National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

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

Please note: Comments received in the course of consultations carried out by NICE 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 submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment 1: the draft remit

Section	Consultee/ Commentator	Comments	Action
Wording	Janssen-Cilag	No. Janssen suggests the wording of the remit should reflect the wording of the anticipated license as follows: To appraise the clinical and cost effectiveness of amivantamab within its marketing authorisation for treating adult patients with [redacted]	Thank you for your comment. The current title and remit should cover the intended population. No action needed.
Timing Issues	Janssen-Cilagvv	There is no licensed medication in this disease setting and outcomes with current standard of care are generally poor. There is, therefore, an urgent need for a treatment option that offers better clinical outcomes. Amivantamab is an innovative bispecific therapy that has been granted Breakthrough Therapy Designation by the Food and Drugs Administration (FDA) and is being considered under the Innovative Licensing and Access Pathway (ILAP) programme.	Thank you, your comment has been noted. No action needed.
Additional comments on the draft remit	Janssen-Cilag	No comment	Noted. No action needed.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments	Action
Background information	Janssen-Cilag	No comment	Noted. No action needed.
The technology/ intervention	Janssen-Cilag	The draft scope incorrectly states that amivantamab targets the hepatocyte growth factor receptor. Please amend sentence to, “Amivantamab is a human bispecific antibody that targets both EGFR and cMet” The draft scope inaccurately states the intervention as “amivantamab alone or in combination with chemotherapy”. Please amend to: Amivantamab monotherapy Please note that CHRYSALIS, the pivotal trial providing the clinical evidence for amivantamab for this submission, investigated several patient cohorts some of which received amivantamab as monotherapy, in combination with Lazertinib or in combination with carboplatin and pemetrexed. The population of interest for this submission as stated below, is a subgroup of cohort D in CHRYSALIS, who received amivantamab monotherapy as the intervention.	Thank you for your comments. Both the technology and intervention sections have been updated.
Population	Janssen-Cilag	To align with the anticipated license: [redacted]	Comment noted. No action needed.
Comparators	Janssen-Cilag	From initial discussions with clinicians in UK practice, it appears that the treatment options for patients with NSCLC with activating EGFR Exon 20 insertion mutations, after failure of platinum-based chemotherapy are chemotherapies, 2mmune-oncology drugs (IOs) and tyrosine kinase inhibitors (TKIs). However, the specific treatments used, and the exact proportions in	Thank you for your comments. All potential comparators are included in the scope. During the development

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		which they are prescribed is currently not known by the company. Specifically, the role of TKIs is particularly unclear at present. Atezolizumab is not anticipated to be a relevant comparator given patients must have received prior chemotherapy and targeted therapy if they are EGFR mutation-positive, which does not align with the anticipated licensed indication for amivantamab (following prior platinum-based chemotherapy only). A clinical advisory board will be conducted by Janssen alongside the NICE submission development in order to provide more clarity on the specific treatments utilised in UK practice. Furthermore, real-world evidence sources will be consulted to further support what the relevant comparators to amivantamab are in the UK. Whilst the exact treatments to include within this scope are not certain at this stage, Janssen agree that chemotherapies (both platinum-based and non-platinum-based), IOs and TKIs, are included in the scope. Although the relevance of TKIs at this stage of the treatment pathway in UK practice is particularly unclear at this stage.	of the appraisal, the appraisal committee will discuss which comparators are most appropriate. No changes have been made.
Outcomes	Janssen-Cilag	Janssen propose some additional outcome measures (in bold) to capture the most important health benefits of amivantamab • overall survival • **progression free survival** • time to treatment discontinuation • **overall response rate** • **duration of response** • **clinical benefit rate** • adverse effects of treatment • health-related quality of life	Thank you for your comments. The outcomes listed are examples and are not intended to be an exhaustive list. Progression-free survival and response rates have been added. It is anticipated that clinical benefit rate and

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			duration of response will be covered under these main outcomes.
Economic analysis	Janssen-Cilag	The genetic test for the EGFR 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/ The EGFR exon 20 insertion-positive mutation is tested as part of the reflexive EGFR test conducted at diagnosis for all NSCLC patients. As such, Janssen, believes 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, Janssen considers that the modelling results should exclude the costs associated with diagnostic testing for EGFR in people with NSCLC	Comment noted. No action needed.
Equality and Diversity		A series of studies have shown the correlation between EGFR positive sub-types and distinct epidemiological sub-groups, of which includes Asian populations.(1) The UK is a culturally diverse country and as such cultural and behavioural factors are relevant to consider. One such study showed that in conventional Chinese culture, awareness of a malignant disease is believed to increase a patient's psychological pressure, leading to anxiety or depression and so for some, the concealment of a diagnosis is beneficial for the patient. In a recent article, the impact of the Covid-19 pandemic on those of Asian descent was well described in various countries around the world including the United Kingdom.(2, 3) People of Asian origin felt they were subjected to racist attacks and reported to have effects on their health and livelihoods.(4) This was also further reported by people of Asian origin living	Comment noted. The committee will discuss potential equality issues that are raised during the development of this appraisal. No action needed.

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		around the United Kingdom. Reports of prejudice and discrimination also links directly to the overlap between early signs and symptoms between Covid-19 and lung cancer, for example persistent cough and breathlessness. This overlap has created an opportunity for misdiagnosis, as one of the key factors involved substantial increase in late-stage presentations of lung cancer during the pandemic, in a patient population, which typically faces poorer prognosis and outcomes.(5, 6) In conclusion, ethnicity is an equality consideration that is relevant for the committees to consider. This has been demonstrated by social and cultural implications of the signs and symptoms of lung cancer, diagnosis and also direct prejudice and discrimination, at a time when patients are facing even poorer outcomes.	
Other considerations		In recent literature, the impact of stigma on people living with lung cancer, including patients and caregivers has been well documented. The impact of stigma is multi-factorial; its perception and effects lead to direct and indirect consequences for the patient, their loved ones, communities and, indeed society itself. In one, descriptive and observational study, lung cancer stigma was seen to be significantly correlated with younger age, greater social deprivation, unemployment, depression, symptom burden and health-related quality of life. In a further qualitative study, barriers to symptom reporting for lung cancer patients; included blame, stigma and cultural influences(7) Perceived stigma and barriers by patients may also affect their interactions and perceived bias by some healthcare professionals. Some patients report feeling uncomfortable communicating their symptoms leading to delay in presentation, diagnosis and treatment (or low uptake of treatment)(8) Patients with lung cancer uniquely experience an added burden from developing an illness that the public recognizes is directly associated with smoking behaviours,(9) despite the fact there is an increasing number of the patient population who are never-smokers.(10) Furthermore, another qualitative study reported that perceived blame by the patient, not only can affect patient depression, but also that of the	Comment noted. No action needed.

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		caregiver.(11) The clinical characteristics of EGFR exon 20 insertion mutation patients show that these patients face a poorer prognosis(12) and by the very nature of the epidemiology of this population, stigma further impacts their own and other individual's outcomes and experiences. The impact of having a new treatment option available to alleviate this condition should be explicitly considered as the effects of stigma should be included within the decision-making process and are not inherently captured within the cost per QALY framework. Stigma is included in the NICE social value judgements principles document and as such, should be considered when deciding whether amivantamab is cost-effective in this underserved population.	
Innovation		There are no approved, targeted therapies for patients with advanced EGFR-mutated NSCLC with Exon 20 insertion mutations and no specific treatment recommendations are provided in clinical treatment guidelines. As stated earlier in the comparators section, there is uncertainty as to the extent of usage of different treatments likely to constitute established clinical management within UK clinical practice: chemotherapy, IOs and TKIs. Patients with advanced NSCLC with EGFR Exon 20 insertions have poorer treatment outcomes with currently available therapies than patients with other types of EGFR mutations or wildtype EGFR (non-mutated, unchanged EGFR gene).(13) Chemotherapy is associated with only a modest increase in survival at the cost of significant toxicity to the patient. Further, unlike classical EGFR mutations (exon 19 deletion and Exon 21 L858R), exon 20 insertions have been associated with resistance to EGFR tyrosine kinase inhibitors (TKIs).(12, 14-16) Together, this highlights the urgent unmet need for targeted, more effective and well tolerated therapies to prolong survival and improve HRQoL in patients with advanced NSCLC and EGFR Exon 20 insertions	Thank you for your comments. During the development of this appraisal, the committee will discuss the extent to which it considers amivantamab to be innovative. No action needed.

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		Amivantamab, a fully human IgG1-based bispecific antibody directed against EGFR and cMet, shows activity against tumours with either the primary activating or the T790M second-site resistance EGFR mutations, overexpressed wildtype EGFR and activation of the cMet pathway. By inhibiting both EGFR and cMet signalling functions, amivantamab may disrupt these signalling pathways, thereby preventing tumour growth and progression in patients with EGFR Exon 20 insertion-positive NSCLC. Amivantamab has already received breakthrough therapy designation by the FDA and presents an important milestone in advancing the treatment of genetically-defined lung cancer, 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. In the UK, amivantamab is also being considered by the MHRA under the Innovative Licensing and Access Pathway (ILAP) programme and the Project Orbis regulatory route, both of which underscore the innovative nature of this technology.	
Questions for consultation		**Below (in bold) are Janssen's responses to the questions for consultation.** Is the current treatment pathway for EGFR mutation-positive disease also used for EGFR Exon 20 insertion-positive NSCLC? **The current treatment pathway is not applicable for EGFR Exon 20 insertion-positive NSCLC. This is because Exon 20 insertion mutations confer primary resistance to most current targeted treatments.** What current treatment is used for people with EGFR Exon 20 insertion-positive NSCLC after chemotherapy? • Are atezolizumab or pembrolizumab used?	Comments noted. No action needed.

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		Please refer to Janssen's response in the comparator section • Have all relevant comparators for amivantamab been included in the scope? **Please refer to Janssen's response in the comparator section** In clinical practice, is amivantamab likely to be used after previous platinum-based chemotherapy? **Yes. Amivantamab is likely to be used after failure of platinum-based chemotherapy.** Are there any subgroups of people in whom amivantamab is expected to be more clinically effective and cost effective or other groups that should be examined separately? **None** Where do you consider amivantamab will fit into the existing NICE pathway, Treating non-small-cell lung cancer? **A clinical advisory board will be conducted by Janssen alongside the NICE submission development in order to provide more clarity on the specific treatments utilised in UK practice and how this impacts the positioning for amivantamab in the existing NICE pathway. Furthermore, real-world evidence sources will be consulted to further support how amivantamab fits in to the existing treatment pathway.** NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the proposed remit and scope may need changing in order to meet these aims. In particular, please tell us if the proposed remit and scope:	

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		• could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which amivantamab will be licensed. **No comment** • could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology. **Please refer to Janssen's response on the equality section presented earlier** • could have any adverse impact on people with a particular disability or disabilities. **No comment** Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts. **Janssen suggests that NICE should consider a stakeholder engagement exercise to establish:** • **The epidemiology of EGFR exon 20 insertion mutation positive NSCLC in Asian patients** • **The differential impact of NSCLC in this patient population** • **The impact of society and cultural factors in living with lung cancer in the population and any correlation to healthcare inequalities seen in the general UK population and whether both**	

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		of these additional aspects associated with ethnicity have any direct impact on patient outcomes Do you consider amivantamab to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)? **Please refer to innovation section presented earlier in this response document.** Do you consider that the use of amivantamab can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation? **Please refer to other considerations section presented earlier in this response document.** **In addition, amivantamab should be considered for the End of Life criteria.** Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits. **Supporting evidence is in development and may include:** • **Literature** • **Reports from in-depth patient interviews and patient surveys conducted by Janssen** To help NICE prioritise topics for additional adoption support, do you consider that there will be any barriers to adoption of this technology into practice? If yes, please describe briefly.	

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		None	
Additional comments on the draft scope		No comment	Noted. No action needed.

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope:

Royal college of Pathologists