National Institute for Health and Care Excellence

Single Technology Appraisal (STA)
Aumolertinib for untreated EGFR mutation-positive non-small cell lung cancer
Response to consultee and commentator comments on the draft remit and draft scope

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Comment 1: the draft remit

Section	Consultee/ Commentator	Comments [sic]	Action
Appropriateness	EQRx	Yes, we believe that this topic is appropriate to refer to NICE for appraisal.	Thank you for your comment. No change to the scope.
	Boehringer Ingelheim	Yes, although we note there are multiple TKIs on the market with similar data and these have registrational trials that are multinational. The data behind Aumolertinib is primarily based out of a single country, China.	Thank you for your comment. No change to the scope.
	AstraZeneca	No comments	Thank you. No change to the scope.
Wording	EQRx	Yes, we believe that the wording of the remit reflects the issue(s) about this technology.	Thank you for your comment. No change to the scope.

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	Boehringer Ingelheim	The clinical trial data does not include patients with uncommon mutations. We would recommend the remit read '**To appraise the clinical and cost effectiveness of aumolertinib for treating epidermal growth factor receptor (EGFR) mutation-positive metastatic non-small-cell lung cancer with common mutations that has not previously been treated'**	Thank you for your comment. The remit has been kept broad and no changes have been made. Further information on the types of mutations aumolertinib targets is included in the technology section of the scope.
	AstraZeneca	No comments	Thank you.
Timing Issues	EQRx	Urgency is high based on the ILAP designation granted to aumolertinib on 6 September, 2021. [redacted]	Thank you for your comment. NICE has scheduled this topic into its work programme. No change to the scope.
	Boehringer Ingelheim	Currently there are five EGFR inhibitors available within the NHS data from these provide broader population groups and data that is comparable e.g. FLAURA data for approved 3rd generation TKI Osimertinib for treating the majority of patients with EGFR positive NSCLC patient population with good efficacy and a manageable side	Thank you for your comment. No change to the scope.

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		effect profile. Therefore, there is no immediate need associated with this new EGFR inhibitor.	
	AstraZeneca	No comments	Thank you.
Additional comments on the draft remit	EQRx	We do not have any additional comments on the draft remit.	Thank you. No change to the scope.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	EQRx	EQRx proposes to use the same disease background information provided in our ILAP application: Around 47,000 people are diagnosed with lung cancer in England and Wales each year of which 87% are aged over 60 years. Approximately 85% of those diagnoses are for non-small cell lung cancer[1], and the majority of those diagnoses (approximately 75%) are at a late stage (stage III and stage IV), which means they are unlikely to be treated with curative intent. Lung cancer is the leading cause of cancer death for both men and women in the UK, with more than 35,000 people dying from the condition each year in England and Wales. In England and Wales, lung cancer incidence and mortality rates are strongly associated with socioeconomic deprivation.[2]	Thank you for your comment. The background section is intended to be an overview of the condition. It is consistent with scopes for other treatments in this disease area. No changes have been made.

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		During the past three decades, genomic characterization of NSCLC has revealed a number of oncogenic driver variants, including gene fusions or rearrangements (ALK, ROS1, RET, NTRK) or activating mutations (EGFR, BRAF, MET). The identification of these oncogenic drivers has led to the development of small molecule inhibitors of the tyrosine kinase region of the respective encoded variant proteins. The predictive value of the presence of these genomic abnormalities for responsiveness to their matched and specific inhibitors has been well-established. Thus, genomic/molecular testing for these oncogenic driver variant genes is considered standard and is used to determine the approach to treatment, as depending on the presence or absence of these genomic abnormalities. Mutations in EGFR, specifically in the regions (exons 18-21) encoding a portion of the tyrosine kinase domain of the EGFR protein, are among the most frequently occurring of the oncogenic driver mutations in NSCLC. Deletions in exon 19 (Exon19del) and a specific mutation in exon 21 (exon 21 L858R) account for approximately 90% of EGFR oncogenic driver variants.[3,4] These mutations confer sensitivity to small molecule EGFR tyrosine kinase inhibitors, and thus are also referred to as EGFR-TKI-sensitizing mutations. The frequency of EGFR driver mutations in patients with NSCLC is correlated to several pathologic, demographic, and epidemiologic factors. These mutations occur more frequently in patients without a history of smoking[5] and are more common in Asian patients (approximately 50% incidence)	

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		versus Caucasian patients (approximately 10% incidence).[6] Additionally, these mutations are thought to occur more frequently in female patients than in men (approximately 60:40 ratio).[7] Approximately 1,800 patients are diagnosed with advanced EGFR-positive NSCLC in England each year.[8] Nonetheless, none of these clinical characteristics is sufficiently predictive to obviate the need for broad based genomic profiling of tumours in NSCLC.	
	Boehringer Ingelheim	This is accurate, however we note there is no mention of the ROS1 mutation and KRAS G12C mutation as druggable options for completeness of this information.	Thank you for your comment. Reference to ROS1 and KRAS mutations has been added to the background section.
	AstraZeneca	No comments	Thank you.
The technology/ intervention *Is the description of the technology or technologies accurate?*	EQRx	We propose to be more specific on the mutant forms of EGFR that aumolertinib can target. This is a major differentiator of third-generation EGFR inhibitors versus earlier generations of drugs in this class. We suggest the following edits to the first paragraph of the technology section:	Thank you for your comments. The technology section has been updated.

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		"Aumolertinib (brand name unknown, EQRx) is a small molecule inhibitor that selectively targets mutant forms of EGFR, including the drug-resistant mutation T790M, and sensitising mutations (exon 19 deletion and L858R mutant). It is administered orally once daily."	
	Boehringer Ingelheim	The description excludes to mention that only common mutations have been tested out in the clinical trial.	Thank you for your comment. The technology section has been updated to include the types of mutations included in the trial.
	AstraZeneca	No comments	Thank you.
Population *Is the population defined appropriately? Are there groups within this population that should be considered separately?*	EQRx	Yes, the population is defined appropriately. Because of the benefit of third-generation tyrosine kinase inhibitors on brain metastases, we will stratify results based on presence of brain metastases at baseline.	Thank you for your comment. The committee will consider the results presented in the submission. No change to the scope.
	Boehringer Ingelheim	No the population includes uncommon mutations which were excluded from the study population. Given the trial took place solely in China it is important to consider how many non-Asian patients were included in the study to understand generalisability	Thank you for your comment. The population in the scope has been kept broad. The committee

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		to the UK. Similarly Asian EGFRm patients are associated with a better prognosis and this bring bias into the data.	will make its recommendations based on the population considered appropriate during the appraisal. The committee will also consider the generalisability of the trial data to UK practice when making its recommendations. No change to the scope is needed.
	AstraZeneca	It should be made clear that the pivotal study of aumolertinib in this indication (AENEAS), is a single-country trial conducted in China. The generalisability of this data to UK clinical practice is a potentially significant limitation and should be addressed in this appraisal.	The committee will consider the generalisability of the trial data to UK practice when making its recommendations. No change to the scope is needed.
Comparators *Is this (are these) the standard treatment(s) currently used in the*	EQRx	We believe that osimertinib is the most appropriate comparator, as it is the most recent NICE recommended treatment option in this setting and current standard of care in the UK.[9]	Thank you for your comment. The comparator list

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NHS with which the technology should be compared? Can this (one of these) be described as 'best alternative care'?		Osimertinib (the only third-generation tyrosine kinase inhibitor (TKI) currently available in the UK) is currently the preferred treatment option as per consensus guidelines such as ESMO and NCCN guidelines. Further, current epidemiology data from the National Lung Cancer Audit in the UK suggests that approximately 1,800 patients are diagnosed with advanced EGFR-positive NSCLC, of which approximately 2/3 of patients with EGFR positive metastatic NSCLC are currently receiving osimertinib as first-line treatment and that this proportion is expected to increase.[8,10,11] Osimertinib was found to be cost-effective compared to afatinib and gefitinib, which were the most commonly used first- and second-generation EGFR TKIs in NHS clinical practice.[11,12] We propose that the relevant comparator for this fast-track appraisal be limited to osimertinib as it is the standard of care in the UK and has been found to be cost-effective and have superior efficacy and safety relative to first and second generation TKIs.[12]	includes all relevant options which may be offered for treatment of this condition. The committee will consider the appropriate comparator(s). See section 6.2 of the NICE Guide to the methods of technology appraisal. No change to the scope is needed.
	Boehringer Ingelheim	Yes. Afatinib and Osimertinib are considered current standards of care as the most prescribed TKIs. We believe Afatinib to be standard of care in those with uncommon mutations based on our interactions with HCPs	Thank you for your comment. No change to the scope.
	AstraZeneca	No comments.	Thank you.
Outcomes *Will these outcome measures capture*	EQRx	The following outcomes measures will be provided: • Progression free survival (Primary)	Thank you for your comment. No change to the scope.

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the most important health related benefits (and harms) of the technology?		• Overall Survival (Secondary) • Response Rate (Secondary) • Response Duration (Secondary) Adverse Effects of Treatment (Safety).	
	Boehringer Ingelheim	Yes.	Thank you for your comment. No change to the scope.
	AstraZeneca	No comments.	Thank you.
Economic analysis	EQRx	We propose conducting a cost comparison analysis and not a cost effectiveness analysis. We are recommending a cost comparison because aumolertinib will provide similar and potentially greater health benefits at similar or lower cost than osimertinib. Wherever possible and appropriate, cost data and sources will be consistent with the data and sources that were used in the previously published NICE guidance for osimertinib to reflect the most up-to-date cost information available for these sources.[12] As both aumolertinib and osimertinib are oral, no administration costs will be included. There will be no changes to the service provision and	Thank you for your comment. No change to the scope.

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		management (e.g., setting of care, differences in frequency of administration, monitoring, and follow-up). We are confident that costs, except for acquisition cost of the medicine, will be similar and this will be demonstrated in the submission. We recommend using three years as the time horizon, with a five-year time horizon in a sensitivity analysis, based on the maximum treatment duration in our clinical trial. Costs will not be discounted. We propose using univariate sensitivity analyses to understand the sensitivity of costs to inputs with uncertainty (e.g., adverse event rates, duration of treatment). For osimertinib, the publicly available list price will be used for acquisition costs.	
	Boehringer Ingelheim	No comment.	Thank you.
	AstraZeneca	No comments.	Thank you.
Equality	EQRx	The proposed remit does not need to be changed in order to meet NICE's stated equality objectives.	Thank you for your comment. No change to the scope.
	Boehringer Ingelheim	Based on data readout at ASCO 2021, all patients included were from China. No information is published on ethnicity of the population so it remains unknown whether Caucasian or African origin patients were evaluated for this drug. The UK population is a broad mix of populations with many ethnic groups living in England. Therefore the applicability of this trial to the UK population is difficult to establish.	The committee will consider the generalisability of the trial data to UK practice when making

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		As above. It is important to understand the ethnic groups recruited into the trial as outcomes between these groups vary	its recommendations. It is not considered that this is an equality issue.
	AstraZeneca	No comments.	Thank you.
Other considerations	EQRx	We have no further suggestions to add.	Thank you for your comment.
	Boehringer Ingelheim	nil	Thank you.
	AstraZeneca	No comments.	Thank you.
Innovation	EQRx	An Innovation Passport was granted to aumolertinib by the MHRA on September 6, 2021. The innovation is primarily on the basis of EQRx pricing to enable affordable access to life-saving drugs.	Thank you for your comment. No change to the scope.
	Boehringer Ingelheim	Mechanism of action, pharmaceutical formulation or efficacy or safety data doesn't provide any distinct features compared to comparators currently available. Therefore, we don't consider this technology as innovative.	Thank you for your comment. The appraisal committee will consider the innovative nature of the technology during the appraisal. No change to scope.

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	AstraZeneca	Aumolertinib is a “me-too” third-generation EGFR-TKI, with an identical mechanism of action to existing standard of care, osimertinib. The technology under appraisal therefore does not represent a step-change in the management of the condition and cannot be considered innovative.	Thank you for your comment. The appraisal committee will consider the innovative nature of the technology during the appraisal. No change to scope
Questions for consultation	EQRx	**Have all relevant comparators for aumolertinib been included in the scope? Which treatments are considered to be established clinical practice in the NHS for EGFR-positive NSCLC?** *EQRx Response:* We believe that osimertinib is the most appropriate comparator, as it is the most recent NICE recommended treatment option in this setting and current standard of care in the UK.[9] Osimertinib (the only third-generation TKI currently available in the UK) is currently the preferred treatment option as per consensus guidelines such as ESMO and NCCN guidelines. Further, current epidemiology data from the National Lung Cancer Audit in the UK suggests that approximately 1,800 patients are diagnosed with advanced EGFR-positive NSCLC, of which approximately 2/3 of patients with EGFR positive metastatic NSCLC are currently receiving osimertinib as first-line treatment and that this proportion is expected to increase.[8,10,11] Osimertinib was found to be cost-effective compared to afatinib and gefitinib, which were the most commonly used first- and second-generation EGFR TKIs in NHS clinical practice are afatinib and gefitinib.[11,12]	Thank you for your comments. The comparator list includes all relevant options which may be offered for treatment of this condition. The economic analysis section has been updated to remove reference to including costs of diagnostic testing. The company may propose a cost-comparison approach as part of the fast-

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		We propose that the relevant comparator for this fast-track appraisal be limited to osimertinib as it is the standard of care in the UK and has been found to be cost-effective and have superior efficacy and safety relative to first and second generation TKIs.[12] **Are the outcomes listed appropriate?** *EQRx Response:* Yes, all outcomes listed are appropriate. **Are there any subgroups of people in whom aumolertinib is expected to be more clinically effective and cost effective or other groups that should be examined separately?** *EQRx Response:* No, we do not believe there are any subgroups of people in whom aumolertinib is expected to be more clinically effective and cost effective. **Is it common practice to test for EGFR mutation status in people with NSCLC, or would the adoption of aumolertinib require additional diagnostic tests to be undertaken?** *EQRx Response:* Testing for EGFR mutations is common practice in the UK in the evaluation of patients diagnosed with non-small cell lung cancer.[9] Additional diagnostic tests would not need to be undertaken. Current epidemiology data from the National Lung Cancer Audit in the UK suggests that approximately 1,800 patients are diagnosed with advanced EGFR-positive NSCLC.[8] **Where do you consider aumolertinib will fit into the existing NICE pathway: Lung cancer?** *EQRx Response:* We recommend aumolertinib be in the same place in the pathway as osimertinib.	track appraisal process as outlined in the NICE process guide. No further changes to the scope are needed.

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		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. *EQRx Response:* As noted above, the proposed remit does not need to be changed in order to meet NICE's stated equality objectives. **Do you consider aumolertinib 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)?** *EQRx Response:* Yes, we consider aumolertinib to be innovative in its potential to make a significant and substantial impact on health-related benefits because NSCLC-related morbidity and mortality continue to remain an area of high unmet need in the UK. We also recognise that the affordability of new treatments is an important consideration for the NHS as it strives to provide innovative, cost-effective, life-extending cancer treatments. **Do you consider that the use of aumolertinib can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?** *EQRx Response:* We do not anticipate any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation.	

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		Please identify the nature of the data which you understand to be available to enable the appraisal committee to take account of these benefits. *EQRx Response:* As noted in the previous question, we do not believe there are any benefits that would not be captured in the QALY calculation. **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.** *EQRx Response:* We do not expect any barriers to adoption. **NICE intends to appraise this technology through its Fast Track Appraisal (FTA) Process. We welcome comments on the appropriateness of appraising this topic through this process.** *EQRx Response:* Because it is likely that aumolertinib provides similar or greater health benefits compared to osimertinib at similar or lower cost than osimertinib, we believe fast track is an appropriate process for this appraisal. **Would it be appropriate to use the cost comparison methodology for this topic?** *EQRx Response:* Based on the response to the comparator section above, we believe aumolertinib provides comparable health benefits versus osimertinib, the standard of care treatment, and therefore a cost comparison analysis is most appropriate. The guidance states that "a cost comparison case can be made if a health technology is likely to provide similar or greater health benefits at similar or lower cost than technologies recommended in published NICE technology appraisal guidance for the same indication." **Is the new technology likely to be similar in its clinical efficacy and resource use to any of the comparators?**	

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		EQRx Response: Yes. Based on the magnitude of progression-free survival benefit observed in the randomized phase III trial of aumolertinib versus gefinitib, which appears similar to that observed in a similarly designed phase III trial of osimertinib versus first-generation EGFR inhibitors. **Is the primary outcome that was measured in the trial or used to drive the model for the comparator(s) still clinically relevant?** *EQRx Response:* Yes, progression free survival remains a relevant endpoint in this indication. **Is there any substantial new evidence for the comparator technology that has not been considered? Are there any important ongoing trials reporting in the next year?** *EQRx Response:* There is no substantial new evidence for the comparator technology as it relates to the initial scoped indications.	
	AstraZeneca	**NICE intends to appraise this technology through its Fast Track Appraisal (FTA) Process. We welcome comments on the appropriateness of appraising this topic through this process.** The FTA process is accelerated and lacks generation of a detailed ERG report as well as a formal consultation stage. The generalisability of the single-country trial (China-only) to UK clinical practice, in addition to the lack of mature OS data are potentially significant limitations of the evidence base, which need to be thoroughly explored and widely consulted on. There is a significant risk that the FTA process may not fully explore these issues.	Thank you for your comment. The company may propose a cost-comparison approach as part of the fast-track appraisal process as outlined in the NICE process guide. No action required.

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Additional comments on the draft scope	EQRx	We do not have any additional comments on the draft scope.	Thank you.