patients, including: Demographics Disease characteristics • Clinical efficacy outcomes, including: OS PFS DFS ORR CBR/DCR Relapse/recurrent free survival DOR TTTD TTNT • Safety outcomes, including but not limited to: AEs SAEs • QoL outcomes • Patient-reported outcomes (RCTs only)	• Economic outcomes • Epidemiological outcomes • Patient-reported outcomes (non-RCTs and observational studies)
Study design	• RCTs • Interventional non-RCTs (i.e., non-randomised and uncontrolled clinical studies),	• Editorials, commentaries, narrative reviews, guidelines, letters (unless they contain novel data)

	Inclusion criteria	Exclusion criteria
	including compassionate use programmes • Observational studies (e.g., prospective/retrospective cohorts, case-control, chart reviews) • Case series • Conference abstracts published in the last 3 years • Post-hoc/pooled analyses • SLRs and (network) meta-analyses These will be considered relevant at the title/abstract review stage and hand searched for relevant primary studies, but will be excluded during the full-text review stage unless they themselves present original research	• Case reports
Language and other restrictions	• Human subjects • English language abstract/full text	N/A
Based on table 7, appendix D, CS[21] AE = adverse event; BSC = best supportive care; CBR = clinical benefit rate; CS = company submission; DCR = disease control rate; DFS = disease-free survival; DOR = duration of response; EGFR = epidermal growth factor receptor; N/A = not applicable; NSCLC = non-small-cell lung cancer; ORR = overall response rate; OS = overall survival; PFS = progression free survival; QoL = quality of life; RCT = randomised controlled trial; RFS = relapse-free survival; SAE = serious adverse event; SLR = systematic literature review; TKI = tyrosine kinase inhibitor, TTNT = time to next treatment; TTTD = Time to treatment discontinuation.		

ERG comment:

Inclusion criteria - The ERG in its clarification letter asked the company to discuss how the SLR eligibility criteria on population is relevant to the NICE final scope for this submission. In discussing the submission population in their response, the company stated that, *"This submission focused on adult patients with locally advanced or metastatic NSCLC with activating EGFR Exon20ins mutations, whose disease has progressed on or after platinum-based chemotherapy. This is in line with the UK marketing authorisation for amivantamab, but is narrower than the population defined in the final scope from NICE as locally advanced or metastatic disease is specified."*[9] The implications of this narrower population have already been discussed in Section 2.1 of this report. Concerning the SLR population, they explained that *"Whilst disease staging eligibility criteria for the SLR were narrower than that of the final scope, the SLR included a slightly broader population than the NICE scope in terms of treatment experience. Specifically, treatment naïve and chemotherapy naïve patients were included in the SLR; however, studies conducted in patients progressing on or after platinum-based chemotherapy were reported separately in the SLR write-up as these data were considered most relevant to the submission."*[9] As the company considered only one of the 88 studies identified during the SLR as being eligible for data extraction, to provide relevant evidence for the efficacy and safety of amivantamab in the submission population, it is unlikely that relevant studies may have been omitted due to a narrower disease staging criteria in the SLR.

Language restrictions - The ERG notes that an English language only restriction was applied to the SLR search. The ERG considers excluding non-English language studies to be inappropriate for obtaining robust evidence on the treatment of adults with advanced NSCLC.

3.1.3 Critique of data extraction

Appendix D of the CS provides clarity on the process of data extraction. Studies that were deemed to meet the inclusion criteria after screening were split into two categories, whereby they underwent either abbreviated or full data extraction.

Studies that reported only qualitative data on patients harbouring EGFR Exon20ins, containing individual participant data (IPD) only, or indicating that patients with Exon 20 insertions had been enrolled but no further details have been provided had an abbreviated data extraction. This involved the collecting of qualitative study characteristics and trial details.

Studies where quantitative data on patients harbouring EGFR Exon20ins were reported, either comprising the entire population studied or a separately reported exon 20 insertion subgroup underwent full data extraction. This involved obtaining detailed characteristics of the study and the participants, along with extracted numerical data on various efficacy, safety, and quality of life outcomes.

The CS reports that data extraction was performed by a single reviewer and then a second reviewer independently checked and verified the extracted data. Any disagreements or discrepancies were discussed between the two reviewers until a consensus could be reached. A third reviewer provided arbitration where consensus between the first two reviewers could not be achieved.

ERG comment: The methodology represents an accepted and viable process although the optimal process would be to ensure two independent data extraction processes. The CS does not clarify whether the third reviewer independently examined and extracted the data and then compared this data to the first extraction and check, or whether a further verification was provided of the initial extraction, before deciding.

3.1.4 Quality assessment

The CS reports that quality assessment of all included RCTs that underwent full data extraction was completed by one reviewer and then verified by a second independent reviewer. RCTs were appraised using the quality assessment tool developed by the York University Centre for Reviews and Dissemination (CRD), while interventional non-RCTs and observational studies that underwent full data extraction was assessed using the ROBINS-1 checklist.

ERG comment: No information is provided to determine how disagreements were resolved. As for data extraction, the optimal process would be to ensure two completely independent quality evaluation processes.

3.1.5 Evidence synthesis

A clinical SLR was conducted in January 2021, and updated September 2021, to identify relevant evidence on clinical efficacy and safety outcomes in patients with EGFR Exon20ins mutated NSCLC. The SLR was designed to capture data specifically in EGFR Exon20ins mutated NSCLC that was reported in both interventional and observational studies. Because the company only used one trial (CHRYSALIS) for their analysis, they did not conduct a meta-analysis.

The CHRYSALIS trial provided data for primary outcome, namely ORR, and secondary outcomes, DOR, PFS, TTF, OS and HRQoL. A subgroup analysis was also conducted on ORR by age (four categories), sex, race (Asian versus non-Asian), ECOG status (0 versus ≥1), history of smoking and prior immunotherapy.

3.2 Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these)

This Section of the report details the sources of evidence in the CS for the clinical effectiveness of amivantamab. According to Section B.2.1 of the CS[4] only one study identified CHRYSALIS (NCT02609776). CHRYSALIS is a Phase 1b, single arm, first-in-human, open-label, multicentre, 2-part trial. The study provided data on efficacy and safety on patients with EGFR-mutated NSCLC with Exon20ins receiving amivantamab treatment. Further details of this study are outlined in this Section.

Comparative evidence for the study was provided via two RWE sources. Data from PHE and a US pooled cohort (pooled data from Flatiron Health Spotlight, ConcertAI and COTA data sources). These datasets are discussed in Section 3.3.

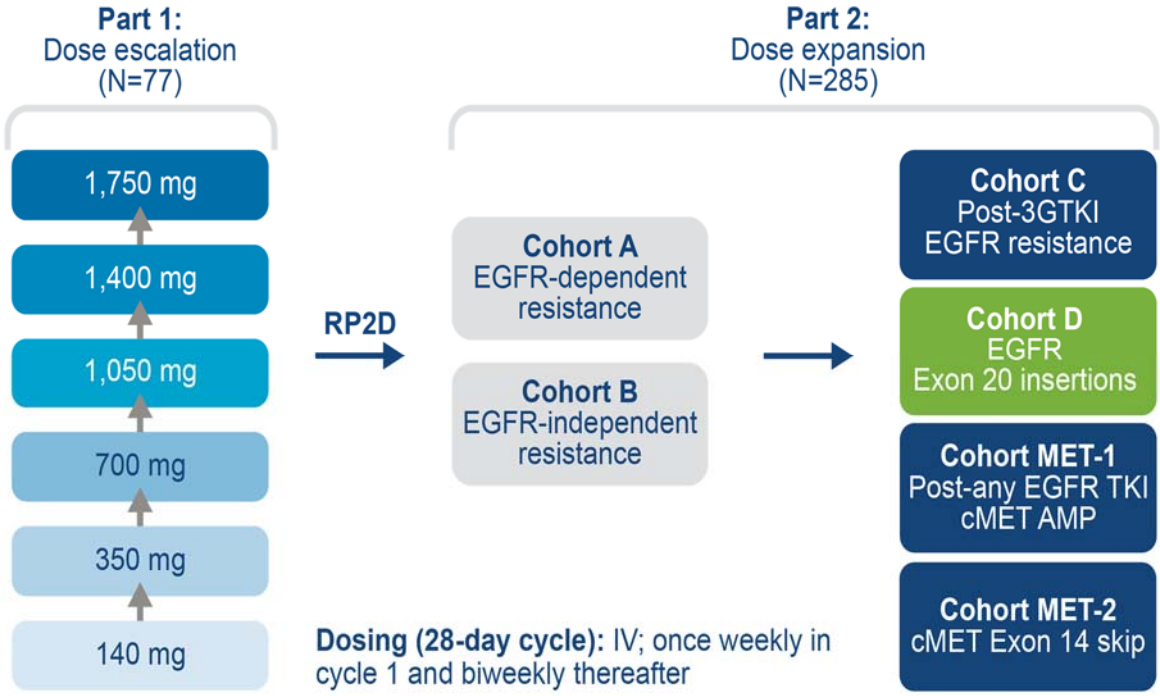
3.2.1 Details of the included trial

The CHRYSALIS trial is an ongoing Phase 1b trial in patients at least 18 years of age, with advanced NSCLC. The study was also used to support the conditional marketing authorisation[8]. The study tested both amivantamab as monotherapy and in combination with lazertinib. In the CS[4] only the monotherapy results are presented and discussed.

CHRYSALIS is a two-part trial consisting of a dose escalation phase (Part 1) and a dose expansion phase (Part 2) (see Figure 3.1 for the study design's overview). The aim of Part 1 (N=77) was to determine the recommended phase 2 dose (RP2D) of amivantamab monotherapy based on safety, pharmacokinetic, pharmacodynamic, and anti-tumour activity data. Six doses were tested from 140 mg to 1,750 mg. It concluded on a weight-based determination of the RP2D at 1,050 mg if baseline weight <80 kg and 1,400 mg if baseline weight ≥80 kg.

The aim of Part 2 (N=285) was to better define the safety and pharmacokinetics at the RP2D, and to examine clinical activity within subgroups defined by tumour molecules. This part of the study consisted of six molecularly defined Cohorts: A, B, C, D, mesenchymal epithelial transition (MET)-1 and MET-2 (Figure 3.1), including patients with locally advanced or metastatic NSCLC patients with activating EGFR and/or MET mutation. Further patient eligibility criteria are provided in Table 3.3 as detailed in Table 8 of the CS[4]. The patients used for the CS are a subset of Cohort A and Cohort D, from now on termed D+ (N=114). It includes patients treated at the RP2D, aligned to the decision problem criteria defined in Table 1 of the CS[4] as *"adult patients with locally advanced or metastatic NSCLC with activating EGFR Exon20ins, whose disease has progressed on or after platinum-based chemotherapy"*.[4]

Figure 3.1: Study design, CHRYSALIS (NCT02609776) study



Source: Figure B.2.1 of the CS [4]
CS = company submission; EGFR = epidermal growth factor receptor; IV = intravenous; MET = mesenchymal epithelial transition; RP2D = recommended Phase 2 dose; TKI = tyrosine kinase inhibitor

Table 3.3: Summary of study methodology, CHRYSALIS

Study design	International, multicentre, Phase 1b, single arm, first-in-human, open-label, 2-part trial
Study objective[29]	Primary objectives Part 1 Dose Escalations • Determine the maximum tolerated dose (MTD), if one exists (Part 1 monotherapy dose escalation only), and the recommended Phase 2 dose (RP2D) for subjects with NSCLC Part 2 (Expansion) • Determine the safety, tolerability, and anti-tumour activity at the RP2D • Estimate the anti-tumour activity at the RP2D, and in selected populations of subjects with documented EGFR or MET mutation(s) who have progressed after treatment with SoC
	Secondary objectives: • Assess additional measures of clinical benefit • Assess the PK and immunogenicity in subjects with NSCLC
Locations	90 sites in 11 countries, including the UK (three sites)
Eligibility criteria for participants	Key inclusion criteria: • Adult patients (≥18 years of age) • Histologically- or cytologically-confirmed NSCLC that was metastatic or unresectable • Progressed on or after prior therapy or were not candidates for currently available approved therapeutic options

	• Must have measurable disease according to RECIST v1.1 • An ECOG performance status of 0 or 1 • Qualifying EGFR mutations or MET mutations or amplifications • Previously diagnosed activating EGFR Exon20ins not previously treated with a TKI having known activity in Exon20ins disease (e.g., poziotinib) but previously treated with a platinum-based chemotherapy regimen • Adequate organ and bone marrow function, as assessed by laboratory measurements of haemoglobin, absolute neutrophil count, platelets, alanine aminotransferase, aspartate aminotransferase, total bilirubin and serum creatine Key exclusion criteria: • Prior chemotherapy, targeted cancer therapy, immunotherapy, or treatment with an investigational anti-cancer agent within 2 weeks or four half-lives whichever is longer, before the first administration of study drug • Untreated or active brain metastases • A history of malignancy other than the disease under study within 3 years before screening • A history of clinically significant cardiovascular disease • Known allergies, hypersensitivity, or intolerance to amivantamab or its excipients • Received an investigational drug (not including anti-cancer therapy) or used an invasive investigational medical device within 6 weeks before the planned first dose of study drug • Uncontrolled inter-current illness, including but not limited to poorly controlled hypertension or diabetes, ongoing or active infection, or psychiatric illness/social situation that would limit compliance with study requirements • Any specifically listed comorbidities such as leptomeningeal disease, human immunodeficiency virus (HIV), hepatitis B or C, and interstitial lung disease (ILD) • Any serious underlying medical or psychiatric condition
Study status	• Ongoing • Efficacy data cut-off date: 30th March 2021
Concomitant medication(s)	Permitted: Symptomatic treatment, prophylactic medications, localised limited radiotherapy of short duration (e.g., 5 days) for palliative purposes may be permitted but only after discussion with approval by the sponsor's medical monitor Disallowed: Any chemotherapy, anti-cancer therapy (other than study treatment(s)), or experimental therapy; radiotherapy to tumour lesions being assessed for tumour response prior to radiographic progression; use of live attenuated vaccines; use of phenytoin or phosphenytoin with carboplatin; nephrotoxic or ototoxic agents should be cautiously used with carboplatin; caution should be exercised when administering pemetrexed concurrently with a nonsteroidal anti-inflammatory drug to a participant whose creatinine clearance is <80 mL/min

RP2D	Amivantamab monotherapy, administered via IV infusion • 1,050 mg for patients with body weight <80 kg • 1,400 mg for patients with body weight ≥80 kg
Study outcome(s) (Part 2)	Primary outcome: • ORR Secondary outcomes: • CBR • DOR • PFS • OS • TTF • The best percentage change from baseline in SoD • HRQoL (exploratory descriptive analyses): PGIS, PGIC, NSCLC-SAQ and EQ-5D-5L VAS
Pre-planned subgroups	• Age: <65 versus ≥65 years and <75 versus ≥75 years • Sex: male versus female • Race: Asian versus non-Asian (patients with unknown race were not included in the subgroup analysis) • Baseline ECOG performance status: 0 versus ≥1 • History of smoking: yes, versus no • Prior immunotherapy: yes, versus no • Key EGFR Exon20ins variants (based on ctDNA analysis of pre-treatment samples). The change in SoD for target lesions was also described for these subgroups using a waterfall plot.

Based on Table 8. of the CS[4]
CBR = clinical benefit rate; CS = company submission; ctDNA = circulating tumour deoxyribonucleic acid; DOR = duration of response; ECOG = Eastern Cooperative Oncology Group; EGFR = epidermal growth factor receptor; EQ-5D-5L VAS = EuroQoL five-dimensions five-levels visual analogue scale; HRQoL = health-related quality of life; HIV = human immunodeficiency virus; ILD = interstitial lung disease; IV = intravenous; MET = mesenchymal epithelial transition; NSCLC = non-small-cell lung cancer; NSCLC-SAQ = Non-Small-Cell Lung Cancer Symptom Assessment Questionnaire; ORR = overall response rate; OS = overall survival; PFS = progression free survival; PGIC = Patient Global Impression of Change; PGIS = Patient Global Impression of Severity; PRO = patient-reported outcomes; RECIST = Response Evaluation Criteria in Solid Tumours; SoC = standard of care; SoD = sum of diameters; TKI = tyrosine kinase inhibitor; TTF = time to treatment failure; UK = United Kingdom

The number of patients coming from different cohorts to comprise Cohort D+ was not clear in the CS. After seeking clarification[30] the company provided these details, reported in Table 3.4. Although the CS stated that Cohort D+ "*consists largely of a subset of Cohort D and small number of patients in Cohort A*", which are both Cohorts of the study's Part 2, in their response they have now reported that five patients came from Part 1.

Table 3.4: Breakdown of patient numbers from CHRYSALIS; post platinum EGFR Exon20ins RP2D expanded efficacy analysis set (N=114)

Part and Cohort	Number of patients (N=114)
Part 1	[redacted]
Part 2 Cohort A	[redacted]
Part 2 Cohort D	[redacted]

Based on Table 17 in the clarification response[9]

ERG comments:

- In a clarification question the ERG inquired why since the decision problem did not specify performance status for the population, the evidence included in the CS was limited to patients with ECOG performance status 0 or 1.[9] The company has responded that "*…the NICE final scope is slightly broader than the marketing authorisation for amivantamab. As NICE appraise within the marketing authorisation, the marketing authorisation for amivantamab represents the population for the decision problem… the CHRYSALIS trial includes patients with an ECOG performance status of 0 or 1; i.e., a narrower population than the marketing authorisation. These data are the data upon which the marketing authorisation was granted and Janssen is requesting access for the licensed indication. That the CHRYSALIS trial, similar to most oncology trials, excludes some patients covered by the marketing authorisation does not mean that this submission is for a restricted population. The decision to treat patients above ECOG 1 is driven by the fitness of the patient and this would be based on the clinical assessment by the oncologist for treatment rather than mandated in the license. In alignment with this, a clinical expert consulted by Janssen during the development of this response document stated that clinicians would consider amivantamab as an option in some patients with ECOG >1*."[9]. The ERG points out that the population used for evidencing the efficacy and safety of the drug in question should match the characteristics of the perspective population under treatment. The standardised criteria which make out the assessment of ECOG status to measure the patient's performance status, are key to defining the population eligibility criteria for inclusion in the study as well as its progress within the study.
- The ERG inquired on the method that was used to identify EGFR Exon20ins mutations, for inclusion in the CHRYSALIS trial and if it was comparable (including with respect to specific mutations detected and limits of detection) with testing currently in place in routine practice in the UK[30]. The company has responded that in "*CHRYSALIS, EGFR Exon20ins mutations were assessed by local testing in the respective clinical trial centre locations or centrally using NGS testing for circulating tumour DNA (ctDNA), or tumour tissue where available. For central testing, Guardant was used for ctDNA while ThermoFischer was used for tumour tissue. The methods used are comparable to those available to patients in the UK as included on the NHS National Genomic Test Directory as part of the services provided by the Genomic Lab Hubs (GLHs)*"[9].
- According to the CHRYSALIS trial protocol[29], pemetrexed is included as concomitant medication to amivantamab, but it is also listed as a comparator. The ERG sought clarification on whether pemetrexed is a comparator, or part of SoC to be used alongside amivantamab, or both. The company has responded that data "*from CHRYSALIS presented in the submission are limited to patients enrolled and treated with amivantamab monotherapy in the dose escalation (Part 1) and dose expansion (Part 2) phases of the clinical trial. Thus, pemetrexed is not included in the intervention technology, and is listed appropriately as an example of treatments comprising "established clinical management without amivantamab" within the scope. The reference to pemetrexed in the CHRYSALIS protocol relates to a separate cohort which is not relevant for this submission. In one of the three cohorts in the dose escalation phase of the trial, patients were treated with amivantamab in combination with standard of care carboplatin and pemetrexed*."[9]. The ERG is satisfied that the company has clarified the use of pemetrexed in the trial and in the CS.
- Five patients in Cohort D+ came from Part 1 of the CHRYSALIS study as reported in Table 17 of the response to the clarification letter[9]. The CS stated that "*Patients enrolled to Part 1 were not required to meet any molecular eligibility requirements*."[4]. Nevertheless, in their response the company stated that Table 17 was a "*breakdown of the patient numbers comprising the efficacy analysis set N=114, patients with EGFR Exon20ins and post platinum chemotherapy who were treated at RP2D*"[9]. The CS also states that "*Part 1 was designed to determine the RP2D of*

amivantamab monotherapy in patients with advanced NSCLC based on safety, pharmacokinetic, pharmacodynamic, and anti-tumour activity data."[4]. The ERG is not entirely confident that the five patients included in Cohort D+, that came from Part 1 (dose escalation) of the study met the molecular eligibility requirements i.e., activating EGFR Exon20ins as well as the rest of the eligibility criteria that define Cohort D+.

- The ERG in its clarification letter asked the company to clarify if any of the patients in Cohort D+ received localised radiotherapy for palliative care, what criteria were used to select patients for this intervention, and what the recovery time between receipt of radiotherapy and amivantamab administration was. In response, the company stated that, *"During the on-treatment period, which was the time interval between the first dose of amivantamab and the end of treatment, 16 patients in the expanded efficacy analysis set (N=114) received palliative radiotherapy… 3 patients received palliative radiotherapy beyond the last dose date but before end-of-treatment, 1 patient received on-treatment salvage local therapy and 2 patients received on-treatment primary local therapy."*[9] They also stated that, *"There were no specific criteria for patient selection and the decision was based on investigator judgement,"*[9] and, *"Among the patients that received on treatment palliative radiotherapy and restarted treatment, treatment with amivantamab was re-started within 6–17 days after the end of radiotherapy."*[9] This did not include the three patients who did not restart amivantamab following palliative radiotherapy.

3.2.2 Statistical analyses of the CHRYSALIS trial

The population included in the CHRYSALIS trial differs from the one used for the CS. The details of the primary and supportive trial populations are presented in Table 3.5. Statistical analyses of the CHRYSALIS trial are summarized in Table 3.6.

The company, after the ERG sought clarification, confirmed that the primary population for safety results, reported in Table 3.3 "*(N=153) included only patients with EGFR Exon20ins NSCLC whose disease had progressed after platinum-based chemotherapy and had received at least one dose of the study drug, amivantamab*."[9]

Due to ambiguity in the CS, the ERG requested a clarification on the data-off dates used for the primary and the supportive clinical efficacy data. The company has now reported that "*the efficacy evidence for the N=114 efficacy population is derived from the 30th of March 2021 data cut-off*" and "*Supportive clinical efficacy data for the N=81 efficacy population is derived from the 8th October 2020 and 30th March 2021 data cut-offs*"[9].

Table 3.5: Trial populations used for the analysis of outcomes of CHRYSALIS

Analysis Set	Definition
Primary trial populations	
Efficacy results	
Post-platinum patients with EGFR Exon20ins RP2D expanded efficacy population (N=114)	Primary population for efficacy results: This population included all patients with EGFR Exon20ins NSCLC who received the RP2D prior to 4th June 2020 data cut-off with ≥3 disease assessments as of the 8th October 2020 data cut-off.
Safety results	
Post-platinum patients with EGFR Exon20ins RP2D safety population (N=153)	Primary population for safety results: This population included all patients with EGFR Exon20ins NSCLC who received prior chemotherapy at the RP2D prior to the 30th March 2021 data cut-off

Analysis Set	Definition
Supportive trial populations	
Efficacy results	
Post-platinum patients with EGFR Exon20ins RP2D initial efficacy population (N=81)	Supportive population for efficacy results: This population included all patients who received the first dose of amivantamab as monotherapy on or before 5th February 2020 and were response-evaluable with ≥3 disease assessments or discontinued treatment for any reason, including disease progression/death, prior to the 8th June 2020 data cut-off
Safety results	
All Treated at RP2D safety population (N=380)	Additional safety population: All patients enrolled in Part 1 (dose escalation) or Part 2 (dose expansion) irrespective of mutation status or prior chemotherapy, who received at least one dose of amivantamab monotherapy consistent with the RP2D (1,050 mg for body weight <80 kg and 1,400 mg for body weight ≥80 kg).
All Treated safety population (N=489)	Additional safety population: All patients enrolled in Part 1 or Part 2 who received at least one dose of amivantamab monotherapy at any dose (i.e., RP2D and non-RP2D).

Based on Tables 12 and 13 of the CS[4]
CS = company submission; EGFR = epidermal growth factor receptor; NSCLC: non-small-cell lung cancer; RP2D: recommended Phase 2 dose
Note: RP2D: 1,050 mg if baseline weight <80 kg and 1,400 mg if baseline weight ≥80 kg.

Table 3.6: Summary of statistical analyses, CHRYSALIS trial

Hypothesis objective	The null hypothesis was that the ORR for amivantamab per RECIST v1.1 was ≤15%; the alternative hypothesis was that the ORR was ≥30%
Sample size, power calculation	The maximum total sample size at a RP2D for Part 2 was set to be approximately 460 patients, including approximately 40 patients in Cohort A, 20 patients in Cohort B, and up to 100 patients each if sufficient efficacy was observed in Cohorts C, D, MET-1, and MET-2 at a RP2D of amivantamab monotherapy. With a one-sided alpha of 2.5%, and a power of 87.5%, the total number of patients needed for each cohort was 86 response-evaluable patients. Assuming a non-evaluable rate of 15%, approximately 100 patients were to be enrolled within each cohort, although the number of patients was to be expanded beyond 100 patients (maximum of approximately 150) to further characterise activity for subpopulations within a cohort. The interim analysis was to be performed when approximately 30 patients were enrolled in each cohort and have sufficient data (i.e., post-baseline disease assessment) to be evaluable for response. Future enrolment into each cohort could have been terminated if it was determined during the first stage that the treatment was considered as ineffective as compared to other treatment options and/or not well tolerated. The sample size consideration for the subgroup in Cohort D who required to have had previous therapy with a combination platinum-doublet chemotherapy regimen was based on the null hypothesis of ORR ≤12%, and the alternative hypothesis of ORR >25%. To have a power of 80% to reject the null hypothesis with a one-sided alpha of 0.025, at least 60 patients were required to be enrolled in the subgroup; approximately 100 patients were targeted for enrolment to characterise the activity of amivantamab in this population.

Statistical analysis	Primary efficacy analysis of ORR with confirmed best overall responses was performed approximately 12 weeks after the last patient received the first infusion or at the end of study, whichever came first. The data cut-off was communicated to the sites. Any additional data were reported to the appropriate health authorities when all patients had finalised treatment with amivantamab. ORR was defined as the proportion of patients who achieved either a CR or PR in all treated analysis set (or response evaluable analysis set for interim monitoring) each expansion cohort (Part 2), as defined by investigator assessment using RECIST v1.1. Observed ORR along with their two-sided 95% exact CIs were presented for each cohort and dose level as appropriate. The null hypothesis for Cohort D was that the ORR was less than or equal to 15%, which was rejected if the lower bound of the 95% CI was greater than 15%. To control the overall type I error rate at 5% within each cohort, a sequential testing strategy was used. The hypotheses testing for subgroup within each cohort was only performed after null hypothesis for the whole cohort was rejected. The null hypothesis for the subgroup in Cohort D who require at least one prior line of platinum-containing chemotherapy is ORR ≤12%, which was rejected if the lower bound of the 95% CI was greater than 12% and was only tested after the null hypothesis for Cohort D (ORR ≤15%) was rejected.
Data management, patient withdrawals	A patient was withdrawn from the study for any of the following reasons: • Lost to follow-up • Withdrawal of consent for follow-up If a patient was lost to follow-up, every reasonable effort was made by the study site personnel to contact the patient and determine the reason for discontinuation/withdrawal. The measures taken to follow up were documented. In accordance with local regulations, information from public records were used to collect any missing survival data.
Based on Table 14 of the CS[4] CI = confidence intervals; CR = complete response; CS = company submission; ORR = overall response rate; PR = partial response; RECIST = response evaluation criteria in solid tumours; RP2D = recommended Phase 2 dose	

ERG comment: The ERG notes that there is a large difference between the efficacy and safety populations in terms of number of participants (N=114 versus N=153, or 34% more participants in the safety populations). This seems to be related to the fact that the efficacy population included only those who received the intervention prior to 4th June 2020 data cut-off with ≥3 disease assessments as of the 8th October 2020 data cut-off. The ERG does not know what the implications of this discrepancy are, but recommends the use of the ITT population for all analysis of all outcomes.

3.2.3 Baseline characteristics of the CHRYSALIS trial

Table 3.7 summarises the key baseline disease and demographic characteristics. The majority of patients were <75 years old (N=105, 92.1%), female (61.4%), Asian (51.8%), of normal weight (57%) and were non-smokers (57%). Most of the population had cancer Stage IV at initial diagnosis (78.9%) and an ECOG performance status 1 (70.2%). All patients had received platinum-based chemotherapy, as per inclusion criteria, while 43.9% had received IO agents. Only [redacted] UK patients were included in Cohort D+.

Table 3.7: Key patient baseline characteristics, CHRYSALIS trial (expanded efficacy population)

Baseline characteristic	Post-platinum patients with EGFR Exon20ins at RP2D (N=114)
Age (years)	
Mean (SD)	61.8 (10.0)
Median (range)	62.0 (36–84)
Age category, n (%)	
<65, n (%)	67 (58.8)
≥65, n (%)	47 (41.2)
<75, n (%)	105 (92.1)
≥75, n (%)	9 (7.9)
Sex, n (%)	
Male	44 (38.6)
Female	70 (61.4)
Race, n (%)	
Asian	59 (51.8)
Black or African American	3 (2.6)
White	42 (36.8)
Not reported	10 (8.8)
Weight, kg	
Mean (SD)	64.8 (15.8)
Median (range)	62.1 (35.4–115.0)
Body mass index, kg/m2	
Mean (SD)	24.1 (4.7)
Median (range)	23.5 (14.0–36.9)
Underweight (<18.5), n (%)	11 (9.6)
Normal (18.5–<25), n (%)	65 (57.0)
Overweight (25–<30), n (%)	25 (21.9)
Obese (≥30), n (%)	13 (11.4)
Initial diagnosis NSCLC subtype, n (%)	
Adenocarcinoma	109 (95.6)
Large cell carcinoma	0 (0)
Squamous cell carcinoma	3 (2.6)
Other	2 (1.8)
Histology grade at initial diagnosis, n (%)	
Moderately differentiated	23 (20.2)
Poorly differentiated	19 (16.7)
Well differentiated	7 (6.1)
Other	64 (56.1)
Not reported	1 (0.9)
Cancer stage at initial diagnosis, n (%)	
0	0 (0)
IA	7 (6.1)
IB	1 (0.9)
IIA	2 (1.8)

Baseline characteristic	Post-platinum patients with EGFR Exon20ins at RP2D (N=114)
IIB	4 (3.5)
IIIA	6 (5.3)
IIIB	4 (3.5)
IV	90 (78.9)
Location of metastasis, n (%)	
Bone	51 (44.7)
Liver	13 (11.4)
Brain	29 (25.4)
Lymph node	62 (54.4)
Adrenal gland	6 (5.3)
Other	62 (54.4)
Time from initial diagnosis of cancer to first dose, months	
Mean (SD)	22.3 (20.0)
Median (range)	17.5 (1.5–130.1)
Time from metastatic disease diagnosis to first dose, months	
Mean (SD)	18.3 (15.5)
Median (range)	15.5 (0.7–116.4)
Number of prior LOTs	
Mean (SD)	2.1 (1.3)
Median (range)	2 (1–7)
ECOG performance status, n (%)	
0	33 (28.9)
1	80 (70.2)
2	1 (0.9)
History of smoking, n (%)	
Yes	49 (43.0)
No	65 (57.0)
Prior systemic therapies of interest in ≥5% of patients, n (%)	
Platinum-based chemotherapy	[redacted]
EGFR TKI (1st generation)	[redacted]
EGFR TKI (2nd generation)	[redacted]
EGFR TKI (3rd generation)	[redacted]
IO agents	[redacted]

Based on Tables 9, 10 and 11 of the CS[4]

Note: RP2D: 1,050 mg if baseline weight <80 kg and 1,400 mg if baseline weight ≥80 kg

CS = company submission; ECOG = Eastern Cooperative Oncology Group; EGFR = epidermal growth factor receptor; IO = immuno-oncology agent; LOT = lines of therapy; NSCLC = non-small-cell lung cancer; RP2D = recommended Phase 2 dose; SD = standard deviation; TKI = tyrosine kinase inhibitor

Generalisability to UK clinical practice

Given the large proportion of Asian patients in Cohort D+ (N=59, 51.8%), the ERG in its clarification letter[30] requested for the breakdown of the characteristics of those participants defined as Asian, as well as a discussion on the implications that this might have to the generalisability of the study population to the UK patient population. The baseline characteristics were provided by the company[9] and are now

presented in Tables 3.8 and 3.9. Regarding generalisability, the company stated that "*Clinical experts consulted by Janssen in the two advisory boards stated that the baseline characteristics of patients recruited to the CHRYSALIS trial broadly reflect those of patients seen in UK clinical practice. EGFR Exon20ins NSCLC is more prevalent in the Asian population than other races.*[14] *A clinical expert consulted by Janssen during the development of responses to this question stated that this was the case regardless of geographical location and that the proportion of Asian patients recruited to CHRYSALIS was broadly in line with what is seen in the UK.*[8] *Most patients with EGFR Exon20ins NSCLC are Stage IV at initial diagnosis.*[15] *The clinical expert also stated that the distribution of cancer stage at initial diagnosis seen in CHRYSALIS is reflective of clinical practice in the UK with most patients being Stage IV.*[9]

Table 3.8: Baseline demographic characteristics for patients defined as Asian (N=59) in CHRYSALIS expanded efficacy population (post-platinum patients with EGFR Exon20ins at RP2D, N=114)

Variable	Level / statistic	
Age	N	[redacted]
	Mean (SD)	[redacted]
	Median	[redacted]
	Range	[redacted]
Age (65 years threshold)	N	[redacted]
	<65	[redacted]
	≥65	[redacted]
Age (75 years threshold)	N	[redacted]
	<75	[redacted]
	≥75	[redacted]
Gender	N	[redacted]
	Male	[redacted]
	Female	[redacted]
Race	N	[redacted]
	Asian	[redacted]
Ethnicity	N	[redacted]
	Not Hispanic or Latino	[redacted]
Weight (kg)	N	[redacted]
	Mean (SD)	[redacted]
	Median	[redacted]
	Range	[redacted]
Height (cm)	N	[redacted]
	Mean (SD)	[redacted]
	Median	[redacted]
	Range	[redacted]
BMI (kg/m)	N	[redacted]
	Mean (SD)	[redacted]
	Median	[redacted]

Variable	Level / statistic	
	Range	[redacted]
BMI category	N	[redacted]
	Underweight (<18.5)	[redacted]
	Normal (18.5- <25)	[redacted]
	Overweight (25- <30)	[redacted]
	Obese (>30)	[redacted]

Based on Table 15 of the clarification letter[9]
Note: If race was not reported, then that subject is excluded from the race subgroup; Ns for each parameter reflect non-missing values.
BMI = body mass index; SD = standard deviation

Table 3.9: Baseline clinical and disease characteristics for patients defined as Asian (n=59) in CHRYSALIS expanded efficacy population (post-platinum patients with EGFR Exon20ins at RP2D, N=114)

Variable	Level / statistic	
Initial diagnosis NSCLC subtype	N	[redacted]
	Adenocarcinoma	[redacted]
	Squamous cell carcinoma	[redacted]
	Other	[redacted]
Histology grade at initial diagnosis	N	[redacted]
	Moderately differentiated	[redacted]
	Poorly differentiated	[redacted]
	Well differentiated	[redacted]
	Other	[redacted]
Cancer stage at initial diagnosis	N	[redacted]
	IA	[redacted]
	IB	[redacted]
	IIA	[redacted]
	IIB	[redacted]
	IIIA	[redacted]
	IIB	[redacted]
	IV	[redacted]
Bone metastasis	N	[redacted]
	No	[redacted]
	Yes	[redacted]
Liver metastasis	N	[redacted]
	No	[redacted]
	Yes	[redacted]
Brain metastasis	N	[redacted]
	No	[redacted]
	Yes	[redacted]

Variable	Level / statistic	
Lymph node metastasis	N	[redacted]
	No	[redacted]
	Yes	[redacted]
Adrenal gland metastasis	N	[redacted]
	No	[redacted]
	Yes	[redacted]
Other metastasis	N	[redacted]
	No	[redacted]
	Yes	[redacted]
Time from initial diagnosis of cancer to first dose	N	[redacted]
	Mean (SD)	[redacted]
	Median	[redacted]
	Range	[redacted]
Time from metastasis disease diagnosis to first dose	N	[redacted]
	Mean (SD)	[redacted]
	Median	[redacted]
	Range	[redacted]
Prior lines of treatment	N	[redacted]
	Mean (SD)	[redacted]
	Median	[redacted]
	Range	[redacted]
Prior lines of treatment (Category)	N	[redacted]
	1	[redacted]
	2	[redacted]
	3	[redacted]
	4	[redacted]
	5	[redacted]
	6	[redacted]
	7	[redacted]
ECOG	N	[redacted]
	ECOG 0	[redacted]
	ECOG 1+	[redacted]
Smoking history	N	[redacted]
	Yes	[redacted]
	No	[redacted]
Hepatic impairment at baseline	N	[redacted]
	Normal (Total bilirubin ≤ ULN and AST ≤ ULN)	[redacted]

Variable	Level / statistic	
	Mild (Total bilirubin ≤ ULN and AST > ULN) or (ULN < Total bilirubin ≤ 1.5 x ULN)	[redacted]
Renal impairment at baseline	N	[redacted]
	Normal (EGFR: ≥ 90 mL/min/1.73m2)	[redacted]
	Mild (EGFR: 60 to < 90 mL/min/1.73m2)	[redacted]
	Moderate (EGFR: 30 to < 60 mL/min/1.73m2)	[redacted]
Based on Table 16 of the clarification letter[9] ECOG = eastern cooperative oncology group; EGFR = epidermal growth factor receptor; NSCLC = non-small-cell lung cancer; SD = standard deviation		

ERG comment:

- In the CS it was not clear how many UK patients were included in Cohort D+. The company has now reported that there were only [redacted] whose *"...baseline demographic characteristics cannot be presented in order to avoid patient identification."*[9]. Although the company maintains that the generalisability of the study population is not affected by the race baseline characteristics, the subgroup analysis has detected differences, please see Section 3.2.5.7 of this report.
- The eligibility criteria stated that only patients with ECOG status 0 or 1 were to be included in the CHRYSALIS trial (Table 3.3), nevertheless, one patient with ECOG status 2 was included (Table 3.7). It is unclear why this patient was included, and how further baseline and clinical characteristics compare to other patients who might have been excluded due to ECOG status.

3.2.4 Risk of bias assessment of the CHRYSALIS trial

Table 3.10 presents the risk of bias assessment of the CHRYSALIS trial conducted using the ROBINS-I[31] tool for assessing risk of bias in non-randomised studies of interventions.Quality assessments were completed by one reviewer and verified by a second independent reviewer. The ERG undertook an independent risk of bias assessment using the same tool (ROBINS-I), whose results are reported in the same table.

Table 3.10: Quality assessment of the CHRYSALIS trial

	Risk of bias	
Source of bias	**CS**	**ERG**
Overall bias due to confounding	Low	Moderate
Overall bias in selection of participants into the study	Low	Low
Overall bias in classification of interventions	Low	Low
Overall bias due to deviations from intended interventions	Low	Low
Overall bias due to missing data	Low	Low
Overall bias in measurement of outcomes	Moderate	Moderate
Overall bias in selection of the reported results	Low	Low
Overall risk of bias	Moderate	Moderate
Based on Table 15 of the CS[4] CS = company submission; ERG = Evidence Review Group		

ERG comment: All parts of the systematic review, including the risk of bias assessment, should be undertaken by a team and not a single person to ensure errors are minimised. It is not clear in the CS whether more than one reviewer was involved in the risk of bias assessment. Nevertheless, the ERG largely agrees with the risk of bias assessment executed by the company. The only difference is the pre-intervention domain of 'bias due to confounding' as the study did not use a method to control for measured confounders. As a result, of only one domain rating change the overall risk of bias rating of the study was not altered.

3.2.5 Efficacy results of the CHRYSALIS trial

The company submitted efficacy results for one primary and several secondary outcomes as presented in Table 3.3. The expanded efficacy population was used (N=114) until the 30th March 2021 data cut-off. In addition, the supportive efficacy trial population (N=81) was used including data until the 30th March 2021. A summary of the outcomes for the expanded efficacy population is presented in Table 3.11. When applicable (all outcomes apart from TTF and OS) both INV and blinded independent committee review assessed (BICR) results were provided in the CS. Further details and critique are provided in the following Sections.

Table 3.11: Summary of key outcomes from the CHRYSALIS trial (30th March 2021 data cut-off)

Outcome	Result
ORR, n (%) [95% CI]	BICR: 49 (43.0) [33.7, 52.6] INV: 42 (36.8) [28.0, 46.4]
CBR, n (%) [95% CI]	BICR: 84 (73.7) [64.6, 81.5] INV: 86 (75.4) [66.5, 83.0]
Median DOR, months (95% CI)	BICR: 10.84 (6.90, 14.98) INV: 12.45 (6.54, 16.13)
Median PFS, months (95% CI)	BICR: 6.74 (5.45, 9.66) INV: 6.93 (5.55, 8.64)
Median TTF, months (95% CI)	8.08 (6.67, 10.64)
Median OS, months (95% CI)	22.77 (17.48, NE)

Based on Table 16 of the CS[4]
Note: DOR is calculated as the time from initial response (either complete or partial response) to PD or death; PFS is defined as the time from first infusion of amivantamab to PD or death; TTF is defined as the time from the first infusion of amivantamab to discontinuation of treatment for any reason, including disease progression, treatment toxicity and death; OS is defined as the time from first infusion of amivantamab to death due to any cause
BICR = blinded independent committee review; CBR = clinical benefit rate; CI = confidence interval; DOR = duration-of-response; INV = investigator assessed; NE = not evaluable; OS = overall survival; ORR = overall response rate; PD = progressive disease; PFS = progression-free survival; TTF = time to treatment failure.

3.2.5.1 Primary outcome: overall response rate (ORR)

The company defined ORR as, "*the proportion of patients with a best overall response of a confirmed CR or PR based on RECIST v1.1 criteria (best response as recorded in the CRF from the start of the amivantamab until disease progression, withdrawal of consent, or start of a subsequent anti-cancer therapy, whichever came first). ORR was based on investigator assessment and BICR assessment*." The results are provided in Table 3.12.

Table 3.12: Summary of best overall response based on RECIST v1.1 from the CHRYSALIS trial (30th March 2021 data cut-off)

	Post-platinum patients with EGFR Exon20ins at RP2D (N=114)	
	BICR	**INV**
Best overall response, n (%)		
CR	3 (2.6)	0 (0)
PR	46 (40.4)	42 (36.8)
SD	47 (41.2)	56 (49.1)
PD	15 (13.2)	14 (12.3)
Not evaluable/unknown	3 (2.6)	2 (1.8)
ORR, n (%) [95% CI]	49 (43.0) [33.7, 52.6]	42 (36.8) [28.0, 46.4]
CBR, n (%) [95% CI]	84 (73.7) [64.6, 81.5]	86 (75.4) [66.5, 83.0]

Based on Table 17 of the CS[4]
Note: CBR is defined as the percentage of patients achieving confirmed complete or partial response, or durable stable disease (duration of at least 11 weeks). RP2D is defined as 1,050 mg if baseline weight <80 kg and 1,400 mg if baseline weight ≥80 kg.
BICR = blinded independent committee review; CBR = clinical benefit rate; CR = complete response; CS = company submission; CI = confidence interval; EGFR = epidermal growth factor receptor; INV = investigator assessed; ORR = overall response rate; PD = progressed disease; PR = partial response; RP2D = recommended Phase 2 dose; SD = stable disease.

In the CS, the company also compared the single arm results to SoC treatments for ORR, by separately comparing to SoC data from a US (RWE) and UK (PHE) Cohort (see Section 3.4 for further details).

Comparing BICR assessed data from CHRYSALIS with the US Cohort, based on an IPW-ATT approach for statistical adjustment (see Section 3.4), the adjusted OR for amivantamab versus SoC was [redacted]. Based on a multivariable proportional hazards regression model the adjusted OR for amivantamab versus SoC was [redacted].

Comparing INV data from CHRYSALIS with the US Cohort, based on an IPW-ATT approach for statistical adjustment (see Section 3.4), the adjusted OR for amivantamab versus SoC [redacted]. Based on a multivariable proportional hazards regression model the adjusted OR for amivantamab versus SoC was [redacted].

The ERG inquired whether the patients were still receiving treatment at the time of the evaluation of best overall response, as reported in Table 3.12. The company in its response to clarification[9] stated that "*Considering INV-assessed best overall response (BOR), all patients for whom a partial response or stable disease was their BOR achieved this whilst receiving treatment. Two patients were recorded as having a non-evaluable BOR since treatment was discontinued before the first disease evaluation.*

For BICR-assessed BOR, all patients with a BOR of complete response, partial response or stable disease achieved this whilst receiving treatment. Two patients were recorded as having a non-evaluable BOR since due to discontinuation of treatment before disease evaluation, and one patient had stable disease on Day 38, but this was not counted given that it did not meet the minimum window of 42 days for standard disease assessment as outlined by the CHRYSALIS trial protocol." The company has also

provided further details on the "*timing for the assessment of best overall response in relation to treatment*" which is reported in Table 3.13.

Table 3.13: Summary of best overall response based on RECIST v1.1 and timing of assessment; Post-platinum EGFR Exon20ins RP2D expanded efficacy population (N=114)

	Best overall response: post-platinum Exon20ins RP2D expanded efficacy population (N=114, 30th March 2021 data cut-off)			
	BICR		INV	
	n (%)	Timing of evaluation	n (%)	Timing of evaluation
CR	[redacted]	[redacted]	[redacted]	[redacted]
PR	[redacted]	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]	[redacted]
PD	[redacted]	[redacted]	[redacted]	[redacted]
Not evaluable/ unknown	[redacted]	[redacted]	[redacted]	[redacted]
ORR, n (%) [95% CI]	[redacted]		[redacted]	
CBR, n (%) [95% CI]	[redacted]		[redacted]	

Based on Table 17 of the CS[9]
AE = adverse event; BICR = blinded independent committee review; BOR = best overall response; CBR = clinical benefit rate; CR = complete response; CS = company submission; CI = confidence interval; EGFR = epidermal growth factor receptor; INV = investigator assessed; N/A = not applicable; ORR = overall response rate; PD = progressed disease; PR = partial response; RP2D = recommended Phase 2 dose; SD = stable disease.
Note: CBR is defined as the percentage of patients achieving confirmed complete or partial response, or durable stable disease (duration of at least 11 weeks). RP2D is defined as 1,050 mg if baseline weight <80 kg and 1,400 mg if baseline weight ≥80 kg.

3.2.5.2 Secondary outcome: duration of response (DOR)

The company calculated DOR as "*time from initial response of CR or PR to PD or death due to underlying disease, whichever comes first, only for patients who achieve CR or PR*". The results are presented in Table 3.14. The Kaplan-Meier (KM) plots according to the BICR and INV assessments are illustrated in Figure 3.2 and

Figure 3.3, respectively. The BICR identified a total of 49 responders while the INV identified 42. The respective median DOR were 10.84 months (95% confidence interval (CI): 6.90, 14.98) and 12.45 months (95% CI: 6.54, 16.13).

Table 3.14: Summary of duration of response (DOR) from the CHRYSALIS trial (30th March 2021 data cut-off)

	Post-platinum patients with EGFR Exon20ins at RP2D (N=114, 30th March 2021 data cut-off)	
	BICR	**INV**
Responders, n	49	42
Event, n (%)	27 (55.1)	21 (50.0)
Censored, n (%)	22 (44.9)	21 (50.0)
Time to event (months)		
25th percentile (95% CI)	5.13 (4.07, 8.21)	4.96 (4.14, 8.31)
Median (95% CI)	10.84 (6.90, 14.98)	12.45 (6.54, 16.13)
75th percentile (95% CI)	21.65 (11.04, NE)	16.13 (12.68, NE)
Range	1.1+, 21.7	1.1+, 19.0+
Duration of response ≥6 months, n (%)	27 (55.1)	27 (64.3)
Duration of study treatment (months)		
N	49	42
Mean (SD)	12.13 (5.77)	12.77 (5.09)
Median	13.37	13.59
Range	1.7, 23.9	2.3, 23.9

Based on Table 18 of the CS[4]
Note: RP2D is defined as 1,050 mg if baseline weight <80 kg and 1,400 mg if baseline weight ≥80 kg.
BICR = blinded independent review; CI = confidence interval; CS = company submission; EGFR = epidermal growth factor receptor; INV = investigator; NE = not evaluable; RP2D = recommended Phase 2 Dose; SD = standard deviation.

Figure 3.2: Kaplan-Meier plot of DOR – the CHRYSALIS trial (30th March 2021 data cut-off) - expanded efficacy population (N=114) by BICR assessment

Source: Figure 7 of the CS[4]
CS = company submission; BICR = blinded independent review; DOR = duration of response

Figure 3.3: Kaplan-Meier plot of DOR – the CHRYSALIS trial (30th March 2021 data cut-off) - expanded efficacy population (N=114) by INV assessment

Source: Figure 8 of the CS[4]
CS = company submission; DOR = duration of response; INV = investigator

3.2.5.3 Secondary outcome: progression-free survival (PFS)

The company defined PFS as "*the time from first infusion of amivantamab to PD or death due to any cause*". The PFS data are provided in Table 3.15,while the KM curves are illustrated in

Figure 3.4 and

Figure 3.5 for the BICR and INV assessments, respectively. Median PFS was 6.74 months (95% CI: 5.45, 9.66) according to BICR and 6.93 months (95% CI: 5.55, 8.64) according to INV; while the median follow was [redacted] months (range: [redacted]).

Table 3.15: Summary of progression-free survival (PFS) from the CHRYSALIS trial (30th March 2021 data cut-off)

	Post-platinum patients with EGFR Exon20ins at RP2D (N=114, 30th March 2021 data cut-off)	
	BICR	**INV**
Event, n (%)	80 (70.2)	81 (71.1)
Censored, n (%)	34 (29.8)	33 (28.9)
Time to event (months)		
25th percentile (95% CI)	3.94 (2.66, 4.83)	3.71 (2.60, 4.34)
Median (95% CI)	6.74 (5.45, 9.66)	6.93 (5.55, 8.64)
75th percentile (95% CI)	12.45 (10.87, NE)	16.56 (12.58, NE)
Range	(0.0+, 23.3)	0.0+, 24.1
3-month event-free rate (95% CI)	0.78 (0.69, 0.85)	0.77 (0.68, 0.84)
6-month event-free rate (95% CI)	0.55 (0.45, 0.64)	0.55 (0.45, 0.64)
9-month event-free rate (95% CI)	0.41 (0.31, 0.50)	0.39 (0.30, 0.48)
12-month event-free rate (95% CI)	0.29 (0.21, 0.39)	0.35 (0.26, 0.44)
15-month event-free rate (95% CI)	0.22 (0.14, 0.31)	0.28 (0.19, 0.37)
18-month event-free rate (95% CI)	0.14 (0.06, 0.26)	0.18 (0.09, 0.30)
21-month event-free rate (95% CI)	0.14 (0.06, 0.26)	0.18 (0.09, 0.30)
24-month event-free rate (95% CI)	0 (NE, NE)	0.18 (0.09, 0.30)
27-month event-free rate (95% CI)	NR	0 (NE, NE)

Based on Table 19 of the CS[4]
Note: RP2D is defined as 1,050 mg if baseline weight <80 kg and 1,400 mg if baseline weight ≥80 kg.
BICR = blinded independent review; CI = confidence interval; CS = company submission; EGFR = epidermal growth factor receptor; INV = investigator; PFS = progression-free survival; NE = not evaluable; NR = not reported; RP2D = recommended Phase 2 dose.

Figure 3.4: Kaplan-Meier plot of PFS – the CHRYSALIS trial (30th March 2021 data cut-off) - expanded efficacy population (N=114) by BICR assessment

Source: Figure 9 of the CS[4]
BICR = blinded independent committee review; CS = company submission; IN = investigator; PFS = progression-free survival; RP2D = recommended Phase 2 dose

Figure 3.5: Kaplan-Meier plot of PFS – the CHRYSALIS trial (30th March 2021 data cut-off) - expanded efficacy population (N=114) by INV assessment

Source: Figure 10 of the CS[4]
BICR = blinded independent committee review; CS = company submission; INV = investigator; PFS = progression-free survival; RP2D = recommended Phase 2 dose

The CS also compared the single arm results to SoC treatments for PFS, by separately comparing to data from a US and UK Cohort (see Section 3.4 for further details).

Comparing BICR data with the US SoC data, based on an IPW-ATT approach for statistical adjustment (see Section 3.4), the adjusted HR for amivantamab versus SoC was [redacted]. Based on a multivariable proportional hazards regression model the adjusted HR for amivantamab versus SoC was [redacted].

Comparing INV data with the US SoC data, based on an IPW-ATT approach for statistical adjustment (see Section 3.4), the adjusted HR for amivantamab versus SoC was [redacted]. Based on a multivariable proportional hazards regression model the adjusted HR for amivantamab versus SoC was [redacted].

3.2.5.4 Secondary outcome: time-to-treatment failure (TTF)

The TTF was defined by the company as "*the time from the first infusion of amivantamab to discontinuation of treatment for any reason, including disease progression, treatment toxicity and death*". The TTF results are presented in Table 3.16, and illustrated in a KM plot in

Figure 3.6. The median TTF was [redacted] (95% CI: [redacted]) with [redacted] of patients censored.

Table 3.16: Summary of TTF from the CHRYSALIS trial (30th March 2021 data cut-off)

	Post-platinum patients with EGFR Exon20ins at RP2D (N=114, 30th March 2021 data cut-off)
Event, n (%)	[redacted]
Censored, n (%)	[redacted]
Time to event (months)	
25th percentile (95% CI)	[redacted]
Median (95% CI)	[redacted]
75th percentile (95% CI)	[redacted]
Range	[redacted]
3-month event-free rate (95% CI)	[redacted]
6-month event-free rate (95% CI)	[redacted]
9-month event-free rate (95% CI)	[redacted]
12-month event-free rate (95% CI)	[redacted]
15-month event-free rate (95% CI)	[redacted]
18-month event-free rate (95% CI)	[redacted]
21-month event-free rate (95% CI)	[redacted]
24-month event-free rate (95% CI)	[redacted]
27-month event-free rate (95% CI)	[redacted]

Based on Table 20 of the CS[4]
Note: RP2D is defined as 1,050 mg if baseline weight <80 kg and 1,400 mg if baseline weight ≥80 kg.
CI = confidence interval; CS = company submission; EGFR = epidermal growth factor receptor; NE = not evaluable; RP2D = recommended Phase 2 dose; TTF = time-to-treatment failure

Figure 3.6: Kaplan-Meier plot of TTF – the CHRYSALIS trial (30th March 2021 data cut-off) - expanded efficacy population (N=114)

Source: Figure 11 of the CS[4]
CS = company submission; TTF = time-to-treatment failure; RP2D = recommended Phase 2 dose

3.2.5.5 Secondary outcome: overall survival (OS)

The OS was defined in the CS as "*the time from first infusion of amivantamab to death due to any cause*". The OS results are presented in Table 3.17 and a KM plot is illustrated in

Figure 3.7. 64.9% of patients was censored and the median OS was 22.77 months (95% CI: 17.48, NE). On the 30th of March 2021 data cut-off (median follow-up of [redacted] [range: [redacted]]), [redacted] ([redacted]) had died.

Table 3.17: Summary of OS from the CHRYSALIS trial (30th March 2021 data cut-off)

	Post-platinum patients with EGFR Exon20ins at RP2D (N=114, 30th March 2021 data cut-off)
Event, n (%)	40 (35.1)
Censored, n (%)	74 (64.9)
Time to event (months)	
25th percentile (95% CI)	9.95 (8.48, 14.59)
Median (95% CI)	22.77 (17.48, NE)
75th percentile (95% CI)	NE (23.00, NE)
Range	(0.2, 30.5+)
3-month event-free rate (95% CI)	0.95 (0.89, 0.98)
6-month event-free rate (95% CI)	0.90 (0.83, 0.94)
9-month event-free rate (95% CI)	0.79 (0.70, 0.86)
12-month event-free rate (95% CI)	0.73 (0.63, 0.80)
15-month event-free rate (95% CI)	0.66 (0.55, 0.75)
18-month event-free rate (95% CI)	0.61 (0.49, 0.71)
21-month event-free rate (95% CI)	0.53 (0.39, 0.66)
24-month event-free rate (95% CI)	0.40 (0.21, 0.58)
27-month event-free rate (95% CI)	0.40 (0.21, 0.58)
30-month event-free rate (95% CI)	0.40 (0.21, 0.58)

Based on Table 21 of the CS[4]

Note: RP2D is defined as 1,050 mg if baseline weight <80 kg and 1,400 mg if baseline weight ≥80 kg.

CI = confidence interval; CS = company submission; EGFR = epidermal growth factor receptor; NE = not evaluable; RP2D: recommended Phase 2 dose; OS = overall survival

Figure 3.7: Kaplan-Meier plot of OS – the CHRYSALIS trial (30th March 2021 data cut-off) - expanded efficacy population (N=114)

Source: Figure 12 of the CS[4]
CS = company submission; TTF = time-to-treatment failure; RP2D = recommended Phase 2 dose

The CS also compared the single arm results to SoC treatments for OS, by separately comparing to data from a US and UK Cohort (see Section 3.4 for further details).

Comparing BICR data with the US SoC data, based on an IPW-ATT approach for statistical adjustment (see Section 3.4), the adjusted HR for amivantamab versus SoC was [redacted]. Based on a multivariable proportional hazards regression model the adjusted HR for amivantamab versus SoC was [redacted].

Comparing BICR data with the UK PHE SoC data, based on a multivariable proportional hazards regression model the adjusted HR for amivantamab versus SoC was [redacted].

ERG comment:

3.2.5.6 Exploratory outcome: Health-related quality of life (HRQoL)

HRQoL consists of exploratory descriptive analyses that were meant to include four patient reported outcomes (PROs): PGIS, PGIC, NSCLC-SAQ and EQ-5D-5L VAS (see Table 3.3). PROs were not part of the original trial protocol but a later addition (protocol Amendment 7), which affected the data availability. Data were available for only a small subset of the population of interest (expanded efficacy population), n=[redacted] of 114 ([redacted]%).

The company opted to present results only for two of the outcomes, the ED-5D VAS and the NSCLC-SAQ results, as illustrated in Figure 3.8 and Figure 3.9, respectively.

NSCLC-SAQ is a 7-item questionnaire-based, PRO measure, used in advanced NSCLC clinical trials. It draws from a 7-day patient recall period and is based on verbal rating scales. The questionnaire assessed the patient reported symptoms of cough, pain, dyspnoea, fatigue and poor appetite. The total score can range from 0 to 20.

ED-5D-5L VAS is also a questionnaire-based PRO measure of health status, but it is designed to be used by the general population. It comprises the five dimensions of mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The system includes five levels of severity for each of the five dimensions indicating no problem, slight problems, moderate problems, severe problems or extreme problems.

Figure 3.8: Change from baseline of NSCLC-SAQ total score over time – the CHRYSALIS trial (30th March 2021 data cut-off) - expanded efficacy population (N=114)

Source: Figure 13 of the CS[4]
CS = company submission; LS = least squares; NSCLC-SAQ = Non-Small-Cell Lung Cancer Symptom Assessment Questionnaire; TOT = time on treatment

Figure 3.9: Change of baseline of EQ-5D-5L VAS over time – the CHRYSALIS trial (30th March 2021 data cut-off) - expanded efficacy population (N=114)

Source: Figure 14 of the CS[4]
CS = company submission; EQ-5D-5L = EuroQoL five-dimensions five-levels; LS = least squares; VAS = visual analogue scale

ERG comments:

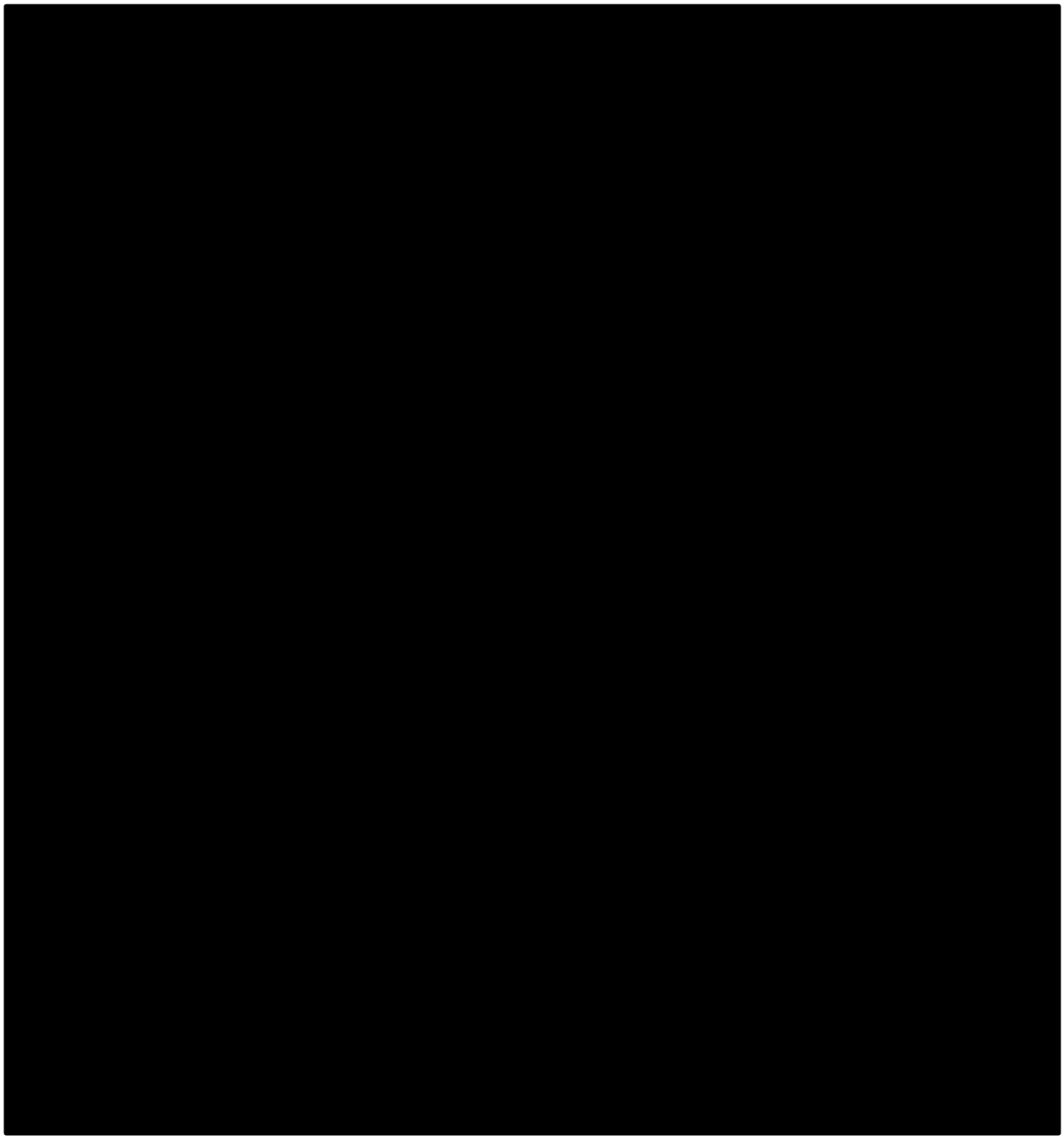
- The company has chosen to present only two out of the four PRO measures that were included in the CHRYSALIS for brevity. The results for PGIS and PGIC were not reported and a justification for their exclusion was not provided.
- In both Figure 3.8 (NSCLC-SAQ) and Figure 3.9 (ED-5D-5L) the included number of patients appears to be very small (n=[redacted]) and different from what was reported in the text (n=[redacted]).
- The number of patients available for this outcome is very small, and the estimates based on this small sample are uncertain. Further comments on the HRQoL outcomes are provided in the cost effectiveness part of this report.

3.2.5.7 Subgroup analysis

The CS presented an ORR subgroup analysis for the following demographic and clinical characteristics: age (four categories), sex, race (Asian versus non-Asian), ECOG status (0 versus ≥1), history of smoking and prior immunotherapy. Forest plots for BICR and INV assessments are illustrated in Figure 3.10 and Figure 3.11, respectively. From the 98 patients whose race could be determined, 59 were Asian (51.8%). The company argues that the results of the subgroup analysis regarding race, illustrate

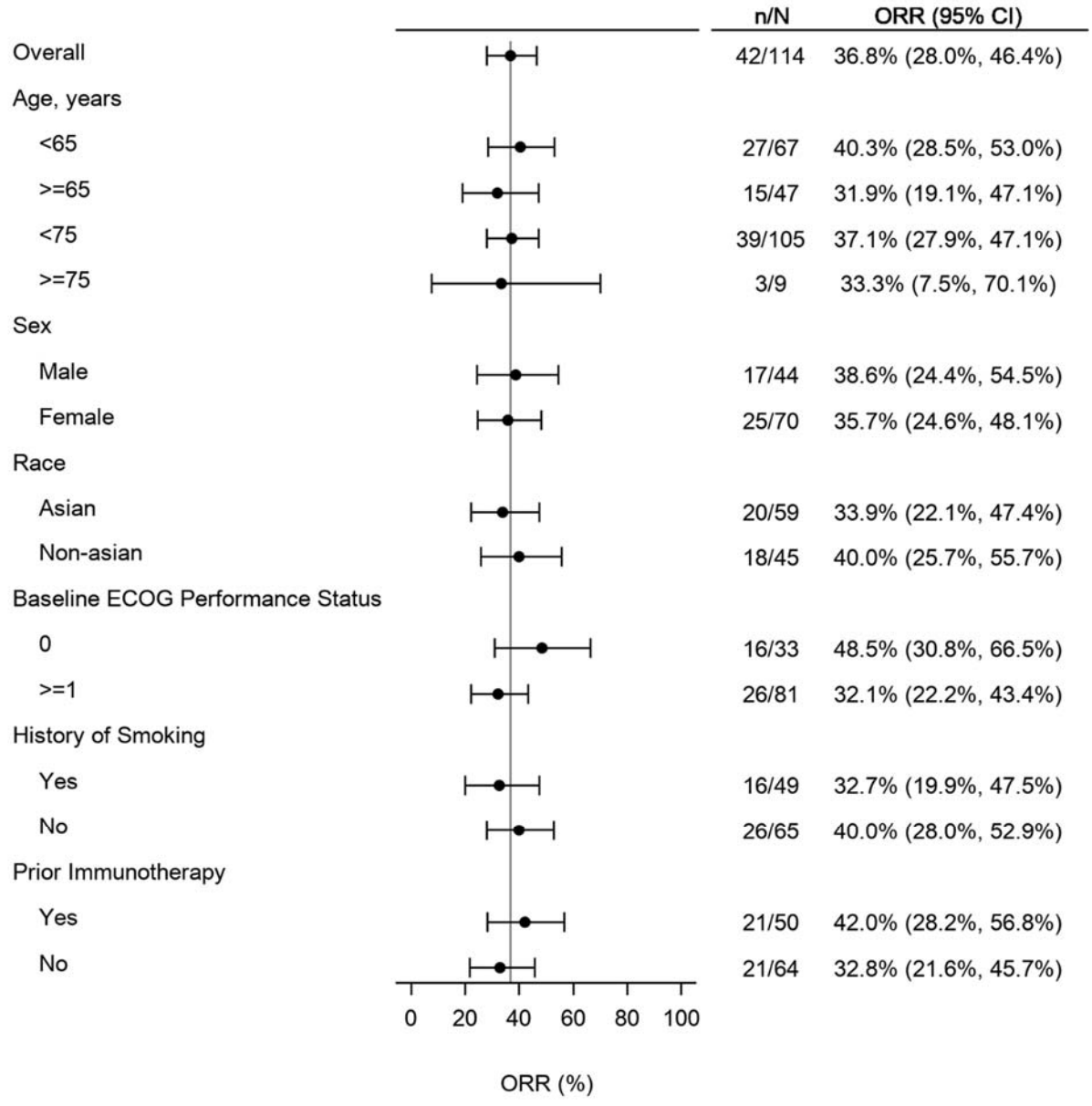
that the high proportion of Asian participants does not influence the generalisability of the efficacy results.

Figure 3.10: Forest plot of ORR based on RECIST v1.1– the CHRYSALIS trial (30th March 2021 data cut-off) - expanded efficacy population (N=114) by BICR assessment



Source: Figure 15 of the CS[4]
Note: n = confirmed CR plus confirmed PR. If race was not reported, then that patient is excluded from the race subgroup. Chinese patients enrolled beyond the initial global cohort enrolment are excluded
CI = confidence interval; CR = complete response; CS = company submission; ECOG = Eastern Cooperative Oncology Group; ORR = overall response rate; PR = partial response

Figure 3.11: Forest plot of ORR based on RECIST v1.1– the CHRYSALIS trial (30th March 2021 data cut-off) - expanded efficacy population (N=114) by INV assessment



Source: Figure 16 of the CS[4]
Note: n = confirmed CR plus confirmed PR. If race was not reported, then that patient is excluded from the race subgroup. Chinese patients enrolled beyond the initial global cohort enrolment are excluded
CI = confidence interval; CR = complete response; CS = company submission; ECOG = Eastern Cooperative Oncology Group; ORR = overall response rate; PR = partial response

ERG comment:

- The results of the subgroup analyses regarding race (Asian versus non-Asian) illustrate that the ORRs vary. In the BICR assessment ORR for Asians is 45.8% (95% CI 32.7, 59.2) and for non-

Asians 40% (95% CI 25.7, 55.7) and in the INV assessment, ORR for Asians is 33.9% (95% CI 22.1, 47.4) and for non-Asians 40% (95% CI 25.7, 55.7).

- The effect of these differences on effectiveness and cost effectiveness, as far as the applicability to the UK population, is unknown.

3.2.6 Safety results of the CHRYSALIS trial

This Section reports on the safety results discussed in Section B.2.10 of the CS.

The CS reports safety results from the CHRYSALIS trial from the 8th October 2020 and 30th March 2021 data cut-offs. Results are presented for the post-platinum patients with Exon20ins at RP2D safety population (N=153) from the 30th March 2021 data cut-off. Additional data from the All Treated at RP2D safety population (N=380) and All Treated safety population (N=489) at the latest data cut-off are presented in Appendix F but are not summarised here.

ERG comment: In its clarification letter, the ERG asked the company to confirm if the safety population only included patients with EGFR Exon20ins NSCLC whose disease had progressed after platinum-based chemotherapy and had received at least one dose of the study drug, amivantamab. In response to clarification, the company stated that, *"Janssen can confirm that the safety population (N=153) included only patients with EGFR Exon20ins NSCLC whose disease had progressed after platinum-based chemotherapy and had received at least one dose of the study drug, amivantamab."*[9] The ERG is satisfied that the results presented in this Section are from a suitable analysis set.

3.2.6.1 Treatment duration and dosage

As of the latest data cut-off date (30th March 2021), from the EGFR Exon20ins RP2D safety population, the median follow up is stated to be [redacted] months. [redacted] of patients had completed the study, 62.1% (95/153) of patients were still in the study and [redacted] had prematurely terminated from study participation. The CS states that at this time 36.6% (56/153) were still receiving amivantamab while 63.4% (97/153) had discontinued treatment. When reviewing reasons for discontinuation 47.7% (73/153) of patients had progressive disease, 7.8% (12/153) had experienced AEs, 4.6% (7/153) were patient selected withdrawals, 1.3% (2/153) withdrew as a result of a physician decision and 2% (3/153) of patients expired. (see Table 3.18 below).

Table 3.18: Study and treatment disposition; post-platinum patients with EGFR Exon20ins at RP2D safety population (N=153)

Event, n (%)	Safety population (N=153, 30th March 2021 data cut-off)
Study disposition	
Patients ongoing	[redacted]
Completed study participation	[redacted]
Terminated study participation prematurely	[redacted]
Treatment disposition	
Patients ongoing	56 (36.6)
Discontinued study treatment	97 (63.4)
Reason for discontinuation	
Progressive disease	73 (47.7)
AE	12 (7.8)
Withdrawal by patient	7 (4.6)

Event, n (%)	Safety population (N=153, 30th March 2021 data cut-off)
Physician decision	2 (1.3)
Death	3 (2.0)

Based on table 26, CS[4]
Note: RP2D is defined as 1,050 mg if baseline weight <80 kg and 1,400 mg if baseline weight ≥80 kg. [a] Patient is considered to have completed the study if the patient died prior to the end of study.
AE = adverse event; CS = company submission; RP2D = recommended Phase 2 dose

The CS states that the median number of treatment cycles received in the safety population was seven, with 34.0% (52/153) subjects having received treatment for ≥10 cycles,[4] and the maximum number of treatment cycles was 27.46.4% (71/153) patients had received treatment for a period of ≥6 months with a median duration of treatment being 5.6 months. The maximum duration of treatment was 23.9% (see Table 3.19).

Table 3.19: Summary of treatment with amivantamab; post-platinum patients with EGFR Exon20ins at RP2D safety population (N=153)

Safety population (N=153, 30th March 2021 data cut-off)	
Duration of study treatment, months[a]	
Mean (SD)	7.28 (5.81)
Median	5.52
Range	(0.03; 23.89)
Duration of study treatment, n (%)	
<2 months	31 (20.3)
2 –<4 months	26 (17.0)
4 –<6 months	25 (16.3)
≥6 months	71 (46.4)
Total number of cycles[b]	
Mean (SD)	8.5 (6.2)
Median	7
Range	(1, 27)

Based on Table 27, CS[4]
Note: RP2D is defined as 1,050 mg if baseline weight <80 kg and 1,400 mg if baseline weight ≥80 kg.
[a]Treatment duration is defined as the duration from the date of the first dose of amivantamab to the date of last dose of amivantamab+1 divided by 30.4375.
[b]A patient is considered as treated in a cycle if the patient received any non-zero dose of study agent in that cycle.
CS = company submission; SD = standard deviation; RP2D = recommended Phase 2 dose.

3.2.6.2 Summary of Treatment emergent adverse events (TEAEs)

The CS states that all patients experienced at least one treatment emergent adverse event (TEAE) while 98.0% had at least one TEAE reported by the investigator to be related to amivantamab. TEAEs at grade 3 or above were experienced by 41.8% of patients while 19.6% patients had TEAEs at grade 3 or above that were deemed to be related to amivantamab. Serious TEAEs were experienced by 28.8% of patients with 2.6% experienced grade 4 TEAEs while 7.2% of patients experienced a grade 5 event (fatal) and expired. Of those 28.8% of patients who experienced a serious TEAE, 8.5% were reported by the investigators. The CS states that all grade 5 fatal events were assessed as being unrelated to

amivantamab (see Table 3.20). The company did not provide a definition of 'serious' AEs within the CS document, however a review of the trial protocol clarified that a 'serious AE' would be based on 'I*CH and EU Guidelines on Pharmacovigilance for Medicinal Products for Human Use is any untoward medical occurrence that at any dose.*

- *Results in death*
- *Is life-threatening (The subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.)*
- *Requires inpatient hospitalization or prolongation of existing hospitalization*
- *Results in persistent or significant disability/incapacity*
- *Is a congenital anomaly/birth defect*
- *Is a suspected transmission of any infectious agent via a medicinal product*
- *Is Medically Important'*[29]

Table 3.20 provides data stating that 14.4% of patients experienced TEAEs that required dose reduction, while 11.8% of patients discontinued treatment as a consequence of AEs. Of the patients, 59.5% experienced a need for infusion modification and 35.9% of patients experiencing events that led to dose interruption. Investigators judged that all events (14.4%) that led to dose reduction were related to amivantamab while 5.2% of events that led to discontinued treatment, 58.8% of events that led to infusion modification and 20.9% of events that led to dose interruption were related to amivantamab.

Table 3.20: Overall summary of TEAEs; Post-platinum patients with EGFR Exon20ins at RP2D safety population (N=153)

Event, n (%)	Safety population (N=153, 30th March 2021 data cut-off)
Patients with ≥1 AE	153 (100.0)
Related AEs[a]	150 (98.0)
AEs leading to death[b]	11 (7.2)
Related AEs leading to death[a,b]	0
Serious AEs	44 (28.8)
Related serious AEs[a]	13 (8.5)
AEs leading to discontinuation of amivantamab	18 (11.8)
Related AEs leading to discontinuation of amivantamab[a]	8 (5.2)
AEs leading to dose reduction	22 (14.4)
Related AEs leading to dose reduction[a]	22 (14.4)
AEs leading to infusion modification[c]	91 (59.5)
Related AEs leading to infusion modification[a, c]	90 (58.8)
AEs leading to dose interruption[d]	55 (35.9)
Related AEs leading to dose interruption[a, d]	32 (20.9)
Grade ≥3 AEs	64 (41.8)
Related grade ≥3 AEs[a]	30 (19.6)
Grade 1	4 (2.6)

Grade 2	85 (55.6)
Grade 3	49 (32.0)
Grade 4	4 (2.6)
Grade 5	11 (7.2)

Based on Table 28, CS[4].
Note: RP2D: 1,050 mg if baseline weight <80 kg and 1,400 mg if baseline weight ≥80 kg
[a]An AE is categorised as related if assessed by the investigator as possibly, probably, or very likely related to study agent
[b]AEs leading to death are based on AE outcome of fatal
[c]AEs leading to infusion modification of study agent are based on infusion interrupted, infusion rate decreased, and infusion aborted due to adverse event on the infusion eCRF page
[d]Excludes infusion related reactions
AE = adverse event; CS = company submission; RP2D = recommended Phase 2 dose

3.2.6.2.1 TEAEs occurring with a frequency of 10% or higher

The TEAEs which occurred with a frequency of 10% or higher in the EGFR Exon20ins at RP2D safety population (N=153) on 30th March 2021 data cut-off are summarised in Table 3.21. The more commonly reported TEAEs included infusion related reactions (63.4%), paronychia (52.9%), rash (43.1%), and dermatitis acneiform (39.2%). Along with stomatitis (22.2%), dry skin (13.7%) and diarrhoea (13.7%) these are stated in the CS to be common on-target events associated with EGFR inhibition. The CS also details that hypoalbuminemia (39.2%), constipation (23.5%) and peripheral oedema (22.9%) which are common on-target events associated with MET inhibition were also reported in >10% of patients in this population.

Table 3.21: TEAEs with a frequency of at least 10% by system organ class and preferred term; post-platinum patients with EGFR Exon20ins at RP2D safety population (N=153, 30th March 2021 cut-off)

Event	n (%)
Patients with one or more AEs	153 (100.0)
Skin and subcutaneous tissue disorders	136 (88.9)
Dermatitis acneiform	60 (39.2)
Rash	66 (43.1)
Pruritus	24 (15.7)
Dry skin	21 (13.7)
Gastrointestinal disorders	114 (74.5)
Constipation	36 (23.5)
Nausea	38 (24.8)
Stomatitis	34 (22.2)
Vomiting	21 (13.7)
Diarrhoea	21 (13.7)
Injury, poisoning and procedural complications	102 (66.7)
Infusion related reaction	97 (63.4)
Infections and infestations	107 (69.9)
Paronychia	81 (52.9)

Event	n (%)
Respiratory, thoracic and mediastinal disorders	88 (57.5)
Dyspnoea	30 (19.6)
Cough	26 (17.0)
General disorders and administration site conditions	96 (62.7)
Oedema peripheral	35 (22.9)
Fatigue	30 (19.6)
Pyrexia	26 (17.0)
Metabolism and nutrition disorders	92 (60.1)
Hypoalbuminaemia	60 (39.2)
Decreased appetite	27 (17.6)
Musculoskeletal and connective tissue disorders	73 (47.7)
Myalgia	18 (11.8)
Back pain	25 (16.3)
Nervous system disorders	50 (32.7)
Dizziness	18 (11.8)
Headache	11 (7.2)
Investigations	63 (41.2)
Alanine aminotransferase increased	34 (22.2)
Aspartate aminotransferase increased	25 (16.3)
Blood alkaline phosphatase increased	16 (10.5)
Psychiatric disorders	29 (19.0)
Insomnia	16 (10.5)

Based on Table 29, CS [4]
AEs = adverse events; CS = company submission; TEAE = treatment emergent adverse event
RP2D: 1,050 mg if baseline weight <80 kg and 1,400 mg if baseline weight ≥80 kg. Patients are counted only once for any given event, regardless of the number of times they actually experienced the event

3.2.6.3 Grade ≥3 Treatment-emergent AEs

The CS provides data on TEAEs at grade ≥3 in the RP2D safety population (N=153) at the 30th March 2021 data cut-off (see Table 3.22 below) and highlights that these are the AEs considered in the cost effectiveness model informing this submission. There were [redacted] patients who experienced one or more grade ≥3 AEs with [redacted] ([redacted]) patients believed to be experiencing grade ≥3 TEAEs considered by the investigator to be related to amivantamab. The most common grade ≥3 AEs were pulmonary embolism and hypokalaemia, occurring in [redacted] and [redacted] patients, respectively. None of the AEs at grade 3 or higher occurred in ≥5% patients.

Table 3.22: Grade 3 or higher TEAE by preferred term: post-platinum patients with EGFR Exon20ins at RP2D safety population (N=153, 30th March cut-off

Event	n (%)
Subjects with one or more grade ≥3 AEs	[redacted]
Preferred term	
Pulmonary embolism	[redacted]

Event	n (%)
Hypokalaemia	[redacted]
Pneumonia	[redacted]
Dyspnoea	[redacted]
Hypoalbuminaemia	[redacted]
Paronychia	[redacted]
Diarrhoea	[redacted]
Infusion related reaction	[redacted]
Neutropenia	[redacted]
Hyponatraemia	[redacted]
Alanine aminotransferase increased	[redacted]
Hypophosphataemia	[redacted]
Hypotension	[redacted]
Gamma-glutamyl transferase increased	[redacted]
Rash	[redacted]
Respiratory failure	[redacted]
Anaemia	[redacted]
Respiratory tract infection	[redacted]
Sepsis	[redacted]
Acne	[redacted]
Cellulitis	[redacted]
Fatigue	[redacted]
Hypoxia	[redacted]
Pleural effusion	[redacted]
Pericardial effusion	[redacted]
Aspartate aminotransferase increased	[redacted]
Dermatitis acneiform	[redacted]
Headache	[redacted]
Hypertension	[redacted]
Oedema peripheral	[redacted]
Syncope	[redacted]
Abdominal pain	[redacted]
Atrial fibrillation	[redacted]
Blood alkaline phosphatase increased	[redacted]
Blood creatine phosphokinase increased	[redacted]
Decreased appetite	[redacted]
Lymphopenia	[redacted]
Mental status changes	[redacted]
Nausea	[redacted]
Pneumonia aspiration	[redacted]

Event	n (%)
Pneumonitis	[redacted]
Stomatitis	[redacted]
Vomiting	[redacted]
Aspiration	[redacted]
Hypocalcaemia	[redacted]
Infected dermal cyst	[redacted]
Insomnia	[redacted]
International normalised ratio increased	[redacted]
Muscular weakness	[redacted]
Pulmonary sepsis	[redacted]
Pulseless electrical activity	[redacted]
Rash papular	[redacted]
Renal vein thrombosis	[redacted]
Sudden death	[redacted]
Thrombocytopenia	[redacted]
Toxic epidermal necrolysis	[redacted]
Transitional cell carcinoma	[redacted]

Based on table 30, CS[4]

Note: Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event. The event experienced by the subject with the worst toxicity is used. RP2D: 1,050 mg if baseline weight <80 kg and 1,400 mg if baseline weight ≥80 kg.

AEs = adverse events; CS = company submission; RP2D = recommended Phase 2 dose; TEAE = treatment-emergent adverse event

3.2.6.4 Treatment related adverse events

The CS states that [redacted] (See Table 3.23 below) patients in the post-platinum patients with EGFR Exon20ins at RP2D safety population (N=153) had AEs reported by the investigator to be related to amivantamab. Skin and subcutaneous tissue disorders comprised the majority of AEs by System Organ Class, with 86.9% of patients affected. Infusion related reaction (IRR) was the most commonly reported with [redacted] of patients experiencing it. Paronychia was the second most reported AE with [redacted] of patients experiencing it. Rash and dermatitis acneiform were experienced by ([redacted]) and ([redacted]) of patients respectively. The CS clarifies that except for IRR, all treatment related AEs were comprised predominantly of on-target events associated with EGFR or MET inhibition and that on-target MET-associated events of hypoalbuminemia and peripheral oedema were reported as related to amivantamab in [redacted] and [redacted] of patients, respectively.

Table 3.23: Treatment-related AEs by system organ class and preferred term; Post-platinum patients with EGFR Exon20ins at RP2D safety population (N=153, 30th March 2021 cut-off)

Preferred term	n (%)
Patients with one or more related AEs	[redacted]
Skin and subcutaneous tissue disorders	[redacted]

Dermatitis acneiform	[redacted]
Rash	[redacted]
Pruritus	[redacted]
Dry skin	[redacted]
Injury, poisoning and procedural complications	[redacted]
Infusion related reaction	[redacted]
Gastrointestinal disorders	[redacted]
Stomatitis	[redacted]
Nausea	[redacted]
Infections and infestations	[redacted]
Paronychia	[redacted]
General disorders and administration site conditions	[redacted]
Fatigue	[redacted]
Oedema peripheral	[redacted]
Metabolism and nutrition disorders	[redacted]
Hypoalbuminaemia	[redacted]
Investigations	[redacted]
Alanine aminotransferase increased	[redacted]
Aspartate aminotransferase increased	[redacted]
Based on table 31, CS[4] AE = adverse event; CS = company submission; RP2D = recommended Phase 2 dose Note: RP2D: 1,050 mg if baseline weight <80 kg and 1,400 mg if baseline weight ≥80 kg. Patients are counted only once for any given event, regardless of the number of times they experienced the event.	

3.2.6.5 Serious TEAEs

Serious TEAEs reported by the investigator for RP2D safety population (N=153) is summarised in Table 3.24 below. There were [redacted] patients that had TEAEs reported by the investigator to be serious. The most common serious TEAE being interstitial lung disease, reported in [redacted] patients ([redacted]).

Table 3.24: Serious TEAEs by system organ class, preferred term; RP2D safety population (N=153)

System organ class/preferred term	Safety population N=153, 30th March 2021 data cut-off, n (%)
Subjects with any serious TEAEs	[redacted]
Skin and subcutaneous tissue disorders	[redacted]
Rash	[redacted]
Toxic epidermal necrolysis	[redacted]
Injury, poisoning and procedural complications	[redacted]
Infusion related reaction	[redacted]
Gastrointestinal disorders	[redacted]
Diarrhoea	[redacted]

System organ class/preferred term	Safety population N=153, 30th March 2021 data cut-off, n (%)
Abdominal pain	[redacted]
Respiratory, thoracic and mediastinal disorders	[redacted]
Interstitial lung disease	[redacted]

Based on Table 32, CS[4]
RP2D: 1,050 mg if baseline weight <80 kg and 1,400 mg if baseline weight ≥80 kg. Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event. The event experienced by the subject with the worst toxicity is used.
ADR = adverse drug reaction; CS = company submission; RP2D = recommended Phase 2 dose; TEAEs = treatment emergent adverse events

ERG comments:

- The ERG notes that 41.8% of patients had experienced a grade 3 or higher AE, which according to the grading criteria of the National Cancer Institute common terminology criteria for adverse events (NCI CTCAE) is defined as being '*Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living*' at a minimum. According to the CS, 19.6% of these AEs were related to the administration of amivantamab when defined as '*assessed by the investigator as possibly, probably, or very likely related to study agent*'. However, events defined as 'serious' by the company (according to the criteria described in Section 3.2.6.2, include the definition 'medically important') occurred in 28.8% of patients, with 8.5% of serious events being related to amivantamab. The ERG would suggest that a grade 3 or above event which is 's*evere or medically significant*' is also 'medically important' and therefore could be defined as 'serious'. The ERG considers that there appears to be a lack of clarity and information leading to uncertainty regarding how 19.6.% of patients are experiencing grade 3 or above events related to amivantamab, yet only 8.5% of patients have experienced what is described as a serious AE**.**
- Concerning the statement in Section B.3.3.3 of the CS[4], *"safety profiles were considered and compared in the context of treatment classes rather than individual treatments, validating this approach,"* the ERG in its clarification letter asked the company to provide AEs specific to amivantamab rather than the class of treatments to which amivantamab belonged. In response, the company stated that, *"The text in the question refers to the approach taken to characterise the safety profile of UK SoC. AE incidence rates for the treatment classes included in the comparator basket were considered and compared in the context of treatment classes rather than individual treatments."*[9] Table 3.25 below reports the incidence of grade ≥3 AEs occurring in ≥5% of patients in the CHRYSALIS trial was also provided.
- Although a wide range of AEs were reported (table 3.22), the CS confirms that none of these were reported in more than 5% of the population. This data suggests that the likelihood of experiencing a severe AE is considerable (41.8%) in this population, and that less than 50% of these will be attributed to amivantamab (19.6%). While the more common AEs in this category included pulmonary embolism (4.6%), and hypokalaemia (3.9%), no incidence of specific or common severe or life-threatening AE's (as defined as grade ≥3 AEs in more than 5% of population) has been explicitly identified to be of concern. The ERG notes that this is based on a small sample and cautions that this should be considered in any interpretation.
- Table 3.24 states that only 7.2% of patients experienced any serious TEAEs. It is also apparent that in Table 3.24 interstitial lung disease is listed as a serious TEAE that has affected 2.6% of the

population, however there is no mention of this as a grade ≥3 TEAE in Table 3.22. We are unsure how a serious TEAE can be identified but yet not also be included in the data on grade 3 or above TEAE's. Furthermore, it is stated in the CS (Section B.2.10) that '*Forty-four patients (28.8%) had serious TEAEs'* however this does not appear to readily tally with the data included in Table 3.24 where it is stated that '*Subjects with any serious treatment-emergent AEs*' amounts to 11 patients (7.2%). The ERG considers that there appears to be a lack of clarity and consistency here on data reporting and defining.

Table 3.25: Incidence of Grade ≥3 AEs occurring in ≥5% of patients

AE, %	AMI	UK SoC				
		IO agents	EGFR TKIs	Pt-based chemotherapy	Non-Pt-based chemotherapy	Weighted average
Anaemia	[redacted]	0.5	0.0	11.8	3.8	3.2
Diarrhoea[a]	[redacted]	15.4	69.9	11.0	24.4	28.4
Fatigue	[redacted]	1.6	1.3	0.7	3.5	2.1
Febrile neutropenia	[redacted]	0.0	0.0	0.0	9.4	3.4
Neutropenia	[redacted]	0.5	0.0	11.8	14.6	7.2
Neutrophil count decreased	[redacted]	0.0	0.0	0.0	11.1	4.0
Rash	[redacted]	0.0	5.9	0.0	0.0	1.1
Thrombo-cytopaenia	[redacted]	0.0	0.0	7.4	0.0	1.1

Based on Table 14 of clarification letter response[9]
Note: [a] Due to its clinical relevance, the incidence of diarrhoea was considered at any grade.
AE = adverse event; AMI = amivantamab; EGFR = epidermal growth factor receptor; IO = immuno-oncology; Pt = platinum; SoC = standard of care; TKI = tyrosine kinase inhibitor; UK = United Kingdom

3.2.6.6 Mortality

The CS emphasises that '*OS is a secondary efficacy endpoint in this study, and survival data continues to be collected on all patients even after discontinuation of amivantamab during the Follow-up Period. In all cases of patient death, regardless of timing, the cause of death was separately reported. For all deaths that occurred during the Treatment Period (and up through 30 days after last dose), specific information regarding the cause of death was to be reported as a Grade 5 TEAE. Thus, patient deaths that are due to progressive disease, if occurring on treatment or within 30 days of the last dose, are also separately reported as an AE having an outcome of death'.*

Data is presented in Table 3.26 below to illustrate a summary of deaths that occurred at any time during the study in the RP2D safety population. The CS emphasises that the median follow-up was [redacted] months (range: [redacted]) and that these deaths were not reported as related to amivantamab by the investigator. Deaths were observed in [redacted] at any time on the study. Progressive disease was the most common cause of death [redacted] expired on treatment or within 30 days of the last dose of amivantamab. Of these, eight ([redacted]) patients died due to a TEAE, and [redacted] patients died due to progressive disease. The CS provides a summary of these deaths by preferred term and system organ class (see Table 34, CS). Briefly, on review of these data it is apparent that respiratory failure and dyspnoea accounted for the more common AEs that led to death with two patients (1.3%), dying of each.

Table 3.26: Summary of deaths during study; Post-platinum patients with RP2D safety population (N=153, 30th March 2021 cut-off)

Preferred term	n (%)
Deaths during study	[redacted]
PD	[redacted]
AE	[redacted]
Other	[redacted]
Deaths during treatment	[redacted]
AE	[redacted]
PD	[redacted]
Other	[redacted]

Based on table 33, CS[4]
RP2D: 1,050 mg if baseline weight <80 kg and 1,400 mg if baseline weight ≥80 kg. Deaths during treatment are presented for patients who died within 30 days of last amivantamab dose.
AE = adverse event; CS = company submission; PD = progressive disease; RP2D = recommended Phase 2 dose

3.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

The CS states that, in the absence of a direct head-to-head trial, and given that the SLR did not identify other relevant trials in this setting, that the two sources for the indirect treatment comparison would be the CHRYSALIS trial and RWE. Two RWE sources were included in the analyses:

- A US cohort that included pooled data from Flatiron Health Spotlight, ConcertAI and COTA data sources. This is referred to as US RWE.
- Data from PHE using routine population-level data available through PHE (now NHS Digital) National Cancer Registration and Analysis Service (NCRAS). These data are referred to as PHE.

A full critique of the CHRYSALIS trial is included in Section 3.2.

ERG comments:

- It was unclear to the ERG whether no other studies might have been suitable for a comparison with amivantamab. The ERG sought further information as to the means and rationale for the identification and selection of these two specific databases and in the request for clarification asked the company to provide insight. The company responded stating that '*The US RWE and the PHE cohort studies were initiated by Janssen with the objective of providing RWE data for patients with EGFR Exon20ins mutations previously treated with platinum-based chemotherapy to inform the external control arm for the CHRYSALIS trial.'* [9]
- The company also stated '*…the SLRs did not identify any studies reporting on clinical outcomes for patients with EGFR Exon20ins mutations positive NSCLC previously treated with platinum-based chemotherapy. As a result, individual patient level data derived from the US RWE and PHE studies were used as the only sources for these data for the adjusted comparison analyses*.' While we do not necessarily consider the data derived from these sources as inappropriate, the ERG expects that there must be a full, justified rationale with clear systematic and scientific robustness for the use of an evidence source.

- The PHE database includes data from a UK based population, while the RWE derived from the US included datasets from three specific databases, namely the Flatiron, COTA, and ConcertAI databases. We sought further information on the suitability of these databases as generalisable to the UK population. In the request for clarification, we asked that the demographic characteristics of the patients in these databases be provided with comparisons to a UK population. The company in its response provided tabulated data for each of the three RWE US databases,[9] as well as emphasising that this data was pooled and compared to the UK based PHE data in Section B.2.9 of the CS. The company also clarified that, '*UK-based clinical experts emphasised the high degree of alignment in the baseline characteristics of patients included in both of these RWE data sources and the CHRYSALIS trial, with the proportion of patients with brain metastases being the only characteristic highlighted as differing notably between them'.*
- While the demographic and patient data may be broadly similar, in the absence of a systematic approach to identifying and selecting this evidence, the impact of selection bias must be considered. The ERG addressed this in its clarification letter to the company and requested further information on how this was mitigated. The company responded acknowledging the presence of selection bias and explaining that this is difficult to avoid due to the rarity of the disease and that RWE cohorts are limited to patients with EGFR Exon20ins mutations for whom data are available. The company clarified that to counteract the impact of such bias, the US RWE data were adjusted to the CHRYSALIS population in terms of key prognostic variables and baseline characteristics. This included [redacted]. The company also stated that according to their clinical experts, '*the characteristics and outcomes broadly aligned with their expectations for the patient population in the UK, and that none of the baseline characteristics showed systematic differences that would confer a substantial selection bias'*[9]
- The ERG understands and appreciates that evidence sources for rare diseases may be difficult to obtain and be limited in their generalisability, however, the systematic approach to identification and selection of evidence must be robust and auditable. In this case we do not consider that this has been properly described. We do not necessarily deny the suitability of these RWE data sources, this is a separate issue, but there must be a clearly described, justified process and criteria, for why source X is identified and used over source Y. In this case the ERG does not feel that this has adequately occurred. Furthermore, while expert clinical opinion is a valuable tool, statements such as '*the characteristics and outcomes broadly aligned with their expectations for the patient population in the UK',* are secondary to the evidence which informs their expectations.

3.4 Critique of the indirect comparison and/or multiple treatment comparison

Because CHRYSALIS is a single arm trial, the company conducted an adjusted treatment comparison to inform the relative efficacy estimates for amivantamab versus a SoC utilising comparator data from RWE sources listed above in Section 3.3.

To account for differences in patient populations between CHRYSALIS and the RWE data sources, the comparisons adjusted for key prognostic variables, which were identified a priori by an SLR and validated by clinical experts. The following covariates were considered: [redacted]

[redacted]

Different statistical approaches were explored to conduct the adjusted comparisons, 1) inverse probability weighting (IPW) method, which uses the propensity score (probability of receiving the treatment) to estimate the average treatment effect on the treated (ATT) (by re-weighting only the comparator data), and 2) a multivariable regression approach with direct adjustment for covariates. Both methods were applied to the US RWE to estimate PFS, TTNT, OS and ORR. Only covariate adjustment was used for the PHE data, the reason given that: "IPW estimates were unstable due to the small sample size". Also, only for TTNT and OS were estimated, with the reason for lack of PFS as "Due to limitations in the data recorded in the PHE datasets, it was not possible to collect PFS for the PHE cohort." No reason was provided for not estimating ORR using the PHE. The US RWE was used in the base case, the reason given that the sample size was larger.

Baseline characteristics of the CHRYSALIS and US RWE cohorts are given in Table 3.27, and those for the UK PHE cohort in Tables 3.26 and 3.27.

The company also provided the results of tests of overlap in Appendix M i.e., plot of propensity scores and standardised mean differences (SMDs).

Table 3.27: Baseline characteristics of treatment lines for patients in CHRYSALIS and the US RWE cohort

Characteristic, n (%)	CHRYSALIS EAS	US RWE cohort	IPW ATT weighted US RWE cohort
N	114	[redacted]	[redacted]
Prior lines of treatment			
1	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]
4+	[redacted]	[redacted]	[redacted]
Brain metastasis			
No	85 (74.6)	[redacted]	[redacted]
Yes	29 (25.4)	[redacted]	[redacted]
Age			
<60	48 (42.1)	[redacted]	[redacted]
60–70	38 (33.3)	[redacted]	[redacted]
≥70	28 (24.6)	[redacted]	[redacted]
ECOG PS			
0	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]
Number of metastatic locations			
1	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]

Characteristic, n (%)	CHRYSALIS EAS	US RWE cohort	IPW ATT weighted US RWE cohort
Missing	[redacted]	[redacted]	[redacted]
Haemoglobin			
Normal/high	[redacted]	[redacted]	[redacted]
Low	[redacted]	[redacted]	[redacted]
Sex			
Male	44 (38.6)	[redacted]	[redacted]
Female	70 (61.4)	[redacted]	[redacted]
Cancer stage at initial diagnosis			
I	[redacted]	[redacted]	[redacted]
II	[redacted]	[redacted]	[redacted]
IIIA	[redacted]	[redacted]	[redacted]
IIIB/IV	[redacted]	[redacted]	[redacted]

Based on Table 24 in CS.[4]
ATT = average treatment effect among the treated; CS = company submission; ECOG PS = Eastern Cooperative Oncology Group performance score; EAS = efficacy analysis set; IPW = inverse probability weighting; RWE = real world evidence; US = United States

Table 3.28: Baseline characteristics of treatment lines for patients in CHRYSALIS and the PHE data source

Characteristic, n (%)	CHRYSALIS EAS	PHE Cohort[a]
N	114	[redacted]
Prior lines of treatment		
1	[redacted]	[redacted]
2	[redacted]	[redacted]
3+	[redacted]	[redacted]
Brain metastasis		
No	85 (74.6)	[redacted]
Yes	29 (25.4)	[redacted]
Age		
≤55	[redacted]	[redacted]
55–≤60	[redacted]	[redacted]
> 60	[redacted]	[redacted]
ECOG PS		
0	33 (28.9)	[redacted]
1	80 (70.2)	[redacted]
Liver metastasis		
No	101 (88.6)	[redacted]
Yes	13 (11.4)	[redacted]
Sex		
Male	44 (38.6)	[redacted]

Characteristic, n (%)	CHRYSALIS EAS	PHE Cohort[a]
Female	70 (61.4)	[redacted]
BMI		
Underweight (<18.5)	11 (9.6)	[redacted]
Normal (18.5- <25)	65 (57.0)	[redacted]
Overweight (25- <30)	25 (21.9)	[redacted]
Obese (>30)	13 (11.4)	[redacted]

Based on Table 25, CS.[4]
Note: [a] Adjusted baseline characteristics are not available for the PHE cohort as only covariate adjustment was applied
BMI = body mass index; CS = company submission; ECOG PS = Eastern Cooperative Oncology Group performance score; EAS = efficacy analysis set; PHE = Public Health England

ERG comment:

- Because CHRYSALIS is non-comparative, an unanchored comparison is necessary. However, considerable potential for risk of bias is entailed in such an indirect comparison. Although methods for confounder adjustment appear robust, as evidenced by the adjusted baseline values in Table 3.27, these are limited by the covariates chosen, and it is highly likely that residual confounding will remain: as stated in TSD 17, the validity of the two methods of adjustment used by the company relies on the assumption of selection on observables.[32] Additionally, the UK data might have been preferred, but apparently this was not possible for PFS outcomes. However, the explanation given for not using the UK data was that the sample size for the US data set (n=206) is larger than the UK data set (n=16). This is a good reason why the data from the US might provide more precise estimates of effect, as well as more valid statistical adjustments, but does not mean the US data are more appropriate, *per se*, for modelling treatment responses for a UK population. The company explains that the US data were deemed relevant to the UK population on the basis of expert opinion, but the exact nature of this opinion was not described. No reason was provided in the cs for not estimating ORR using the PHE, but the FAC check stated that these data were not collected. The ERG agrees that, given the limitation in the UK data, the US RWE was probably more appropriate.
- The IPW method to estimate the ATT was also the most appropriate method, given a less stringent requirements for ignorability and overlap of covariates, essentially because only the comparator data need to be adjusted.[32] Also, there did seem to be sufficient adjustment given overlap in the distribution of propensity scores and SMDs, which were all below 0.25.[32] The ERG did also ask for a comparison with the IPW method to estimate the ATE, which showed very little difference in any outcome (PFS, OS or TTNT).[30] However, there remains doubt whether all appropriate data sources were found and so this constitutes a key issue.

Table 3.29: Comparison of HRs for overall population and subgroups by LOT. The HRs denote the relative effect between amivantamab and SoC (adjusted, based on US RWE).

HR (95% CI), ATT approach	OS	PFS (BICR)	TTNT
Base case (2L+)	[redacted]	[redacted]	[redacted]
2L subgroup	[redacted]	[redacted]	[redacted]
3L+ subgroup	[redacted]	[redacted]	[redacted]

Based on Table 5 in clarification response.[9]

HR (95% CI), ATT approach	OS	PFS (BICR)	TTNT
2L = second line; 3L+ = third line and beyond; ATT = average treatment effect among the treated; CI = confidence interval; HR = hazard ratio; BICR = blinded independent committee review; LOT = line of therapy; OS = overall survival; PFS = progression-free survival; TTNT = time to next treatment.			

The company also examined the effect of line of therapy using other methods, gaining qualitatively similar results. However, the company did not provide sub-group comparisons using only the comparators that would be standard of care for that particular PD-L1 sub-group as specifically requested in the ERG clarification question.

ERG comment:

- Adjustment of the US RWE resulted in a decrease in the treatment effect, albeit only slightly, due to better comparator outcomes. Using the PHE, the treatment effect on OS increased. Of course, it is impossible to know how much reduction in bias there was, but the choice of the US RWE does at least seem conservative relative to the PHE. In terms of the request for sub-grouping around PD-L1 status, the company's response was as follows: *"For the PD-L1 subgroup analyses, a test for PD-L1 status was performed for [redacted] patients in the CHRYSALIS population, and [redacted] tested positive. In the US cohort, [redacted] lines of therapy corresponded to patients who tested PD-L1 positive. Of these, only [redacted] lines of therapy consisted of nivolumab or pembrolizumab monotherapies. In the PHE cohort, [redacted] patient had a positive PD-L1 status and was not treated with nivolumab or pembrolizumab monotherapies. It is therefore not feasible to conduct a comparative analysis on this subgroup."*
- The ERG agrees that PD-L1 sub-group analyses would have been unfeasible for the reasons given.

3.5 Additional work on clinical effectiveness undertaken by the ERG

Not applicable.

3.6 Conclusions of the clinical effectiveness Section

The CS and response to clarification provided full details for the ERG to appraise the literature searches conducted to identify studies about clinical efficacy and safety outcomes in patients with advanced NSCLC with EGFR Exon 20 insertion mutations.[4, 9, 21] The searches were conducted in January 2021 and updated in September 2021. Searches were transparent and reproducible, and comprehensive search strategies were used. A good range of databases and grey literature resources were searched. Despite the use of a focused population facet of search terms, the literature searches were comprehensive, and it was unlikely that relevant studies were missed.

The CS presented the results of one study, the CHRYSALIS trial[4] a Phase 1b, single arm, first-in-human, open-label, multicentre, 2-part trial. The trial included 77 participants in Part 1 (to determine recommended dose, median [redacted] months) and 285 participants in Part 2 (to determine safety and pharmacokinetics, 9.9 months)

Detailed efficacy results are presented in Section 3.2.5 while detailed safety results are presented in Section 3.2.6. The results are summarised below for the cut-off date of 30th March 2021 (median follow up time [redacted] months):

- **ORR** rates were 43% (95% CI 33.7% to 52.6%) for BICR and 36.8% (95% CI 28.0% to 46.4%) for INV.
- **CBR** rates were 73.7% (95% CI 64.6% to 81.5%) for BICR and 75.4% (95% CI 66.5% to 83.0%)

- **DOR** (median) was 10.84 months for BICR (95% CI 6.90 to 14.98) and 12.45 months for INV (95% CI 6.54 to 16.13)
- **PFS** (median) was 6.74 months for BICR (95% CI 5.45 to 9.66) and 6.93 months for INV (95% CI 5.55 to 8.64)
- **OS** (median) was 22.77 months (95% CI 17.48 to 'not evaluable')
- **TTF** (median) was 8.08 months (95% CI 6.67 to 10.64)

HRQoL was also evaluated as an exploratory analysis. Four PROMs were meant to be included, but only two were reported - the ED-5D VAS and the NSCLC-SAQ results. In neither of these analyses was a significant change in QoL from baseline observed. It should be noted that the graphical data reported in the CS are both limited in size (n=26) and different from what was reported in the text (n=30). The small number of patients available for this outcome may explain the high levels of uncertainty observed.

Due to the single-arm nature of the CHRYSALIS trial, an adjusted treatment comparison was conducted to derive comparative efficacy for amivantamab versus SoC treatments – a basket of treatments comprising treatments currently used for this population. Using US SoC data, these additional analyses showed that amivantamab offers statistically significant benefits over SoC in terms of PFS [HR [redacted]] and OS [HR [redacted]]. Although methods for confounder adjustment appear robust, these analyses are inevitably limited by the covariates chosen. However, the biggest limitation is that only a subset of results based on different data sources and methods used have been reported. For example, results based on UK data should have been presented more fully, and this is believed to have increased the risk of reporting bias.

The ERG raised a number of concerns with the clinical effectiveness evidence, including issues with the choice of populations for efficacy and safety, comparators, short follow-up time, and the real-world data used to identify comparators (see Section 1).

4. COST EFFECTIVENESS

4.1 ERG comment on company's review of cost effectiveness evidence

One set of systematic literature searches was performed to identify cost effectiveness studies, health-state utility values, and cost and healthcare resource use studies (CS, Appendix G, Appendix H and Appendix I).[21]

4.1.1 Searches performed for cost effectiveness Section

The following paragraphs contain summaries and critiques of all searches related to cost effectiveness presented in the CS.[4, 21] The CADTH evidence-based checklist for PRESS was used to inform this critique.[22, 23] The CS was checked against the STA specification for company/sponsor submission of evidence.[24]

Appendix G, Appendix H and Appendix I of the CS reported the literature searches used to identify cost effectiveness studies, health-state utility values, and cost and healthcare resource use studies.[21] Searches were conducted in May 2020, then updated in February 2021, and updated again in November 2021.

A summary of the resources searched is provided in Table 4.1.

Table 4.1: Resources searched for the cost effectiveness literature review (as reported in the CS)

Resource	Host/Source	Date Ranges	Dates searched
Electronic databases			
MEDLINE, MEDLINE In-Process, MEDLINE Daily, Epub Ahead of Print	Ovid SP	Latest update: 1946 to November 01, 2021	04/05/20 04/02/21 02/11/21
Embase	Ovid SP	Latest update: Embase 1974 to November 1st, 2021	04/05/20 04/02/21 02/11/21
NHS EED	CRD website	NHS EED: Issue 2 of 4, April 2015	04/05/20
HTA Database	CRD website	Issue 4 of 4, October 2016	04/05/20
INAHTA HTA database	INAHTA website	Latest update: up to Nov 1 2021	04/02/21 02/11/21
Additional resources			
HERC Database of Mapping Studies	https://www.herc.ox.ac.uk/downloads/herc-database-of-mapping-studies	Latest update: up to November 1 2021	04/06/20 24/02/21 10/11/21
CEA Registry	http://healtheconomicsdev.tuftsmedicalcenter.org/cear2/search/search.aspx	Latest update: up to November 1 2021	04/06/20 24/02/21 10/11/21

Resource	Host/Source	Date Ranges	Dates searched
ScHARRHUD	http://www.scharrhud.org/	Latest update: up to November 1 2021	04/06/20 24/02/21 10/11/21
EQ-5D Publications Database	http://eq-5dpublications.euroqol.org/?noheader=true	Latest update: up to November 1 2021	04/06/20 24/02/21 10/11/21
Conference proceedings			
AACR annual meeting	Online abstract books	2018-2021	Not reported
ASCO annual meeting	https://meetinglibrary.asco.org/	2018-2021	Not reported
ESMO congress	Online abstract books	2018-2021	Not reported
ESMO ELCC	Online abstract books	2018-2021	Not reported
ISPOR annual international and European meetings	https://www.ispor.org/heor-resources/presentations-database/search	2018-2021	Not reported
HTA organisations			
AEMPS	https://www.aemps.gob.es/home.htm	Latest update: up to Nov 2021	08/06/20 01/03/21 11/11/21
AIFA	http://www.agenziafarmaco.gov.it	Latest update: up to Nov 2021	08/06/20 01/03/21 11/11/21
AWMSG	http://www.awmsg.org/	Latest update: up to Nov 2021	05/06/20 18/03/21 12/11/21
BAG	https://www.bag.admin.ch/bag/de/home.html	Latest update: up to Nov 2021	08/06/20 01/03/21 11/11/21
Danish Medicine Council	https://medicinraadet.dk/igangvaerende-vurderinger	Latest update: up to Nov 2021	08/06/20 01/03/21 12/11/21
FinCCHTA	https://www.ppshp.fi/Tutkimus-ja-opetus/FinCCHTA/Sivut/default.aspx	Latest update: up to Nov 2021	08/06/20 01/03/21 11/11/21
G-BA	https://www.g-ba.de/	Latest update: up to Nov 2021	08/06/20 01/03/21 12/11/21
HAS	https://www.has-sante.fr/portail/	Latest update: up to Nov 2021	08/06/20 01/03/21 11/11/21
MSCBS	http://www.mscbs.gob.es/	Latest update:	08/06/20

Resource	Host/Source	Date Ranges	Dates searched
	home.htm	up to Nov 2021	01/03/21 11/11/21
NCPE	http://www.ncpe.ie/	Latest update: up to Nov 2021	08/06/20 01/03/21 11/11/21
NICE	https://www.nice.org.uk/	Latest update: up to Nov 2021	08/06/20 01/03/21 12/11/21
NIPH	https://www.fhi.no/en/	Latest update: up to Nov 2021	08/06/20 01/03/21 12/11/21
SMC	https://www.scottishmedicines.org.uk/	Latest update: up to Nov 2021	08/06/20 01/03/21 12/11/21
SBU	https://www.sbu.se/en/	Latest update: up to Nov 2021	08/06/20 01/03/21 12/11/21
Zorginstituut Nederland	https://www.zorginstituut nederland.nl/	Latest update: up to Nov 2021	08/06/20 01/03/21 12/11/21
Additional resources: CEA = Cost-Effectiveness Analysis Registry; HERC = Health Economics Research Centre; ScHARRHUD = School of Health and Related Research Health Utilities Database **Conference proceedings**: AACR = American Association for Cancer Research; ASCO = American Society of Clinical Oncology; ESMO = European Society for Medical Oncology; ELCC = European Lung Cancer Annual Congress; HTA = Health Technology Assessment; ISPOR = International Society for Pharmacoeconomics and Outcomes Research **HTA organisations**: AEMPS = Agencia Española de Medicamentos y Productos Sanitarios; AIFA = Agenzia Italiana del Farmaco; AWMSG = All Wales Medicines Strategy Group; BAG = Bundesamt für Gesundheit; FinCCHTA = Finnish Coordinating Center for Health Technology Assessment; G-BA = Gemeinsamer Bundesausschuss; HAS = Haute Autorité de Santé; MSCBS = Ministerio de Sanidad, Consumo y Bienestar Social; NCPE = National Centre for Pharmacoeconomics; NICE = National Institute for Health and Care Excellence; NIPH = Norwegian Institute of Public Health; SBU = Swedish Agency for Health Technology Assessment and Assessment of Social Services; SMC = Scottish Medicines Consortium		

ERG comment:

- The CS provided full details of the literature searches for the ERG to appraise.[4, 21]
- A comprehensive range of databases, supplementary resources, conference proceedings, and HTA organisation websites were searched.
- Full details of the database searches, including the database name, host platform, date range and date searched, were provided.
- Full details of the supplementary economic specific resources searched were provided, including url links, search terms used, date searched, and results.
- Full details of the conference proceeding searches were provided. The search terms used, url links, date range, and results, were reported.
- Full details of the comprehensive list of HTA organisation websites searched were provided, including the url links, search terms used, date searched, and results.

- The database search strategies were well structured, transparent and reproducible. They included truncation, proximity operators, synonyms, and subject headings (MeSH in MEDLINE and the CRD databases, and EMTREE in Embase). There were no language or date limits for the economic evaluation and health-state utility values elements of the searches. A 5-year date limit was included for the cost and resource use element of the searches in MEDLINE and Embase.
- It would have been preferable for the database search strategies to be presented exactly as run, rather than copied into a tabular format, as item eight of the PRISMA-S checklist recommends.[25] The Cochrane Handbook also recommends that *"...bibliographic database search strategies should be copied and pasted into an appendix exactly as run and in full, together with the search set numbers and the total number of records retrieved by each search strategy. The search strategies should not be re-typed, because this can introduce errors"*.[26]
- The population facet used for the cost effectiveness searches was much broader than that used for the clinical effectiveness searches: NSCLC plus advanced/metastatic. To further ensure sensitivity, the search strategies did not include a facet for interventions/comparators.
- The search strategies did not include the MeSH or EMTREE terms for NSCLC: *Carcinoma, Non-Small-Cell Lung/* or *exp non small cell lung cancer/*.
- The final line from the NHS EED/HTA database search strategy was missing. This was likely to be a reporting error rather than a searching error.
- Study design search filters for economic evaluations, utilities and HRQoL, and cost and resource use were included. The Scottish Intercollegiate Guidelines Network (SIGN) filter for economic studies was used, with additional terms derived from other sources.[33] It would have been helpful if the other sources of additional terms had been cited.[25]
- The update search results were de-duplicated against the original results, as limiting by publication date risks missing relevant studies.[34, 35]

4.1.2 Inclusion/exclusion criteria

In- and exclusion criteria for the review on cost effectiveness studies, utilities and costs and resource use are presented in Table 4.2.

Table 4.2: Eligibility criteria for the systematic literature reviews

Category	Inclusion criteria	Exclusion criteria
Population	Patients with metastatic or surgically unresectable NSCLC. Patients with stage IIIB, IIIC or IV disease. Studies with patients only specified as "stage 3" eligible only if stage 4 patients were also included within the study population .	Patients without metastatic or unresectable NSCLC or studies where outcomes were not presented separately for the patients of interest. Patients with locally advanced disease. Patients with stage 3 disease, if sub-stage b or c not specified.
Intervention	IOs as monotherapy or in combination with chemotherapy. Chemotherapy (platinum or non-platinum-based regimens). Nintedanib in combination with chemotherapy. TKIs[a]	Any other intervention.
Comparators	Any comparator (or none).	–

Category	Inclusion criteria	Exclusion criteria
Outcomes	Cost effectiveness outcomes, including but not limited to: ICERs Cost per clinical outcome Total QALYs Total LYGs Total costs Incremental costs and QALYs	Studies not presenting relevant outcomes for the population of interest.
Study design	Any of the following analysis types: Cost-utility Cost effectiveness Cost-consequence Cost-benefit Cost-minimisation	Any other types of study design.
Publication type	Original research studies (including economic evaluations, observational, interventional and real-world evidence studies). HTAs Congress abstracts published in or after 2018	Any other publication type, including studies not reporting any original research. Congress abstracts published before 2018.
	SLRs were included in the SLR at title/abstract for bibliography searching, these were then subsequently excluded for being an irrelevant study design at full-text review.	
Other considerations	Human subjects English language abstract/full text OECD countries	–

Based on Table 24 of Appendix G of CS.[4]

Note: [a] *Initially, due to the large volume of evidence in the field of NSCLC, the results were limited to publications relevant to OECD countries. However, due to the emerging real-world evidence that has identified TKIs as a constituent of the UK standard of care treatments deemed the relevant comparator for amivantamab, the scope was updated as part of the second SLR update to include economic evaluations reporting on TKIs. Due to the large number of additional economic evaluations included based on this expanded scope, evaluations conducted from a UK perspective were prioritised for extraction. For consistency, these prioritisation criteria were applied across all interventions in the economic evaluations stream. Economic evaluations from a non-UK perspective were still included but are presented as a list.*

CS = company submission; EGFR = epidermal growth factor receptor; HTA = health technology assessment; ICER = incremental cost-effectiveness ratio; IO = immune-oncology; LYG = life years gained; NSCLC = non-small-cell lung cancer; OECD = Organisation for Economic Co-operation and Development; QALY = quality-adjusted life years; SLRs = systematic literature reviews; TKI = tyrosine kinase inhibitor; UK = United Kingdom

ERG comment: The ERG agrees that the eligibility criteria are broadly suitable to fulfil the company's objective to identify cost effectiveness studies. However, the exclusion of non-English studies could have led to some relevant studies being missed.

In addition, there appeared to be some issues with the review methodology which potentially impinge on the ability of the review to ensure that the eligibility criteria were adhered to, including:

- The data extraction was not completed by two independent reviewers, which increases the risk of mistakes made at this stage. In the FAC, the company clarified two independent reviewers were used.

- It is unclear whether the quality assessment was conducted by independent reviewers, which makes the quality assessments less robust. In the FAC, it was clarified that quality assessments were completed by one reviewer and verified by a second independent reviewer.

4.1.3 Conclusions of the cost effectiveness review

The CS provides an overview of the included cost effectiveness, utility and resource use and costs studies, but no specific conclusion was formulated.

ERG comment:

- The CS and response to clarification provided full details for the ERG to appraise the literature searches conducted to identify economic, health-state utility values, and cost and healthcare resource use studies.[4, 9, 21] Searches were conducted in May 2020, then updated in February 2021, and updated again in November 2021. The searches were transparent and reproducible, and comprehensive search strategies were used. A good range of databases and grey literature resources were searched. Search strategies included validated study design search filters. Overall, the ERG has no concerns about the literature searches conducted.
- The eligibility criteria were broadly suitable for the SLR performed. However, the ERG raised several concerns, including about the exclusion of non-English studies, the comparators, and the review methodology (see Section 4.1.2).

4.2 Summary and critique of company's submitted economic evaluation by the ERG

4.2.1 NICE reference case checklist

Table 4.3: NICE reference case checklist

Element of HTA	Reference case	ERG comment on CS
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	In line with reference case
Perspective on costs	NHS and PSS	In line with reference case
Type of economic evaluation	Cost utility analysis with fully incremental analysis	Partly in line with reference case (i.e., no fully incremental analysis was performed)
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	In line with reference case
Synthesis of evidence on health effects	Based on systematic review	In line with reference case
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of HRQoL in adults.	In line with reference case
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	Partly in line with reference case (QoL data from the CHRYSALIS trial was only used in a scenario analysis).

Element of HTA	Reference case	ERG comment on CS
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	In line with reference case
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	In line with 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	In line with reference case
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	In line with reference case

CS = company submission; ERG = Evidence Review Group; HTA = health technology assessment; NHS = National Health Service; PSS = Personal Social Services; QALY = quality-adjusted life year; UK = United Kingdom

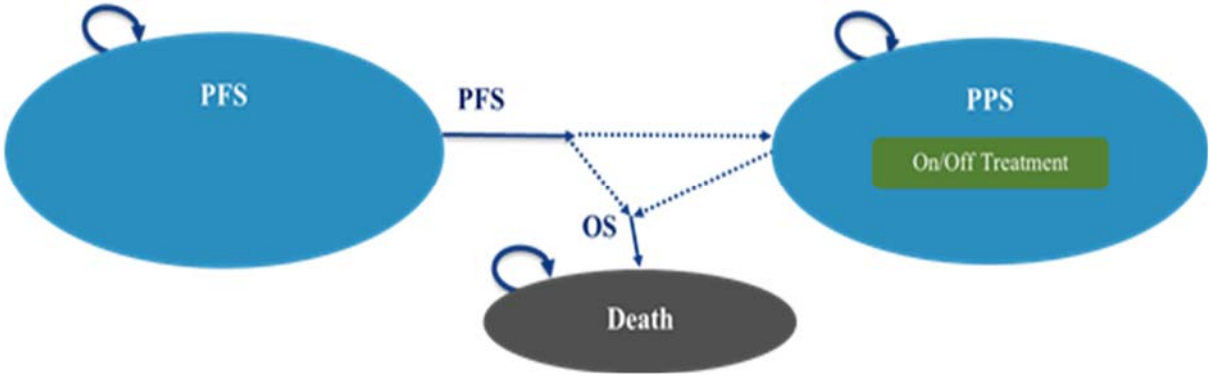
4.2.2 Model structure

A partitioned survival model (PSM) was developed including three health states: a PFS state, a PPS state, and death (Figure 4.1). The company stated that a partitioned survival analysis approach was chosen because it permits the use of outcome data from the adjusted treatment comparison presented in Section B.2.9 of the CS and permits the clinical benefits of amivantamab to be captured by reflecting the increased proportion of patients expected to be alive and/or progression-free over time. In addition, it was deemed in line with previous cost effectiveness models in metastatic NSCLC with EGFR. The model was developed in Microsoft Excel.

The allocation of patients into health states was directly based on treatment-specific PFS and OS functions. The model considers up to two distinct lines of treatment: current-line treatment while in the PFS state, and a subsequent line while in the PPS state. Time on treatment was assumed to be equal to progression. Upon disease progression patients could receive a basket of subsequent treatments. The proportion of patients receiving these treatments and the composition of the subsequent treatment basket was based on US RWE pooled data. Only costs of subsequent treatments were considered in the model, as it was assumed that efficacy was implicitly captured in OS extrapolations.

A lifetime horizon (i.e., 15 years) with a cycle length of 4 weeks (including half-cycle correction) was applied to ensure all costs and QALYs were captured. This was considered appropriate given that the mean starting age of the patients (61.75 years) and their poor prognosis.

Figure 4.1: Model structure



Source: Figure 23 of the CS

CS = company submission; PFS = progression-free survival

ERG comment: The main concern of the ERG relates to the use of a PSM without exploring a state transition model (STM) alongside it. The NICE Decision Support Unit (DSU) TSD 19 recommends the use of STMs alongside PSMs to verify the plausibility of PSM extrapolations and to explore key clinical uncertainties in the extrapolation period. In response to clarification question B2, the company stated that although over- or underestimation of long-term outcomes is a potential limitation of a PSM, the CHRYSALIS trial data were relatively mature and the risk of long-term over- or under-estimation of outcomes with a PSM was therefore likely limited. In addition, the company validated their approach based on literature comparing PSM and STM approaches and other NSCLC NICE submissions. Although the ERG ideally would have liked to see a STM to verify the PSM results, the ERG agrees the company's arguments are reasonable.

4.2.3 Population

The population considered in the CS (CS, Table 1) was adult patients with locally advanced or metastatic NSCLC with activating EGFR Exon20ins, whose disease has progressed on or after platinum-based chemotherapy, which is different from the population defined in the final NICE scope and may not be generalisable to the England and Wales NHS population.

The modelled baseline patient characteristics were presented in Table 43 of the CS. These have been taken from the patients in the CHRYSALIS trial, as clinical experts indicated that they were largely generalisable to the patient population in the UK.

ERG comment: The main concern of the ERG relates to the population considered by the company being slightly narrower than the population defined in final NICE scope. The narrower population may not be generalisable to the England and Wales NHS population and may for example have led to an underestimation of AEs. More details regarding this issue are provided in Sections 2.1 and 3.2.

4.2.4 Interventions and comparators

The intervention considered in the CS was amivantamab monotherapy. Amivantamab was administered via IV infusion at 1,050 mg for patients with body weight <80 kg and 1,400 mg for patients with body weight ≥80 kg once weekly for the first 4 weeks and then once every 2 weeks starting at week 5, consistent with the regimen used in the CHRYSALIS trial and the SmPC for amivantamab. Although the protocol of the CHRYSALIS trial allowed patients to continue to receive treatment following disease progression, UK clinical experts considered this does not reflect clinical practice and treatment discontinuation was therefore assumed upon disease progression.

The NICE scope listed the following comparators: established clinical management without amivantamab, including but not limited to atezolizumab, nivolumab (subject to an ongoing NICE appraisal), pembrolizumab (for disease with PD-L1 >1%) and chemotherapy such as docetaxel alone or with nintedanib, pemetrexed and carboplatin. As the CHRYSALIS trial is a single arm study, data informing comparator efficacy in the economic model were derived from pooled US RWE data. According to clinical experts, there is no established standard treatment pathway for patients with EGFR Exon20ins mutated NSCLC in the UK and amivantamab was therefore compared to a basket of treatments termed UK SoC within the model. The treatment classes included in this basket were IO agents ([redacted]), EGFR TKIs ([redacted]), platinum-based chemotherapy regimens ([redacted]), non-platinum-based chemotherapy regimens ([redacted]) and other ([redacted]), as reported in Table 5 of the CS (transposition of the values for IO agents and EGFR TKIs corrected by the ERG). After redistribution of the 9% in the 'other' category, the four treatment classes included in this basket were IO agents ([redacted]), EGFR TKIs ([redacted]), platinum-based chemotherapy regimens ([redacted]) and non-platinum-based chemotherapy regimens ([redacted]), as reported in Table 38, CS. For costing purposes, the individual treatments considered in each of these four treatment classes were as follows:

- IO agents: atezolizumab (45%), pembrolizumab (45%) and nivolumab (10%)
- EGFR TKIs: afatinib (100%)
- Platinum-based chemotherapy: carboplatin plus gemcitabine (33.3%), carboplatin plus pemetrexed (33.3%) and carboplatin plus vinorelbine (33.3%)
- Non-platinum-based chemotherapy: docetaxel plus nintedanib (75%) and docetaxel monotherapy (25%)

Scenario analyses were performed to assess the impact of varying the treatments and treatment proportions implemented in the model.

The composition of the basket for subsequent treatments received following amivantamab or UK SoC was sourced from the subsequent treatment distribution of patients receiving third-line or later therapy in the pooled US RWE database and are presented in Tables 39 and 40 of the CS. In line with this study, [redacted] of patients are modelled to receive subsequent treatments (calculated from the proportion of second line patients receiving a third-line treatment upon progression), with the remaining [redacted] of patients receiving no active treatment and assumed to receive best supportive care (BSC). A scenario analysis was explored in which the subsequent treatment composition for patients following amivantamab was sourced from the subsequent treatment distribution of patients receiving third-line or later therapy in the CHRYSALIS trial.

ERG comment: The main concern of the ERG relates to the effectiveness of the comparator basket being representative of UK clinical practice.

Due to considerable heterogeneity in treatments due to lack of specifically recommended treatments in the UK, data informing comparator efficacy were derived from a basket of treatments from a US RWE database study. The comparator effectiveness and costs are therefore based on the average clinical effectiveness and weighted average costs across all the treatments included in the comparator basket. As reported in Table 38 of the CS, the company assumed [redacted] of the comparator basket to exist of EGFR TKIs. It is, however, unclear to the ERG whether this is consistent with UK clinical practice, especially given that, as reported on page 23 of the CS, Exon20ins mutations have been associated with resistance to EGFR TKIs. In addition, the results of the indirect treatment comparison excluding TKIs in response to clarification question A6c show that the HRs are slightly higher than the base case HRs, indicating that the effectiveness of EGFR TKIs for Exon20ins mutations may indeed be questionable. Therefore,

the inclusion of the substantial proportion of EGFR TKI in the US RWD is considered as a source of uncertainty by the ERG, potentially underestimating outcomes for the comparator basket. This means that ICERs might be under-estimated. The ERG would like to see an analysis where EGFR TKI therapies are excluded from the US RWD informing the comparator basket. In addition, although the ERG acknowledges the limitation of small sample sizes of patients receiving individual treatments in the RWE sources, a fully incremental analysis of all relevant comparators in the comparator basket would be informative (as was requested in the clarification letter, but not provided) to address the uncertainty of assuming average effectiveness and costs of a basket of treatments.

4.2.5 Perspective, time horizon and discounting

The analysis is performed from the NHS and PSS perspective. Discount rates of 3.5% are applied to both costs and benefits. The model cycle length is 4 weeks with a lifetime time horizon (15 years).

ERG comment: The approach is in concordance with the NICE reference case.

4.2.6 Treatment effectiveness and extrapolation

The main source of evidence on treatment effectiveness used for amivantamab and SoC are the CHRYSALIS trial and US RWE data respectively. The baseline characteristics of the modelled population were based on the CHRYSALIS trial. To account for differences in the treatment populations of CHRYSALIS and the US RWE used to inform comparator efficacy, the treatment comparisons were adjusted for differences in key prognostic variables at baseline (identified a priori by an SLR and validated by clinical experts). For the US RWE an ATT approach (IPW) was used while for the scenario analysis using the PHE data a covariate adjustment approach was used.

The main outcomes regarding treatment effectiveness were OS and PFS. The company stated that the criteria that were used to decide on the best parametric fit were 1) visual fit to the observed KM curve, 2) statistical fit based on AIC and BIC statistics, and 3) face validity based on expert opinion.

4.2.6.1 Company's base case

The company selected the Weibull model in its base case for the extrapolation of OS in the amivantamab arm. For amivantamab PFS, the company selected the generalised gamma model. Progression in the base case was assessed with a BICR. For more details regarding the company's survival curve selection see Table 4.4 (criteria based on NICE DSU TSD 14).

For both OS and PFS for patients receiving SoC the KM curve was directly used rather than selecting a parametric model. The company argued that extrapolation of OS and PFS for SoC was not necessary, as the KM data was based on a 'robust' population size (n=206) and all patients had reached the end point for both outcomes.

Table 4.4: Criteria for choice of survival curves

Criteria for choice of survival curve	OS	PFS	TTD
General considerations	SoC Extrapolation of the US RWE data informing efficacy for UK SoC was not deemed necessary	SoC Extrapolation of the US RWE data informing efficacy for UK SoC was not deemed necessary	Amivantamab The company assumed that time on treatment was equal to PFS. SoC

Criteria for choice of survival curve	OS	PFS	TTD
	due to the maturity of the available data.	due to the maturity of the available data.	It was assumed that SoC time on treatment is equal to SoC PFS.
Reporting of log-cumulative hazard plots, quantile-quantile plots or suitable residual plots to allow initial selection of appropriate models	Log-cumulative hazard plots, Schoenfeld residuals were provided. Proportional hazards assumption does not hold.*	Log-cumulative hazard plots, Schoenfeld residuals were provided Proportional hazards assumption does not hold.*	*Not reported by the company*
Fit to the observed data based on AIC and BIC	Amivantamab Lowest AIC: Weibull Lowest BIC: Exponential SoC (US RWE - scenario) Lowest AIC & BIC: Weibull	Amivantamab Lowest AIC: Log-logistic Lowest BIC: Log-logistic SoC (US RWE - scenario) Lowest AIC & BIC: Log-logistic	*Not reported by the company*
Fit to the observed data based on visual comparison with the Kaplan-Meier curves	Plots including KM curve and all parametric curves were provided for amivantamab and SoC. No further comment was made based on their visual fit.	Plots including KM curve and all parametric curves were provided for amivantamab and SoC. No further comment was made based on their visual fit.	*Not reported by the company*
Clinical plausibility of the extrapolation based on comparison with data	*Not reported by the company*	*Not reported by the company*	*Not reported by the company*
Clinical plausibility of the extrapolation based on clinical expert opinion	5-year OS expectation of 7-8%.	5-year PFS expectation less than 1%. 2-year PFS expectation about 10%.	Assumption that PFS equals TT
Base case approach	Based on expert opinion and best fit with AIC the Weibull curve was chosen. KM curves were considered directly for SoC in the CS base case.	Generalised gamma curve was selected based on expectation of 2-year and 5-year PFS. KM curves were considered directly	TTD was set equal to PFS based on expert opinion

Criteria for choice of survival curve	OS	PFS	TTD
		for SoC in the CS base case.	
Based on CS Section 3.3 CS = company submission; KM = Kaplan-Meier; OS = overall survival; PFS = progression=free survival; RWE = real world evidence; SoC = standard of care; TTD = time to treatment discontinuation; UK = United Kingdom; US = United States; *provided in response to clarification letter			

4.2.6.2 Scenario analyses

To explore the impact of alternative assumptions the company conducted several scenario analyses:

- For the amivantamab treatment population the impact of using IA progression instead of BICR-assessed progression was explored. A log-normal model was selected for the scenario based on AIC and BIC fit.
- For SoC OS, based on the US RWE, the impact of using a Weibull model (based on statistical fit) and a generalised gamma model (based on expert expectations of survival) were explored. Further the UK PHE data was explored as an alternative source of data. Here, the KM curve was directly implemented in the model.
- For SoC PFS, based on the US RWE, the impact of using a log-logistic model (based on statistical fit) was explored. Again, using the impact of the UK PHE data was explored by implementing the KM curve directly into the model. In this case TTNT was used as a proxy as progression data was unavailable.

4.2.6.3 Time to treatment discontinuation

To calculate treatment costs (i.e., drug acquisition and drug administration costs), TTD was implemented in the model. While the median treatment duration ([redacted] months) in the CHRYSALIS trial was longer than the median PFS ([redacted] months), clinical experts stated that time to discontinuation would usually be the same as time to progression. Therefore, the company base case assumed that time-on-treatment was equal to PFS.

ERG comment: The main concerns of the ERG relate to: a) using KM data for SoC survival analyses of PFS and OS; b) assumption that treatment discontinuation is equal to PFS; c) lack of transparency and choice of curve for the modelled treatment discontinuation; d) adherence of the company to the NICE DSU TSD 14[36]; e) a lack of exploration around uncertainty of the parametric survival curves; f) no inclusion of treatment waning in the model; g) alternative methods to perform indirect treatment comparison; and h) external validation of parametric curves.

a) For survival analyses of OS and PFS in the SoC arm, the company argued that due to the maturity of the data and all patients reaching the specified end point or being censored within the timeframe of data collection, KM data could be directly implemented rather than fitting a parametric survival model. However, this is not necessarily in line with NICE DSU TSD 14, which states that "*parametric models are likely to represent the preferred method for incorporating survival data into health economic models in the majority of cases*". For example, the 'stepped' nature of KM curves, resulting from follow-up only occurring at pre-specified time intervals, means that events are only observed to have occurred at specific intervals which could create bias in survival analysis results. Moreover, the implementation of KM data may introduce overfitting of the modelled survival outcomes. Implementing KM curves biases the SoC treatment effectiveness as patients do not transition smoothly. Instead at each measurement point all patients who have died or progressed

will leave the health state at once, which is not valid. Hence, the ERG requested a scenario analysis in which the most appropriate parametric models were selected for OS and PFS in the SoC arm including a PSA with 5,000 iterations. The company complied with this request, implementing a Weibull model for OS and a log-logistic model for PFS. The ICER of the resulting probabilistic analysis including the PAS price was £40,353. The ERG therefore chose to implement these parametric models into its base case.

b) For the estimation of TTD, the company assumed that treatment would be discontinued when a patient progresses, setting TTD equal to PFS. The CHRYSALIS trial, however, allowed patients to remain on treatment after disease progression and median TTD ([redacted]) was substantially longer than median PFS ([redacted]). The ERG questions the company's approach. The assumption reduces the estimated treatment costs of amivantamab without reducing the estimated effectiveness after progression of amivantamab. The ICER is therefore likely underestimated. The ERG therefore requested a scenario analysis in which TTD would be informed by the CHRYSALIS trial protocol for amivantamab, which increased the ICER to £50,549 per QALY gained. An additional scenario analysis was conducted in which TTNT was used as a proxy for TTD in the SoC arm, decreasing the ICER to £33,708 per QALY gained. The company argued that the second scenario analysis was more valid, as in this case the assumptions made for each treatment arm would be in line with each other. The ERG disagrees with this judgement. TTNT likely overestimates TTD, as the time to the start of a next treatment is per definition longer than the time to discontinue treatment. Additionally, no compelling evidence was provided by the company to demonstrate the TTNT as a good approximation to TTD. While acknowledging that this approach may be conservative, the ERG therefore chose to implement parametric survival curves for TTD in the amivantamab arm and take PFS as a proxy for TTD in the SoC arm.

c) Upon request, the company conducted two scenario analyses using parametric survival curves to reflect treatment discontinuation (as described in critique b)). The choice of survival curves for these analyses was not transparent (i.e., lacked details regarding the NICE DSU TSD 14 criteria). For amivantamab a Gompertz model was implemented, while the KM-curve was used for SoC. The limited indicators that are available to the ERG showed that the Gompertz model had the fourth best statistical fit (exponential, Weibull and log-logistic models all had a better fit) and did not clearly have the best visual fit. The Gompertz model distinguished itself from other models by being the most pessimistic curve (i.e., resulting in the lowest number of patients on-treatment over time). For SoC, the generalised gamma model had the best statistical fit. The ERG therefore implemented an exponential model for amivantamab, which had the best statistical fit and was in between the most optimistic and pessimistic curves, hence not presenting an extreme of early discontinuation or late discontinuation. For a scenario analysis exploring TTNT as a proxy for TTD in the SoC arm, the generalised gamma model was chosen.

d) In the initial CS, there was substantial uncertainty surrounding the adherence of the company to the NICE DSU TSD 14[36]. Upon request for clarification, log-cumulative hazard plots and Schoenfeld residual plots were submitted by the company. However, for other additional analyses conducted for other clarification requests, NICE DSU TSD 14 details were again not submitted. The ERG could therefore only judge the new analyses on statistical measures of fit and visual fit, rather than all relevant NICE DSU TSD 14 criteria.

e) For the modelling of PFS in amivantamab even though AIC and BIC indicated that a log-logistic curve would be the best fit, a generalised gamma curve was implemented based on the fit to expected progression-free rates based on expert opinion. The resulting uncertainty was not explored. Upon clarification, the company elaborated that while log-logistic curves had a better statistical fit and the log-logistic curves would be consistent with a decreasing hazard, log-logistic curves had a long tail, which did not seem like a valid assumption to the analysts. The ERG has

looked into the impact of assuming the log-logistic curve for PFS in the amivantamab arm and this did not seem to have a large impact on the ICER.

f) The ERG considered that the assumption of a lifelong treatment effect may not be warranted and requested the company to explore treatment waning in the model. Upon request to do so, the company refused with the arguments that 1) treatment waning would be implicitly captured in the selected curves, 2) due to the poor prognosis patients receive treatment for a relatively short amount of time, and 3) amivantamab is a treat to progression treatment. It is unclear to the ERG whether this assumption holds true in clinical practice as there is limited evidence provided on treatment waning by the company. The follow-up of the CHRYSALIS study is notably shorter than the time horizon in the economic model. Hence, it is unclear to the ERG whether the benefits of amivantamab could be assumed to last over the full-time horizon. This has also been acknowledged in other STAs. For example, in TA520, the appraisal committee concluded that a lifetime treatment effect was implausible. The ERG would like to see an updated economic model in which the company explores treatment waning scenarios. Additional evidence to support the company's statement that treatment waning would be implicitly captured in the selected curves would also be informative to address this issue.

g) The comparative effectiveness of amivantamab versus SoC was explored via covariate adjustment and IPW. However, alternative approaches to address confounding in the indirect treatment comparison are possible. Hence, the ERG requested the company to implement matching instead of IPW to examine the potential uncertainty introduced by different methodological choices. In response to clarification question B4, the company performed a PSM analysis in which SoC patients from the US RWE and those from CHRYSALIS have been matched to estimate the relative efficacy of amivantamab versus UK SoC. This resulted in an ICER of £45,092 per QALY gained. The ERG acknowledges the concerns of the company that the matching results in a smaller sample size and that the IPW results therefore might be slightly more robust. However, the ERG implemented the results of the PSM analysis as second ERG base case.

h) In response to clarification question B5, the company provided an overview of the validity of the extrapolated OS and PFS rates beyond the trial data for both amivantamab and SoC. The company stated that, to this extent, "*clinicians were presented with both KM data and curve extrapolation options for OS and PFS for both amivantamab and UK SoC (as informed by US RWE or PHE cohort data). The clinicians were then asked whether the KM curves and the available extrapolations broadly aligned with their clinical expectations for EGFR Exon20ins mutated NSCLC patients in UK clinical practice receiving either amivantamab or UK SoC after the failure of platinum-based chemotherapy*". The resulting estimates are presented in Table 29 of the company's response to clarification. In Table 30 of the company's response to clarification, the corresponding modelled long-term OS and PFS rates assumed in the base case economic analysis are presented. Although the modelled results seem to be in line with clinical expectations, the ERG would like to emphasise that rates of OS and PFS in the model seem to be slightly underestimated for SoC and overestimated for amivantamab compared to estimations made by the clinicians.

4.2.7 Adverse events

The economic model included grade ≥3 AEs that were reported in more than 5% of patients in key trials, except for incidence of diarrhoea, which was considered at any grade due to its clinical relevance (see Table 49 of the CS). In the CS, it was stated that "*clinical expert opinion received by Janssen supports that these AEs are relevant for inclusion and that no relevant events expected to affect more than 5% of patients have been omitted*".[4] AEs were only considered for current-line treatments, and AEs associated with subsequent-line treatments were not included. The main sources of evidence on treatment AEs used for intervention and comparators were clinical trials (CHRYSALIS for

amivantamab, AURA3 for platinum-based chemotherapy (as per TA653) and LUX-Lung-8 for EGFR TKIs) or previous NICE appraisals (TA520 for IO agents and non-platinum-based chemotherapy).[10, 37, 38]

The consequences of AEs were modelled in terms of the accrual of associated management costs and disutilities. The percentage of patients who experienced AEs was calculated at the start of the model and one-off costs and disutilities were incurred at this stage.

ERG comment: In the CS base case, disutilities associated with grade ≥3 AEs were based on a weighted average based on the treatment class proportions in the US RWE. Considering that SoC is a basket of treatments including IO agents, EGFR TKIs and platinum and non-platinum-based chemotherapies, it is uncertain whether this basket is representative of UK clinical practice (see Section 4.2.4). Hence, the ERG would have liked to see a scenario analysis where EGFR TKI therapies are excluded from the US RWD informing the comparator basket AEs disutilities.

4.2.8 Health-related quality of life

The company stated that EQ-5D-5L data were collected in CHRYSALIS at day 1 of each cycle, at the end of treatment and during post-treatment follow-up. However, in the CS, the company states that "*the number of responses to the EQ-5D-5L questionnaire was low at the time of data cut-off and were therefore not used in the model*" [4].

4.2.8.1 Health-related quality of life data identified in the review

According to the CS, the SLR identified 50 articles reporting on 47 unique studies. Although an appendix was provided with more details, the company did not summarise in the CS whether any of these studies could be used in the economic model.

4.2.8.2 Health state utility values

Health state utility values used in the economic model have been sourced from TA484/TA713, a previous NICE appraisal in advanced non-squamous NSCLC after chemotherapy[11, 39]. In the CS, the company stated that "*this was considered a suitable source for utility data given the similarity of this population to the population of interest in this submission*". Furthermore, the company stated that UK clinical experts consulted as part of this appraisal confirmed that the utility values used are appropriate[4].

Utilities were not age-adjusted, which the company justified by stating that the time horizon of the economic model is relatively short, and the impact of age-adjustment on the results is therefore likely to be marginal.

The company stated in the CS that the standard error for utilities was assumed to be ±10% of the mean.

A summary of all utility values used in the cost effectiveness analysis is provided in Table 4.5.

Table 4.5: Health state utility values

Health state	Utility value	Standard error
Progression-free survival	0.713	0.0713
Post-progression survival	0.569	0.0569

Based on TA484/TA713.93
Based on CS, Table 51
CS = company submission

4.2.8.3 Disutility values

The company implemented one-off disutilities for AEs, sourced from TA520, TA484/TA713 and the published literature (see Table 4.6).

Table 4.6: Summary of AE disutilities applied in the cost effectiveness model

AE	Disutility (SE)	Source
Anaemia	−0.073 (0.018)	Nafees et al. (2008) as per TA484/TA713 and TA52094[10, 39, 40]
Diarrhoea	−0.047 (0.016)	Nafees et al. (2008) as per TA484/TA71394[39, 40]
Fatigue	−0.073 (0.018)	Nafees et al. (2008) as per TA484/TA713 and TA52094[10, 39, 40]
Febrile neutropenia	−0.090 (0.016)	Nafees et al. (2008) as per TA484/TA713 and TA52094[10, 39, 40]
Neutropenia	−0.090 (0.015)	Nafees et al. (2008) as per TA484/TA713 and TA52094[10, 39, 40]
Neutrophil count decreased	0	TA484/TA713 and TA52094[10, 39, 40]
Rash	−0.032 (0.012)	Nafees et al. (2008)[40]
Thrombocytopaenia	−0.108 (0.011)	Tolley et al. (2013)[41]
Based on CS, Table 50 AEs = adverse events; CS = company submission		

ERG comment: The main concerns of the ERG relate to a) exclusion of age-adjustment to the health state utilities; and b) source of health state utilities.

a) The company stated that given the relatively short time horizon of the model, the impact of age-adjustment on results is likely to be marginal and as such, utilities were not age-adjusted. In response to clarification question B12, the company provided an updated model which included the possibility to run the model with age-adjusted utilities, which slightly increased the ICER to £40,293 per QALY gained. This adjustment was included in the ERG base case.
b) Although EQ-5D-5L data were collected in CHRYSALIS, health state utilities in the economic model were sourced from TA484/TA713 as the number of EQ-5D-5L responses from the CHRYSALIS trial was low at the time of data cut-off. In response to clarification question B11, the company provided a scenario analysis informing health state utilities based on the collected HRQoL data in CHRYSALIS. This resulted in a slight increase in the ICER (£42,117 per QALY gained compared to £39,764 per QALY gained in its base case). Given the small sample from which utilities were collected, the ERG is not necessarily against the use of utilities from TA484/TA713. In response to clarification question B11, the company presented scenario analyses investigating the effect of using health state utilities from TA428 and TA347. This resulted in an ICER of £35,617 per QALY gained and £38,086 per QALY gained. The ERG acknowledges the limitations of the HRQoL data in CHRYSALIS and is satisfied with the additional analyses the company provided, which only had a minor impact on the ICER.

4.2.9 Resource use and costs

The cost categories included in the model were drug acquisition costs, drug administration costs, costs of subsequent treatments, medical & monitoring costs (i.e., liver function test, renal function test, full blood test, outpatient oncologist visit, CT scan (chest), General Practitioner (GP) surgery visit, GP home

visit, non-admitted monitoring consultation, and palliative care), costs of managing AEs, and end-of-life costs[4].

Unit prices were based on the NHS reference prices, British National Formulary (BNF), Personal Social Services Research Unit (PSSRU) and pharmaceutical electronic market information tool (eMIT).

4.2.9.1 Resource use and costs data identified in the review

According to the CS, the SLR identified seven articles reporting on seven unique studies in patients with lung cancer. The company stated that no studies reporting on cost and healthcare resource use were conducted in the population considered in this submission (adult patients with locally advanced or metastatic NSCLC with activating EGFR Exon20ins, whose disease has progressed on or after platinum-based chemotherapy).

4.2.9.2 Drug acquisition and administration costs (with PAS)

Drug acquisition costs for every 4-week model cycle were calculated for each treatment based on the dosing schedule and the UK list price of each pack or vial. The company stated that, in the base case, no vial sharing is assumed given the small patient population.

All drugs administered orally or via IV infusion were assumed to be administered in an outpatient setting. The administration-related costs were derived according to data available from the NHS Reference Costs 2019/20.

Dosing regimens and cost per model cycle of intervention and comparators, including amivantamab PAS discount can be found in Table 4.7. A summary of drug costs, administration costs, AE management costs, disease management costs, and subsequent treatment costs per cycle can be found in Table 4.8.

Table 4.7: Dosing regimens and cost per model cycle of intervention and comparators, inclusive of amivantamab PAS discount

Treatment	Dosing regimen	Stopping rule	Cost per dose	Admins per cycle	Cost per treatment cycle	Weeks per cycle	Cost per model cycle
Amivantamab (1,050 mg)	1,050 mg or 1,400 mg (weight dependent) weekly for 4 weeks and bi-weekly thereafter	Treat to progression	£[redacted]	Initial cycle: 4 Subsequent cycles: 2	Initial cycle: £[redacted] Subsequent cycles: £[redacted]	4	Initial cycle: £[redacted] Subsequent cycles: £[redacted]
Amivantamab (1,400 mg)		Treat to progression	£[redacted]		Initial cycle: £[redacted] Subsequent cycles: £[redacted]	4	Initial cycle: £[redacted] Subsequent cycles: £[redacted]
EGFR TKIs (note: in the CS base case, only the costs for afatinib were assumed)							
Afatinib	Oral, 40 mg daily	Treat to progression	£72.26	28	£2,023.28	4	£ 2,023.28
Osimertinib	Oral, 80 mg daily	Treat to progression	£192.33	28	£5,385.33	4	£5,385.33
IO agents							
Atezolizumab	1,200 mg every 3 weeks	Treat to progression	£3,807.69	1	£3,807.69	3	£5,076.92
Pembrolizumab	200 mg every 3 weeks	Treat to progression	£5,260.00	1	£5,260.00	3	£7,013.33
Nivolumab	240 mg every 2 weeks	Treat to progression	£3,291.00	1	£3,291.00	2	£6,582.00
Platinum-based chemotherapy regimens							
Carboplatin + gemcitabine							Initial cycle: £84.92 Subsequent cycles: £0

Treatment	Dosing regimen	Stopping rule	Cost per dose	Admins per cycle	Cost per treatment cycle	Weeks per cycle	Cost per model cycle
Carboplatin	Area under curve 6 mg/mL per minute administered every 3 weeks	Four treatment cycles or progression	£27.03	1	£108.10	12	Initial cycle: £36.03 Subsequent cycles: £0
Gemcitabine	1,250 mg/m^2 on days 1 and 8 every 3 weeks		£18.33	2	£146.65	12	Initial cycle: £48.88 Subsequent cycles: £0
Carboplatin + vinorelbine							Initial cycle: £76.74 Subsequent cycles: £0
Carboplatin	Area under curve 5 mg/mL per minute administered every 3 weeks	Four treatment cycles or progression	£25.67	1	£102.66	12	Initial cycle: £34.22 Subsequent cycles: £0
Vinorelbine	25 mg/m^2 on days 1 and 8 every 3 weeks		£15.95	2	£127.56	12	Initial cycle: £42.52 Subsequent cycles: £0
Carboplatin + pemetrexed							Initial cycle: £1,459.22 Subsequent cycles: £0
Carboplatin	Area under curve 5 mg/mL per minute administered every 3 weeks	Four treatment cycles or progression	£25.67	1	£102.66	12	Initial cycle: £34.22 Subsequent cycles: £0
Pemetrexed	500 mg/m^2 on day 1 every 3 weeks		£1,068.75	1	£4,275.00	12	Initial cycle: £1,425.00 Subsequent cycles: £0
Non-platinum-based chemotherapy regimens							
Docetaxel + nintedanib							First six cycles: £1,935.83 Subsequent cycles: £1,912.09
Docetaxel	75 mg/m^2 repeat cycle every 3 weeks	Fixed duration (six cycles)	£17.81	1	£18.26	3	£24.35
Nintedanib	200 mg twice daily on days 2–21 of cycle	Treat to progression	£35.85	40	£1,434.07	3	£1,912.09

Treatment	Dosing regimen	Stopping rule	Cost per dose	Admins per cycle	Cost per treatment cycle	Weeks per cycle	Cost per model cycle
Docetaxel	75 mg/m^2 repeat cycle every 3 weeks	Treat to progression	£17.81	1	£18.26	3	£24.35

Based on CS, Table 53
CS = company submission; EGFR = epidermal growth factor receptor; IO = immune-oncology; TKIs = tyrosine kinase inhibitor

4.2.9 Resource use & monitoring costs

The types of resource use incorporated in the model were based on TA520[10]. The company stated that "*this was considered to be a suitable source for healthcare resource use given that it is a relatively recent NICE appraisal that considered a patient population analogous to that of this submission*".

4.2.10 Adverse reaction unit costs and resource use

The cost of managing AEs experienced by patients receiving treatments was included as a one-off cost in the economic model. The company stated that the costs per event were based on NHS Reference Costs 2019–20 as per TA653[42].

4.2.11 End-of-life costs

A one-off cost representing the cost of terminal care was applied in the model in the first cycle post-death. The cost applied in the model (£3,803.36) was derived as per the assumptions in TA520, using costs from the NHS Reference Costs (2019/20) and PSSRU (2021) [10].

Table 4.8: Summary of drug costs, administration costs, AE management costs, disease management costs, and subsequent treatment costs per cycle

Drug costs, initial cycle		**Measurement of uncertainty (distribution)**
Amivantamab	£13,780.99	Assumed to be ±10% of the mean (Gamma)
IO agents	£6,098.81	
EGFR TKIs	£2,023.28	
Pt-based chemotherapy	£540.29	
Non-Pt-based chemotherapy	£1,457.81	
Drug costs, subsequent cycles		**Measurement of uncertainty (distribution)**
Amivantamab	£6,890.49	Assumed to be ±10% of the mean (Gamma)
IO agents	£6,098.81	
EGFR TKIs	£2,023.28	
Pt-based chemotherapy	£0.00	-
Non-Pt-based chemotherapy	£1,440.00	Assumed to be ±10% of the mean (Gamma)
Administration costs, initial cycle		
Amivantamab	£885.39	Assumed to be ±10% of the mean (Gamma)
IO agents	£309.89	
EGFR TKIs	£207.79	
Pt-based chemotherapy	£666.41	
Non-Pt-based chemotherapy	£295.13	
Administration costs, subsequent cycles		
Amivantamab	£442.70	Assumed to be ±10% of the mean (Gamma)
IO agents	£309.89	
EGFR TKIs	£0.00	-
Pt-based chemotherapy	£0.00	-
Non-Pt-based chemotherapy	£73.78	Assumed to be ±10% of the mean (Gamma)
AE management costs		
Amivantamab	£242.43	Assumed to be ±10% of the mean (Gamma)

UK SoC	£628.82	
Disease management costs, progression-free		
Amivantamab	£648.19	Assumed to be ±10% of the mean (Gamma)
UK SoC	£823.35	
Disease management costs, post-progression		
Amivantamab	£536.28	Assumed to be ±10% of the mean (Gamma)
UK SoC	£536.28	
Disease management costs, one-off cost		
Mortality	£3,803.36	Assumed to be ±10% of the mean (Gamma)
Subsequent treatment costs		
Amivantamab	£8,200.12	Assumed to be ±10% of the mean (Gamma)
UK SoC	£8,469.41	
Based on CS Table 60 AEs = adverse events; CS = company submission; EGFR = epidermal growth factor receptor; IO = immuno-oncology; Pt = platinum; SoC = standard of care; TKIs = tyrosine kinase inhibitor; UK = United Kingdom		

ERG comment: The main concerns of the ERG relate to a) treatment costs for EGFR TKIs solely being based on afatinib and b) exclusion of costs for diagnostic testing for EGFR in people with NSCLC.

a) In the CS base case, treatment costs for EGFR TKIs are solely based on afatinib (e.g., excluding osimertinib) rather than calculating this based on the proportion of patients per EGFR TKI in the US RWE. This is likely not in line with UK clinical practice (see Section 4.2.4). Furthermore, the company provided a scenario analysis in which the costs of EGFR TKIs were solely based on osimertinib, which decreased the ICER to £31,224 per QALY gained. Although the ERG prefers EGFR TKIs to be removed from the model (Section 4.2.4), if the company decides to include them, the EGFR TKI treatment costs should be based on proportions in line with clinical evidence.
b) In the final scope issues by NICE, it is stated that "*The use of amivantamab is conditional on the presence of an EGFR mutation. The economic modelling should therefore include the costs associated with diagnostic testing for EGFR in people with NSCLC who would not otherwise have been tested. A sensitivity analysis should be provided without the cost of the diagnostic test*". However, in response to clarification question B13, the company argued: "*EGFR Exon20ins mutations can be tested as part of the EGFR test conducted at diagnosis for all NSCLC patients. As such, Janssen, considers there are no additional costs likely to be incurred by the NHS over and above the current standard of care EGFR testing requirements for all NSCLC patients*". The ERG is satisfied with this justification.

5. COST EFFECTIVENESS RESULTS

5.1 Company's cost effectiveness results

5.1.1 Company's deterministic base case results

In the company's probabilistic cost effectiveness results (probabilistic) indicated that amivantamab is both more costly (additional costs of [redacted]) and more effective (incremental QALYs of [redacted]) UK SoC, amounting to an ICER of £40,246 per QALY gained (see Table 5.1). The probability of amivantamab being cost effective at a threshold of £50,000 per QALY gained was around 68% (i.e., due to variation in the PSA results when running the model multiple times).

Overall, the technology is modelled to affect QALYs by (deterministic):

- Increased PPS, with an increment of 0.526 years (63% of total incremental LYs) in the amivantamab arm (1.349 years) compared with UK SoC (0.823 years)
- Increasing PFS, with an increment of 0.314 years (37% of total incremental LYs) in the amivantamab arm (0.818 years) compared with UK SoC (0.504 years)

Overall, the technology is modelled to affect costs by (deterministic):

- The higher drug costs (additional cost of [redacted], [redacted] of total incremental costs), administration costs (additional cost of [redacted], [redacted] of total incremental costs) and post-progression disease management costs (additional cost of [redacted], [redacted] of total incremental costs)

Table 5.1: Company's probabilistic base case results (with PAS)

Technology	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	ICER (£/QALY)
UK SoC	[redacted]	1.32	[redacted]	-	-	-	-
Amivantamab	[redacted]	2.21	[redacted]	[redacted]	0.88	[redacted]	£40,246

Sources: CS Table 64 and Table 65[4]

CS = company submission; ICER = incremental cost-effectiveness ratio; LYs = life years; QALY = quality-adjusted life year; SoC = standard of care; UK = United Kingdom

ERG comment: The main concern of the ERG relates to the lack of a fully incremental analysis for all relevant comparators in the comparator basket. Although the ERG acknowledges the limitation of small sample sizes of patients receiving individual treatments in the RWE sources, a fully incremental analysis of all relevant comparators in the comparator basket would be informative (as was requested in the clarification letter, but not provided) to address the uncertainty of assuming average effectiveness and costs of a basket of treatments.

5.2 Company's sensitivity analyses

The company performed and presented the results of PSA, DSA as well as scenario analyses. The parameters that had the greatest effect on the ICER based on the company's DSA were:

- PFS KM curve for the UK SoC arm
- Drug costs in subsequent cycles for the amivantamab arm
- Health state utilities for PFS and PPS

The CS scenarios that have the greatest impact on the ICER (not including scenarios related to discount rates and time horizon) were:

- UK SoC efficacy based on PHE data (decreased ICER to £25,865)
- Using osimertinib to represent EGFR TKIs (decreased ICER to £31,224)
- Using INV as a measure of progression (increased ICER to £42,249)

ERG comment: The main concern of the ERG related to the fact that the majority ([redacted]) of the incremental QALY gain was accrued post-progression. Upon a request for justification, the company argued that this was in line with the submitted evidence. The company added that UK clinical experts agreed with this judgement as amivantamab offered another line of treatment leading to the list of available treatments becoming exhausted later. The ERG is satisfied with this response.

5.3 Model validation and face validity check

5.3.1 Face validity assessment

The company states that expert clinical input was sought during the development of the cost effectiveness model to ensure that the inputs and assumptions used in the analysis were relevant to UK clinical practice and to validate the clinical plausibility of the outcomes predicted by the model. Moreover, feedback was obtained in two advisory boards and in total, input was gathered from seven UK clinical experts. The CS provides limited information on these clinical experts or advisory boards (i.e., how issues were presented, what topics were discussed, whether there was disagreement).

5.3.2 Technical verification

In the CS, it is stated that the model programming was checked by an analyst who was not involved in the original development of the model. Moreover, the company reports to have held a model challenge session with health economic experts to gain insights and advice regarding the most appropriate assumptions and inputs to consider for the cost effectiveness model. In the CS, it is mentioned that the model was validated "using a validation checklist similar that reported in the published literature". This checklist was not provided in the CS. In response to clarification question B18b, the company indicated that this checklist was based on the TECH-VER checklist. Furthermore, in response to clarification question B18a, the company provided additional information on the stress test checklist used to validate the model.

5.3.3 Comparisons with other technology appraisals

In the CS base case, no cross-validation with other technology appraisals was performed by the company regarding the modelled outcomes (e.g., comparisons of extrapolated PFS or OS curves, QALY gains, or total cost estimates).

In response to clarification question B19, the company provided comparisons with other relevant NICE TAs focused on similar, potentially relevant, diseases. To this extent the company provided a summary of key previous appraisals as per the NICE final scope and NG122 (TA347, TA428, TA484/TA713, TA520 and TA653).

5.3.4 Comparison with external data used to develop the economic model

No external data was used to validate outcomes in the CS base case model. In the CS, it is stated that parametric distributions were selected based on clinical expert input. This selection process did not involve external data.

5.3.5 Comparison with external data not used to develop the economic model

Not performed.

ERG comment: The main concern of the ERG relates to differences between the probabilistic results when running the same model multiple times (without changing model settings). This is likely due to the lack of a fixed random seed in the model PSA, which results in slightly different random draws each time the model runs. When running the model multiple times, the ERG estimates the ICER to fluctuate roughly with £500 to £1,000 per QALY gained.

6. EVIDENCE REVIEW GROUP'S ADDITIONAL ANALYSES

6.1 Exploratory and sensitivity analyses undertaken by the ERG

Table 6.1 summarises the key issues related to the cost effectiveness categorised according to the sources of uncertainty as defined by Grimm et al. 2020[43]:

- Transparency (e.g., lack of clarity in presentation, description, or justification)
- Methods (e.g., violation of best research practices, existing guidelines, or the reference case)
- Imprecision (e.g., particularly wide confidence intervals, small sample sizes, or immaturity of data)
- Bias and indirectness (e.g., there is a mismatch between the decision problem and evidence used to inform it in terms of population, intervention/comparator and/or outcomes considered)
- Unavailability (e.g., lack of data or insight)

Identifying the source of uncertainty can help determine what course of action can be taken (i.e., whether additional clarifications, evidence and/ or analyses might help to resolve the key issue). Moreover, Table 6.1 lists suggested alternative approaches, expected effects on the cost effectiveness, whether it is reflected in the ERG base case as well as additional evidence or analyses that might help to resolve the key issues.

Based on all considerations in the preceding Sections of this ERG report, the ERG defined a new base case. This base case included multiple adjustments to the original base case presented in the previous Sections. These adjustments made by the ERG form the ERG base case and were subdivided into three categories (derived from Kaltenthaler 2016):[44]

- Fixing errors (FE) (correcting the model where the company's submitted model was unequivocally wrong)
- Fixing violations (FV) (correcting the model where the ERG considered that the NICE reference case, scope or best practice had not been adhered to)
- Matters of judgement (MJ) (amending the model where the ERG considers that reasonable alternative assumptions are preferred)

6.1.1 ERG base case

Adjustments made by the ERG, to derive the ERG base case (using the CS base case as starting point) are listed below. Table 6.2 shows how individual adjustments impact the results plus the combined effect of all abovementioned adjustments simultaneously, resulting in the ERG base case. The 'fixing error' adjustments were combined, and the other ERG analyses were performed also incorporating these 'fixing error' adjustments given the ERG considered that the 'fixing error' adjustments corrected unequivocally wrong issues.

6.1.1.1 Fixing errors

There were no errors identified by the ERG.

6.1.1.2 Fixing violations

1. Exclusion of age-adjustment to the health state utilities (Section 4.2.8): In the CS base case, the company did not include an age-adjustment to the health state utilities given the relatively short time horizon of the model. However, the ERG decided to include age-adjustments as it is in line with good modelling practice.

6.1.1.3 Matters of judgement

2. Indirect treatment comparison approach for the comparative effectiveness of amivantamab versus SoC (Section 4.2.6): The comparative effectiveness was explored via covariate adjustment and IPW and propensity score matching (PSM). The ERG decided to opt for two ERG base cases because it remains undecided regarding the best way to determine the comparative effectiveness of amivantamab versus SoC. Hence, the ERG opted for two separate ERG base cases in which ERG base case one was based on the IPW approach and ERG base case two was based on the propensity score matching approach.
3. Implementation of parametric survival curves in SoC arm (Section 4.2.6): In line with the company's scenario analyses, the ERG implemented a Weibull curve for OS and a log-logistic curve for PFS.
4. TTD for amivantamab was informed by the CHRYSALIS trial protocol instead of assuming TTD is equal to PFS (Section 4.2.6): Instead of assuming TTD being equal to PFS, the ERG implemented TTD using an exponential curve informed by CHRYSALIS trial data.

6.1.2 ERG exploratory scenario analyses

The ERG performed the following exploratory scenario analyses to explore the impact of alternative assumptions conditional on the ERG base case.

6.1.2.1 Exploratory scenario analyses

5. Informing health state utilities based on the collected HRQoL data in CHRYSALIS (Section 4.2.8): health state utilities in the economic model were sourced from TA484/TA713 as the number of EQ-5D-5L responses from the CHRYSALIS trial was low at the time of data cut-off. Nevertheless, an ERG scenario informing utilities based on CHRYSALIS data was conducted to assess the impact on the ICER.
6. Assuming TTNT as a proxy for treatment discontinuation in the SoC population (Section 4.2.6): For this scenario, TTNT estimates were used as a proxy for TTD in the SoC arm. For this analysis the generalised gamma model was chosen. For amivantamab, the ERG implemented the exponential model for TTD in its base case (see ERG change 4).

6.1.3 ERG subgroup analyses

No subgroup analyses were performed by the ERG.

Table 6.1: Overview of key issues related to the cost effectiveness (conditional on fixing errors highlighted in Section 5.1)

Key issue	Section	Source of uncertainty	Alternative approaches	Expected impact on ICER[a]	Resolved in ERG base case[b]	Required additional evidence or analyses
Representativeness of the comparator basket effectiveness to UK clinical practice	4.2.4	Bias and indirectness	Exclude EGFR TKIs from comparator basket.	+/-	No	Updated economic model excluding the costs and effects of EGFR TKIs.
Implementation of parametric survival curves instead of KM curves for SoC	4.2.6	Methods	Implement parametric models for survival analyses of OS and PFS in the SoC arm.	+	Yes	N/A
TTD assumed equal to PFS	4.2.6	Methods	Apply parametric survival model to TTD based on CHRYSALIS evidence.	+	Partly	Details of NICE DSU TSD 14 criteria assessment to support TTD curve selection.
Treatment waning	4.2.6	Bias and indirectness	Updated economic model including treatment waning scenarios. Additional evidence that treatment waning would be implicitly captured in the selected curves.	+/-	No	Updated economic model including treatment waning scenarios. Additional evidence that treatment waning would be implicitly captured in the selected curves
Exclusion of age-adjusted health state utilities in the CS base case	4.2.8	Methods	Include age-adjusted health state utilities	+	Yes	N/A
Lack of a fully incremental analysis for all relevant comparators in the comparator basket	5.1	Methods	Fully incremental analysis of all relevant comparators in the comparator basket.	+/-	No	Fully incremental analysis of all relevant comparators in the comparator basket.
Lack of a fixed random seed in model PSA	5.3	Imprecision	Implement fixed random seed to model PSA.	+/-	No	Implement fixed random seed to model PSA.

Note: [a] Likely conservative assumptions (of the intervention versus all comparators) are indicated by '-'; while '+/-' indicates that the bias introduced by the issue is unclear to the ERG and '+' indicates that the ERG believes this issue likely induces bias in favour of the intervention versus at least one comparator; [b] Explored

Key issue	Section	Source of uncertainty	Alternative approaches	Expected impact on ICER[a]	Resolved in ERG base case[b]	Required additional evidence or analyses
CS = company submission; DSU = Decision Support Unit; EGFR = epidermal growth factor receptor; ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; KM = Kaplan-Meier; N/A = not applicable; NICE = National Institute for Health and Care Excellence; PFS = progression-free survival; PSA = probabilistic sensitivity analysis; SoC = standard of care; TKI = tyrosine kinase inhibitor; TSD = Technical Support Document; TTD = time to treatment discontinuation; UK = United Kingdom						

6.2 Impact on the ICER of additional clinical and economic analyses undertaken by the ERG

In Section 6.1 the ERG base case was presented, which was based on various changes compared to the company base case. Table 6.2 shows how individual changes impact the results plus the combined effect of all changes simultaneously. The exploratory scenario analyses are presented in Table 6.3. These are all conditional on the ERG base case. The analyses numbers in Tables 6.2 and 6.3 correspond to the numbers reported in Section 6.1. The submitted model file contains technical details on the analyses performed by the ERG (e.g., the "ERG" sheet provides an overview of the cells that were altered for each adjustment).

Table 6.2: ERG base case 1 (IPW approach) and base case 2 (PSM approach) (with PAS)

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
CS deterministic base case					
Amivantamab	[redacted]	[redacted]	[redacted]	[redacted]	39,764
UK SoC	[redacted]	[redacted]			
Fixing violation (1-Exclusion of age-adjustment to the health state utilities)					
Amivantamab	[redacted]	[redacted]	[redacted]	[redacted]	40,293
UK SoC	[redacted]	[redacted]			
Matter of judgement (2-Use of PSM approach)					
Amivantamab	[redacted]	[redacted]	[redacted]	[redacted]	45,790
UK SoC	[redacted]	[redacted]			
Matter of judgement (3-Implementation of parametric survival curves in SoC arm)					
Amivantamab	[redacted]	[redacted]	[redacted]	[redacted]	41,401
UK SoC	[redacted]	[redacted]			
Matter of judgement (4-Time to treatment discontinuation informed by the CHRYSALIS trial protocol)					
Amivantamab	[redacted]	[redacted]	[redacted]	[redacted]	55,695
UK SoC	[redacted]	[redacted]			
Deterministic ERG base case 1 (IPW approach)					
Amivantamab	[redacted]	[redacted]	[redacted]	[redacted]	56,799
UK SoC	[redacted]	[redacted]			
Probabilistic ERG base case 1 (IPW approach)					
Amivantamab	[redacted]	[redacted]	[redacted]	[redacted]	54,418
UK SoC	[redacted]	[redacted]			
Deterministic ERG base case 2 (PSM approach)					
Amivantamab	[redacted]	[redacted]	[redacted]	[redacted]	52,185
UK SoC	[redacted]	[redacted]			
Probabilistic ERG base case 2 (PSM approach)					
Amivantamab	[redacted]	[redacted]	[redacted]	[redacted]	49,880
UK SoC	[redacted]	[redacted]			

CS = company submission, ERG = Evidence Review Group, ICER = incremental cost-effectiveness ratio, IPW = inverse probability weighting, PSM = propensity score matching, QALY = quality-adjusted life year, SoC = standard of care; UK = United Kingdom

Table 6.3: Probabilistic scenario analyses (conditional on ERG base case) (with PAS)

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
ERG base case 1 (IPW approach)					
Amivantamab	[redacted]	[redacted]	[redacted]	[redacted]	54,418
UK SoC	[redacted]	[redacted]			
Scenario analysis base case 1 (5-Health state utilities based on CHRYSALIS HRQoL data)					
Amivantamab	[redacted]	[redacted]	[redacted]	[redacted]	58,764
UK SoC	[redacted]	[redacted]			
Scenario analysis base case 1(6-Assuming TTNT as proxy for treatment discontinuation in SoC)					
Amivantamab	[redacted]	[redacted]	[redacted]	[redacted]	39,567
UK SoC	[redacted]	[redacted]			
ERG base case 2 (PSM approach)					
Amivantamab	[redacted]	[redacted]	[redacted]	[redacted]	49,880
UK SoC	[redacted]	[redacted]			
Scenario analysis base case 2 (5-Health state utilities based on CHRYSALIS HRQoL data)					
Amivantamab	[redacted]	[redacted]	[redacted]	[redacted]	53,390
UK SoC	[redacted]	[redacted]			
Scenario analysis base case 2 (6-Assuming TTNT as proxy for treatment discontinuation in SoC)					
Amivantamab	[redacted]	[redacted]	[redacted]	[redacted]	36,169
UK SoC	[redacted]	[redacted]			

ERG = Evidence Review Group; HRQoL = health-related quality of life; ICER = incremental cost-effectiveness ratio; IPW = inverse probability weighting; PSM = propensity score matching; QALY = quality-adjusted life year; TTNT = time to next treatment; SoC standard of care; UK = United Kingdom

6.3 ERG's preferred assumptions

The estimated ERG base case ICERs (probabilistic), based on the ERG preferred assumptions highlighted in Section 5.1, were £54,418 per QALY gained for ERG base case 1 and £49,880 per QALY gained for ERG base case 2. The probabilistic ERG base case 1 and ERG base case 2 analyses indicated cost effectiveness probabilities of 38% and 47% at a willingness to pay threshold of £50,000 per QALY gained. The most influential adjustments were implementing TTD using an exponential curve informed by CHRYSALIS trial data and selecting the PSM indirect treatment comparison approach for the comparative effectiveness of amivantamab versus SoC. The ICER increased most in the scenario analysis assuming TTNT (generalised gamma curve) as a proxy for treatment discontinuation in the SoC population.

6.4 Conclusions of the cost effectiveness Section

The company's cost effectiveness model partly complied with the NICE reference case. Deviations from the NICE reference case related to the exclusion of a fully incremental analysis which would include all UK SoC comparators separately (rather than a "basket" of comparators). The most prominent issues highlighted by the ERG were 1) the representativeness of the comparator basket effectiveness to UK clinical practice; 2) the assumption that treatment would be discontinued when a patient progresses (i.e. assuming TTD equal to PFS in the model); 3) using the KM curves to inform survival analyses for

UK SoC; 4) the exclusion of age-adjustment to the health state utilities; and 5) the company's assumption of a lifelong treatment effect. As a general source of uncertainty, the ERG was undecided regarding the best way to determine the comparative effectiveness of amivantamab versus SoC (i.e., IPW or PSM approach). To this extent, the ERG opted for two ERG base cases in its ERG analyses.

First, due to considerable heterogeneity in treatments due to lack of specifically recommended treatments in the UK, data informing comparator efficacy were derived from a basket of treatments from a US RWE database study. The comparator effectiveness and costs are therefore based on the average clinical effectiveness and weighted average costs across all the treatments included in the comparator basket. It is, however, unclear to the ERG whether this is consistent with UK clinical practice. This is especially important as Exon20ins mutations have been associated with resistance to EGFR TKIs, which are now included in the CS base case. In addition, the results of the indirect treatment comparison excluding TKIs show that the HRs are slightly higher than the base case HRs, indicating that the effectiveness of EGFR TKIs for Exon20ins mutations may indeed be questionable. An updated economic model excluding EGFR TKI therapies from the US RWD could resolve this issue. Moreover, although the ERG acknowledges the limitation of small sample sizes of patients receiving individual treatments in the RWE sources, a fully incremental analysis of all relevant comparators in the comparator basket would be informative to address the uncertainty of assuming average effectiveness of a basket of treatments.

Second, for the estimation of TTD the company assumed that treatment would be discontinued when a patient progresses, setting TTD equal to PFS. The CHRYSALIS trial, however, allowed patients to remain on treatment after disease progression and median TTD ([redacted]) was significantly longer than median PFS([redacted]). This assumption reduces the estimated cost of amivantamab without reducing the estimated effectiveness after progression of amivantamab. Upon request the company implemented a scenario examining the impact of separate TTD curves (i.e., assuming PFS is not necessarily equal to PFS). In its base case, the ERG implemented an exponential curve to model TTD for amivantamab.

Third, OS and PFS in the SoC arm were modelled based on the KM data. The company argued that due to the maturity of the data and all patients reaching the specified end point or being censored within the timeframe of data collection, KM data could be directly implemented rather than fitting a parametric survival model. However, this is not necessarily in line with NICE DSU TSD 14, which states that "*parametric models are likely to represent the preferred method for incorporating survival data into health economic models in the majority of cases*". The ERG decided that the implementation of KM data may introduce overfitting of the modelled survival outcomes. Implementing KM curves biases the SoC treatment effectiveness as patients do not transition smoothly. The ERG therefore implemented parametric models to inform survival analysis of OS and PFS for SoC in its base case.

Fourth, in the CS base case, the company did not include an age-adjustment to the health state utilities. It was argued that given the relatively short time horizon of the model, the impact of age-adjustment on the model results was likely to be marginal and as such, utilities were not age-adjusted. However, in line with good modelling practice, the ERG decided to include age-adjustments in its base case.

Fifth, the ERG considered that the assumption of a lifelong treatment effect may not be warranted and requested that the company explored treatment waning in the model, which the company did not implement. It is unclear to the ERG whether the assumption of a lifelong treatment effect holds true in clinical practice as there is limited evidence provided on the presence (or absence) of treatment waning by the company.

Finally, the ERG decided to opt for two ERG base cases because it remained undecided regarding the most appropriate approach to determine the comparative effectiveness of amivantamab versus SoC. The comparative effectiveness was explored via IPW and PSM approaches. Hence, the ERG opted for two separate ERG base cases in which one was based on the IPW approach (ERG base case 1) and the other one based on the PSM approach (ERG base case 2).

The CS base case probabilistic and deterministic ICERs were £40,246 and £39,764 per QALY gained, respectively. According to the company's model amivantamab is set to influence cost effectiveness by 1) increased PPS, with an increment of 0.526 years (63% of total incremental LYs) in the amivantamab arm (1.349 years) compared with UK SoC (0.823 years); 2) increased PFS, with an increment of 0.314 years (37% of total incremental LYs) in the amivantamab arm (0.818 years) compared with UK SoC (0.504 years); and 3) the higher drug costs, administration costs and post-progression disease management costs.

The two (probabilistic) ERG base case analyses resulted in ICERs of £55,043 per QALY gained (when assuming all ERG changes and the IPW approach to determine comparative effectiveness) and £49,273 per QALY gained (when assuming all ERG changes and the PSM approach to determine comparative effectiveness). The TTD informed by parametric curves based on the CHRYSALIS trial protocol had the biggest impact in the ICER compared to the CS base case. The ICER increased most in the scenario analysis in which health state utilities were based on CHRYSALIS HRQoL data. The ICER decreased most when assuming TTNT as a proxy for treatment discontinuation in SoC. It should be noted that the latter scenario assumes that TTNT is a good approximation to TTD, which is questionable according to the ERG (as discussed in Section 4.2.6. of this report).

In conclusion, there remains uncertainty about the effectiveness and relative effectiveness of amivantamab, which can be at least partly resolved by the company by conducting further analyses (e.g., incorporate the results of the indirect treatment comparison excluding EGFR TKIs in the model, perform a fully incremental analysis, and explore treatment waning). Moreover, the current assessment does not provide an appropriate estimation of the comparators listed in the scope. Therefore, the ERG believes that the CS nor the ERG report contains an unbiased ICER of amivantamab compared with relevant comparators.

7. END OF LIFE

The company states that amivantamab fulfils the first NICE end of life criteria (that the population's life expectancy is less than 24 months) and the second (that the survival benefit of amivantamab exceeds 3 months), see Table 7.1.

Table 7.1: End of life criteria

Criterion	Data available			Section in Document B of the CS
	Comparator	Median OS	Mean undis-counted life years	
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	UK SoC	US RWE: [redacted] CEM: [redacted]	1.38 LYs	B.2.9 (62), B.3.3 (101)
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment	Amivantamab	CHRYSALIS: 22.77 (17.48, NE) CEM: [redacted]	2.31 LYs	B.2.6 (48), B.3.3 (101)
	Difference versus amivantamab	US RWE: [redacted] CEM: [redacted]	0.93 LYs	

Based on Table 36 of CS[4]
[a] Median OS is presented based on adjusted comparison with US data (US RWE), unadjusted comparison with UK data (PHE), the output of the cost effectiveness model (CEM) or the CHRYSALIS trial (CHRYSALIS).
CEM = cost effectiveness model; CS = company submission; NE = not evaluable; NHS = National Health Service; OS = overall survival; RWE = real-world evidence; SoC = standard of care; UK = United Kingdom

In Section 5.1 above, the ERG reports figures that also suggest that amivantamab satisfy both end of life criteria. Specifically, the ERG found that the life expectancy of patients without the treatment (SoC) is 1.33 LYs. On this basis, the ERG analysis confirms that criteria that patients do not survive more than 24 months is met. Relatedly, the ERG calculated that patients taking amivantamab have an additional 0.84 LYs, so the second criteria also appears to be met.

ERG comment:

- The ERG confirms that amivantamab fulfils the first NICE end of life criterion (that the population's life expectancy is less than 24 months).
- The ERG notes that there is uncertainty regarding the estimates of clinical effectiveness, and also that the reported values appear to be well over 3 months). Therefore, the ERG considers the 2nd end-of-life also to have been met.

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National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

ERG report – factual accuracy check and confidential information check

Amivantamab for treating EGFR Exon 20 insertion-positive non-small-cell lung cancer after platinum-based chemotherapy [ID3836]

'*Data owners will be asked to check that confidential information is correctly marked in documents created by others in the technology appraisal process before release; for example, the technical report and ERG report.*' (Section 3.1.29, Guide to the processes of technology appraisals).

You are asked to check the ERG 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 **5pm on Tuesday 3 May 2022** 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 '[redacted]' in turquoise, all information submitted as '[redacted]' in yellow, and all information submitted as '[redacted]' in pink.

Issue 1 Potential misinterpretations from the company submission

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 13 of the ERG report gives an overview of the key model outcomes without specifying whether the costs presented are list price or PAS price.	A statement should be added to clarify whether these costs are list price or PAS price. This should also be applied throughout the ERG report where cost and cost-effectiveness outcomes from the cost-effectiveness model are reported.	It is important to be clear whether costs are being reported at list or PAS price to prevent misinterpretation of results.	All reported cost and cost-effectiveness outcomes from the cost-effectiveness model include the amivantamab PAS price. Not a factual error, but 'with PAS' added for clarity in relevant parts of section 6.
Page 14 of the ERG report states: *"Population considered by company is narrower than the population defined in final National Institute for Health and Care Excellence (NICE) scope; the narrower population may not be generalisable to the England and Wales National Health Service (NHS) population; and (because the company's population was "fitter"), may have led to an underestimate of adverse events (AEs)."*	The ERG should detail the difference in the populations between the final scope and the population addressed within the Company submission (CS).	It is important to describe the exact deviations in order to prevent this statement being misinterpreted as saying that the Company addressed an inappropriate population in the CS.	The differences in populations are clearly spelled out in section 2.1. Section 1 is a short summary. Not a factual error and no change made to report.
Page 18 of the ERG report states: *"In the company submission (CS) base case, the company did not include an age-adjustment to the health state utilities given the relatively short time horizon of the model, which is not in line with, good*	Please could the paragraph be amended as follows: *"In the company submission (CS) base case, the company did not include an age-adjustment to the health state utilities given the relatively short time horizon of the model, which is not in line with, good modelling*	This statement is potentially misleading and implies an omission by the Company. A scenario analysis exploring this issue was added at clarification question stage at the request of the ERG.	Change made to text.

modelling practice, and exaggerated the cost effectiveness of amivantamab."	*practice, and exaggerated the cost effectiveness of amivantamab.* ***This was subsequently provided by the company at clarification question stage.*** *"*		
Page 19 of the ERG report states: *"Amivantamab was compared to a basket of treatments. The comparator effectiveness and costs are therefore based on the average clinical effectiveness and costs across all the treatments included in the comparator basket, rather than a fully incremental analysis of all relevant comparators in the comparator basket."*	Please could the paragraph on Page 19 be amended as follows: *"Amivantamab was compared to a basket of treatments,* ***as there is no established SoC for patients with EGFR Exon20ins mutated NSCLC in the UK****. The comparator effectiveness and costs are therefore based on the average clinical effectiveness and costs across all the treatments included in the comparator basket, rather than a fully incremental analysis of all relevant comparators in the comparator basket.* ***The company did not consider a fully incremental analysis to be appropriate given the lack of definition of SoC, as this means there is no robust methodological basis for decision-making at the margin****."* These qualifying statements should be included throughout when referring to the comparator basket and the request for a fully incremental analysis.	This additional wording should be added to provide context as to why the UK SoC comparator is considered the most appropriate and why a fully incremental analysis was not presented. The Company consider the SoC comparator to be most appropriate given the heterogeneous nature of treatment patterns in UK practice, as a basket of therapies is a true representation of what would be displaced should amivantamab be recommended by NICE. Relatedly, a fully incremental analysis was not considered appropriate as a comparison between amivantamab and individual treatments is inappropriate and would not provide estimates suitable for decision-making.	The implication of variation in SoC is either inefficient allocation of resources if those treatments are mutually exclusive or that those treatments are not mutually exclusive. If the latter than a subgroup analysis should be performed. Neither case implies comparison to a basket of treatments. Not a factual error, no change made to report.
Page 26 of the ERG report states: *"Whereas the final NICE scope includes all those with EGFR Exon 20 insertion-positive NSCLC, the company limits the population to those with locally advanced or*	The statement should be amended as follows: *"Whereas the final NICE scope includes all those with EGFR Exon 20 insertion-positive NSCLC, the company limits the population to those with locally advanced or metastatic NSCLC with activating EGFR Exon20ins* ***to***	It is important to include rationale as to why the population addressed in the CS is narrower than the final scope in order to prevent misinterpretation that this is an unusual approach or a	This text in the ERG report is about the difference between the final NICE Scope and the CS. Not a factual error, no change made to report.

metastatic NSCLC with activating EGFR Exon20ins."	***align with the population of CHRYSALIS and the licensed indication for amivantamab**."*	mistake from the Company in scope interpretation.	
Page 26 of the ERG report states: *"On 15th November 2021, the Medicines & Healthcare Products Regulatory Agency granted an innovation passport to amivantamab for adult patients with advanced NSCLC with activating EGFR Exon 20 insertion mutations, after failure of platinum-based therapy."*	The statement should be amended as follows: *"**Amivantamab was granted an innovation passport by the Medicines & Healthcare Products Regulatory Agency (MHRA) on 8th April 2021**. On 15th November 2021, the MHRA granted a **marketing authorisation for** amivantamab for adult patients with **locally** advanced **or metastatic** NSCLC with activating EGFR Exon 20 insertion mutations, **whose disease has progressed on or after** platinum-based **chemo**therapy."* In addition, the reference cited by the ERG to support this information is inaccurate and should be amended to EMC 2022.[1]	The date originally given refers to the date the marketing authorisation for amivantamab was granted rather than when the innovation passport was granted. Both the innovation passport and marketing authorisation should be mentioned here. In addition, the indication wording should be updated to accurately reflect the text of the marketing authorisation, and the cited reference should be amended for accuracy.	Change made to text and reference corrected.
Page 27 of the ERG report states: *'the company acknowledge that the patients in the trial might be "fitter"'*	The statement should be amended as follows: *'the company acknowledge that the patients in the trial might be "fitter", **as is common for oncology trials**"*	The Company acknowledge that patients in the trial may be slightly fitter than the population in UK clinical practice; however, this statement has been taken out of the context of the paragraph which noted that this issue is common across oncology trials and is therefore not an unusual aspect of this submission.	Not a factual error, no change made to report.
Page 28 of the ERG report states: *"The comparator chosen by the company is a pooled treatment*	The statement should be amended as follows:	The statement in its current form is unclear and does not clearly specify the source of the efficacy	Not a factual error, no change made to report.

basket in the form of real-world data to estimate clinical effectiveness and SoC in the cost effectiveness analysis…"	*"The comparator chosen by the company is a pooled treatment basket.* ***Efficacy for this basket is informed by real-world data and costs are based on the treatments available in UK practice for those treatment classes included in the real-world evidence****…"*	and costs associated with the pooled treatment basket.	
Page 28 of the ERG report states: *"In their response, the company provided hazard ratios (HRs) for PFS, OS, and TTNT for the base case, and a scenario excluding all TKIs (including nintendanib)."* Page 29 of the ERG report states: *"The ERG does not understand why the company reports in the clarification letter excluding all TKIs rather than all TKIs other than nintendanib (as per the ERG request, which aligns with the final NICE scope)."*	The statement should be amended as follows: *"In their response, the company provided hazard ratios (HRs) for PFS, OS, and TTNT for the base case, and a scenario excluding all TKIs (****apart from nintedanib****)."* All similar statements throughout the ERG report should be similarly amended. This statement should be removed from the ERG report: *"The ERG does not understand why the company reports in the clarification letter excluding all TKIs rather than all TKIs other than nintendanib (as per the ERG request, which aligns with the final NICE scope)."*	Beginning at submission and at any timepoint afterwards, nintedanib was not treated as a TKI in the Company's classification of treatments. As such, when providing an analysis excluding TKIs, nintedanib was not excluded. It is unclear to the Company why the ERG have made this conclusion; however, the Company can confirm that all TKIs apart from nintedanib were excluded.	Change made to the error on page 28. Statement on page 29 removed. Table 2.1 and Section 2.3 also amended, and 'EGFR' added to 'TKI' throughout the report to improve clarity.
Page 28 of the ERG report states the following in reference to the Company not providing a PD-L1 subgroup analysis: *"In short, the company provided some, but not all, of the evidence requested by the ERG."* Page 29 of the ERG report states:	The statement should be amended as follows: *"In short, the company* ***provided an analysis by line of therapy, but not an analysis by PD-L1 status, as the latter was not feasible due to small sample sizes within the data****."*	These statements fail to acknowledge that the PD-L1 subgroup analyses were not feasible due to the small sample sizes within both the CHRYSALIS and RWE cohorts and should be amended to reflect this. The ERG acknowledge this later in the ERG report (Page 84):	Not a factual error, no change made to report.

"Regarding the company's refusal to fully respond to the ERG's request to provide separate clinical effectiveness analyses by line of therapy and PD-L1 subgroup (to align with the final NICE scope)…" *"…Therefore, the ERG believes that the data should be presented according to different lines of therapy and PD-L1 status"*	All similar statements throughout the ERG report should be amended. The second statement should be amended as follows: *"**The company could not provide an analysis by PD-L1 status as this was not feasible given that within the US RWE data sources, only [redacted] lines of therapy corresponded to patients who tested PD-L1 positive, and of these, only [redacted] consisted of nivolumab or pembrolizumab. Within the CHRYSALIS data set, only [redacted] patients in the trial had their PD-L1 status recorded. An analysis by line of therapy was provided**"* The third statement should be removed.	*"The ERG agrees that PD-L1 sub-group analyses would have been unfeasible for the reasons given"* Further, an analysis by line of therapy was provided by the Company.	
Page 29 of the ERG report states: *"Given the limited activity in this population, existing EGFR TKIs are not used in patients with EGFR Exon20ins mutation-positive NSCLC following platinum-based chemotherapy (i.e., the position of the anticipated mobocertinib licence)."*	This statement should be removed from the ERG report.	As evidenced by the RWE data presented within the CS and in response to clarification question A6, this statement is incorrect as TKIs are used in patients with advanced NSCLC with activating EGFR Exon20ins mutations after failure of platinum-based chemotherapy.	Changed to "not used" to "rarely used"
Page 29 of the ERG report states: *"Hence, excluding all TKIs (rather than all TKIs other than nintendanib) as comparators will lead to an exaggeration of the benefits of amivantamab."*	The statement should be removed.	As explained earlier, the Company did not exclude nintedanib from the analyses that requested the exclusion of TKIs other than nintedanib and as such, the	Statement removed. See response above.

		conclusion implied by this statement is invalid.	
Page 30 of the ERG report states: "In addition, invasive disease-free survival (iDFS) and distant recurrence-free interval were included as outcome measures."	This statement should be removed.	These outcome measures were not included in the CHRYSALIS trial and are therefore not included in the CS.	Statement removed.
Page 30 of the ERG report states: *"With respect to the additional outcomes used by the company that go over and above those listed in the final NICE scope, the ERG notes that these increase the risk of false positive results."*	Additional information needs to be added to this statement to clarify why this would be the case, or otherwise this statement should be removed.	It is unclear to the Company why presenting data for clinical outcomes beyond those in the final scope would lead to an increase in the likelihood of false positive results.	Statement modified.
Page 37 of the ERG report states: *"The ERG notes that an English language only restriction was applied to the SLR search. The ERG considers excluding non-English language studies to be inappropriate for obtaining robust evidence on the treatment of adults with advanced NSCLC."*	Justification should be added here as to why the approach conducted is inappropriate.	It is unclear to the Company why this approach would be inappropriate. Therefore, this should be justified in the ERG report to prevent misinterpretation.	Not a factual error, no change made to report.
Page 42 of the ERG report states: *"The ERG is satisfied that the company has clarified the use of pemetrexed in the trial and in the CS."*	As the ERG is satisfied with the Company's clarification, statements concerning pemetrexed potentially being a confounding factor (such as on Page 15) should be removed.	As stated in the clarification response, the CHRYSALIS cohort providing clinical data for the submission received amivantamab monotherapy. As such, pemetrexed is not included as part of the intervention treatment.	Table 1.4, Table 2.1 and Section 2,3 amended.

Page 15 of the CS (and elsewhere throughout the document) states: *"In addition, pemetrexed appears to have been used by both the patients in the treatment and control groups, which could have confounded the results."*		Given the confirmation from the ERG that the clarification response from the Company regarding this has clarified this issue, it is inappropriate to raise this throughout the ERG report as a key issue.	
Page 45 of the ERG report states: *"The ERG notes that there is a large difference between the efficacy and safety populations in terms of number of participants (N=114 versus N=153, or 34% more participants in the safety populations) and cut-off dates (4th June 2020 versus 30th March 2021)."*	The cut-off date for the efficacy population is stated incorrectly, efficacy data reported in the submission are from the 30th March 2021 data cut. The 4th June 2020 date refers to the definition of the patient population for efficacy results, which is as follows: this population included all patients with EGFR Exon20ins NSCLC who received the RP2D prior to 04 June 2020 data cut-off with ≥3 disease assessments as of the 08 October 2020 data cut-off. All mentions of a difference in data cut-off dates between the safety and efficacy populations difference should be removed.	The content of the ERG report implies that an inconsistent data cut-off date has been used for efficacy and safety data in the CS; however, this is not the case. Different dates refer to the definitions of the relevant analysis sets as a certain degree of follow-up was required to assess efficacy outcomes.	Table 1.1, Table 1.6, Section 3.2.2 and Section 3.6 amended.
Page 51 of the ERG report states: *"Table 3.10 presents the risk of bias assessment of the CHRYSALIS trial conducted using the ROBINS I33 tool for assessing risk of bias in non-randomised studies of interventions. It is not clear if one or more reviewers were involved in the assessment."*	This statement should be amended as follows: *"Table 3.10 presents the risk of bias assessment of the CHRYSALIS trial conducted using the ROBINS I[33] tool for assessing risk of bias in non-randomised studies of interventions.* ***Quality assessments were completed by one reviewer and verified by a second independent reviewer****."*	The existing statement implies that the risk of bias assessment was not verified by a second team member whereas this is incorrect, as described in Appendix D.1.3.2 of the CS, and Section 3.1.4 of the ERG report.	Modification made.

	This should be updated throughout the ERG report as needed.		
Page 54 of the ERG report states, in reference to ORR data: *"PHE comparative data (from the UK) were collected but results using those data for this outcome were not reported in the CS, nor were they reported in the appendices."* The same statement is made on Page 60 in reference to PFS data.	This statement should be amended as follows: "*PHE comparative data (from the UK) were collected but results using those data for this outcome were not* ***collected by PHE and are therefore not available***." Other statements around the lack of ORR and PFS data for the PHE cohort should also be amended to clarify that this is due to the data not being collected by PHE.	ORR and PFS data were not collected for the PHE dataset and were therefore not available to be presented. All available UK data were presented.	Amended.
Page 54 and Page 60 of the ERG report state: *"The company states that the US data are representative of the UK population, but there seems little reason to use US data when UK data were available. The question remains as to why the UK data were not used for this outcome"*	This statement should be amended to reflect the reason given by the Company as to why the UK data were not used, i.e. that there were limitations with the sample size of the PHE data, and data were not available for all outcomes.	The justification for why the US data are considered more appropriate for the base case analysis should be made clear throughout the ERG report.	Amended – see previous response. Sentence also deleted on p.65 and one added on p.84.
Page 64 of the ERG report states: *"The INV data were not used for this outcome, but this is not explained."*	The statement should be amended as follows: *"The INV data were not used for this outcome* ***as the method of assessment for OS prevents data being classed as INV or BICR****."*	As OS is not assessed by RECIST criteria, the INV and BICR distinction is not applicable. The statement is therefore potentially misleading.	Sentence deleted.

Page 83 of the ERG report states: *"Although methods for confounder adjustment appear robust, as evidenced by the adjusted baseline values in Table 3.27, these are limited by the finite number of covariates chosen, and it is highly likely that residual confounding will remain"* This limitation is also stated elsewhere in the report.	The statement should be amended as follows: *"Although methods for confounder adjustment appear robust, as evidenced by the adjusted baseline values in Table 3.27,* ***and all clinically relevant confounding variables were adjusted for given the available data and as identified via an SLR and validated by clinical experts, bias due to residual confounding cannot be entirely excluded as with any non-randomised comparison****"* This should be updated throughout the ERG report as needed.	Use of '*the finite number of covariates chosen'* implies that key variables were excluded. This is not the case as covariates were included if they were identified by the SLR, validated by clinicians and had available data from CHRYSALIS and the RWE sources. Therefore, all clinically relevant covariates that could be considered were adjusted for in the analysis.	'finite number of' deleted.
Page 83 of the ERG report states: *"The company explains that the US data were deemed relevant to the UK population on the basis of expert opinion, but the exact nature of this opinion was not described."*	The statement should be removed.	The expert opinion surrounding the relevance of the US data is detailed in the advisory board minutes provided as part of the reference pack for the CS.	Not a factual error, no change made to report.
Table 4.1 on Page 87 of the ERG report states that conference proceedings search dates are *"Not reported"*.	A footnote should be added with the following text: *"****The Company did not report these search dates as these sources were searched following the conclusion of each conference, meaning that the conference programme would not change thereafter. Therefore, the date of when searches were conducted is not necessary to ensure the searches are reproducible****."*	This footnote is necessary for clarity that this is not an omission or methodological error in the SLR, but rather is not necessary information for reproducibility of results as it relates to conference proceedings (in contrast to other sources where the date searched would influence the number of hits).	Not a factual error, no change made to report.

Page 91 of the ERG report states: *"However, there were a number of problems with the eligibility criteria (listed below) which introduce uncertainty to the SLR's results.* • *TKIs were included as comparators (see Sections 1, 2, 3 for the potential problems with this).* • *It is unclear why original research studies published before 2018 were acceptable whereas congress abstracts published before 2018 were not.* • *The exclusion of non-English studies could have led to some relevant studies being missed.* • *In addition, there were some issues with the review methodology which potentially impinge on the ability of the review to ensure that the eligibility criteria were adhered to, including:* o *The data extraction was not completed by two independent reviewers, which increases the risk of*	The first, second and fourth bullet points should be removed.	For the first bullet point, whilst the ERG may have concerns with the inclusion of TKIs in the SoC basket from a clinical and cost-effectiveness perspective, their inclusion in the SLR has no impact on the validity of the SLR and does not introduce additional uncertainty in the SLR results. For the second bullet point, the rationale for this is stated in the Appendices of the CS: *"The rationale for limiting these searches to the last four years (i.e. 2018 to 2021) was that it was anticipated that any relevant, high-quality conference research published prior to this date would have since been developed into a full manuscript and would therefore have been found in the electronic database searches."* For the fourth bullet, although not stated explicitly in the CS, the extraction of data for the economic SLR was conducted by two independent reviewers. For quality assessment, as highlighted in a previous row of this table relating to Page 51 of the ERG report, quality assessments were completed by one reviewer and	Amended.

mistakes made at this stage. o *It is unclear whether the quality assessment was conducted by independent reviewers, which makes the quality assessments less robust."*		verified by a second independent reviewer.	
Page 94 of the ERG report states: *"As reported in Table 38 of the CS, the company assumed [redacted] of the comparator basket to exist of EGFR TKIs. It is, however, unclear to the ERG whether this is consistent with UK clinical practice, especially given that, as reported on Page 23 of the CS, Exon20ins mutations have been associated with resistance to EGFR TKIs."*	This statement should be amended as follows: *"As reported in Table 38 of the CS, the company assumed [redacted] of the comparator basket to exist of EGFR TKIs. It is, however, unclear to the ERG whether this is consistent with UK clinical practice, especially given that, as reported on Page 23 of the CS, Exon20ins mutations have been associated with resistance to EGFR TKIs.* ***UK RWE suggests that despite the limitations of TKI treatment, patients within UK clinical practice are still given TKIs.****"*	Evidence has been provided by the Company to support that TKIs are being used in this setting in UK practice. This should be reflected in the ERG report. The [redacted] reported here is also factually inaccurate and must have academic in confidence highlighting applied to it (as done here) – please see the typographical errors and confidentiality highlighting errors sections, respectively.	Not a factual error, no change made to report.
Table 4.8 on Page 105 of the ERG report provides the summary of drug costs, administration costs, AE management costs, disease management costs and subsequent treatment cycle costs. However, the	The initial cycle drug costs should be added here.	As both initial cycle drug costs and subsequent cycle drug costs are included in the model, both should be presented in the table for completeness.	Change made to table.

table does not include the initial cycle drug costs as per Table 60 of the CS.			
Page 95 of the ERG report states: *"For amivantamab PFS, the company selected the log-logistic model."*	This statement should be amended to: *For amivantamab PFS, the company selected the **generalised gamma** model.*	This change is to accurately reflect the parametric distribution used to model amivantamab PFS in the Company base case.	Change made to text.
Page 108 of the ERG report states: *"The CS does not provide any information on these clinical experts or advisory boards (i.e., what kind of experts, how issues were presented, what topics were discussed)."*	This statement should be amended to reflect that further information was provided on the advisory boards in response to question B20 at clarification question stage.	This change should be made to prevent misinterpretation that further details on the elicitation of clinical expert opinion was not provided by the Company.	The ERG believes that the company is referring to question B21. Text amended.
Page 108 of the ERG report states: *"No external data was used to validate outcomes in the CS base case model. In the CS, it is stated that parametric distributions were selected based on clinical expert input. This selection process did not involve external data."*	This statement should be amended as follows, to reflect the context given in clarification question B20: *No external data was used to validate outcomes in the CS base case model. **External data from previous NICE evaluations and one published paper was provided in response to clarification questions. [reference Dersarkissian et al. (2019)] However, the ability to conduct external validation is limited due to the rare nature of EGFR Exon20ins mutations leading to a scarcity of published data in the relevant population with which to validate outcomes.** In the CS, it is stated that parametric distributions were selected based on clinical expert input. This selection process did not involve external data."*	This change should be made to prevent misinterpretation that further external validation of model outcomes was not provided by the Company.	Not a factual error, no change made to report.

Issue 2 Typographical errors

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 12 of the ERG report states: *"The company assumed [redacted] of the comparator basket to consist of epidermal growth factor receptor tyrosine kinase inhibitors (EGFR TKIs) which may not be consistent with UK clinical practice; the relative cost effectiveness of amivantamab is therefore unclear."*	The statement on Page 12 should be amended as follows: *"The company assumed [redacted] of the comparator basket to consist of epidermal growth factor receptor tyrosine kinase inhibitors (EGFR TKIs) which may not be consistent with UK clinical practice; the relative cost effectiveness of amivantamab is therefore unclear."* All other instances of this value error should also be corrected.	The statement contains a typographical error.	Corrected.
Nintedanib is misspelt throughout the document. The first instance of this is found on Page 15 of the ERG report: *"Some of the comparators (especially tyrosine kinase inhibitors (TKIs) other than **nintendanib**) lack justification and could have exaggerated the benefits of amivantamab."*	The statement on Page 15 should be amended as follows: *"Some of the comparators (especially tyrosine kinase inhibitors (TKIs) other than **nintedanib**) lack justification and could have exaggerated the benefits of amivantamab."* All other instances of this spelling error should also be corrected.	The statement contains a typographical error.	Corrected.
Table 1.15 on Page 20 of the ERG states: *"Matter of judgement (4-**TTTD** informed by the CHRYSALIS trial protocol)"*	The statement in Table 1.15 should be amended as follows: *"Matter of judgement (4-**TTD** informed by the CHRYSALIS trial protocol)"*	The statement contains a typographical error.	Corrected.

Page 26 of the ERG report states: *"The main difference between the population defined in the NICE scope listed below (CS, Table 1, Page 10)"*	This sentence is incomplete and thus unclear, so should be amended. Since the meaning of the statement is unclear, the Company cannot provide a suggested amendment.	Amendment is necessary for this statement to be interpreted correctly.	Corrected.
Page 30 of the ERG report states: *"According to the company, **trastuzumab emtansine** is innovative because it is the first targeted treatment for adult patients with EGFR Exon20ins mutated NSCLC."*	The statement is should be amended as follows: *"According to the company, **amivantamab** is innovative because it is the first targeted treatment for adult patients with EGFR Exon20ins mutated NSCLC."*	The statement contains a typographical error.	Corrected.
Page 51 of the ERG report states: "In addition, the supportive efficacy trial population (N=81) was used including data until the 8th June 2020."	The statement should be amended as follows: *"In addition, the supportive efficacy trial population (N=81) was used including data until the **30th March 2021**."*	The statement contains a typographical error.	Corrected.
Page 72 of the ERG report states: *"The more commonly reported TEAEs included infusion related reactions (63.4%), paronychia (**52.9**), rash (43.1%), and dermatitis acneiform (39.2%)."*	The statement should be amended as follows: *"The more commonly reported TEAEs included infusion related reactions (63.4%), paronychia (**52.9%**), rash (43.1%), and dermatitis acneiform (39.2%)."*	The statement contains a typographical error.	Corrected.
Page 84 of the ERG report states: *"PFS (median) was 6.74 months for BICR (**05%** CI 5.45 to 9.66) and 6.93 months for INV (95% CI 5.55 to 8.64)"*	The statement should be amended as follows: *"PFS (median) was 6.74 months for BICR (**95%** CI 5.45 to 9.66) and 6.93 months for INV (95% CI 5.55 to 8.64)"*	The statement contains a typographical error.	Corrected.

Table 3.7 on Page 46 of the ERG report gives the following values: *"Sex, n (%); Male: 70 (61.4); Female: 44 (38.6)"*	The values should be amended as follows: *"Sex, n (%); Male: **44 (38.6)**; Female: **70 (61.4)**"*	The statement contains typographical errors.	Corrected.
Page 94 of the ERG report states: *"The four treatment classes included in this basket were IO agents ([redacted]), EGFR TKIs ([redacted]), platinum-based chemotherapy regimens ([redacted]) and non-platinum-based chemotherapy regimens ([redacted]). For costing purposes, the individual treatments considered in each of these four treatment classes were as follows:"*	The values should be amended as follows: *"The four treatment classes included in this basket were IO agents ([redacted]), EGFR TKIs ([redacted]), platinum-based chemotherapy regimens ([redacted]) and non-platinum-based chemotherapy regimens ([redacted]). For costing purposes, the individual treatments considered in each of these four treatment classes were as follows:"*	The statement contains typographical errors.	Corrected.
Table 5.1 on Page 107 of the ERG report gives the following values: *"UK SoC; Total costs: [redacted]; Total LYs: [redacted]"*	The values should be amended as follows: *"UK SoC; Total costs: [redacted]; Total LYs: [redacted]"*	The statement contains typographical errors.	Corrected.

References

1. EMC. Rybrevant (amivantamab) 50mg/mL concentrate for solution for infusion. Available at: https://www.medicines.org.uk/emc/product/13084 [Accessed: 20 January 2022].

NICE National Institute for Health and Care Excellence

Technical engagement response form

Amivantamab for treating EGFR Exon 20 insertion-positive non-small-cell lung cancer after platinum-based chemotherapy [ID3836]

As a stakeholder you have been invited to comment on the evidence review group (ERG) report for this appraisal.

Your comments and feedback on the key issues below are really valued. The ERG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the ERG report that are likely to be discussed by the committee. The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the ERG report.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

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.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under [redacted], all information submitted under [redacted], and all information submitted under [redacted] in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

Deadline for comments by **5pm** on **Monday 13 June**. 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

About you

Your name	[redacted]
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	Janssen-Cilag Ltd
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	N/A

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the ERG report.

Key issue	Does this response contain new evidence, data or analyses?	Response
Issue 1: The narrower population considered by company may not be generalisable to the England and Wales NHS population and may have led to an underestimate of adverse events	No	The NICE final scope defines the population as "adults with EGFR Exon 20 insertion-positive non-small-cell lung cancer after previous platinum-based chemotherapy."[1] However, as outlined in response to Clarification Question A3, the marketing authorisation for amivantamab from the Medicines and Healthcare products Regulatory Agency (MHRA) is narrower than the population defined in the scope, and considers adult patients with locally advanced or metastatic NSCLC with activating EGFR Exon20ins mutations, whose disease has progressed on or after platinum-based chemotherapy. The population considered within this submission is aligned with the marketing authorisation, and the clinical effectiveness evidence for these patients is sourced from the Cohort D+ of the CHRYSALIS trial. As noted by the ERG, minor differences exist between this Cohort D+ population of the CHRYSALIS trial and the marketing authorisation of amivantamab due to the inclusion criteria of the CHRYSALIS trial: patients in the CHRYSALIS trial had to have histologically- or cytologically-confirmed NSCLC that was metastatic or unresectable and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. Restrictions such as limiting a clinical trial to patients with ECOG status of 0 or 1, are common for oncology treatments.

		The population of the CHRYSALIS trial, recruited from 11 countries including the UK, is generalisable to UK clinical practice despite being slightly narrower than the marketing authorisation. This was validated by feedback from UK-based clinicians at a Janssen-led advisory board who confirmed that the baseline characteristics of patients included in the study were comparable to the characteristics of patients with EGFR-mutated Exon20ins NSCLC that they would expect to treat in their typical clinical practice. The clinicians further validated that the baseline characteristics of the CHRYSALIS trial were consistent with those of the UK-based patients included in the Public Health England (PHE) dataset (see Section 2.9 of the company submission [CS]), additionally supporting their generalisability to the UK population of interest.[2] In addition, Janssen wish to emphasise that as compared with typical patients with late-stage lung cancer, patients with non-smoking lung cancers (which is the majority of EGFR Exon20ins NSCLC) are generally younger and fitter, which is often reflected by lower ECOG performance scores than would be typical for patients with other late-stage lung cancers. Indeed, data from the market research study that assessed medical records for 50 patients with EGFR Exon20ins NSCLC showed that 94% had ECOG status 0 or 1 with only 6% having ECOG status 2.[3] As such, unlike other cancer indications where the exclusion of patients with lower ECOG performance scores could lead to an underestimation of adverse events, as is the concern of the ERG, this will likely not be the case for patients in the CHRYSALIS trial where even patients with relatively late-stage disease could have maintained lower ECOG performance scores. Overall, as acknowledged by the ERG on Page 28 of the ERG report, this should not be regarded as a key issue given that NICE can appraise and recommend interventions within the licensed population only which permits equitable access to new therapies for patients who are not able to enrol in clinical trials. This is reflected by prior NICE recommendations in which the licensed indication is broader than the inclusion criteria of the pivotal clinical trial (Table 1).

Table 1: Examples of previous NICE technology appraisals in NSCLC in which the licensed indication is broader than the clinical trial population

NICE TA (intervention)	Population as per scope	Licensed population	Population as per clinical trial
TA520 (atezolizumab)[4]	Adult patients with locally advanced or metastatic NSCLC after prior chemotherapy	Adult patients with locally advanced or metastatic NSCLC after prior chemotherapy. *(Patients with EGFR-activating mutations or ALK-positive tumour mutations should also have received targeted therapy before receiving atezolizumab)*	Adult patients with locally advanced or metastatic NSCLC after prior chemotherapy, patients within the clinical trial were also subject to inclusion/exclusion criteria including ECOG score of 0 or 1, life expectancy ≥12 weeks and adequate hematologic and end-organ function
TA484/TA713 (nivolumab)[5, 6]	People with PD-L1–positive previously treated locally advanced or metastatic non-squamous non-small-cell lung cancer after prior chemotherapy	Adult patients with locally advanced or metastatic NSCLC after prior chemotherapy	Patients aged ≥18 with advanced or metastatic non-squamous NSCLC after failure of prior platinum doublet-based chemotherapy and an ECOG score or 0 or 1
TA347 (nintedanib in combination with docetaxel)[7]	Patients with locally advanced, metastatic or recurrent NSCLC of	Adult patients with locally advanced, metastatic or locally recurrent NSCLC of	Patients with histologically or cytologically confirmed stage IIIB

		<table><tr><td></td><td>adenocarcinoma tumour histology after first-line chemotherapy</td><td>adenocarcinoma tumour histology after first-line chemotherapy</td><td>or IV, or recurrent NSCLC with relapse or failure of 1 prior first-line chemotherapy. Patients must also have an ECOG score of 0 or 1 and be ≥18 years</td></tr></table> **Abbreviations:** ECOG: Eastern Cooperative Oncology Group; NSCLC: non-small cell lung cancer; PD-L1: programmed death ligand 1; TA: technology appraisal.
Issue 2: Patients in the intervention group received concomitant medications (including targeted radiotherapy) that could have exaggerated the benefits of amivantamab	Yes	As per the CHRYSALIS trial protocol, permitted medications and therapies that could be received by patients during the trial were strictly controlled and defined:[8] • Symptomatic treatment: supportive care, such as antibiotics or analgesics, or concomitant medications for the symptomatic treatment of related toxicities (Grades I–IV) at the treating physician's discretion and as clinically indicated • Prophylactic medications: appropriate antiemetic regiments, rash prophylaxis, pre- and post-infusion medications and prophylaxis for chemotherapeutic agents • Localised, limited radiotherapy of short duration (e.g., five days) for palliative purposes, which could be permitted only after discussion with, and approval by, the medical monitor. As such, given their considerable clinical relevance, it would have been ethically inappropriate for these medications not to be provided, particularly in the case of short-term radiotherapy as part of palliative care. With respect to the potential confounding of amivantamab efficacy results due to receipt of concomitant medications, Janssen consider that as an active anti-cancer

		treatment, targeted radiotherapy may confound efficacy results, whereas medications used for the treatment or prevention of disease symptoms and treatment-related reactions are less likely to do so as they would be given in clinical practice anyway. To investigate this further, Janssen conducted an updated adjusted treatment comparison excluding the three patients who received targeted radiotherapy and versus the US RWE using the IPW ATT methodology. These results show that, when incorporating the updated amivantamab overall survival data and excluding patients who received targeted radiotherapy from the amivantamab arm amivantamab is associated with an adjusted hazard ratio (HR) versus UK SoC of [redacted] for overall survival (OS), [redacted] for progression-free survival (PFS) and [redacted] for time to next treatment (TTNT). The results are very similar to those from the analysis of the full population including updated data from CHRYSALIS for OS ([redacted] for OS, [redacted] for PFS and [redacted] for TTNT. Thus, the exclusion of patients who received targeted radiotherapy has a negligible impact. Detailed results for this analysis are presented in Appendix 2. Additionally, a cost-effectiveness scenario analysis has been conducted in which these patients are excluded. The results of the cost-effectiveness scenario in which patients who received targeted radiotherapy were excluded from the amivantamab treatment arm are presented in Appendix 5. These results show that exclusion of the three patients who received targeted radiotherapy marginally reduces the with-PAS ICER from £38,021/QALY gained to £37,440/QALY gained. To retain clinical effectiveness from the full population, and given this scenario produced results that are in close alignment with the base case approach indicating it

does not impact overall cost-effectiveness conclusions, this approach has not been implemented in the updated base case.

Note: As requested by the ERG as part of this issue, in the scenario described above, safety data for the equivalent population were implemented in the model, as presented in **Error! Reference source not found.**. As outlined in Section B.3.3.3 of the CS, the AEs considered in the model were Grade ≥3 AEs that were reported in more than 5% of patients in any of the key clinical trials for amivantamab or any of the comparator treatment classes. The exception was the incidence of diarrhoea, which was considered at any grade due to its clinical relevance.

Table 2: Incidence of Grade ≥3 AEs occurring in the amivantamab treatment arm in the CHRYSALIS population excluding patients who received concomitant targeted radiotherapy (N=111) scenario population

AE, %	Scenario analysis population (N=111, 30th March 2022 data cut-off)
Anaemia	[redacted]
Diarrhoea[a]	[redacted]
Fatigue	[redacted]
Febrile neutropenia	[redacted]
Neutropenia	[redacted]
Neutrophil count decreased	[redacted]
Rash	[redacted]
Thrombocytopaenia	[redacted]

[a] Due to its clinical relevance, the incidence of diarrhoea was considered at any grade.
Abbreviations: AE: adverse event.

Issue 3: Some of the comparators lack justification and could have obscured or exaggerated the benefits of amivantamab	Yes	This issue appears to relate mainly to the inclusion of TKIs in UK SoC for the adjusted comparison analysis versus amivantamab. It is linked to Key Issue 7, which we believe relates to the inclusion of TKIs in the cost-effectiveness analysis. Janssen acknowledge that EGFR tyrosine kinase inhibitors (TKIs) have relatively limited efficacy in the population of interest. However, market research and RWE supports that TKIs are used within this population. Market research of oncologists and pulmonologists from the UK found that TKIs are clearly used for patients with Exon20ins mutated NSCLC at second line and beyond.[3] TKI use is also supported by RWE from both the US and UK, where TKIs represent [redacted] and [redacted] of treatment lines in the pooled US databases and the UK database, respectively. As such, Janssen maintain that inclusion of TKIs in the comparator basket is reflective of UK clinical practice. However, to address the ERG's concerns that, due to limited efficacy of TKIs, their inclusion in the comparator basket could favour amivantamab, an updated ITC was performed at the Clarification Questions stage in which TKIs are removed from the RWE data. The results of this scenario analysis have now been updated to include the updated amivantamab OS data (as given in response to Key Issue 4) and are presented in Table 3 and Appendix 2. The updated results for the base case adjusted treatment comparison analysis (with the full CHRYSALIS population and including TKIs in the basket comparator) are also presented in Appendix 2. Whilst this analysis has been conducted in response to the ERG request, Janssen emphasises that the analysis and its results cannot be relied on for decision making as excluding TKIs does not represent the reality of current clinical practice in the UK. We have presented compelling evidence that TKIs are being used within this population (their clinical effectiveness notwithstanding) meaning the analyses do not reflect real-

		world clinical practice. Further, the current analysis does not account for the following factors: • There is no evidence to support which treatments patients currently treated with TKIs would receive if they did not receive TKIs, whether their inclusion in other treatment classes would alter the efficacy of that treatment class (if patients receiving TKIs have specific characteristics that distinguish them from those receiving other regimens), or how the exclusion of TKIs would impact the use of amivantamab at the margin. • Although Exon 20ins mutations may confer resistance to EGFR TKIs, published evidence suggests that TKIs may be associated with a modest anti-tumour effect in some of these patients.[9] However, it is unknown whether the patients within the UK SoC cohort who respond to TKIs systematically differ from those who do not, adding to the considerable uncertainty associated with redistributing these patients to other treatments. As such, this analysis cannot be meaningfully interpreted in the context of current UK clinical practice, instead it represents theoretical best practice in a hypothetical situation in which patients are completely interchangeable. Therefore, Janssen maintain that this analysis is methodologically inappropriate and thus insufficiently robust to inform decision-making. The results of the updated adjusted treatment comparison show that, compared with the updated base case approach (see Appendix 1), the exclusion of TKIs from the comparator basket had a minimal impact on the HRs and produced an adjusted OS HR for amivantamab versus SoC of [redacted]), versus [redacted] when considering the base case analysis. Therefore, these results indicate that the efficacy of the SoC arm is consistent regardless of the inclusion of TKIs, and is even more consistent when compared to the results from the previous data cut-off

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<td>from CHRYSALIS, as per Clarification Question A6 ([redacted] for the base case versus [redacted] when excluding TKIs).

Table 3: Comparison of adjusted treatment comparison results for scenario analysis for CHRYSALIS vs. US RWE excluding TKIs
<table>
<tr><th rowspan="2">HR (95% CI)</th><th colspan="2">Original analysis (30th March 2021 data cut)</th><th colspan="2">Updated analysis (7th March 2022 data cut)</th></tr>
<tr><th>Base case</th><th>Scenario excluding TKIs</th><th>Base case</th><th>Scenario excluding TKIs</th></tr>
<tr><td>OS</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>PFS BICR[a]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>TTNT[a]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
</table>
[a] PFS and TTNT data remain unchanged as compared with the previous data cut.
Abbreviations: BICR: blinded independent committee review; CI: confidence interval; HR: hazard ratio; OS: overall survival; TKI: tyrosine kinase inhibitor; TTNT: time to next treatment.

Consideration of the impact of excluding TKIs on the cost-effectiveness data is discussed in Issue 7, with a scenario analysis demonstrating that including TKIs in the comparator basket is a conservative approach.</td>
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<td>Issue 4: The short follow-up time of the CHRYSALIS trial makes medium- and longer-term results uncertain</td>
<td>Yes</td>
<td>In order to address the ERG's concerns regarding the relatively short follow-up of the CHRYSALIS trial, an updated OS data cut from CHRYSALIS that has become available since the time of submission has now been incorporated. These data are from a 7th March 2022 data cut and represent an additional 12 months of follow up compared with the originally submitted data (Table 4). This data cut was conducted to</td>
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<td>provide more mature OS data, which were relatively immature compared with the other outcomes at the time of the previous data cut-off.

Table 4: CHRYSALIS OS data
<table>
<tr><th></th><th>Previous data-cut (30th March 2021)</th><th>Updated data cut (7th March 2022)</th></tr>
<tr><td>Median follow-up, months</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Median OS, months (95% CI)</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Censoring rate</td><td>[redacted]</td><td>[redacted]</td></tr>
</table>
OS is defined as the time from first infusion of amivantamab to death due to any cause.
Abbreviations: CI: confidence interval; NE: not evaluable; OS: overall survival.

Data from this updated data cut are broadly in alignment with the data cut-off used to inform the original submission but demonstrate a slightly extended median OS. They also show a reduction in censoring rates to [redacted], as compared with [redacted] at the previous data cut-off.

These data are included in the updated economic base case (see Table 7). In addition, the following are provided in Appendix 1 in relation to these updated OS data:

• Updated diagnostic and hazard plots
• Updated adjusted treatment comparison for amivantamab versus UK SoC in the full CHRYSALIS population</td>
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<td>Issue 5: The efficacy and safety populations differ in a way that is likely to exaggerate the benefits and understate harms</td>
<td>Yes</td>
<td>In their report, the ERG note that the efficacy (N=114) and safety (N=153) populations implemented within the economic model differ in a way that is likely to exaggerate benefits and understate harms. Although a larger safety population was used in order to gather safety data from as large a group of patients as possible, we present the safety results for the efficacy population (N=114) at the March 2021 data cut so as to</td>
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reassure the ERG that the difference in population sizes does not have a large impact on the safety profile of amivantamab. These safety data for the N=114 population have been incorporated into the updated economic base case (Table 7).

Safety data that inform the economic model are presented in Table 5 for the N=114 population at the March 2021 data cut. For ease of comparison, the N=153 data implemented in the CS are also presented. AEs considered in the model were Grade ≥3 AEs that were reported in more than 5% of patients in any of the key clinical trials for amivantamab or any of the comparator treatment classes, except for diarrhoea, which was considered at any grade due to its clinical relevance. The full safety data from the N=114 population are presented in Appendix 1.

These N=114 data show that the safety profile of amivantamab is very similar between the N=114 and N=153 populations. A similar percentage of patients experienced Grade ≥3 AEs ([redacted] and [redacted]) and serious AEs related to amivantamab ([redacted] and [redacted]) in the N=153 and N=114 populations, respectively.

Table 5: Incidence of Grade ≥3 AEs occurring in ≥5% of patients

AE, %	Safety population (N=153, 30th March 2021 data cut-off)	Efficacy population (N=114, 30th March 2021 data cut-off)
Anaemia	[redacted]	[redacted]
Diarrhoea[a]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]
Febrile neutropenia	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]
Neutrophil count decreased	[redacted]	[redacted]
Rash	[redacted]	[redacted]

		Thrombocytopaenia | [redacted] | [redacted] [a] Due to its clinical relevance, the incidence of diarrhoea was considered at any grade. **Abbreviations:** AE: adverse event.
Issue 6: The real-world evidence (RWE) sources to identify comparators for the indirect treatment comparison were not comprehensive, leading to uncertainty in the benefits of amivantamab compared with relevant comparators	No	As discussed in Section B.1.3 of the CS, the rarity of Exon20ins mutations coupled with the single arm nature of the CHRYSALIS trial meant there are limited comparative data available for these patients. This was demonstrated by the results of the clinical SLR which did not identify any relevant studies comparing amivantamab to other treatments in this indication. Therefore, it was necessary to conduct an indirect comparison in order to obtain comparative efficacy data for use within this submission. In order to identify studies with which to conduct this comparison, the results of the clinical SLR were considered. Specifically, the search sought to identify any relevant clinical or real-world evidence in the form of randomised controlled trials (RCTs), interventional non-RCTs (i.e. non-randomised and uncontrolled clinical studies, including compassionate use programmes), observational studies such as prospective/retrospective cohorts, case-control or chart reviews, or case series. No relevant evidence sources with which to conduct the adjusted treatment comparison were identified. As such, Janssen opted for a pragmatic approach of initiating RWE studies utilising accessible data sources from the US (Flatiron, COTA and ConcertAI) and the UK (PHE, NHS Digital) RWE cohorts. Such databases are commonly used to inform comparator data in similar analyses, particularly in rare disease indications where data are sparse. Additionally, PHE data are the most relevant to the UK, directly reflecting UK clinical practice. Although it cannot be guaranteed that all possible sources of data were identified (as although a systematic search for RWE *studies* was conducted, a systematic search for RWE *sources* [i.e. databases] was not), Janssen are pleased to read acknowledgement by the ERG that the sources of data used are not unsuitable or inappropriate (ERG report pages 79 and 80). Based on the above and due to the short

		time frame of technical engagement, a systematic search for further data sources has not been conducted.
Issue 7: The company assumed [redacted]% of the comparator basket to consist of epidermal growth factor receptor tyrosine kinase inhibitors (EGFR TKIs) which may not be consistent with UK clinical practice; the relative cost effectiveness of amivantamab is therefore unclear	Yes	Whilst Janssen maintains that the inclusion of TKIs in the comparator basket is appropriate as outlined in response to Key Issue 3 above, a cost-effectiveness scenario analysis in which the clinical efficacy and costs associated with TKIs are excluded from the UK SoC comparator has been conducted in order to address the concerns of the ERG regarding their inclusion. Results of this scenario analysis are presented in Appendix 5 and indicate that removing TKIs from the comparator arm is not considerably impactful on the ICER (with amivantamab PAS), reducing it from £38,021/QALY gained to £33,272/QALY gained. However, Janssen would like to reiterate that analyses excluding TKIs cannot be meaningfully interpreted in the context of UK clinical practice, nor is it reflective of the treatments that real-world evidence shows to be used in these patients, and as such is inappropriate for decision making (see response to Key Issue 3).
Issue 8: The company implemented Kaplan-Meier (KM) curves instead of parametric survival models for the survival analyses of overall survival (OS) and progression-free survival (PFS) in the standard of care (SoC) arm, leading to potential overfitting of modelled survival outcomes	No	Based on NICE DSU TSD 14, the ERG stated that they would prefer parametric models to be implemented rather than using KM curves to inform OS and PFS for the UK SoC arm. Parametric survival modelling was presented as a scenario in Clarification Question B5, demonstrating the minimal impact of the assumption on the results of the cost-effectiveness analysis. Janssen maintain that KM curves are more appropriate for the base case, as the mature OS and PFS data means all events are captured.

Issue 9: time to treatment discontinuation (TTD) was assumed to be equal to the duration of PFS, while evidence from the CHRYSALIS trial showed that amivantamab treatment had a longer median duration than PFS, leading to a possible underestimate of amivantamab's relative cost	Yes	As discussed in Section B.3.3.2.3 of the CS and in response to Clarification Question B.8, Janssen wish to emphasise that UK-based clinicians stated that patients would discontinue treatment with amivantamab upon experiencing a progression event, and thus we maintain that the assumption that time to treatment discontinuation (TTD) is equal to PFS is appropriate. However, in acknowledgement of the concerns of the ERG regarding this assumption, two scenario analyses were presented in response to Clarification Question B.8 in which time on treatment (ToT) for amivantamab was modelled using TTD data from the CHRYSALIS trial. In both scenarios, the Gompertz curve was selected for amivantamab, while ToT for UK SoC was implemented using KM PFS data (as per the base case approach) or by KM time to next treatment (TTNT) data, since TTD data are not available. To address the concerns of the ERG regarding the amivantamab TTD curve choice, additional information as per NICE DSU TSD 14 criteria is presented in Appendix 4. The smoothed hazard curve for TTD in the CHRYSALIS trial (Figure 24) shows that the hazard does not remain constant over time, instead decreasing initially before increasing from around Month 5, in line with the Weibull or Gompertz distributions. This would rule out the exponential curve given its inherent assumption of a constant hazard over time means that it does not represent an appropriate curve choice As further outlined at the Clarification Question response stage, Janssen consider that the use of TTD for amivantamab whilst maintaining an assumption that ToT is equal to PFS for the UK SoC treatment arm penalises the amivantamab arm unfairly given it assumes treatment beyond progression only in the amivantamab arm and we welcome acknowledgement by the ERG that this approach may indeed be conservative (ERG report, page 98). To investigate the impact of a less pessimistic approach, a novel economic analysis was explored, in which the proportion of patients in the amivantamab or UK SoC arm for whom ToT is assumed to be equal to PFS can be varied between 0% and 100%. For patients for whom this assumption does not apply,

		ToT is modelled using TTD data from CHRYSALIS (amivantamab arm, Gompertz distribution) or TTNT data from the US RWE cohort (UK SoC, KM data). In order to reflect the opinion of the ERG that clinical reality is likely to fall somewhere between the two approaches considered so far (that ToT is equal to PFS for all patients, or that ToT is equal to TTD/TTNT for all patients), a scenario analysis was performed in which 50% of all patients, regardless of treatment arm, discontinue treatment at progression. The with-PAS ICER is £35,231/QALY gained, which is decreased from the base case ICER of £38,021/QALY gained and lies between the ICERs of the two extremes. In addition, it is important to note that patients in clinical trials are monitored more closely than in the real world and as such, progression in CHRYSALIS would have been detected earlier than it would in real-world clinical practice. Progression is not a hard stop, rather it evolves at the cellular level before impacting patient health-related quality of life (HRQoL). Therefore, the use of early detected progression to inform HRQoL may underestimate the benefit of amivantamab. Janssen consider that the proposed data collection plan if amivantamab were placed on the CDF, as outlined in Section B.2.11 of the original CS, would help to reduce the uncertainty associated with real world time on treatment by permitting assessment of when patients discontinue treatment in practice.
Issue 10: The company did not explore treatment waning in the model, whereas the Evidence Review Group (ERG) considered that the assumption of a lifelong	Yes	As discussed in detail in response to Clarification Question B6, and as there is no evidence to suggest the waning of treatment effect, Janssen maintain that the incorporation of explicit treatment effect waning for amivantamab is inappropriate. Amivantamab is a continuous, treat-to progression treatment and as such, patients receive the intervention until they experience a progression event, rather than for a pre-specified period of time, and the poor prognosis of patients with EGFR Exon20ins

treatment effect may not be warranted		mutated NSCLC means that they are unlikely to experience treatment effect waning within their lifespan. Furthermore, as illustrated in Figure 5, the updated data cut for OS (presented in response to Key Issue 4 and in Appendix 1) shows that the treatment benefit of amivantamab has remained consistent as the follow up period has increased. The maintenance, and marginal improvement, of the observed median OS between this data cut ([redacted] months at [redacted] months of follow up) and the previous data cut ([redacted] months at [redacted] months of follow up) supports that the treatment effect for amivantamab is durable. However, if any treatment effect waning were to be observed, Janssen reiterate that it would be captured implicitly within the modelled curves because UK clinicians consulted in an advisory board confirmed that the long-term outcomes in terms of the proportion of patients alive or progression-free at the 2- and 5-year timepoints, were aligned with their clinical expectation. As such, there is no reason to add treatment effect waning on top of the modelled curves. An approach in which treatment waning is not explicitly applied is in line with the approach taken and accepted by the NICE Committee in a recent NICE appraisal for tepotinib in advanced NSCLC with MET gene alterations (TA789), and similarly, explicit waning was not implemented or discussed within the NICE appraisals for afatinib (TA310) or osimertinib (TA653).[10-12] By contrast, treatment waning assumptions have been implemented in prior appraisals of treatments with a fixed treatment duration, such the nivolumab (TA655) and atezolizumab (TA520) appraisals which considered waning after a two year stopping rule, reflecting that these patients are not modelled to receive continuous treatment.[4, 13] However, to respond to the ERG's request, a scenario analysis is presented in which waning is applied to the OS and PFS treatment effect of amivantamab. In this scenario, treatment effect waning is modelled to begin three years after the cessation of amivantamab treatment, from which point it wanes linearly until it reaches the same

		efficacy as the UK SoC comparator (hazard ratio: 1) at the end of the time horizon (15 years). The three-year starting point of treatment waning is in line with the most conservative time point explored in TA428 and TA713.[6, 14] Results of this scenario analysis are presented in Appendix 5. These results show that the implementation of treatment waning has a minimal effect on the overall cost-effectiveness results, increasing the with PAS ICER from £38,021/QALY gained to £39,012/QALY gained.
Issue 11: The company's failure to include an age-adjustment to the health state utilities in their company submission (CS) base case is not in line with good modelling practice and may have exaggerated the cost effectiveness of amivantamab	Yes	Given the short time horizon of the economic model, which reflects the limited life expectancy of the population of interest, age adjustment was not applied to the health state utility values in the submitted base case. However, at the request of the ERG, the economic model has been updated to include age adjustment of utilities, as per Hernandez Alava et al. (2022), and this change has been incorporated into the base case (see Table 7).[15]
Issue 12: Lack of a fully incremental analysis for all relevant comparators in the comparator basket, increasing the uncertainty of estimates of amivantamab's cost effectiveness	No	As discussed in detail in response to Part I of Clarification Question B3, RWE and expert clinician feedback confirm that the treatments currently received by patients with EGFR mutated Exon20ins NSCLC are heterogeneous, with no established standard of care. This heterogeneity is reflective of the lack of treatment guidelines or treatment options specifically recommended for these patients. As such, a basket of treatments is the most relevant comparator in this appraisal. As discussed in response to Issue 3 above, the lack of an established standard of care means that there is no rationale for identifying any single treatment which would be displaced by amivantamab. This lack of robust methodology for decision making at the margin means that we could mechanistically conduct the steps for identifying the ratio between incremental costs and effects, but the number of assumptions needing to be

made mean that any such analysis could not be interpreted in a meaningful way, nor would it be clinically relevant. Furthermore, if a fully incremental analysis were to be conducted, the number of patients from the RWE cohort receiving each individual treatment would be small, and therefore, the analysis would be inappropriate to use for decision making.

In addition, a basket comparator has previously been accepted by NICE for decision making, without a fully incremental analysis, in previous appraisals as outlined in Table 6, underscoring the inappropriate nature of this analysis when a basket comparator is considered.[16-20]

Table 6: Examples of previous appraisals that used a basket comparator

NICE TA (intervention)	Comparator	Committee opinion
TA677 (autologous anti-CD19-transduced CD3+ cells)[20]	Standard of care consists of multi-agent chemotherapy and is modelled as a blended comparator comprising rituximab-based therapies	The committee accepted that there was no universally agreed standard of care and that the model containing the basket comparator was appropriate for decision making
TA491 (ibrutinib)[16]	A physician's choice comparator encompassing rituximab with a range of chemotherapy options	The committee concluded that there was no agreed standard of care for treatment and a basket comparator was appropriate
TA559 (axicabtagene ciloleucel)[17]	A blended comparator (termed BSC) comprising salvage chemotherapy (excluding pixantrone)	The committee concluded that there was no standard treatment option and that BSC would be used, usually including salvage chemotherapy

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<tr><td>TA567 (tisagenlecleucel)[18]</td><td>Salvage chemotherapy (excluding pixantrone) without or without rituximab</td><td>The committee concluded that this was the most appropriate comparator as there was no standard salvage chemotherapy regimen used</td></tr>
<tr><td>TA642 (gilteritinib)[19]</td><td>Blended comparator including salvage chemotherapy</td><td>The committee concluded that the blended comparator alongside BSC was the most appropriate comparator</td></tr>
</table>
Abbreviations: BSC: best supportive care; TA: technology appraisal.

As such, a fully incremental analysis is not presented as Janssen consider it is not in line with best methodological practice in situations where there is no established standard of care.
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<td>Issue 13: Lack of a fixed random seed in model probabilistic sensitivity analysis (PSA) leads to fluctuations in probabilistic results and hence increased uncertainty of estimates of amivantamab’s cost-effectiveness</td>
<td>Yes</td>
<td>At the request of the ERG, a fixed random seed has been implemented in the model PSA. Updated probabilistic base case results are presented in Table 9.</td>
</tr>
</table>

Additional issues

All: Please use the table below to respond to additional issues in the ERG report that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this appraisal (for example, at the clarification stage).

Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: The ERG noted a lack of clarity and information surrounding "how 19.6% of patients are experiencing grade 3 or above events related to amivantamab, yet only 8.5% of patients have experienced what is described as a serious AE."	Section 3.2.6.5 (page 77)	No	Janssen would like to clarify that there was a difference between the definitions of serious AEs and Grade ≥3 AEs within the CHRYSALIS trial. The definition of a serious AE was one which resulted in death, was life-threatening, caused hospitalisation, resulted in persistent or significant disability, or was a congenital anomaly or birth defect. By contrast, the grading of AEs was a separate system. For example, the definition of a Grade 3 acneiform rash in CHRYSALIS was "*Papules and/or pustules covering >30% BSA with moderate or severe symptoms; limiting self-care ADL; associated with local superinfection with oral antibiotics indicated*". None of these criteria would meet the definition of seriousness.

			Therefore, an AE in the CHRYSALIS trial could be classed as a Grade ≥3 event but not be considered serious. This underlies the difference noted between the two percentages, but Janssen can confirm that no data discrepancies have been identified.
Additional issue 2: The ERG were not confident that "the five patients included in Cohort D+, that came from Part 1 (dose escalation) of the study met the molecular eligibility requirements."	Section 3.2.1 (page 42)	No	Janssen can confirm that the five patients included in Cohort D+ from Part 1 (dose escalation) of the study met the molecular eligibility criteria requirements and tested positive for the EGFR Exon20ins mutation.
Additional issue 3: The ERG noted that "in both Figure 3.8 (NSCLC-SAQ) and Figure 3.9 (ED-5D-5L) the included number of patients appears to be very small (n=[redacted]) and different from what was reported in the text (n=[redacted])."	Section 3.2.5.6 (page 66)	No	Janssen apologise for this typographical error in the text and can confirm that the correct sample size is [redacted].
Additional issue 4: The ERG noted that "the eligibility criteria stated that only patients with ECOG status 0 or 1 were to be included in the CHRYSALIS trial (Table 3.3), nevertheless, one patient with ECOG status 2 was included (Table 3.7)."	Section 3.2.3 (page 51)	No	This patient had an ECOG status within the eligible range of 0 or 1 at the time of enrolment to the trial. However, by the time treatment with amivantamab was commenced, the patient's performance had changed to ECOG status 2. As this was not considered a protocol deviation, the patient was retained within the trial.

Summary of changes to the company's cost-effectiveness estimate(s)

Base case

Table 7: Changes to the Company's base case cost-effectiveness analysis

Key issue(s) in the ERG report that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact of each change on the company's base-case ICER
		Previously submitted Company base case ICER (with amivantamab PAS): ***£39,764/QALY gained***	
Key Issue 4	OS data for amivantamab sourced from the 31st March 2021 data cut of the CHRYSALIS trial	OS data for amivantamab have been updated to data from the 7th March 2022 data cut of the CHRYSALIS trial, providing a 12-month increase in the follow up time as compared with the previously submitted approach. OS data for the UK SoC arm remain unchanged from the previously submitted base case given they are adjusted to the baseline characteristics of patients from CHRYSALIS, which remain unchanged.	−£2,506
Key Issue 5	Safety data for amivantamab sourced from the CHRYSALIS trial N=153 safety population	Safety data for amivantamab have been updated to data from the N=114 efficacy population of the CHRYSALIS trial	+£264
Key Issue 11	Health state utility values are not age-adjusted	Health state utility values are age-adjusted as per Hernandez Alava *et al*. (2022).[15]	+£529
		Updated Company base case ICER (with amivantamab PAS): ***£38,021/QALY gained***	

Abbreviations: ICER: incremental cost-effectiveness ratio; OS: overall survival; PAS: patient access scheme; SoC: standard of care.

Table 8: Updated base case results at amivantamab PAS price (deterministic)

	Total			Incremental			ICER (£/QALY)
	Costs	QALYs	LYs	Costs	QALYs	LYs	
UK SoC	[redacted]	[redacted]	[redacted]	-	-	-	-
AMI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£38,021

Abbreviations: AMI: amivantamab; ICER: incremental cost-effectiveness ratio; LY: life years; PAS: patient access scheme; QALYs: quality-adjusted life years; SoC: standard of care.

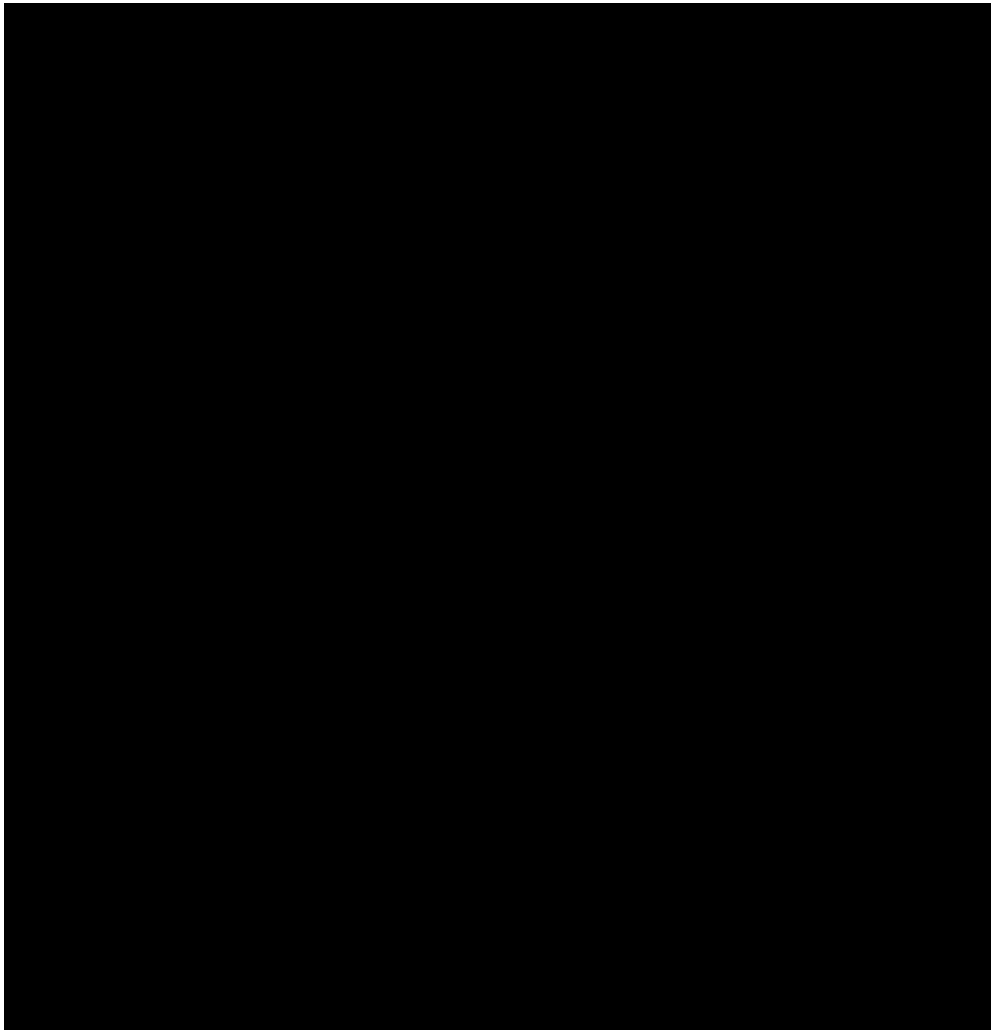
Sensitivity analyses around revised base case: PSA

Table 9: Updated base case results at amivantamab PAS price (probabilistic)

	Total			Incremental			ICER (£/QALY)
	Costs	QALYs	LYs	Costs	QALYs	LYs	
UK SoC	[redacted]	[redacted]	[redacted]	-	-	-	-
AMI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£38,841

Abbreviations: AMI: amivantamab; ICER: incremental cost-effectiveness ratio; LY: life years; PAS: patient access scheme; QALYs: quality-adjusted life years; SoC: standard of care.

Figure 1: Cost effectiveness plane scatterplot at amivantamab PAS price



Abbreviations: ICER: incremental cost-effectiveness ratio; PAS: patient access scheme; QALY: quality-adjusted life year; SoC: standard of care.

Figure 2: Cost-effectiveness acceptability curve at amivantamab PAS price

Abbreviations: CE: cost-effectiveness; PAS: patient access scheme; SoC: standard of care.

Sensitivity analyses around revised base case: scenario analyses

In Section B.3.8.3 of the CS, a scenario analysis was presented in which an alternative extrapolation (generalised gamma) was selected for amivantamab OS data, in place of the base case setting of a Weibull extrapolation. Results for this scenario analysis, updated to account for the updated base case settings presented above, which include updated amivantamab OS data, are presented in Table 10. These results show that applying a generalised gamma extrapolation marginally reduces the with-PAS ICER from £38,021/QALY gained to £37,594/QALY gained.

Table 10: Scenario analysis results – exclusion of patients receiving targeted radiotherapy from the amivantamab treatment arm

Scenario analysis	LIST PRICE			WITH PAS		
	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)
Base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£38,021
Alternative extrapolation method for OS (generalised gamma)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£37,594

Abbreviations: ICER: incremental cost-effectiveness ratio; LY: life years; Incr: incremental; PAS: patient access scheme; QALYs: quality-adjusted life years.

Appendix 1 Updated amivantamab overall survival data (Key Issue 4)

Updated Kaplan-Meier curve

The Kaplan-Meier for the OS data from the updated data cut (7th March 2022), as described in Key Issue 4, is presented in Figure 3. As described in Table 4, after a median follow-up of [redacted], the median OS at the updated data cut-off of 7th March 2022 is [redacted], compared to [redacted] at the 30th March 2021 data cut-off.

Parametric extrapolations fit to the updated data are presented in Figure 4. The impact of these updated data on the cost-effectiveness results is described in Table 7.

Figure 3: Kaplan-Meier curve for OS for CHRYSALIS

Abbreviations: CI: confidence interval; OS: overall survival

Figure 4: Kaplan-Meier data and parametric extrapolations for updated amivantamab OS data from CHRYSALIS

Abbreviations: OS: overall survival.

Overlaid Kaplan-Meier curve

The overlaid OS KM curves for the March 2021 and March 2022 data cuts of the CHRYSALIS trial are presented in Figure 5. The latest data cut provides 12 months of additional follow-up and, together with the updated comparison results presented in the section immediately below Figure 5, demonstrate a continued treatment effect of amivantamab versus UK SoC over time.

Figure 5: Overlaid OS Kaplan-Meier curves from the 30th March 2021 and 7th March 2022 data cuts of the CHRYSALIS trial

Abbreviations: OS: overall survival.

Updated adjusted treatment comparison results

The results of the adjusted treatment comparison (updated with the March 2022 OS data) are presented in Figure 6, utilising the IPW ATT approach as per the base case for the Company Submission. Data from the 30th of March 2021 data cut-off led to a median OS [redacted] and [redacted] (95% CI: [redacted]) for amivantamab and UK SoC, respectively (adjusted HR: [redacted]). For the updated OS analysis, this was [redacted]) (adjusted HR: [redacted], for amivantamab and UK SoC, respectively.

Figure 6: Kaplan-Meier curve for OS for CHRYSALIS versus US RWE cohort – IPW (ATT)

Abbreviations: ATT: average treatment effect among the treated; OS: overall survival; IPW: inverse probability weighting; PC: physicians' choice (referred to as UK SoC in submission); RWE: real world evidence.

Diagnostic and hazard plots

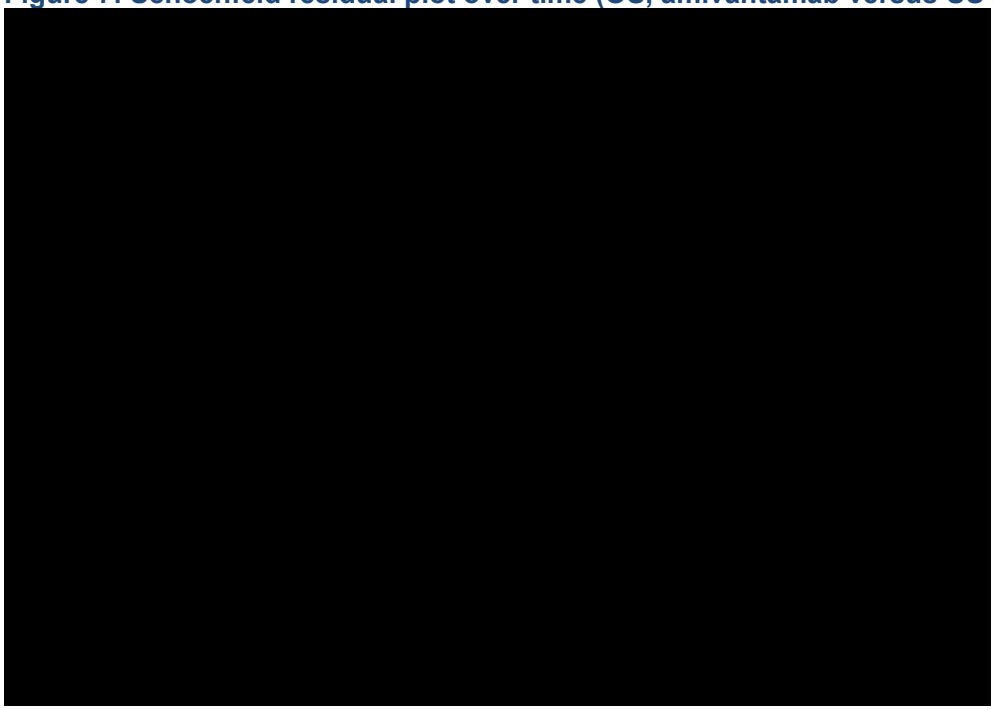
The Schoenfeld residual plot over time for OS is presented in Figure 7, with SoC data informed by the ATT-weighted US RWE cohort. As presented in the figure, the Schoenfeld test for OS is not significant (p=[redacted]), which suggests that the assumption of proportional hazards (PH) holds. However, the estimate of hazard ratio over time (represented by the solid blue line) varies over time, decreasing and increasing twice before remaining stable after Month 20. As such, there is considerable uncertainty regarding the assumption of proportional hazards. Please note that the cost effectiveness analysis base case compares CHRYSALIS OS and PFS outcomes to an sATT-weighted US RWE cohort and does not rely on an assumption of proportional hazards.

When looking at the log-cumulative hazard plot, the hazards associated with amivantamab and UK SoC cross, indicating a violation of the proportional hazard assumption in the early stages of follow up.

The smoothed hazard curve suggests that the hazard is first increasing then slightly decreasing. Towards the end of the follow up there is an increase in the unsmoothed hazard, likely due to a combination of the small bin size (one month) and there being very few (five) patients at risk by this time. As such, the results should be interpreted with caution due to increased uncertainty.

Weibull has lowest AIC and long-term extrapolations with loglogistic and lognormal have long tails. Weibull can be considered as a conservative choice.

Figure 7: Schoenfeld residual plot over time (OS, amivantamab versus US RWE cohort)



Abbreviations: OS: overall survival; RWE: real-world evidence.

Figure 8: Log cumulative hazard plot (OS, amivantamab versus US RWE cohort)

Abbreviations: OS: overall survival; PC: physicians' choice (referred to as UK SoC in the submission); RWE: real-world evidence.

Figure 9: CHRYSALIS OS – parametric models and smoothed hazard

Abbreviations: OS: overall survival.

Figure 10: CHRYSALIS OS – smooth and unsmoothed

Abbreviations: OS: overall survival.

The loglogistic, lognormal and Gompertz diagnostic curves deviate from a linear trend. Weibull and exponential diagnostic curves conform better with linear trend compared with the other three

parametric curves. Extrapolation of the US RWE data informing efficacy for UK SoC was not deemed necessary in the base case due to the maturity of the available data. However, at the request of the ERG, diagnostic curves are presented for SoC OS (informed by the US RWE cohort). Greater deviation from a linear trend is observed for the loglogistic, lognormal and Gompertz diagnostic curves, than there is for Weibull and exponential curves.

Figure 11: Exponential (cumulative hazard versus time) – OS

Abbreviations: Ami: amivantamab; OS: overall survival; PC: physicians' choice (referred to as UK SoC in the submission).

Figure 12: Loglogistic (negative log survival odds versus log time) – OS

Abbreviations: Ami: amivantamab; OS: overall survival; PC: physicians' choice (referred to as UK SoC in the submission).

Figure 13: Weibull (log cumulative hazard versus log time) – OS

Abbreviations: Ami: amivantamab; OS: overall survival; PC: physicians' choice (referred to as UK SoC in the submission).

Figure 14: Gompertz (log hazard versus time) – OS

Abbreviations: Ami: amivantamab; OS: overall survival; PC: physicians' choice (referred to as UK SoC in the submission).

Figure 15: Lognormal (inverse cumulative standard normal probability versus log time) – OS

Abbreviations: Ami: amivantamab; OS: overall survival; PC: physicians' choice (referred to as UK SoC in the submission).

Appendix 2 Adjusted treatment comparison results with updated amivantamab OS data

Key Issue 2 (exclusion of patients receiving targeted radiotherapy from the amivantamab treatment arm)

Results of the comparison between CHRYSALIS and the US RWE cohort when excluding patients from CHRYSALIS who received concomitant targeted radiotherapy are presented below. Results are presented using both unadjusted and adjusted via the IPW (ATT) approach for OS in Figure 16 (unadjusted) and Figure 17 (adjusted), for PFS in Figure 18 (unadjusted) and Figure 19 (adjusted) and for TTNT in Figure 20 (unadjusted) and Figure 21 (adjusted).

These results demonstrate consistent hazard ratios when compared to the full population results, supporting that the concomitant medications have a limited impact on the efficacy of amivantamab in the CHRYSALIS trial.

OS – CHRYSALIS vs US RWE cohort

Figure 16: Kaplan-Meier curve for OS for CHRYSALIS versus US RWE cohort excluding patients receiving targeted radiotherapy from the amivantamab treatment arm (amivantamab versus SoC) – unadjusted results

Abbreviations: OS: overall survival; PC: physicians' choice (referred to as UK SoC in the submission); RWE: real world evidence; SoC: standard of care.

Figure 17: Kaplan-Meier for OS for CHRYSALIS versus US RWE cohort excluding patients receiving targeted radiotherapy from the amivantamab treatment arm (amivantamab vs SoC) – IPW (ATT)

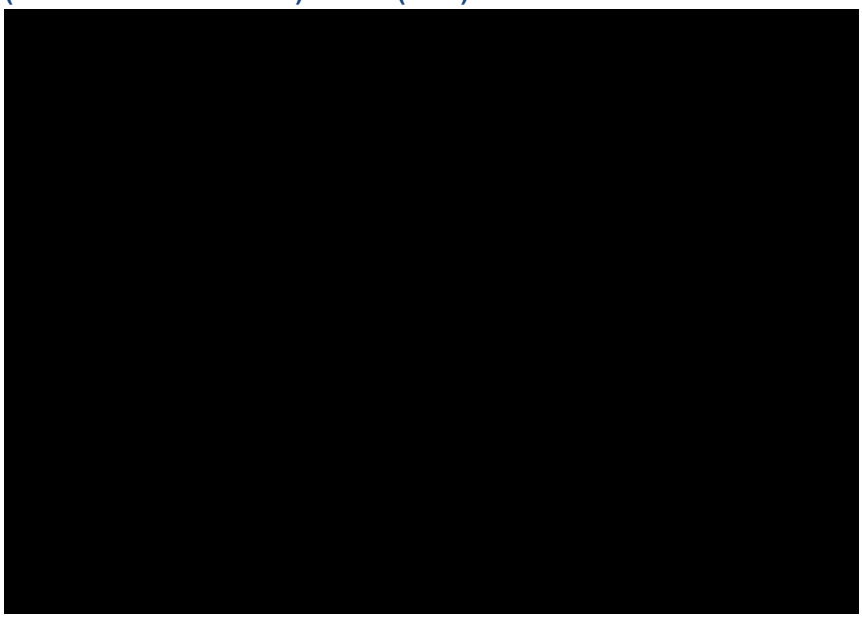
Abbreviations: ATT: average treatment effect among the treated; IPW: inverse probability weighting; OS: overall survival; PC: physicians' choice (referred to as UK SoC in the submission); RWE: real world evidence; SoC: standard of care.

PFS – CHRYSALIS vs US RWE cohort

Figure 18: Kaplan-Meier for PFS for CHRYSALIS versus US RWE cohort excluding patients receiving targeted radiotherapy from the amivantamab treatment arm (amivantamab vs SoC) – unadjusted

Abbreviations: PC: physicians' choice (referred to as UK SoC in the submission); PFS: progression-free survival; RWE: real world evidence; SoC: standard of care.

Figure 19: Kaplan-Meier for PFS for CHRYSALIS versus US RWE cohort excluding patients receiving targeted radiotherapy from the amivantamab treatment arm (amivantamab vs SoC) – IPW (ATT)



Abbreviations: ATT: average treatment effect among the treated; IPW: inverse probability weighting; PC: physicians' choice (referred to as UK SoC in the submission); PFS: progression-free survival; RWE: real world evidence; SoC: standard of care.

TTNT – CHRYSALIS vs US RWE cohort

Figure 20: Kaplan-Meier for TTNT for CHRYSALIS versus US RWE cohort excluding patients receiving targeted radiotherapy from the amivantamab treatment arm (amivantamab vs SoC) – unadjusted

Abbreviations: PC: physicians' choice (referred to as UK SoC in the submission); RWE: real world evidence; SoC: standard of care; TTNT: time-to-next treatment.

Figure 21: Kaplan-Meier for TTNT for CHRYSALIS versus US RWE cohort excluding patients receiving targeted radiotherapy from the amivantamab treatment arm (amivantamab vs SoC) – IPW (ATT)

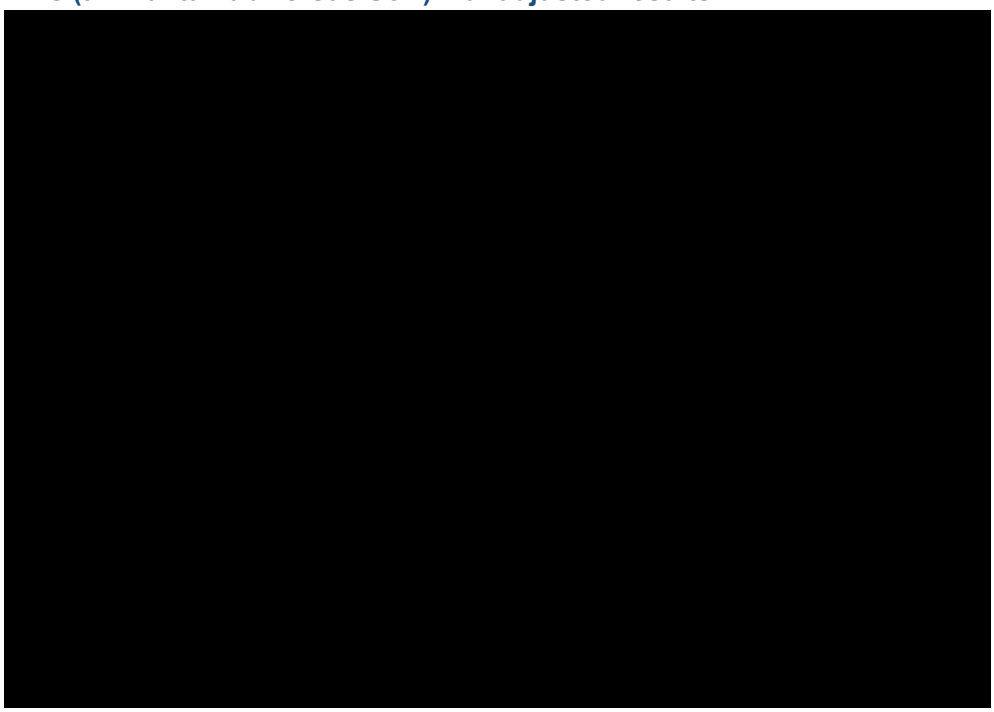
Abbreviations: **Abbreviations**: ATT: average treatment effect among the treated; IPW: inverse probability weighting; PC: physicians' choice (referred to as UK SoC in the submission); RWE: real world evidence; SoC: standard of care; TTNT: time-to-next treatment.

Key Issue 3 (exclusion of TKIs from the comparator basket)

OS results of the comparison comparing CHRYSALIS and the US RWE cohort, both unadjusted and adjusted via the IPW (ATT) approach, when excluding patients from CHRYSALIS who received TKIs are presented in Figure 22 and Figure 23 below. These results show that excluding TKIs from the comparator basket is minimally impactful on the HRs. As described in Issue 3 above, Janssen maintain that this analysis is methodologically inappropriate and thus insufficiently robust to inform decision-making.

OS – CHRYSALIS vs US RWE cohort

Figure 22: Kaplan-Meier curve for OS for CHRYSALIS versus US RWE cohort excluding TKIs (amivantamab versus SoC) – unadjusted results



Abbreviations: OS: overall survival; PC: physicians' choice (referred to as UK SoC in the submission); RWE: real world evidence; SoC: standard of care.

Figure 23: Kaplan-Meier for OS for CHRYSALIS versus US RWE cohort excluding TKIs (amivantamab vs SoC) – IPW (ATT)

Abbreviations: ATT: average treatment effect among the treated; IPW: inverse probability weighting; OS: overall survival; PC: physicians' choice (referred to as UK SoC in the submission); RWE: real world evidence; SoC: standard of care.

Appendix 3 Additional safety data for the N=114 population of the CHRYSALIS trial (Key Issue 5)

Safety results from CHRYSALIS are presented below for the post-platinum patients with Exon20ins at RP2D safety population (N=153) and the efficacy analysis set (N=114) from the 30th March 2021 data cut-off.

Treatment duration and dosage

Patient disposition and completion/withdrawal information

Table 11 summarises study and treatment disposition for the post-platinum patients with EGFR Exon20ins at RP2D safety population (N=153) and efficacy analysis set (N=114) at the 30th of March 2021 data cut-off.

Table 11: Study and treatment disposition; Post-platinum patients with EGFR Exon20ins at RP2D safety population (N=153) and efficacy population (N=114)

Event, n (%)	Safety population (N=153, 30th March 2021 data cut-off)	Efficacy population (N=114, 30th March 2021 data cut-off)
Study disposition		
Patients ongoing	[redacted]	[redacted]
Completed study participation	[redacted]	[redacted]
Terminated study participation prematurely	[redacted]	[redacted]
Treatment disposition		
Patients ongoing	56 (36.6)	[redacted]
Discontinued study treatment	97 (63.4)	[redacted]
Reason for discontinuation		
Progressive disease	73 (47.7)	[redacted]
AE	12 (7.8)	[redacted]
Withdrawal by patient	7 (4.6)	[redacted]
Physician decision	2 (1.3)	[redacted]
Death	3 (2.0)	[redacted]

RP2D is defined as 1,050 mg if baseline weight <80 kg and 1,400 mg if baseline weight ≥80 kg. [a] Patient is considered to have completed the study if the patient died prior to the end of study.
Abbreviations: AE: adverse event; RP2D: recommended Phase 2 dose.
Source: Janssen CHRYSALIS Clinical Overview (30th March 2021 data cut-off).[21, 22]

Extent of exposure

The extent of exposure for the post-platinum patients with EGFR Exon20ins at RP2D safety population (N=153) and efficacy analysis set (N=114) is summarised in Table 12.

Table 12: Summary of treatment with amivantamab; Post-platinum patients with EGFR Exon20ins at RP2D safety population (N=153) and efficacy population (N=114)

	Safety population (N=153, 30th March 2021 data cut-off)	Efficacy population (N=114, 30th March 2021 data cut-off)
Duration of study treatment, months[a]		
Mean (SD)	7.28 (5.81)	[redacted]
Median	5.52	[redacted]
Range	(0.03; 23.89)	[redacted]
Duration of study treatment, n (%)		
<2 months	31 (20.3)	[redacted]
2 –<4 months	26 (17.0)	[redacted]
4 –<6 months	25 (16.3)	[redacted]
≥6 months	71 (46.4)	[redacted]
Total number of cycles[b]		
Mean (SD)	8.5 (6.2)	[redacted]
Median	7	[redacted]
Range	(1, 27)	[redacted]

RP2D is defined as 1,050 mg if baseline weight <80 kg and 1,400 mg if baseline weight ≥80 kg. [a] Treatment duration is defined as the duration from the date of the first dose of amivantamab to the date of last dose of amivantamab+1 divided by 30.4375. [b] A patient is considered as treated in a cycle if the patient received any non-zero dose of study agent in that cycle.
Abbreviations: SD: standard deviation; RP2D: recommended Phase 2 dose.
Source: Amivantamab EPAR.[22]

Adverse events

Overview of treatment-emergent AEs

An overall summary of treatment-emergent AEs (TEAEs) for the post-platinum patients with EGFR Exon20ins at RP2D safety population (N=153) and for the efficacy analysis set (N=114) at the 30th March 2021 data cut-off is presented in Table 13.

Table 13: Overall summary of TEAEs; Post-platinum patients with EGFR Exon20ins at RP2D safety population (N=153) and efficacy population (N=114)

Event, n (%)	Safety population (N=153, 30th March 2021 data cut-off)	Efficacy population (N=114, 30th March 2021 data cut-off)
Patients with ≥1 AE	153 (100.0)	[redacted]
Related AEs[a]	150 (98.0)	[redacted]
AEs leading to death[b]	11 (7.2)	[redacted]
Related AEs leading to death[a,b]	0	[redacted]
Serious AEs	44 (28.8)	[redacted]
Related serious AEs[a]	13 (8.5)	[redacted]

AEs leading to discontinuation of amivantamab	18 (11.8)	[redacted]
Related AEs leading to discontinuation of amivantamab[a]	8 (5.2)	[redacted]
AEs leading to dose reduction	22 (14.4)	[redacted]
Related AEs leading to dose reduction[a]	22 (14.4)	[redacted]
AEs leading to infusion modification[c]	91 (59.5)	[redacted]
Related AEs leading to infusion modification[a, c]	90 (58.8)	[redacted]
AEs leading to dose interruption[d]	55 (35.9)	[redacted]
Related AEs leading to dose interruption[a, d]	32 (20.9)	[redacted]
Grade ≥3 AEs	64 (41.8)	[redacted]
Related grade ≥3 AEs[a]	30 (19.6)	[redacted]
Grade 1	4 (2.6)	[redacted]
Grade 2	85 (55.6)	[redacted]
Grade 3	49 (32.0)	[redacted]
Grade 4	4 (2.6)	[redacted]
Grade 5	11 (7.2)	[redacted]

RP2D: 1,050 mg if baseline weight <80 kg and 1,400 mg if baseline weight ≥80 kg. [a] An AE is categorised as related if assessed by the investigator as possibly, probably, or very likely related to study agent. [b] AEs leading to death are based on AE outcome of Fatal. [c] AEs leading to infusion modification of study agent are based on infusion interrupted, infusion rate decreased, and infusion aborted due to adverse event on the infusion eCRF page. [d] Excludes infusion related reactions.
Abbreviations: AE: adverse event; RP2D: recommended Phase 2 dose.
Source: Amivantamab EPAR.[22]

Treatment-emergent AEs by preferred term

Common TEAEs (i.e., frequency of 10% or higher) for the post-platinum patients with EGFR Exon20ins at RP2D safety population (N=153) and efficacy analysis set (N=114) at 30th March 2021 data cut-off are summarised in Table 14.

Table 14: Number of patients with TEAEs with a frequency of at least 10% by system organ class and preferred term; Post-platinum patients with EGFR Exon20ins at RP2D safety population (N=153) and efficacy population (N=114)

Event, n (%)	Safety population (N=153, 30th March 2021 data cut-off)	Efficacy population (N=114, 30th March 2021 data cut-off)
Patients with 1 or more AEs	153 (100.0)	[redacted]
Skin and subcutaneous tissue disorders	136 (88.9)	[redacted]
Dermatitis acneiform	60 (39.2)	[redacted]
Rash	66 (43.1)	[redacted]

Pruritus	24 (15.7)	[redacted]
Dry skin	21 (13.7)	[redacted]
Rash maculo-papular	N/A*	[redacted]
Gastrointestinal disorders	114 (74.5)	[redacted]
Constipation	36 (23.5)	[redacted]
Nausea	38 (24.8)	[redacted]
Stomatitis	34 (22.2)	[redacted]
Vomiting	21 (13.7)	[redacted]
Diarrhoea	21 (13.7)	[redacted]
Injury, poisoning and procedural complications	102 (66.7)	[redacted]
Infusion related reaction	97 (63.4)	[redacted]
Infections and infestations	107 (69.9)	[redacted]
Paronychia	81 (52.9)	[redacted]
Pneumonia	N/A*	[redacted]
Respiratory, thoracic and mediastinal disorders	88 (57.5)	[redacted]
Dyspnoea	30 (19.6)	[redacted]
Cough	26 (17.0)	[redacted]
Productive cough	N/A*	[redacted]
General disorders and administration site conditions	96 (62.7)	[redacted]
Oedema peripheral	35 (22.9)	[redacted]
Fatigue	30 (19.6)	[redacted]
Pyrexia	26 (17.0)	[redacted]
Asthenia	N/A*	[redacted]
Metabolism and nutrition disorders	92 (60.1)	[redacted]
Hypoalbuminaemia	60 (39.2)	[redacted]
Decreased appetite	27 (17.6)	[redacted]
Hypokalaemia	N/A*	[redacted]
Hypomagnesaemia	N/A*	[redacted]
Musculoskeletal and connective tissue disorders	73 (47.7)	[redacted]
Myalgia	18 (11.8)	[redacted]
Back pain	25 (16.3)	[redacted]
Arthralgia	N/A*	[redacted]
Musculoskeletal pain	N/A*	[redacted]
Nervous system disorders	50 (32.7)	[redacted]
Dizziness	18 (11.8)	[redacted]
Headache	11 (7.2)	[redacted]

Investigations	63 (41.2)	[redacted]
Alanine aminotransferase increased	34 (22.2)	[redacted]
Aspartate aminotransferase increased	25 (16.3)	[redacted]
Blood alkaline phosphatase increased	16 (10.5)	[redacted]
Psychiatric disorders	29 (19.0)	[redacted]
Insomnia	16 (10.5)	[redacted]

RP2D: 1,050 mg if baseline weight <80 kg and 1,400 mg if baseline weight ≥80 kg. Patients are counted only once for any given event, regardless of the number of times they actually experienced the event. *Values are not reported for these events as they did not occur at a frequency of >10% relative to the N=153 population.
Abbreviations: TEAE: treatment emergent adverse event.
Source: Amivantamab EPAR.[22]

Treatment-emergent AEs Grade ≥3 by preferred term

TEAEs at Grade ≥3 for the post-platinum patients with EGFR Exon20ins at RP2D safety population (N=153) and efficacy analysis set (N=114) at the 30th March 2021 data cut-off are summarised in Table 15.

Table 15: Number of patients with grade 3 or higher TEAE by preferred term: Post-platinum patients with EGFR Exon20ins at RP2D safety population (N=153) and efficacy population (N=114)

Event, n (%)	Safety population (N=153, 30th March 2021 data cut-off)	Efficacy population (N=114, 30th March 2021 data cut-off)
Subjects with 1 or more Grade ≥3 AEs	[redacted]	[redacted]
Preferred term		
Pulmonary embolism	[redacted]	[redacted]
Hypokalaemia	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]
Dyspnoea	[redacted]	[redacted]
Hypoalbuminaemia	[redacted]	[redacted]
Paronychia	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]
Infusion related reaction	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]
Hyponatraemia	[redacted]	[redacted]
Alanine aminotransferase increased	[redacted]	[redacted]
Hypophosphataemia	[redacted]	[redacted]
Hypotension	[redacted]	[redacted]
Gamma-glutamyltransferase increased	[redacted]	[redacted]

Event, n (%)	Safety population (N=153, 30th March 2021 data cut-off)	Efficacy population (N=114, 30th March 2021 data cut-off)
Rash	[redacted]	[redacted]
Respiratory failure	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]
Respiratory tract infection	[redacted]	[redacted]
Sepsis	[redacted]	[redacted]
Acne	[redacted]	[redacted]
Cellulitis	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]
Hypoxia	[redacted]	[redacted]
Pleural effusion	[redacted]	[redacted]
Pericardial effusion	[redacted]	[redacted]
Aspartate aminotransferase increased	[redacted]	[redacted]
Dermatitis acneiform	[redacted]	[redacted]
Headache	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]
Oedema peripheral	[redacted]	[redacted]
Syncope	[redacted]	[redacted]
Abdominal pain	[redacted]	[redacted]
Atrial fibrillation	[redacted]	[redacted]
Blood alkaline phosphatase increased	[redacted]	[redacted]
Blood creatine phosphokinase increased	[redacted]	[redacted]
Decreased appetite	[redacted]	[redacted]
Lymphopenia	[redacted]	[redacted]
Mental status changes	[redacted]	[redacted]
Nausea	[redacted]	[redacted]
Pneumonia aspiration	[redacted]	[redacted]
Pneumonitis	[redacted]	[redacted]
Stomatitis	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]
Aspiration	[redacted]	[redacted]
Hypocalcaemia	[redacted]	[redacted]
Infected dermal cyst	[redacted]	[redacted]
Insomnia	[redacted]	[redacted]
International normalised ratio increased	[redacted]	[redacted]
Muscular weakness	[redacted]	[redacted]

Event, n (%)	Safety population (N=153, 30th March 2021 data cut-off)	Efficacy population (N=114, 30th March 2021 data cut-off)
Pulmonary sepsis	[redacted]	[redacted]
Pulseless electrical activity	[redacted]	[redacted]
Rash papular	[redacted]	[redacted]
Renal vein thrombosis	[redacted]	[redacted]
Sudden death	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]
Toxic epidermal necrolysis	[redacted]	[redacted]
Transitional cell carcinoma	[redacted]	[redacted]

Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event. The event experienced by the subject with the worst toxicity is used. RP2D: 1,050 mg if baseline weight <80 kg and 1,400 mg if baseline weight ≥80 kg.
Abbreviations: RP2D: recommended Phase 2 dose; (TE)AE: (treatment-emergent) adverse event.
Source: Amivantamab EPAR;[22] Janssen data on file.

Treatment-related AEs

AEs reported by the investigator to be related to amivantamab in the post-platinum patients with EGFR Exon20ins at RP2D safety population (N=153) and efficacy analysis set (N=114) are reported in Table 16.

Table 16: Number of patients with treatment-related AEs by system organ class and preferred term; Post-platinum patients with EGFR Exon20ins at RP2D safety population (N=153) and efficacy population (N=114)

Preferred term, n (%)	Safety population (N=153, 30th March 2021 data cut-off)	Efficacy population (N=114, 30th March 2021 data cut-off)
Patients with 1 or more related AEs	[redacted]	[redacted]
Skin and subcutaneous tissue disorders	[redacted]	[redacted]
Dermatitis acneiform	[redacted]	[redacted]
Rash	[redacted]	[redacted]
Pruritus	[redacted]	[redacted]
Dry skin	[redacted]	[redacted]
Injury, poisoning and procedural complications	[redacted]	[redacted]
Infusion related reaction	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]
Stomatitis	[redacted]	[redacted]
Nausea	[redacted]	[redacted]
Infections and infestations	[redacted]	[redacted]
Paronychia	[redacted]	[redacted]

General disorders and administration site conditions	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]
Oedema peripheral	[redacted]	[redacted]
Metabolism and nutrition disorders	[redacted]	[redacted]
Hypoalbuminaemia	[redacted]	[redacted]
Investigations	[redacted]	[redacted]
Alanine aminotransferase increased	[redacted]	[redacted]
Aspartate aminotransferase increased	[redacted]	[redacted]

RP2D: 1,050 mg if baseline weight <80 kg and 1,400 mg if baseline weight ≥80 kg. Patients are counted only once for any given event, regardless of the number of times they actually experienced the event.
Abbreviations: AE: adverse event; RP2D: recommended Phase 2 dose.
Source: Amivantamab EPAR;[22] Janssen data on file.

Serious treatment-emergent AEs

The incidence of treatment-emergent AEs reported by the investigator to be serious for the post-platinum patients with EGFR Exon20ins at RP2D safety population (N=153) and efficacy analysis set (N=114) is summarised in Table 17.

Table 17: Incident of serious treatment-emergent serious adverse drug reactions (ADRs) by system organ class, preferred term; Post-platinum patients with EGFR Exon20ins at RP2D safety population (N=153) and efficacy population (N=114)

System organ class/Preferred term, n (%)	Safety population (N=153, 30th March 2021 data cut-off)	Efficacy population (N=114, 30th March 2021 data cut-off)
Subjects with any serious treatment-emergent AEs	[redacted]	[redacted]
Skin and subcutaneous tissue disorders	[redacted]	[redacted]
Rash	[redacted]	[redacted]
Toxic epidermal necrolysis	[redacted]	[redacted]
Injury, poisoning and procedural complications	[redacted]	[redacted]
Infusion related reaction	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]
Abdominal pain	[redacted]	[redacted]
Respiratory, thoracic and mediastinal disorders	[redacted]	[redacted]
Interstitial lung disease	[redacted]	[redacted]

RP2D: 1,050 mg if baseline weight <80 kg and 1,400 mg if baseline weight ≥80 kg. Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event. The event experienced by the subject with the worst toxicity is used.

Abbreviations: ADR: adverse drug reaction; RP2D: recommended Phase 2 dose.
Source: Janssen Data on File: CHRYSALIS Clinical Overview (30th March 2021 data-cut).[21]

Deaths

A summary of deaths that occurred at any time during the study through the data cut-off for the post-platinum patients with EGFR Exon20ins at RP2D safety population (N=153) and efficacy analysis set (N=114) at the 30th of March data cut-off is presented in Table 18.

Table 18: Summary of deaths during study; Post-platinum patients with EGFR Exon20ins at RP2D safety population (N=153) and efficacy population (N=114)

Preferred term, n (%)	Safety population (N=153, 30th March 2021 data cut-off)	Efficacy population (N=114, 30th March 2021 data cut-off)
Deaths during study	[redacted]	[redacted]
PD	[redacted]	[redacted]
AE	[redacted]	[redacted]
Other	[redacted]	[redacted]
Deaths during treatment	[redacted]	[redacted]
AE	[redacted]	[redacted]
PD	[redacted]	[redacted]
Other	[redacted]	[redacted]

RP2D: 1,050 mg if baseline weight <80 kg and 1,400 mg if baseline weight ≥80 kg. Deaths during treatment are presented for patients who died within 30 days of last amivantamab dose.
Abbreviations: AE: adverse event; PD: progressive disease; RP2D: recommended Phase 2 dose.
Source: Janssen Data on File: CHRYSALIS Clinical Overview (30th March 2021 data-cut).[21]

Table 19: Number of patients with TEAEs leading to death by system organ class and preferred term; Post-platinum patients with Exon20ins at RP2D safety population (N=153) and efficacy population (N=114)

Preferred term, n (%)	Safety population (N=153, 30th March 2021 data cut-off)	Efficacy population (N=114, 30th March 2021 data cut-off)
Patients with 1 or more AEs leading to Death	[redacted]	[redacted]
Infections and infestations	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]
Adenovirus infection	[redacted]	[redacted]
Pulmonary sepsis	[redacted]	[redacted]
Respiratory, thoracic and mediastinal disorders	[redacted]	[redacted]
Respiratory failure	[redacted]	[redacted]
Dyspnoea	[redacted]	[redacted]
Aspiration	[redacted]	[redacted]
Pneumonia aspiration	[redacted]	[redacted]

Cardiac disorders	[redacted]	[redacted]
Cardio-respiratory distress	[redacted]	[redacted]
General disorders and administration site conditions	[redacted]	[redacted]
Sudden death	[redacted]	[redacted]

RP2D: 1,050 mg if baseline weight <80 kg and 1,400 mg if baseline weight ≥80 kg. AEs leading to death are based on AE outcome of Fatal. Patients are counted only once for any given event, regardless of the number of times they actually experienced the event.
Abbreviations: AE: adverse event; RP2D: recommended Phase 2 dose; TEAE: treatment emergent adverse event.
Source: Janssen Data on File: CHRYSALIS Clinical Overview (30th March 2021 data-cut).[21]

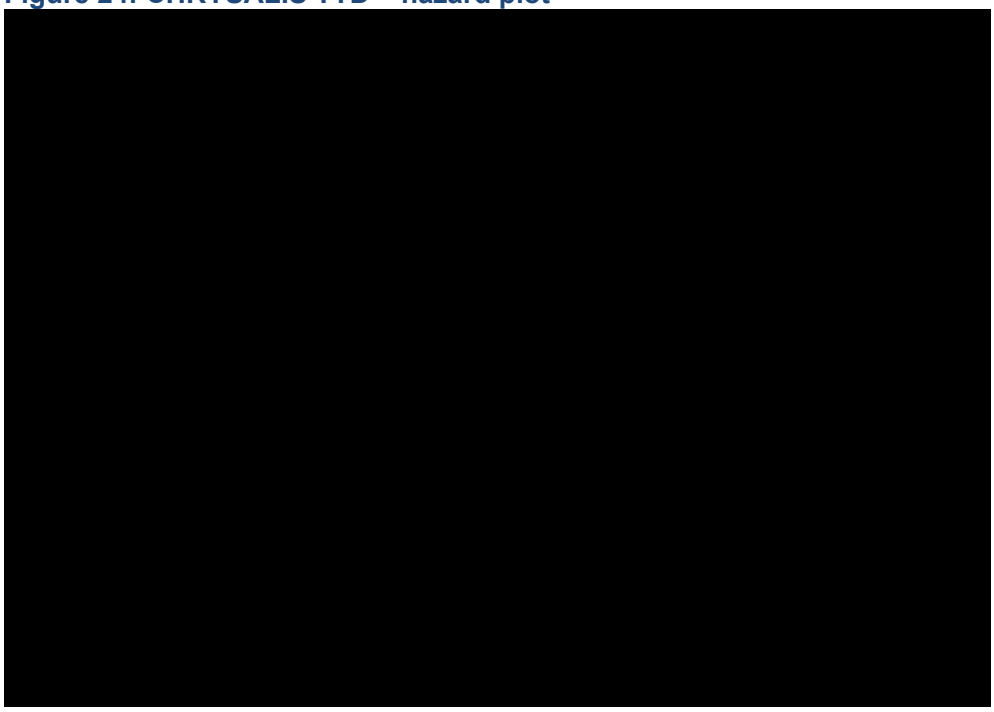
Infusion-related reactions

In the All Treated at RP2D safety population (N=[redacted]), IRRs occurred in 67.4% of post-platinum patients with Exon20ins and in the efficacy analysis set (N=114), IRRs occurred in [redacted] of the population with [redacted] events reported.

Appendix 4 Supportive information for selected curve choices (Key Issue 9)

The smoothed hazard curve for TTD presented in Figure 24 suggests that the hazard initially decreases before increasing from around Month 5, which is in line with the Weibull or Gompertz distributions. Despite the exponential curve having the lowest AIC and BIC, given the assumption of constant hazards is inherent to the exponential curve, this selection is not considered appropriate in this instance given the changes in hazard over time observed with amivantamab. Towards the end of the follow up there is an increase in the unsmoothed hazard (Figure 25), likely due to a combination of the small bin size (one month) and there being very few (three) patients at risk by this time. As such, the results should be interpreted with caution due to increased uncertainty.

Figure 24: CHRYSALIS TTD – hazard plot



Abbreviations: TTD: time to treatment discontinuation.

Figure 25: CHRYSALIS TTD – smooth and unsmoothed

Abbreviations: TTD: time to treatment discontinuation.

Figure 26: Weibull (log cumulative hazard versus log time) – TTD

Abbreviations: Ami: amivantamab; TTD: time to treatment discontinuation.

Figure 27: Exponential (cumulative hazard versus time) – TTD

Abbreviations: Ami: amivantamab; TTD: time to treatment discontinuation.

Figure 28: Lognormal (inverse cumulative standard normal probability versus log time) – TTD

Abbreviations: Ami: amivantamab; TTD: time to treatment discontinuation.

Figure 29: Loglogistic (negative log survival odds versus log time) – TTD

Abbreviations: Ami: amivantamab; TTD: time to treatment discontinuation.

Figure 30: Gompertz (log hazard versus time) – TTD

Abbreviations: Ami: amivantamab; TTD: time to treatment discontinuation.

Appendix 5 Scenario analyses

Key Issue 2 (exclusion of patients receiving targeted radiotherapy from the amivantamab treatment arm)

Results for the scenario analysis in which patients receiving targeted radiotherapy are excluded from the amivantamab treatment arm are presented in Table 20. These results show that exclusion of the three patients who received targeted radiotherapy marginally reduces the with-PAS ICER from £38,021/QALY gained to £37,440/QALY gained.

Table 20: Scenario analysis results – exclusion of patients receiving targeted radiotherapy from the amivantamab treatment arm

Scenario analysis	LIST PRICE			WITH PAS		
	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)
Base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£38,021
Exclusion of patients receiving targeted radiotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£37,440

Abbreviations: ICER: incremental cost-effectiveness ratio; LY: life years; Incr: incremental; PAS: patient access scheme; QALYs: quality-adjusted life years.

Key Issue 7 (exclusion of TKIs from the comparator basket)

Results for the scenario analysis in which the cost and efficacy of EGFR TKIs are excluded from the comparator basket are presented in Table 21. These results show that exclusion of TKIs from the comparator basket reduces the with-PAS ICER from £38,021/QALY gained to £33,272/QALY gained, demonstrating that their inclusion in the comparator basket is a conservative approach.

Table 21: Scenario analysis results – exclusion of TKIs from the comparator basket

Scenario analysis	LIST PRICE			WITH PAS		
	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)
Base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£38,021
Exclusion of TKIs from the comparator basket	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£33,272

Abbreviations: ICER: incremental cost-effectiveness ratio; LY: life years; Incr: incremental; PAS: patient access scheme; QALYs: quality-adjusted life years; TKI: tyrosine kinase inhibitors.

Key Issue 10 (treatment effect waning)

Results for the scenario analysis in which the treatment effect of amivantamab (OS and PFS) is waned linearly from three years after the cessation of amivantamab treatment until it reaches the same efficacy as the UK SoC comparator (hazard ratio: 1) at the end of the time horizon (15 years) are presented in Table 22. This scenario shows that the implementation of treatment waning has a minimal effect on the overall cost-effectiveness results and the with-PAS ICER remains under a WTP threshold of £40,000/QALY gained.

Table 22: Scenario analysis results – treatment waning implemented

Scenario analysis	LIST PRICE			WITH PAS		
	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)
Base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£38,021
Implementation of treatment waning	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£39,012

Abbreviations: ICER: incremental cost-effectiveness ratio; LY: life years; Incr: incremental; PAS: patient access scheme; QALYs: quality-adjusted life years.

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NICE National Institute for Health and Care Excellence

Clinical expert statement and technical engagement response form

Amivantamab for treating EGFR Exon 20 insertion-positive non-small-cell lung cancer after platinum-based chemotherapy [ID3836]

Thank you for agreeing to comment on the evidence review group (ERG) report for this appraisal, and 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 ERG report and stakeholder responses are used by the appraisal committee to help it make decisions at the appraisal 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 for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking for your views on key issues in the ERG report that are likely to be discussed by the committee. The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the ERG report (Section 1). You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

A clinical perspective could help either:

- resolve any uncertainty that has been identified OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

In part 3 we are asking you to provide 5 summary sentences on the main points contained in this document.

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. Please type information directly into the form.

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.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

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 replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

Please note, part 1 can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

Deadline for comments by **5pm** on **Monday 13 June**. 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: Treating EGFR Exon 20 insertion-positive NSCLC and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Alastair Greystoke
2. Name of organisation	Newcastle upon Tyne Hospitals NHS Trust
3. Job title or position	Senior Lecturer and Honorary Consultant in Medical Oncology
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 EGFR Exon 20 insertion-positive NSCLC? ☒ A specialist in the clinical evidence base for EGFR Exon 20 insertion-positive NSCLC or amivantamab? ☐ 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 is the main aim of treatment for EGFR Exon 20 insertion-positive NSCLC?	Maintain quality of life and prevent disability, improve survival, improve or prevent cancer related symptoms

(For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	
9. 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)	An improvement in survival by 2 months. A response rate of over 30% maintained for over 2 months. A significant improvement in health related quality of life maintained for over two months.
10. In your view, is there an unmet need for patients and healthcare professionals in EGFR Exon 20 insertion-positive NSCLC?	Yes in general these patients have poor outcomes with standard therapies and there is a need for novel therapies that can help control the cancer and improve prognosis. Toxicity with chemotherapy and immunotherapy combinations can be problematic, restricting treatment to the very fittest populations. Whether these patients benefit from single agent immunotherapy is unclear and the additional benefit of adding immunotherapy two chemotherapy is uncertain
11. How is EGFR Exon 20 insertion-positive NSCLC? currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • 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.) • What impact would the technology have on the current pathway of care?	Fit patients with performance status 0-1 will normally receive either chemotherapy and immunotherapy in combination. The role of single agent immunotherapy if the cancer tumour proportion score for PDL1 is >50% is uncertain from the evidence but may be used by some clinicians as within present approvals and guidelines. Chemotherapy and immunotherapy regimens include Regardless of PDL1: carboplatin-pemetrexed-pembrolizumab PDL1<50%: carboplatin-paclitaxel-atezolizumab-bevacizumab Patients may also receive carboplatin and pemetrexed based chemotherapy in the first line setting if so they will be eligible for single-agent immunotherapy following this with agents available including pembrolizumab if PDL1 +ve or atezolizumab regardless of PDL1 expression.

	Lastly patients may receive nintedanib and docetaxel after previous lines of treatment Treatment is based around the technology appraisals for the regimens above The NICE guideline NG122 (https://www.nice.org.uk/guidance/ng122/resources) also outlines these treatment options as does The European Society of Medical Oncology guideline (https://www.esmo.org/guidelines/lung-and-chest-tumours/clinical-practice-living-guidelines-metastatic-non-small-cell-lung-cancer: however this includes regimens that are not licensed or funded in the NHS). The pathways of care are defined. Clinicians may vary in their use of chemo-immunotherapy combinations (over single agent immunotherapy) in the patients with cancer with PDL1 >50%; and in their preferred chemotherapy regimen for non-squamous cancers with PDL1< 50% (with both carboplatin-pemetrexed-pembrolizumab and carboplatin-paclitaxel-atezolizumab-bevacizumab approved for use). The main areas of uncertainty and differences in opinion between conditions are as to whether single-agent immunotherapy has a role in this disease. Although limited the available data suggests that response rates are poor. This addition is also associated with a non-smoking status where immunotherapies have poor response rates. Therefore clinicians that who are more familiar with the emerging literature would suggest that single-agent immune therapy should not be used. This technology would be used before current second line options i.e. after either first line chemotherapy or chemotherapy and immunotherapy combination. Subsequent treatments such as nintedanib and docetaxel would move into later lines of treatment after failure.

12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	The technology will be used in Specialist cancer centres or units, and administered on chemotherapy day units by appropriately trained nurses. These will need to be trained in the management of the infusion reactions that commonly occur with this agent but this should be relatively easy to accomplish. This technology will require frequent attendance on chemotherapy day unit using treatment slot particularly in the first few weeks of treatment when it is given weekly (and the first week is a split over two days).
13. 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?	Yes. These patients need better treatments for their lung cancer. This will provide an additional line of treatment which is likely to be associated with an improvement in overall survival Patient with lung cancer quality of life is in the main driven by symptoms related to the disease. In general using an effective treatment that shrinks the cancer is associated with improvements in quality of life. Given this agent is more effective than other treatments available it is likely to be associated with an improvement in health related quality of life.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	No
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than	As described above the main issues that will be encountered is the frequent infusion reactions during the first treatment and the need for multiple intravenous

current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	infusions particularly during the first four weeks of therapy. Patience and for healthcare professionals.
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Treatment will normally be continued until disease progression (normally demonstrated by a CT scan) but sometimes continued beyond progression on CT scans until there is a lack of clinical benefit. Treatment may also stopped due to excess toxicity.
17. 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	No
18. 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?	Yes This is a novel form of treatment for a rare but difficult to treat form of lung cancer. It is also the first licensed agent of its type (a bi-specific antibody) which may lead to future treatment advances as another way of treating cancer. In some patients responses can be long-lasting, although selecting these patients in advance at present is not possible as we do not fully understand the biology.

19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The main side-effect is infusion reaction at time of first administration. This is unpleasant but short lived. Other side effects that may impact on quality of the life are rash which can be significant and unsightly and require treatment with antibiotics and steroids. Diarrhoea can occur but tends to be less problematic then with some other agents Ankle oedema can occur and be problematic in some patients due to its impact on mobility
20. 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?	Yes
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
22. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance TA520?	No
23. How do data on real-world experience compare with the trial data?	There is limited real-world data available as to the efficacy of this agent.

	There is real-world data that has been presented as to the outcomes with standard therapies in this rare population. This is in general has been included in the company submission.
24. NICE considers whether there are any equalities issues at each stage of an appraisal. 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 appraisal could • 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.	No

Find more general information about the Equality Act and equalities issues here.	

Part 2: Technical engagement questions for clinical experts

We welcome your comments on the key issues below, but you may want to concentrate on issues that are in your field of expertise. If you think an issue that is important to clinicians or patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section.

The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting.

For information: the professional organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report. These will also be considered by the committee.

Table 2 Issues arising from technical engagement

Issue 1: generalisability and potential underestimation of adverse events, i.e.: • *The clinical trial population is likely to be fitter than the population in clinical practice (for example, only people with ECOG status of 0 or 1 were included within the trial population). What*	I do not think this is a major issue. It is likely that funding will be restricted to a similar population as involved in the clinical trial i.e. performance status 0 to 1. Although these patients may have additional comorbidities that prevented entry into studies; given the pattern of toxicity I still think this would be tolerable in the general population.

impact do you consider this to have?	
Issue 2: use of concomitant medications, i.e.: • *People within the intervention group of the clinical trial, received a number of concomitant medicines (including targeted radiotherapy). What impact do you consider this may have had on results?*	I do not think this will have had any major impact on outcomes. Palliative radiotherapy is unlikely to impact majorly on survival, and these patients didn't receive any additional systemic treatment whilst on study. I think the outcomes presented would be achievable within the UK population. Although these patients may have received EGFR TKIs after this treatment for reasons described below I do not think this would impact on outcomes in a significant manner.
Issue 3: comparators, i.e.: • *In clinical practice, what is typically used after platinum-based chemotherapy?* • *Are EGFR TKIs typically used in clinical practice for EGFR Exon20ins mutations?*	In the UK population single-agent immunotherapy if not used before will probably be the predominant treatment used by clinicians. As discussed above clinicians who are more familiar with the emerging literature may not use this treatment and would instead treat patients directly with nintedanib and docetaxel. I do not think these patients should be treated with standard EGFR inhibitors available in the NHS such as Afatinib and Osimertinib. This mutation is described as a resistance mechanism to these agents.

	There have been small studies presented of these agents in this setting showing low response rate. These patients would have been excluded from the pivotal trials of these drugs which led to that nice approval. Some clinicians internationally have suggested higher doses of Osimertinib can be used in patients particularly where the insertion is proximal in Exon 20. This is not licensed or funded and the evidence is relatively sparse Yang JCH, et al. *Lancet Oncol.* 2015;16:141–51; Vyse S, Huang PH. *Sig Transduct Target Ther*. 2019;4:5 van Veggel B, et al. *Lung Cancer.* 2020;141:9–13; 8.
Issue 4: short follow-up of CHRYSALIS trial	
Issue 5: cut-off dates for efficacy and safety populations	
Issue 6: RWE data sources	
Issue 7: EGFR TKIs in comparator basket, i.e.: • *What percentage of people (if any) have EGFR TKIs in clinical practice?*	The company produced some data suggesting EGFR TKI use in the UK environment. I have no reason to believe this data is not correct but I would not use these agents in clinical practice and I do not think their use is justified by license or funding.

Issue 8: use of KM curves instead of parametric survival models	
Issue 9: time to treatment discontinuation, i.e.: • *What is the expected treatment duration of amivantamab?* • *Is treatment with amivantamab likely to continue beyond disease progression?*	it is likely that as with other targeted treatments that treatment may continue beyond progression; particularly if the subsequent options is docetaxel based chemotherapy. This will be due to reluctance of both patients and clinicians to use docetaxel based chemotherapy. In addition it may be possible to ablate areas of locally progressive disease using radiotherapy and this is probably an appropriate strategy that is commonly used in the UK. In general I would expect that the time on treatment on average will be two to three months beyond progression, but this could vary markedly between patients, with some patients stopping on progression and some patients continuing for more prolonged periods.
Issue 10: treatment waning, i.e.: • *How long do you expect treatment effect of amivantamab to last? Is treatment waning expected?*	
Issue 11: utilities age-adjustment	
Issue 12: lack of fully incremental analysis for all comparators	

Issue 13: lack of fixed random seed in model PSA	
Are there any important issues that have been missed in ERG report?	

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Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

An important new option for patients with a rare form of lung cancer

These patients are poorly served by present treatment options

This will require treatment time on chemotherapy day units which are already stretched particularly the first four weeks of treatment

A basket approach may be appropriate given the various options that may be used by clinicians but in my opinion should not include standard EGFR inhibitors

Click or tap here to enter text.

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

NICE National Institute for Health and Care Excellence

Clinical expert statement and technical engagement response form

Amivantamab for treating EGFR Exon 20 insertion-positive non-small-cell lung cancer after platinum-based chemotherapy [ID3836]

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NICE National Institute for Health and Care Excellence

Part 1: Treating EGFR Exon 20 insertion-positive NSCLC and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	[redacted]
2. Name of organisation	Royal College of Pathologists
3. Job title or position	Consultant Thoracic Pathologist, [redacted]
4. Are you (please tick all that apply)	X An employee or representative of a healthcare professional organisation that represents clinicians? ☐ A specialist in the treatment of people with EGFR Exon 20 insertion-positive NSCLC? ☐ A specialist in the clinical evidence base for EGFR Exon 20 insertion-positive NSCLC or amivantamab? ☐ 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 X 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 is the main aim of treatment for EGFR Exon 20 insertion-positive NSCLC?	To slow progression of malignancy by targeted therapy in patients with locally advanced or metastatic NSCLC with activating EGFR Exon20ins mutations after previous platinum based chemotherapy

(For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	
9. 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)	Unable to comment
10. In your view, is there an unmet need for patients and healthcare professionals in EGFR Exon 20 insertion-positive NSCLC?	Yes, there is definitely an unmet need. There are currently no targeted therapies for Exon 20 insertion non small cell lung cancers and this mutation is associated with poor prognosis when compared to similar malignancies with activating mutations (eg exon 19, 21 mutations). Current EGFR TKIs are not effective in exon 20 insertion-positive tumours. In addition, patients are less likely to respond to immunotherapy compared to patients with wild-type EGFR.
11. How is EGFR Exon 20 insertion-positive NSCLC? currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • 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.) • What impact would the technology have on the current pathway of care?	I am not an oncologist but to the best of my knowledge they receive routine therapy similar to patients in which no driver mutation is identified. Introduction of Amivantanab would provide a new, targeted therapeutic option for this specific group of patients in whom current therapeutic options are limited.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic)	Unable to comment

• What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	
13. 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?	Yes – based on data from the CHRYSALIS trial when compared to routine standard of care there appears to be an improvement in progression-free survival and overall survival.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Amivantanab is only effective in patients with EGFR Exon 20ins NSCLC however this mutation is more frequent in never smokers and individuals of Asian heritage.
15. 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 affecting patient acceptability or ease of use or additional tests or monitoring needed)	Unable to comment
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	No additional testing is required provided exon 20 mutation status is routinely reported in molecular reports on all NSCLC biopsies tested. As stated several times in the submission documentation "EGFR Exon 20 insertions mutations are included in the National Genomic Test Directory for cancer and can be routinely tested in clinical practice in the Genomic Lab Hubs, as part of the diagnosis and treatment selection for patients with EGFR

	alterations." As outlined in comment 24 there is anecdotal evidence that reporting of exon 20 status is not routine across all site in England & Wales
17. 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	Unable to comment
18. 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?	Yes – I think that this technology is innovative as there are no other targeted therapies for this specific mutation in NSCLC and therefore has the potential to fulfil an unmet need in care of these patients.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Unable to comment
20. 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?	Yes

• 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?	
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
22. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance TA520?	No
23. How do data on real-world experience compare with the trial data?	Unable to comment
24. NICE considers whether there are any equalities issues at each stage of an appraisal. 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 appraisal could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation	As outlined clearly in the submission documentation (B.1.4) the frequency of EGFR mutations in NSCLC is greater in those of Asian heritage. Given the multiple barriers to accessing appropriate and timely healthcare that can be faced by this group special attention should be paid to ensuring equity of access. As stated several times in the submission documentation "EGFR Exon 20 insertions mutations are included in the National Genomic Test Directory for cancer and can be routinely tested in clinical practice in the Genomic Lab Hubs, as part of the diagnosis and treatment selection for patients with EGFR alterations." Anecdotally however there is geographic variation in the routine reporting of exon 20 EGFR mutation status. If Amivantanab is approved then routine reporting of rare EGFR mutations is necessary across the country to ensure equity of access to this therapy.

• 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: Technical engagement questions for clinical experts

We welcome your comments on the key issues below, but you may want to concentrate on issues that are in your field of expertise. If you think an issue that is important to clinicians or patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section.

The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting.

For information: the professional organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report. These will also be considered by the committee.

Table 2 Issues arising from technical engagement

Issue 1: generalisability and potential underestimation of adverse events, i.e.: • *The clinical trial population is likely to be fitter than the population in clinical practice (for example, only people with ECOG status of 0 or 1 were included within the trial population). What*	

impact do you consider this to have?	
Issue 2: use of concomitant medications, i.e.: • *People within the intervention group of the clinical trial, received a number of concomitant medicines (including targeted radiotherapy). What impact do you consider this may have had on results?*	
Issue 3: comparators, i.e.: • *In clinical practice, what is typically used after platinum-based chemotherapy?* • *Are EGFR TKIs typically used in clinical practice for EGFR Exon20ins mutations?*	

Issue 4: short follow-up of CHRYSALIS trial	
Issue 5: cut-off dates for efficacy and safety populations	
Issue 6: RWE data sources	
Issue 7: EGFR TKIs in comparator basket, i.e.: • *What percentage of people (if any) have EGFR TKIs in clinical practice?*	
Issue 8: use of KM curves instead of parametric survival models	
Issue 9: time to treatment discontinuation, i.e.: • *What is the expected treatment duration of amivantamab?* • *Is treatment with amivantamab likely to continue beyond disease progression?*	

Issue 10: treatment waning, i.e.: • *How long do you expect treatment effect of amivantamab to last? Is treatment waning expected?*	
Issue 11: utilities age-adjustment	
Issue 12: lack of fully incremental analysis for all comparators	
Issue 13: lack of fixed random seed in model PSA	
Are there any important issues that have been missed in ERG report?	

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Amivantanab has a potential role in meeting an unmet need of patients with EGFR exon20ins positive NSCLC for whom there are no current targeted therapies
In order to ensure geographical equity of access molecular pathology results need to routinely include exon 20 mutation status in reporting of EGFR status in NSCLC testing.

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

NICE National Institute for Health and Care Excellence

Patient expert statement and technical engagement response form

Amivantamab for treating EGFR Exon 20 insertion-positive non-small-cell lung cancer after platinum-based chemotherapy [ID3836]

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 evidence review group (ERG) report and stakeholder responses are used by the appraisal committee to help it make decisions at the appraisal 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 EGFR Exon 20 insertion-positive NSCLC or caring for a patient with EGFR Exon 20 insertion-positive NSCLC. The text boxes will expand as you type.

In part 2 we are asking for your views on key issues in the ERG report that are likely to be discussed by the committee. The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the ERG report (Section 1).

A patient perspective could help either:

- resolve any uncertainty that has been identified OR

- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise. We have given guidance on the issues in which we expect this to be the case and advice on what you could consider when giving your response.

In part 3 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.

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. Please type information directly into the form.

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.

Please note, **part 1** can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

Deadline for comments by **5pm** on **Monday 13 June**. 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.

Part 1: Living with this condition or caring for a patient with EGFR Exon 20 insertion-positive NSCLC

Table 1 About you, EGFR Exon 20 insertion-positive NSCLC, current treatments and equality

1. Your name	Angela Terry
2. Are you (please tick all that apply)	☐ A patient with EGFR Exon 20 insertion-positive NSCLC ? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with EGFR Exon 20 insertion-positive NSCLC? ☒ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	EGFR Positive 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) ☒ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☒ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☒ I agree with it and **will be** completing
5. 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 have completed part 2 of the statement **after attending** the expert

	engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with EGFR Exon 20 insertion-positive NSCLC? **If you are a carer (for someone with EGFR Exon 20 insertion-positive NSCLC) please share your experience of caring for them**	Non-small cell lung cancer with an EGFR mutation is an aggressive disease that has a considerable physical, psychological, economic and social impact on patients and their families. Late diagnosis at Stage 4 is common and reflects that EGFR patients are generally younger than typical lung cancer patients, non-smokers, more likely to be female, often still working and with dependent children. The diagnosis is particularly devastating and affects all aspects of life. Lung Cancer patients carry the additional stigma of contracting a disease that is thought to be linked to smoking. Of our EGFR positive UK members (85%) have never smoked (59%) or gave up over 10 years ago (26%). Living with stage IV disease is extremely difficult. Many of our members are still working, in the prime of their lives, and have dependent children. For families, facing the loss of a parent and breadwinner, causes immense strain and many of our members suffer from anxiety and depression. This coupled with the burden of disease and treatment, impacts enormously on their quality of life and that of their families. The causes of poor quality of life are frequently treatment and disease related symptoms such as diarrhoea, fatigue, pain, shortness of breath and cough. Together these have a negative impact on daily activities including household chores and self-care, social activities, work, and family life. Psychologically, socially and economically life can be extremely challenging. Progression free survival and quality of life are key to patients - the ability to

	take part fully in family life and to support the family for as long as possible is vital. EGFR positive patients have a very high probability of developing brain metastases. Evidence suggests that patients in whom brain metastases are treated early have improved overall survival. Only 42% of our members have regular routine brain scans. This impacts directly on treatment options, particularly if patients become symptomatic before brain metastases are discovered. Additionally once brain metastases are identified the patient must stop driving, this has implications for both the patient and their families. Family and carers of patients may have a considerable burden providing care and assistance with the activities of daily living. This could affect the ability of family members to continue employment, have a detrimental effect on household income, and cause financial strain. This may add to the stress and anxiety of caring for a loved one with significant disease burden. For younger family members, educational choices may be affected which could have an impact for years to come. .
7a. What do you think of the current treatments and care available for EGFR Exon 20 insertion-positive NSCLC on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	7a.EGFR Exon 20 insertion is a distinct population. It is recommended that patients are offered platinum-based chemotherapy 1st line and there are no specific treatment recommendations beyond this. There are currently no approved targeted therapies available for EGFR Exon 20 insertion patients and EGFR Exon 20 insertion mutations are known to be associated with resistance/insensitivity to the currently available TKIs. The poor prognosis coupled with knowing that there are fewer treatments than those available to other EGFR patients, has a devastating impact. EGFR positive patients have a very high probability of developing brain metastases. No treatment currently offered to EGFR Exon 20 insertion

	patients offers protection to the brain and patients fear the inevitable CNS progression. We have found that following initial chemotherapy, there is little conformity in the treatment offered in the 2nd line setting. Patients were offered a range of treatments: TKI's approved for other EGFR mutations, chemotherapy and immunotherapy. This is surprising as it is known that these therapies offer limited clinical benefit to EGFR Exon 20 insertion patients. Patients however have a strong preference for targeted therapies and upon progression they are pressing for another treatment so perhaps trying one that is available but not optimal, is preferable to nothing. 7b. The views are a summary of those interviewed for this submission.
8. If there are disadvantages for patients of current NHS treatments for EGFR Exon 20 insertion-positive NSCLC (for example, how amivantamab is given or taken, side effects of treatment, and any others) please describe these	There is little conformity in the treatment offered in the 2nd line setting. Patients are offered a range of treatments: TKI's approved for other EGFR mutations, chemotherapy and immunotherapy even though it is known that these therapies offer limited clinical benefit to EGFR Exon 20 insertion patients. PxP: 'I feel very isolated, I don't know anyone else who has this type of EGFR and I am not sure my Oncologist does either. My treatment feels like trial and error.' PxL: 'I am really positive about targeted therapies. I don't like this one size fits all approach (Chemo). We are becoming much better educated about our disease and I really dislike chemo, there must be other treatment available to us' PxJ: I know from other patients that their targeted therapies are less toxic and more effective. I am angry and disappointed knowing they are available to others in the group but not to me.'

	These patients have poorer treatment outcomes compared with patients with other EGFR mutations across different currently available therapy options and treatment lines. PxB: I have already had chemotherapy earlier on and I believe an Exon 20 targeted therapy would be another level of treatment to slow the progression of the disease.' PxL: 'I am really positive about targeted therapies. I don't like this one size fits approach (Chemo). We are becoming much better educated about our disease and I really dislike chemo, there must be other treatments available to us' PxN:'I am a fighter, I can't believe this (Chemo) is all there is for me!' Without approved targeted therapies in the 2nd line setting, EGFR Exon 20 insertion patients are offered treatments that seem to be 'what is available' and 'will give hope'. Sadly these treatments are unlikely to give patients longer progression free survival. Meanwhile the treatment they are living with has significant side effects that impact every aspect of their lives. PxK: ''It had all been doom and gloom until we found out that I was EGFR positive Exon 20 insertion. I was prescribed Afatinib. The side effects are horrible, constant diarrhoea meant I can't go out, my skin is like a pizza and I am so tired all the time but I have to keep going on this but I don't know what will be next for me.' In terms of prognostic impact and clinical burden, there is a high unmet need for novel, effective therapies for patients with EGFR Exon 20 insertion.

9a. If there are advantages of amivantamab 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 amivantamab 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**	9a. Amivantamab is proposed for use after the failure of platinum-based chemotherapy. It is well tolerated and has a low toxicity burden. It is an IV therapy that is delivered in a hospital or Clinic. There are few side effects with Amivantamab and those there are, are mainly linked to an infusion related reaction which often happens on the 1st infusion only. PxG: 'I started reacting when I was given my first dose but I wasn't frightened as the team had talked us through what might happen. They weren't alarmed and knew exactly what to do and that calmed me down. I ended up having the first dose over 2 days.' Amivantamab is not just important for post-chemo treatment but potentially important when used in sequence with the other new drugs that target EGFR Exon 20 patients. In addition, some patients may be better candidates for Amivantamab rather than the other targeted drugs and vice versa. PxL: 'I am really positive about targeted therapies. I don't like this one size fits approach (chemo). We are becoming much better educated about our disease and I really dislike chemo, there must be other treatment available to us' 9b. It is crucial to have alternative treatments available for these patients. 9c. This new treatment would change the clinical, mental and emotional state of the EGFR Exon 20 patients and give them hope. Treatment with Amivantamab would allow patients to live progression free for longer. This would likely result in more independence with day-to-day life and selfcare, which would reduce dependence on family and support services. This drug offers a lifeline of hope for the first time for these patients.

10. If there are disadvantages of amivantamab over current treatments on the NHS please describe these. For example, are there any risks with amivantamab? If you are concerned about any potential side effects you have heard about, please describe them and explain why	As a charity we see no disadvantages for patients in Amivantamib being available as a 2nd line treatment but there are some issues. Patients have a fear of Chemotherapy and may need to be persuaded that this IV therapy is the best option for them. Taking time to help the patient fully understand what the treatment is, how it will be administered and predicable reactions is key. PxQ: 'The 1st infusion is scaring a lot of people. I was told that the body is seeing the antibody as something it will reject. Patients need to know that this will happen and it should not be a deterrent to having the treatment. It is a 100% expected side effect.' PxG: 'I started reacting when I was given my first dose but I wasn't frightened as the team had talked us through what might happen. They weren't alarmed and knew exactly what to do and that calmed me down. I ended up having the first dose over 2 days.' IV therapy is delivered in a hospital or Clinic. The time required for the treatment and travelling to and from the hospital may present challenges especially for those patients who have mobility issues or live a long distance from their hospital/clinic. Amivantamib does not offer CNS penetration. Brain metastases are common with this disease and patients who are on this drug will fear the inevitable progression to the brain.
11. Are there any groups of patients who might benefit more from amivantamab or any who may benefit less? If so, please describe them and explain why	All EGFR positive Exon 20 insertion patients would benefit from Amivantamab being approved for use in the 2nd line setting.

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	Amivantamab would give Clinicians more choice and flexibility in the treatment of their EGFR positive Exon 20 insertion patients. Amivantamab would, for the first time, offer EGFR Exon 20 positive patients access to a targeted therapy. This would bring them emotionally and clinically in line with their fellow EGFR patients who have had access to targeted treatments for some time.
12. Are there any potential equality issues that should be taken into account when considering EGFR Exon 20 insertion-positive NSCLC and amivantamab? 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.	A major equality issue for patients is often one of equal access to the best treatment available.
13. Are there any other issues that you would like the committee to consider?	The success of a targeted approach is dependent on understanding the genomic state of the tumour cells. It is imperative to identify EGFR patients with Exon 20 insertion so that they can be matched up with the right treatment. Patients who are EGFR Exon 20 insertion positive are a small and distinct group whose number may have been significantly underestimated. Detection rates are currently increasing with the advent of more sensitive NGS testing. In essence they are an under-diagnosed and under-served population.

	Amivantamab is an excellent addition to the EGFR Exon 20 insertion patient's treatment options however there is still a need for new drugs with intracranial activity and resistance mechanisms. EGFR Exon 20 insertion patients are a small population with a significant unmet need. They are outliers in the EGFR group. A niche group who are often under or mis-diagnosed and have an urgent need for targeted, more effective and well tolerated therapies to prolong survival and improve quality of life.

Part 2: Technical engagement questions for patient experts

Issues arising from technical engagement

The issues raised in the ERG report are listed in table 2. We welcome your comments on the issues, but you do not have to provide a response to every issue, such as the ones that are technical, that is, cost effectiveness-related issues. We have added a comment to the issues where we consider a patient perspective would be most relevant and valuable. If you think an issue that is important to patients has been missed in the ERG report, please let us know in the space provided at the end of this section.

For information: the patient organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report, the patient organisation responses will also be considered by the committee.

Table 2 Issues arising from ERG report

Issue 1: generalisability and potential underestimation of adverse events, i.e.: *The clinical trial population is likely to be fitter than the population in clinical practice (for example, only people with ECOG status of 0 or 1 were included within the trial population). What*	EGFR positive lung cancer patients are different from traditional lung cancer patients. They are younger, fitter, non/never smokers and predominantly female.

impact do you consider this to have?	
Issue 2: use of concomitant medications, i.e.: *People within the intervention group of the clinical trial, received a number of concomitant medicines (including targeted radiotherapy). What impact do you consider this may have had on results?*	
Issue 3: comparators, i.e.: • *In clinical practice, what is typically used after platinum-based chemotherapy?* • *Are EGFR TKIs (e.g. afatinib) typically used in clinical practice for EGFR Exon20ins mutations?*	
Issue 4: short follow-up of CHRYSALIS trial	

Issue 5: cut-off dates for efficacy and safety populations	
Issue 6: RWE data sources	
Issue 7: EGFR TKIs in comparator basket, i.e.: *What percentage of people (if any) have EGFR TKIs in clinical practice?*	
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Issue 10: treatment waning, i.e.:	

• *How long do you expect treatment effect of amivantamab to last? Is treatment waning expected?*	
Issue 11: utilities age-adjustment	
Issue 12: lack of fully incremental analysis for all comparators	
Issue 13: lack of fixed random seed in model PSA	
Are there any important issues that have been missed in ERG report?	

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Amivantamab would begin to meet a significant unmet need. For the first time, EGFR Exon 20ins positive patients would have access to a targeted therapy. This would bring them emotionally and clinically in line with some of the treatment options their fellow EGFR patients have had access to for some time.
- Amivantamab offers Progression Free Survival and Quality of Life Benefits
- Amivantamab has a low toxicity profile and infusion related reactions are manageable
- Amivantamab has the potential to be used in sequence or in combination with other new treatments for EGFR Exon 20ins positive patients
- Whilst taking Amivantamab patients can be expected to have a good quality of life for longer, be able to live independently, continue to work and drive and participate fully in family life and social activities.

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Patient expert statement and technical engagement response form

Amivantamab for treating EGFR Exon 20 insertion-positive non-small-cell lung cancer after platinum-based chemotherapy [ID3836]

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

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Information on completing this form

In part 1 we are asking you about living with EGFR Exon 20 insertion-positive NSCLC or caring for a patient with EGFR Exon 20 insertion-positive NSCLC. The text boxes will expand as you type.

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A patient perspective could help either:

- resolve any uncertainty that has been identified OR

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Deadline for comments by **5pm** on **Monday 13 June**. 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.

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Part 1: Living with this condition or caring for a patient with EGFR Exon 20 insertion-positive NSCLC

Table 1 About you, EGFR Exon 20 insertion-positive NSCLC, current treatments and equality

1. Your name	Deborah Littell
2. Are you (please tick all that apply)	☐ A patient with EGFR Exon 20 insertion-positive NSCLC ? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with EGFR Exon 20 insertion-positive NSCLC? ☒ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	EGFR Positive 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) ☒ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☐ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☒ I agree with it and **will be** completing
5. 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 have completed part 2 of the statement **after attending** the expert

	engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with EGFR Exon 20 insertion-positive NSCLC? **If you are a carer (for someone with EGFR Exon 20 insertion-positive NSCLC) please share your experience of caring for them**	6. Living with stage IV disease is extremely difficult. Many of our members are still working, in the prime of their lives, and have dependent children. For families, facing the loss of a parent and breadwinner, causes immense strain and many of our members suffer from anxiety and depression. This coupled with the burden of disease and treatment, impacts enormously on their quality of life and that of their families. The diagnosis is often late at Stage 4, and the patients are typically non-smokers, female, still working and have children. This then gives rise to considerable physical, psychological, economic and social impact on patients and their families. The diagnosis is particularly devastating and affects all aspects of life. Lung Cancer patients carry the additional stigma of contracting a disease that is thought to be linked to smoking. Of our EGFR positive UK members (85%) have never smoked (59%) or gave up over 10 years ago (26%). The causes of poor quality of life from both treatment and disease related symptoms such as diarrhoea, fatigue, pain, shortness of breath and cough. Together these have a negative impact on daily activities including household chores and self-care, social activities, work, and family life. Psychologically, socially and economically life can be extremely challenging. Progression free survival and quality of life are key to patients - the ability to

	take part fully in family life and to support the family for as long as possible is vital.
7a. What do you think of the current treatments and care available for EGFR Exon 20 insertion-positive NSCLC on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	7a. Although there is a clear and effective pathway for several of the EGFR variants there is no formal effective pathway for Exon 20 insertion-positive patients. Therefore, we often see patients being treated in the same way as EGFR patients with the more common profiles such as Exon 19 and other variants in the hope that something may stick and work. Resulting in poor quality of life from both the treatment and disease related symptoms such as diarrhoea, fatigue, pain, shortness of breath, cough and of course progression. Together these have a negative impact on daily activities including household chores and self-care, social activities, work, family life and mental wellbeing of the patient. 7b. EGFR Exon 20 insertion is a distinct population. It is recommended that patients are offered platinum-based chemotherapy 1st line and there are no specific treatment recommendations beyond this. There are currently no approved targeted therapies available for EGFR Exon 20 insertion patients and EGFR Exon 20 insertion mutations are known to be associated with resistance/insensitivity to the currently available TKIs and early mortality. The poor prognosis coupled with knowing that there are fewer treatments than those available to other EGFR patients, has a devastating impact.
8. If there are disadvantages for patients of current NHS treatments for EGFR Exon 20 insertion-positive NSCLC (for example, how amivantamab is given or	8. Some clinics offer another chemo variant, however, this is not consistent in clinical practice in the 2nd line setting.

taken, side effects of treatment, and any others) please describe these	Patients are offered a range of treatments: TKI's approved for other EGFR mutations, chemotherapy and immunotherapy despite not knowing whether these therapies will offer any clinical benefit to EGFR Exon 20 insertion patients. The current regime means that patients are switched from one treatment to another in some vague hope that they may make a difference to the point of no return. The Chemo offered is more aggressive and the quality of life diminishes with limited overall benefit. It may have an overall survival benefit but at what cost to the patient and family.
9a. If there are advantages of amivantamab 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 amivantamab 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**	9a. Amivantamab is proposed for use after the failure of platinum-based chemotherapy. It is well tolerated and has a low toxicity burden. It is an IV therapy that is delivered in a hospital or Clinic and therefore easy to administer. There are few side effects with Amivantamab and those there are, mainly linked to an infusion related reaction which often happens on the 1st infusion only. 9b. It is crucial that patients have an effective treatment pathway to provide a progression free survival that is more effective than the current guess work. 9c. This new treatment would change the clinical, mental and emotional state of the EGFR Exon 20 patients and give them hope. Treatment with Amivantamab would allow patients to live progression free for longer. This would likely result in more independence with day-to-day life and selfcare, which would reduce dependence on family and support services.

	This drug offers a lifeline of hope for the first time for these patients.
10. If there are disadvantages of amivantamab over current treatments on the NHS please describe these. For example, are there any risks with amivantamab? If you are concerned about any potential side effects you have heard about, please describe them and explain why	10. There are no disadvantages for patients on Amivantamib IV therapy is delivered in a hospital or Clinic. The time required for the treatment and travelling to and from the hospital may present challenges especially for those patients who have mobility issues or live a long distance from their hospital/clinic but are similar to that of or better than the current proposed approach of Chemo.
11. Are there any groups of patients who might benefit more from amivantamab 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	All EGFR positive Exon 20 insertion patients would benefit from Amivantamab being approved for use in the 2nd line setting. Amivantamab would give Clinicians a clear pathway for a treatment plan of their EGFR positive Exon 20 insertion patients. Amivantamab would, for the first time, offer EGFR Exon 20 positive patients access to a targeted therapy. This would bring them emotionally and clinically in-line with their fellow EGFR patients who have had access to targeted treatments for some time. Amivantiamab may also be effective on other Exon groups and therefore patients with a combination of Exon mutations would also benefit even if Exon 20 insertion is not their driving Exon.
12. Are there any potential equality issues that should be taken into account when considering EGFR Exon 20 insertion-positive NSCLC and amivantamab? Please explain if you think any groups of people with this condition are particularly disadvantaged	Equality in supporting lung cancer patients when perception can be that there was a causative effect such as smoking. In EGFR patients this is NOT true and they should be afforded the best clinical treatment for a group which is likely to comprise of women of a working age with young families.

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.	Non-small cell lung cancer with an EGFR mutation is an aggressive disease that has a considerable physical, psychological, economic and social impact on patients and their families. Late diagnosis at Stage 4 is common and reflects that EGFR patients are generally younger than typical lung cancer patients, non-smokers, more likely to be female, often still working and with dependent children. The diagnosis is particularly devastating and affects all aspects of life. Lung Cancer patients carry the additional stigma of contracting a disease that is thought to be linked to smoking. Of our EGFR positive UK members (85%) have never smoked (59%) or gave up over 10 years ago (26%).
13. Are there any other issues that you would like the committee to consider?	The success of a targeted approach is dependent on understanding the genomic state of the tumour cells. It is imperative to identify EGFR patients with Exon 20 insertion so that they can be matched up with the right treatment. Patients who are EGFR Exon 20 insertion positive are a small and distinct group whose number may have been significantly underestimated. Detection rates are currently increasing with the advent of more sensitive NGS testing. In essence they are an under-diagnosed and under-served population.

Part 2: Technical engagement questions for patient experts

Issues arising from technical engagement

The issues raised in the ERG report are listed in table 2. We welcome your comments on the issues, but you do not have to provide a response to every issue, such as the ones that are technical, that is, cost effectiveness-related issues. We have added a comment to the issues where we consider a patient perspective would be most relevant and valuable. If you think an issue that is important to patients has been missed in the ERG report, please let us know in the space provided at the end of this section.

For information: the patient organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report, the patient organisation responses will also be considered by the committee.

Table 2 Issues arising from ERG report

Issue 1: generalisability and potential underestimation of adverse events, i.e.: *The clinical trial population is likely to be fitter than the population in clinical practice (for example, only people with ECOG status of 0 or 1 were included within the trial population). What*	EGFR patients as a whole are generally fitter and present with a ECOG status 0 – 1 but in the advent of progression quickly decline and typically die within a 3 – 6 month period.

impact do you consider this to have?	
Issue 2: use of concomitant medications, i.e.: *People within the intervention group of the clinical trial, received a number of concomitant medicines (including targeted radiotherapy). What impact do you consider this may have had on results?*	Concomitant medications are part of the clinical picture for other EGFR groups and provide an opportunity for a TKI "to get the upper hand" and stabilise a position. This is an accepted treatment practice and do not believe that Amivantamab would replace this practice.
Issue 3: comparators, i.e.: • *In clinical practice, what is typically used after platinum-based chemotherapy?* • *Are EGFR TKIs (e.g. afatinib) typically used in clinical practice for EGFR Exon20ins mutations?*	As there is not a consistent treatment plan after platinum based chemo therapy I don't believe there is currently a comparator.
Issue 4: short follow-up of CHRYSALIS trial	

Issue 5: cut-off dates for efficacy and safety populations	Anecdotally, we have seen patients in the US have this treatment for 3 years plus with great effect.
Issue 6: RWE data sources	
Issue 7: EGFR TKIs in comparator basket, i.e.: *What percentage of people (if any) have EGFR TKIs in clinical practice?*	A very high percentage (all) of our EGFR positive members have TKIs. It is gold standard practice for EGFR patients. Currently, EXON 20 insertion patients receive a mix of Chemo, or TKIs in the hope that something may work with little or no great effect.
Issue 8: use of KM curves instead of parametric survival models	
Issue 9: time to treatment discontinuation, i.e.: • *What is the expected treatment duration of amivantamab?* • *Is treatment with amivantamab likely to continue beyond disease progression?*	Anecdotally, we have seen patients in the US have this treatment for 3 years plus with great effect.
Issue 10: treatment waning, i.e.:	All TKIs eventually get resistance and there is no reason to suppose this is any different. 3rd gen TKI in my case has continued to be effective PFS for 42 months.

• *How long do you expect treatment effect of amivantamab to last? Is treatment waning expected?*	
Issue 11: utilities age-adjustment	Most patients are in their 50's and therefore have many productive working years of life ahead.
Issue 12: lack of fully incremental analysis for all comparators	
Issue 13: lack of fixed random seed in model PSA	
Are there any important issues that have been missed in ERG report?	

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Amivantamab offers Progression Free Survival and Quality of Life Benefits
- Amivantamab is proposed for use after the failure of platinum-based chemotherapy. It is well tolerated and has a low toxicity burden. It is an IV therapy that is delivered in a hospital or Clinic and therefore easy to administer.
- Amivantamab provides an effective treatment pathway to provide a progression free survival that is more effective than the current guess work.
- Amivantamab would extend patients' lives. This would likely result in more independence with day-to-day life and selfcare, which would reduce dependence on family and support services.
- Amivantamab has a low toxicity profile and infusion related reactions are manageable.

Thank you for your time.

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Erasmus School of Health Policy & Management

Maastricht University

Amivantamab for treating EGFR Exon 20 insertion-positive non-small-cell lung cancer after platinum-based chemotherapy (review of TA10729) [ID3836]

Produced by

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Authors

Jeremy Howick, Reviews Manager, KSR Ltd, United Kingdom (UK)
Willem Witlox, Health Economist, Maastricht UMC+, The Netherlands
Kevin McDermott, Systematic Reviewer, KSR Ltd, UK
Ben Wijnen, Health Economist, Maastricht UMC+, The Netherlands
Evangelos Danopoulos, Systematic Reviewer, KSR Ltd, UK
Thomas Otten, Health Economist, Maastricht UMC, The Netherlands
Charlotte Ahmadu, Health Economist, KSR Ltd, UK
Steven Duffy, Information Specialist, KSR Ltd, UK
Marie Westwood, Reviews Manager, KSR Ltd, UK
Nigel Armstrong, Health Economics Manager, KSR Ltd, UK
Mark Perry, Reviews Manager, KSR Ltd, UK
Robert Wolff, Managing Director, KSR Ltd, UK
Manuela Joore, Health Economist, Maastricht UMC+, The Netherlands
Jos Kleijnen, Founder and Owner, KSR Ltd

Correspondence to Jeremy Howick, Kleijnen Systematic Reviews Ltd
Unit 6, Escrick Business Park
Riccall Road, Escrick
York, YO19 6FD
United Kingdom

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Any de-personalised data are highlighted in pink throughout the report.

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

Jeremy Howick acted as project lead and systematic reviewer on this assessment, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Willem Witlox and Ben Wijnen acted as health economic project leads, critiqued the company's economic evaluation, and contributed to the writing of the report. Thomas Otten, Charlotte Ahmadu, and Nigel Armstrong acted as health economists on this assessment, critiqued the company's economic evaluation and contributed to the writing of the report. Kevin McDermott, Evan Danopoulos, Mark Perry, and Marie Westwood acted as systematic reviewers, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Steven Duffy critiqued the search methods in the submission and contributed to the writing of the report. Manuela Joore acted as health economist on this assessment, critiqued the company's economic evaluation, contributed to the writing of the report and provided general guidance. Robert Wolff and Jos Kleijnen critiqued the company's definition of the decision problem and their description of the underlying health problem and current service provision, contributed to the writing of the report and supervised the project.

Abbreviations

AACR	American Association for Cancer Research
AE	Adverse event
AEMPS	Agencia Española de Medicamentos y Productos Sanitarios
AIFA	Agenzia Italiana del Farmaco
AMI	Amivantamab
ASCO	American Society of Clinical Oncology
ATT	Average treatment effect among the treated
AWMSG	All Wales Medicines Strategy Group
BAG	Bundesamt für Gesundheit
BICR	Blinded independent committee review assessed
BMI	Body mass index
BNF	British National Formulary
BOR	Best overall response
BSC	Best supportive care
CADTH	Canadian Agency for drugs and Technologies in Health
CBR	Clinical benefit rate
CDSR	Cochrane Database of Systematic Reviews
CENTRAL	Cochrane Central Register of Controlled Clinical Trials
CI	Confidence interval
cm	Centimetre
CR	Complete response
CRD	Centre for Reviews and Dissemination
CS	Company submission
DARE	Database of Abstracts of Reviews of Effects
DFS	Disease free survival
DOR	Duration of response
DSA	Deterministic sensitivity analysis
DSU	Decision Support Unit
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal growth factor receptor
EMA	European Medicines Agency
EQ-5D-5L	EuroQoL 5-dimensions 5-levels
EQ-5D-5L VAS	EuroQol-5 dimensions 5-levels visual analogue score
ERG	Evidence Review Group
ESMO	European Society for Medical Oncology
Exon20ins	Exon 20 insertion mutations
FE	Fixing errors
FinCCHTA	Finnish Coordinating Center for Health Technology Assessment
FDA	Food and Drugs Administration
FV	Fixing violations
G-BA	Gemeinsamer Bundesausschuss
HAS	Haute Autorité de Santé
HER2	Human epidermal growth factor receptor 2
HIV	Human immunodeficiency virus
HR	Hazard ratio
HRQoL	Health-related quality of life

HTA	Health technology assessment
IASLC	International Association for the Study of Lung Cancer
ICER	Incremental cost-effectiveness ratio
iDFS	Invasive disease-free survival
ILD	Interstitial lung disease
INV	Investigator-assessed
IPD	Individual participant data
IPW	Inverse probability weighting
IRR	Infusion related reaction
IO	Immuno-oncology
ITC	Indirect treatment comparison
ITT	Intention to treat
IV	Intravenous
kg	Kilogram
KM	Kaplan-Meier
LOT	Line of therapy
LS	Least squares
LY	Life year
mg	Milligram
MET	Mesenchymal epithelial transition
MHRA	Medicines and Healthcare Products Regulatory Agency
MJ	Matters of judgement
MSCBS	Ministerio de Sanidad, Consumo y Bienestar Social
MTD	Maximum tolerated dose
NCI CTCAE	National Cancer Institute common terminology criteria for adverse events
NCPE	National Centre for Pharmacoeconomics
NCRAS	National Cancer Registration and Analysis Service
NE	Not evaluable
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIPH	Norwegian Institute of Public Health
NR	Not reported
NSCLC	Non-small-cell lung cancer
NSCLC-SAQ	Non-small-cell lung cancer Symptom Assessment Questionnaire
ORR	Overall response rate
OS	Overall survival
PAS	Patient Access Scheme
pCR	Pathological complete response
PD	Progressed disease
PFS	Progression-free survival
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
PHE	Public Health England
PPS	Post-progression survival
PR	Partial response
PRESS	Peer Review of Electronic Search Strategies
PRO	Patient-reported outcome

PSA	Probabilistic sensitivity analysis
PSM	Propensity score matching
PSSRU	Personal Social Services Research Unit
Pt	Platinum
QALY	Quality-adjusted life year
QoL	Quality of life
RCT	Randomised controlled trial
RECIST	Response Evaluation Criteria in Solid Tumours
RID	Residual invasive disease
RP2D	Recommended Phase 2 dose
RWD	Real world data
RWE	Real world evidence
SBU	Swedish Agency for Health Technology Assessment and Assessment of Social Services
SCLC	Small cell lung cancer
SD	Standard deviation
SLR	Systematic literature review
SMC	Scottish Medicines Consortium
SMD	Standardised mean difference
SoC	Standard of Care
SoD	Sum of diameters
STM	State transition model
STA	Single technology appraisal
TEAE	Treatment-emergent adverse event
TKI	Tyrosine kinase inhibitor
TSD	Technical Support Document
TTD	Time to treatment discontinuation
TTF	Time to treatment failure
TTNT	Time to next treatment
UK	United Kingdom
US	United States
VAS	Visual analogue scale

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Issue 10 – The company did not explore treatment waning in the model, whereas the Evidence Review Group (ERG) considered that the assumption of a lifelong treatment effect may not be warranted 13

Issue 11 – The company's failure to include an age-adjustment to the health state utilities in their company submission (CS) base case is not in line with good modelling practice and may have exaggerated the cost 14

Issue 12 - Lack of a fully incremental analysis for all relevant comparators in the comparator basket, increasing the uncertainty of estimates of amivantamab's cost effectiveness 14

Issue 13 - Lack of a fixed random seed in model probabilistic sensitivity analysis (PSA) leads to fluctuations in probabilistic results and hence increased uncertainty of estimates of amivantamab's cost-effectiveness 14

Additional issue 1 - The ERG noted a lack of clarity and information surrounding "how 19.6% of patients are experiencing grade 3 or above events related to amivantamab, yet only 8.5% of patients have experienced what is described as a serious AE." 14

Additional issue 2 - The ERG were not confident that "the five patients included in Cohort D+, that came from Part 1 (dose escalation) of the study met the molecular eligibility requirements." 14

Additional issue 3 - The ERG noted that "in both Figure 3.8 (NSCLC-SAQ) and Figure 3.9 (ED-5D-5L) the included number of patients appears to be very small [redacted]) and different from what was reported in the text [redacted])." 15
Additional issue 4 - The ERG noted that "the eligibility criteria stated that only patients with ECOG status 0 or 1 were to be included in the CHRYSALIS trial (Table 3.3), nevertheless, one patient with ECOG status 2 was included (Table 3.7)." 15

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Issue 1 – The narrower population considered by company may not be generalisable to the England and Wales NHS population and may have led to an underestimate of adverse events

The company acknowledge again that the population in the CHRYSALIS trial is relatively fit with lower ECOG status (0 or 1). They explain that, although this is narrower than the marketing authorisation, it is consistent with the UK EGFR-mutated Exon20ins NSCLC population: "*This was validated by feedback from UK-based clinicians at a Janssen-led advisory board who confirmed that the baseline characteristics of patients included in the study were comparable to the characteristics of patients with EGFR-mutated Exon20ins NSCLC that they would expect to treat in their typical clinical practice.*"

ERG comment:

The ERG would simply point out that, notwithstanding how common this is, the most relevant population in clinical practice is those with ECOG 0 or1.

Issue 2 – Patients in the intervention group received concomitant medications (including targeted radiotherapy) that could have exaggerated the benefits of amivantamab

The company argued that all concomitant medications except targeted radiotherapy might be considered UK standard care and therefore performed an updated adjusted treatment comparison excluding the three patients who received targeted radiotherapy and versus the US real world evidence (RWE) using the inverse probability weighting to estimate the average treatment effect on the treated (IPW ATT) methodology, also based on update overall survival (OS) data provided for Key Issue 4. Based on the results for OS, progression free survival (PFS) and time to next treatment (TTNT), the company claimed that exclusion of patients who received targeted radiotherapy has a negligible impact. The company also presented results for the eight adverse events (AEs) included in the economic model (see Table 1: the ERG have added the also including the AE results from the old data-cut).

Table 1: Incidence of Grade ≥3 AEs occurring in ≥5% of patients in the amivantamab treatment arm in the CHRYSALIS population

AE, %	Scenario analysis population[b] (N=111, 30th March 2022 data cut-off)	Safety population (N=153, 30th March 2021 data cut-off)	Efficacy population (N=114, 30th March 2021 data cut-off)
Anaemia	[redacted]	[redacted]	[redacted]
Diarrhoea[a]	[redacted]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]
Febrile neutropenia	[redacted]	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]	[redacted]
Neutrophil count decreased	[redacted]	[redacted]	[redacted]
Rash	[redacted]	[redacted]	[redacted]
Thrombocytopaenia	[redacted]	[redacted]	[redacted]

Source: Tables 2 and Table 5, TE response
[a] Due to its clinical relevance, the incidence of diarrhoea was considered at any grade.
[b]Excluding patients who received concomitant targeted radiotherapy (N=111) scenario population
Abbreviations: AE: adverse event.

ERG comment:

The ERG acknowledges that most of the concomitant treatments were for symptomatic or palliative treatment and would probably have little impact on OS, PFS or TTNT, the exception being targeted radiotherapy. The ERG also notes that there was effectively no difference in outcome due to exclusion of targeted radiotherapy for up to two decimal places for PFS and TTNT and only a 0.01 and 0.02 difference in the point estimate and lower 95% confidence (CI) limit for OS. The exclusion of those three patients seems to have had little effect on AE rates, although there is no comparison between with and without for the same data-cut.

Issue 3 – Some of the comparators lack justification and could have obscured or exaggerated the benefits of amivantamab

The company argued that inclusion of EGFR TKIs in the RWD appropriately reflected UK clinical practice. Nevertheless, they conducted an updated adjusted treatment comparison excluding patients in receipt of these treatments versus the US RWE using the IPW ATT methodology, also based on update survival data provided for Issue 4. Based on the results for OS, PFS and TTNT, the company claimed that exclusion of patients who received EGFR TKIs has a minimal impact (see Table 2).

Table 2: Comparison of adjusted treatment comparison results for scenario analysis for CHRYSALIS vs. US RWE excluding TKIs

HR (95% CI)	Original analysis (30th March 2021 data cut)		Updated analysis (7th March 2022 data cut)	
	Base case	Scenario excluding TKIs	Base case	Scenario excluding TKIs
OS	[redacted]	[redacted]	[redacted]	[redacted]
PFS BICR[a]	[redacted]	[redacted]	[redacted]	[redacted]
TTNT[a]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Table 3, TE response
[a] PFS and TTNT data remain unchanged as compared with the previous data cut.
Abbreviations**:** BICR: blinded independent committee review; CI: confidence interval; HR: hazard ratio; OS: overall survival; TKI: tyrosine kinase inhibitor; TTNT: time to next treatment.

ERG comment:

The ERG remains uncertain as to the appropriateness of EGFR TKIs to UK clinical practice. However, the ERG also notes that there was effectively no difference in outcome due to exclusion of these therapies for up to two decimal places for PFS and TTNT and only a 0.01, 0.01 and 0.04 difference in the point estimate, lower and upper 95% CI limit for OS.

Issue 4 – The short follow-up time of the CHRYSALIS trial makes medium- and longer-term results uncertain

The company has updated OS data from CHRYSALIS from a 7th March 2022 data cut, which represents an additional 12 months of follow up compared with the originally submitted data i.e., 30th March 2021. The results are shown in Table 3.

Table 3: CHRYSALIS OS data

	Previous data-cut (30th March 2021)	Updated data cut (7th March 2022)
Median follow-up, months	[redacted]	[redacted]
Median OS, months (95% CI)	22.77 (17.48, NE)	[redacted]
Censoring rate	[redacted]	[redacted]

Source: Table 4, TE response.
OS is defined as the time from first infusion of amivantamab to death due to any cause.
Abbreviations: CI: confidence interval; NE: not evaluable; OS: overall survival.

ERG comment:

The ERG notes that median OS increased slightly and, given that there was considerably reduced censoring, the 95% CI could be estimated. The company stated that these data were incorporated into the analysis for issues 2 and 3.

Issue 5 – The efficacy and safety populations differ in a way that is likely to exaggerate the benefits and understate harms

The company presented a comparison between AE rates in the safety (n=153) and efficacy (n=114) populations (see Table 1) at the older 30th March data cut, concluding that the profiles were similar. A more detailed comparison was presented in Appendix 3.

ERG comment:

It is unclear to the ERG as to how the company chose the efficacy population which was defined as all patients with EGFR Exon20ins NSCLC who received the RP2D prior to 4th June 2020 data cut-off with ≥3 disease assessments as of the 8th October 2020 data cut-off, as opposed to the safety population, which did not apply those two date criteria. It is also unclear why the AE rate comparison was made between the two populations only for the earlier data cut. However, Table 1 shows that, except for thrombocytopaenia, the rate was higher for the efficacy population. The ERG speculates that it would probably be higher again for the later data cut given increased exposure time. However, given the lack of justification for the difference in populations, the ERG recommends an analysis of efficacy for the safety population unless the company can provide adequate justification for not doing this.

Issue 6 – The real-world evidence (RWE) sources to identify comparators for the indirect treatment comparison were not comprehensive, leading to uncertainty in the benefits of amivantamab compared with relevant comparators

The company acknowledged that *"it cannot be guaranteed that all possible sources of data were identified (as although a systematic search for RWE studies was conducted, a systematic search for RWE sources [i.e. databases] was not)"*. They also stated that *"Based on the above* [the ERG opinion that the sources used were neither unsuitable nor inappropriate] *and due to the short time frame of technical engagement, a systematic search for further data sources has not been conducted."*

ERG comment:

The ERG considers that the uncertainty remains, although no solution can be offered.

Issue 7 – The company assumed [redacted]% of the comparator basket to consist of epidermal growth factor receptor tyrosine kinase inhibitors (EGFR TKIs) which may not be consistent with UK clinical practice; the relative cost effectiveness of amivantamab is therefore unclear

The company provided a scenario analysis in which the clinical efficacy and costs associated with EGFR TKIs are excluded from the UK SoC comparator in order to address the concerns of the ERG regarding their inclusion. The results of this scenario analysis (Appendix 5) reduced the company's base-case ICER from £38,021/QALY gained to £33,272/QALY gained. The company added that analyses excluding EGFR TKIs cannot be meaningfully interpreted in the context of UK clinical practice, nor is it reflective of the treatments that real-world evidence shows to be used in these patients, and as such is inappropriate for decision making.

ERG comment:

The ERG is satisfied that the company provided a scenario analysis excluding EGFR TKIs from the UK SoC comparator. However, as excluding the clinically efficacy of these TKIs from the UK SoC comparator may impact the survival analyses of OS and PFS, the ERG also requested an updated assessment of the NICE DSU TSD14 criteria for survival analyses without EGFR TKIs in the SoC basket to support curve selection. The company did not provide this, and it is therefore unclear whether the selected OS and PFS curves are appropriate for the survival modelling of the UK SoC comparator without EGFR TKIs. Nevertheless, it is unlikely that the choice of survival curves would be any different given the lack of difference made to the HRs as shown in Table 2.

Issue 8 – The company implemented Kaplan-Meier (KM) curves instead of parametric survival models for the survival analyses of overall survival (OS) and progression-free survival (PFS) in the standard of care (SoC) arm, leading to potential overfitting of modelled survival outcomes

The company maintain that KM curves are more appropriate for the base case, as the mature OS and PFS data means all events are captured.

ERG comment:

No compelling new arguments or evidence have been provided. Hence, the ERG perspective as described in the ERG report remains unchanged.

Issue 9 – time to treatment discontinuation (TTD) was assumed to be equal to the duration of PFS, while evidence from the CHRYSALIS trial showed that amivantamab treatment had a longer median duration than PFS, leading to a possible underestimate of amivantamab's relative cost

The company emphasises that UK-based clinicians stated that patients would discontinue treatment with amivantamab upon experiencing a progression event, and thus the assumption that time to treatment discontinuation (TTD) is equal to PFS is maintained in their base case.

To address the concerns of the ERG regarding the amivantamab TTD curve choice, additional information as per NICE DSU TSD 14 criteria is presented in Appendix 4. The company states that the smoothed hazard curve for TTD in the CHRYSALIS trial (Figure 24) shows that the hazard does not remain constant over time, instead decreasing initially before increasing from around month 5, in line with the Weibull or Gompertz distributions. This would rule out the exponential curve, which was used in the ERG base case, given its inherent assumption of a constant hazard over time.

Furthermore, the company considers that the use of TTD for amivantamab whilst maintaining an assumption that ToT is equal to PFS for the UK SoC treatment arm penalises the amivantamab arm unfairly given it assumes treatment beyond progression only in the amivantamab arm. The company

explored an analysis in which the proportion of patients in the amivantamab or UK SoC arm for whom ToT is assumed to be equal to PFS can be varied between 0% and 100%. For patients for whom this assumption does not apply, ToT is modelled using TTD data from CHRYSALIS (amivantamab arm, Gompertz distribution) or TTNT data from the US RWE cohort (UK SoC, KM data). A scenario analysis was performed in which 50% of all patients, regardless of treatment arm, discontinue treatment at progression. The with-PAS ICER is £35,231/QALY gained, which is decreased from the base case ICER of £38,021/QALY gained and lies between the ICERs of the two extremes.

ERG comment

Despite the UK-based clinicians stating that patients would discontinue treatment with amivantamab upon progression, the ERG considers that this assumption reduces the estimated treatment costs of amivantamab without reducing the estimated effectiveness, which was based on CHYSALIS, in which median TTD was substantially longer than median PFS. The ERG agrees that based on the smoothed hazard curve for TTD, the exponential curve may not be the most appropriate curve, despite its best statistical fit. However, the Gompertz curve (selected by the company) is the most pessimistic curve with the 4th best statistical fit. The ERG therefore considers the Weibull curve to be the most appropriate alternative to the exponential curve for the modelling of amivantamab TTD.

Furthermore, the ERG does not agree with the company's statement that assuming treatment beyond progression only in the amivantamab arm is unfair. Evidence from the CHRYSALIS trial showed that patients were allowed to remain on treatment after disease progression, whereas this is not clear for the comparator arm. The ERG acknowledges that assuming treatment beyond progression for amivantamab only may be conservative, and additional evidence demonstrating that this also applies to (part of) the comparators in the comparator basket would be informative to resolve this issue.

Finally, the ERG appreciates the novel exploratory scenario analysis the company explored. However, this analysis requires an additional assumption, and the ERG therefore prefers the modelling of TTD as per its ERG base-case.

Issue 10 – The company did not explore treatment waning in the model, whereas the Evidence Review Group (ERG) considered that the assumption of a lifelong treatment effect may not be warranted

The company maintains that the incorporation of explicit treatment effect waning for amivantamab is inappropriate, and states that the updated data cut for OS (Figure 5, presented in response to Key Issue 4 and in Appendix 1) shows that the treatment benefit of amivantamab has remained consistent as the follow up period has increased. In addition, the company states that the maintenance, and marginal improvement, of the observed median OS between this data cut ([redacted] months at [redacted] months of follow up) and the previous data cut (22.77 months at [redacted] months of follow up) supports that the treatment effect for amivantamab is durable.

Upon the ERG's request, the company presented a scenario analysis in which waning is applied to the OS and PFS treatment effect of amivantamab. In this scenario, treatment effect waning is modelled to begin three years after the cessation of amivantamab treatment, from which point it wanes linearly until it reaches the same efficacy as the UK SoC comparator (hazard ratio: 1) at the end of the time horizon (15 years). This scenario analysis increased the ICER from £38,021/QALY gained to £39,012/QALY gained.

ERG comment

Although the ERG appreciates the scenario analysis provided by the company, it would have liked to see a scenario analysis where the time to reach a hazard ratio of 1 was reduced e.g., to 5 or 10 years, rather than assuming a linear waning effect until the end of the time horizon.

Issue 11 – The company's failure to include an age-adjustment to the health state utilities in their company submission (CS) base case is not in line with good modelling practice and may have exaggerated the cost

The company updated the economic to include age adjustment of utilities, as per Hernandez Alava et al. (2022), and this change has been incorporated into the company's base case.

ERG comment

The ERG is satisfied with the company's response.

Issue 12 - Lack of a fully incremental analysis for all relevant comparators in the comparator basket, increasing the uncertainty of estimates of amivantamab's cost effectiveness

A fully incremental analysis is not presented as the company considers it is not in line with best methodological practice in situations where there is no established standard of care.

ERG comment

No compelling new arguments or evidence have been provided. Hence, the ERG perspective as described in the ERG report remains unchanged.

Issue 13 - Lack of a fixed random seed in model probabilistic sensitivity analysis (PSA) leads to fluctuations in probabilistic results and hence increased uncertainty of estimates of amivantamab's cost-effectiveness

The company implemented a fixed random seed in the model PSA, and updated probabilistic base case results are presented in Table 9.

ERG comment

The ERG is satisfied with the company´s response.

Additional issue 1 - The ERG noted a lack of clarity and information surrounding "how 19.6% of patients are experiencing grade 3 or above events related to amivantamab, yet only 8.5% of patients have experienced what is described as a serious AE."

The company explained that 'serious' is not the same as Grade 3 or above, citing acneiform rash as an example.

ERG comment:

The ERG understands this discrepancy and notwithstanding the definition of Grade 3 in the Common Terminology Criteria for Adverse Events to essentially imply severe or at least 'medically significant',[1] the ERG is satisfied that at least the more common definition was applied in the economic model.

Additional issue 2 - The ERG were not confident that "the five patients included in Cohort D+, that came from Part 1 (dose escalation) of the study met the molecular eligibility requirements."

The company confirmed that the five patients included in Cohort D+ from Part 1 (dose escalation) of the study met the molecular eligibility criteria requirements and tested positive for the EGFR Exon20ins mutation.

ERG comment: nothing further to add.

Additional issue 3 - The ERG noted that "in both Figure 3.8 (NSCLC-SAQ) and Figure 3.9 (ED-5D-5L) the included number of patients appears to be very small [redacted]) and different from what was reported in the text [redacted])."

The company have clarified that the correct number is [redacted].

ERG comment: nothing further to add.

Additional issue 4 - The ERG noted that "the eligibility criteria stated that only patients with ECOG status 0 or 1 were to be included in the CHRYSALIS trial (Table 3.3), nevertheless, one patient with ECOG status 2 was included (Table 3.7)."

The company explained that the ECOG status of that particular patient changed from 0 or 1 at enrolment, which was not a protocol violation.

ERG comment: nothing further to add.

1. REFERENCES

[1] National Cancer Institute, Cancer Therapy Evaluation Program, U.S. Department of Health and Human Services. *Common Terminology Criteria for Adverse Events (CTCAE). Version 5.0. Published: November 27, 2017*. Washington, D.C.: U.S. Department of Health and Human Services, 2017 Available from: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_5x7.pdf

NICE National Institute for Health and Care Excellence

Clinical expert statement and technical engagement response form

Amivantamab for treating EGFR Exon 20 insertion-positive non-small-cell lung cancer after platinum-based chemotherapy [ID3836]

Thank you for agreeing to comment on the evidence review group (ERG) report for this appraisal, and 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 ERG report and stakeholder responses are used by the appraisal committee to help it make decisions at the appraisal 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 for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking for your views on key issues in the ERG report that are likely to be discussed by the committee. The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the ERG report (Section 1). You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

A clinical perspective could help either:

- resolve any uncertainty that has been identified OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

In part 3 we are asking you to provide 5 summary sentences on the main points contained in this document.

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. Please type information directly into the form.

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.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

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 replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

Please note, part 1 can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

Deadline for comments by **5pm** on **Monday 13 June**. 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: Treating EGFR Exon 20 insertion-positive NSCLC and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Alastair Greystoke	ERG comment
2. Name of organisation	Newcastle upon Tyne Hospitals NHS Trust	
3. Job title or position	Senior Lecturer and Honorary Consultant in Medical Oncology	
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 EGFR Exon 20 insertion-positive NSCLC? ☒ A specialist in the clinical evidence base for EGFR Exon 20 insertion-positive NSCLC or amivantamab? ☐ 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 is the main aim of treatment for EGFR Exon 20 insertion-positive NSCLC? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	Maintain quality of life and prevent disability, improve survival, improve or prevent cancer related symptoms	
9. 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)	An improvement in survival by 2 months. A response rate of over 30% maintained for over 2 months. A significant improvement in health related quality of life maintained for over two months.	
10. In your view, is there an unmet need for patients and healthcare professionals in EGFR Exon 20 insertion-positive NSCLC?	Yes in general these patients have poor outcomes with standard therapies and there is a need for novel therapies that can help control the cancer and improve prognosis. Toxicity with chemotherapy and immunotherapy combinations can be problematic, restricting treatment to the very fittest populations. Whether these patients benefit from single agent immunotherapy is unclear and the additional benefit of adding immunotherapy two chemotherapy is uncertain	
11. How is EGFR Exon 20 insertion-positive NSCLC? **currently treated in the NHS?** • Are any clinical guidelines used in the treatment of the condition, and if so, which? • 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.)	Fit patients with performance status 0-1 will normally receive either chemotherapy and immunotherapy in combination. The role of single agent immunotherapy if the cancer tumour proportion score for PDL1 is >50% is uncertain from the evidence but may be used by some clinicians as within present approvals and guidelines. Chemotherapy and immunotherapy regimens include Regardless of PDL1: carboplatin-pemetrexed-pembrolizumab PDL1<50%: carboplatin-paclitaxel-atezolizumab-bevacizumab	

• What impact would the technology have on the current pathway of care?	Patients may also receive carboplatin and pemetrexed based chemotherapy in the first line setting if so they will be eligible for single-agent immunotherapy following this with agents available including pembrolizumab if PDL1 +ve or atezolizumab regardless of PDL1 expression. Lastly patients may receive nintedanib and docetaxel after previous lines of treatment Treatment is based around the technology appraisals for the regimens above The NICE guideline NG122 (https://www.nice.org.uk/guidance/ng122/resources) also outlines these treatment options as does The European Society of Medical Oncology guideline (https://www.esmo.org/guidelines/lung-and-chest-tumours/clinical-practice-living-guidelines-metastatic-non-small-cell-lung-cancer: however this includes regimens that are not licensed or funded in the NHS). The pathways of care are defined. Clinicians may vary in their use of chemo-immunotherapy combinations (over single agent immunotherapy) in the patients with cancer with PDL1 >50%; and in their preferred chemotherapy regimen for non-squamous cancers with PDL1< 50% (with both carboplatin-pemetrexed-pembrolizumab and carboplatin-paclitaxel-atezolizumab-bevacizumab approved for use). The main areas of uncertainty and differences in opinion between conditions are as to whether single-agent immunotherapy has a role in this disease. Although limited the available data suggests that response rates are poor. This addition is also associated with a non-smoking status where immunotherapies have poor response rates. Therefore clinicians that who	

	are more familiar with the emerging literature would suggest that single-agent immune therapy should not be used. This technology would be used before current second line options i.e. after either first line chemotherapy or chemotherapy and immunotherapy combination. Subsequent treatments such as nintedanib and docetaxel would move into later lines of treatment after failure.	
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	The technology will be used in Specialist cancer centres or units, and administered on chemotherapy day units by appropriately trained nurses. These will need to be trained in the management of the infusion reactions that commonly occur with this agent but this should be relatively easy to accomplish. This technology will require frequent attendance on chemotherapy day unit using treatment slot particularly in the first few weeks of treatment when it is given weekly (and the first week is a split over two days).	
13. 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?	Yes. These patients need better treatments for their lung cancer. This will provide an additional line of treatment which is likely to be associated with an improvement in overall survival Patient with lung cancer quality of life is in the main driven by symptoms related to the disease. In general using an effective treatment that shrinks the cancer is associated with improvements in quality of life. Given this agent is more effective than other treatments available it is likely to be associated with an improvement in health related quality of life.	

14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	No	
15. 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 affecting patient acceptability or ease of use or additional tests or monitoring needed)	As described above the main issues that will be encountered is the frequent infusion reactions during the first treatment and the need for multiple intravenous infusions particularly during the first four weeks of therapy. Patience and for healthcare professionals.	
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Treatment will normally be continued until disease progression (normally demonstrated by a CT scan) but sometimes continued beyond progression on CT scans until there is a lack of clinical benefit. Treatment may also stopped due to excess toxicity.	
17. 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	No	
18. Do you consider the technology to be innovative in its potential to make a	Yes	

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 is a novel form of treatment for a rare but difficult to treat form of lung cancer. It is also the first licensed agent of its type (a bi-specific antibody) which may lead to future treatment advances as another way of treating cancer. In some patients responses can be long-lasting, although selecting these patients in advance at present is not possible as we do not fully understand the biology.	
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The main side-effect is infusion reaction at time of first administration. This is unpleasant but short lived. Other side effects that may impact on quality of the life are rash which can be significant and unsightly and require treatment with antibiotics and steroids. Diarrhoea can occur but tends to be less problematic then with some other agents Ankle oedema can occur and be problematic in some patients due to its impact on mobility	
20. 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?	Yes	

• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?		
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No	
22. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance TA520?	No	
23. How do data on real-world experience compare with the trial data?	There is limited real-world data available as to the efficacy of this agent. There is real-world data that has been presented as to the outcomes with standard therapies in this rare population. This is in general has been included in the company submission.	
24. NICE considers whether there are any equalities issues at each stage of an appraisal. 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 appraisal could	No	

• 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: Technical engagement questions for clinical experts

We welcome your comments on the key issues below, but you may want to concentrate on issues that are in your field of expertise. If you think an issue that is important to clinicians or patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section.

The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting.

For information: the professional organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report. These will also be considered by the committee.

Table 2 Issues arising from technical engagement

Issue 1: generalisability and potential underestimation of adverse events, i.e.: • *The clinical trial population is likely to be fitter than the population in clinical practice (for example, only people with ECOG status of 0 or 1 were*	I do not think this is a major issue. It is likely that funding will be restricted to a similar population as involved in the clinical trial i.e. performance status 0 to 1. Although these patients may have additional comorbidities that prevented entry into studies; given the pattern of toxicity I still think this would be tolerable in the general population.	This is consistent with the ERG comment on the company response.

included within the trial population). What impact do you consider this to have?		
Issue 2: use of concomitant medications, i.e.: • *People within the intervention group of the clinical trial, received a number of concomitant medicines (including targeted radiotherapy). What impact do you consider this may have had on results?*	I do not think this will have had any major impact on outcomes. Palliative radiotherapy is unlikely to impact majorly on survival, and these patients didn't receive any additional systemic treatment whilst on study. I think the outcomes presented would be achievable within the UK population. Although these patients may have received EGFR TKIs after this treatment for reasons described below I do not think this would impact on outcomes in a significant manner.	This is consistent with the ERG comment on the company response.
Issue 3: comparators, i.e.: • *In clinical practice, what is typically used after platinum-based chemotherapy?*	In the UK population single-agent immunotherapy if not used before will probably be the predominant treatment used by clinicians. As discussed above clinicians who are more familiar with the emerging literature may not use this treatment and	This response seems to suggest that EGFR TKIs should not be comparators and that they should not be included in effectiveness data, notwithstanding the effect of their exclusion as mentioned in the ERG comment on the company response.

• *Are EGFR TKIs typically used in clinical practice for EGFR Exon20ins mutations?*	would instead treat patients directly with nintedanib and docetaxel. I do not think these patients should be treated with standard EGFR inhibitors available in the NHS such as Afatinib and Osimertinib. This mutation is described as a resistance mechanism to these agents. There have been small studies presented of these agents in this setting showing low response rate. These patients would have been excluded from the pivotal trials of these drugs which led to that nice approval. Some clinicians internationally have suggested higher doses of Osimertinib can be used in patients particularly where the insertion is proximal in Exon 20. This is not licensed or funded and the evidence is relatively sparse Yang JCH, et al. *Lancet Oncol.* 2015;16:141–51; Vyse S, Huang PH. *Sig Transduct Target Ther*. 2019;4:5 van Veggel B, et al. *Lung Cancer.* 2020;141:9–13; 8.	
Issue 4: short follow-up of CHRYSALIS trial		
Issue 5: cut-off dates for efficacy		

and safety populations		
Issue 6: RWE data sources		
Issue 7: EGFR TKIs in comparator basket, i.e.: • *What percentage of people (if any) have EGFR TKIs in clinical practice?*	The company produced some data suggesting EGFR TKI use in the UK environment. I have no reason to believe this data is not correct but I would not use these agents in clinical practice and I do not think their use is justified by license or funding.	The ERG have nothing further to add.
Issue 8: use of KM curves instead of parametric survival models		
Issue 9: time to treatment discontinuation, i.e.: • *What is the expected treatment duration of amivantamab?* • *Is treatment with amivantamab likely to continue beyond disease progression?*	it is likely that as with other targeted treatments that treatment may continue beyond progression; particularly if the subsequent options is docetaxel based chemotherapy. This will be due to reluctance of both patients and clinicians to use docetaxel based chemotherapy. In addition it may be possible to ablate areas of locally progressive disease using radiotherapy and this is probably an appropriate strategy that is commonly used in the UK.	This seems to be consistent with the ERG approach of using TTD as opposed to PFS for time to discontinuation, as mentioned in the ERG comment on the company response.

	In general I would expect that the time on treatment on average will be two to three months beyond progression, but this could vary markedly between patients, with some patients stopping on progression and some patients continuing for more prolonged periods.	
Issue 10: treatment waning, i.e.: • *How long do you expect treatment effect of amivantamab to last? Is treatment waning expected?*		
Issue 11: utilities age-adjustment		
Issue 12: lack of fully incremental analysis for all comparators		
Issue 13: lack of fixed random seed in model PSA		
Are there any important issues that have been missed in ERG report?		

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

An important new option for patients with a rare form of lung cancer

These patients are poorly served by present treatment options

This will require treatment time on chemotherapy day units which are already stretched particularly the first four weeks of treatment

A basket approach may be appropriate given the various options that may be used by clinicians but in my opinion should not include standard EGFR inhibitors

Click or tap here to enter text.

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

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