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Sent by e-mail only: [redacted]

19 May 2023

Dear [redacted]

Re: Final Appraisal Document — Lorlatinib for untreated ALK-positive advanced non-small-cell lung cancer [ID3896]

Thank you for your letter of 12 May 2023, lodging an appeal against the above Final Appraisal Document (FAD).

Introduction

The Institute's appeal procedures provide for an initial scrutiny of points that an appellant wishes to raise, to provide an initial view on whether they are within the permitted grounds of appeal ("valid") and are at least arguable. The permitted grounds of appeal are:

- 1(a) NICE has failed to act fairly, or
- 1(b) NICE has exceeded powers;
- (2) the recommendation is unreasonable in the light of the evidence submitted to NICE.

This letter sets out my initial view of the points of appeal you have raised: principally whether they fall within any of the grounds of appeal, or whether further clarification is required of any point. Only if I am satisfied that your points contain the necessary information, are arguable, and fall within any one of the grounds will your appeal be referred to the Appeal Panel.

You have the opportunity to comment on this letter in order to elaborate on or clarify any of the points raised before I will make my final decision as to whether each appeal point should be referred on to the Appeal Panel.

Initial View

I assess each of your points in turn.

Ground 1(a): In making the assessment that preceded the recommendation, NICE has failed to act fairly

Appeal point 1(a).1 [numbered 1.1 in your appeal letter]: The committee has failed to explain how (if at all) it has taken into account the benefits of lorlatinib in preventing CNS progression in its decision making

I am minded to refer this appeal point to the Appeal Panel. I anticipate that the Panel will wish to explore: whether "the potential benefit of lorlatinib in preventing CNS progression" was a relevant factor that the committee ought to have taken into account (noting the committee's position on this at para 3.14 of the FAD); whether the committee in fact took this into account; and whether the committee provided adequate reasons / explanation of its decision-making in the FAD. See also my comments on point 2.3.

Ground 2: the recommendation is unreasonable in the light of the evidence submitted to NICE

Appeal point 2.1: The committee has been unreasonable in concluding that the original model structure could never be accepted, even with further data collection

I do not regard this as a valid appeal point. That is because only two decisions are reported in the FAD, namely that lorlatinib is not recommended for either routine commissioning in the NHS or managed access in the Cancer Drugs Fund. The latter decision is explained in para 3.27, which says in terms that while the committee considered that a recommendation through managed access may resolve some of the uncertainties, it still thought that, at the price proposed by the company, lorlatinib did not have plausible potential to be cost-effective. In other words, price was the key determinant for the decision relating to managed access.

Having reached that decision, the committee goes on to make the statement against which you appeal, as follows:

> *"It also noted the EAG's view that the original model structure did not represent a plausible alternative approach to modelling overall survival, even if further data was collected. So, it excluded any application of that model from its decision making. The committee concluded that it was unable to recommend lorlatinib for managed access."*

In my view it is clear that the "decision making" from which the committee excluded application of the original model relates to the two decisions I've identified above. Your appeal point does not argue that the committee is unreasonable to reject the model in respect of these two decisions. Rather, it argues that it is unreasonable for the committee to conclude that the original model could never be accepted in the future, i.e. in any CDF exit appraisal. In my judgement the committee has not reached that conclusion.

Put another way, as lorlatinib has not been recommended for the CDF, there can be no decision in the FAD about how lorlatinib's (hypothetical) exit from the CDF may be conducted. I therefore see no arguable point here.

Regarding the final paragraph in your appeal letter under this point 2.1, stating that para 3.12 of the FAD misrepresents the company's position, this does not change my initial view that there is no arguable unreasonableness here. I do however wish to alert you to the opportunity afforded to all stakeholders to request that NICE make factual corrections to the FAD. To make a factual correction request, please contact the project manager, Kate Moore by emailing TAteam5@nice.org.uk as soon as possible. The technical lead and associate director for this appraisal will consider the proposed changes. Where appropriate these may be discussed with the Chair of the appraisal committee. If changes are made, the amended FDG may be submitted to NICE's Guidance Executive for ratification. Corrections will only be made after the end of the appeal period (in the event that no appeals are made) or following completion of any action arising from an appeal panel decision. Before the guidance is issued NICE will notify all consultees and commentators of any change to the FDG that has been made to correct a factual inaccuracy.

Appeal point 2.2: The committee has been unreasonable in determining that future CROWN data is not generalisable to UK clinical practice on the basis of the currently available data

I am not minded to refer this appeal point to the Appeal Panel. That is because this appeal point as set out in your appeal letter of 12 May 2023 purports to challenge the following extract from paragraph 3.27 of the FAD:

> *"They also noted that, although more mature overall survival data will become available from CROWN, it will not be generalisable to NHS practice. This is because the subsequent treatments used in CROWN do not align with those used in the NHS. This means that overall survival in CROWN could be confounded or driven by subsequent use of second-generation ALK TKIs."*

It is important to consider the above in its context. The FAD at paragraph 3.27 in fact states as follows (with my emphasis added):

> *"3.27… At the second committee meeting,* ***the clinical lead for the Cancer Drugs Fund*** *noted that more mature progression-free survival data from CROWN might reduce uncertainty about the most appropriate progression-free survival extrapolations for use in the model.* ***They also noted that, although more mature overall survival data will become available from CROWN, it will not be generalisable to NHS practice. This is because the subsequent treatments used in CROWN do not align with those used in the NHS*** *(see section 3.5)… The committee agreed that more mature progression-free and overall survival data from CROWN might reduce some of the resolvable uncertainty associated with treatment-effect duration and comparative effectiveness. But it recognised that the treatment sequences in the CROWN trial are not generalisable to the NHS. The committee acknowledged that, despite significant uncertainty, lorlatinib may offer improved clinical benefit for some people. It considered that a recommendation through a managed access agreement may resolve some of the uncertainties. But the company's and EAG's ICERs were substantially above the threshold that NICE considers to be a cost effective use of NHS resources. The committee considered its preferred assumptions and allowed for uncertainty in the clinical evidence. But it still thought that, at the price proposed by the company, lorlatinib did not have plausible potential to be cost-effective..."*

Following receipt of your appeal, it has been confirmed by the committee that the term "They" that I have underlined in bold in the extract above is a reference to the clinical lead for the Cancer Drugs Fund (not, as your letter appears to suggest, the committee itself). The committee reports the position of the clinical lead and goes on to reach its own, different, conclusion (namely, that while "*the treatment sequences in the CROWN trial are not generalisable to the NHS"* and despite significant uncertainty, lorlatinib may offer improved clinical benefit for some people and a recommendation through a managed access agreement may resolve some of the uncertainties. As your point 2.2 appeals against the committee "determining that future CROWN data is not generalisable to UK clinical practice" and the committee made no such determination, I see no arguable point here.

I will however ensure that NICE amends the FAD to ensure this is unambiguous by substituting "The clinical lead for the Cancer Drugs Fund" for "They" in the relevant sentence of para 3.27 of the FAD.

For completeness, I note that the statement cited in your appeal letter that "*This means that overall survival in CROWN could be confounded or driven by subsequent use of second-generation ALK TKIs"* is not in paragraph 3.27 but in paragraph 3.5 of the FAD as follows (my emphasis added):

> *3.5 … **The EAG** highlighted that the treatment sequences in CROWN do not align with those currently used in the NHS. **This means that overall survival in CROWN could be confounded or driven by subsequent use of second-generation ALK TKIs**…The committee considered that the comparator in the trial and subsequent treatments in both arms do not represent NHS practice, meaning a high level of uncertainty in the clinical evidence from CROWN. The committee concluded that it would take this into account during decision making."*

As the statement you have cited reports the position of the EAG, I see no arguable point that the committee reached a conclusion that is unreasonable in light of the submitted evidence.

Appeal point 2.3: The committee has been unreasonable in not capturing the benefits of preventing CNS progression and concluding that this would not materially affect its decision, given the high impact on the ICER of excluding the CNS-PD health state

I am not minded to refer this appeal point to the Appeal Panel under ground 2. That is because I do not consider the apparent change in the committee's view between the first appraisal committee meeting (ACM) and the drafting of para 3.28 of the FAD is sufficient to demonstrate arguable unreasonableness.

I am however minded to permit you to refer to the conclusion at paragraph 3.28 of the FAD (that the committee "*concluded that allowing for lorlatinib's potential uncaptured benefits would not materially affect its decision*") and the apparent inconsistency between this and slide 9 of the first ACM slides in support of your point 1a.1 that the committee has provided inadequate reasons / explanation of its decision-making around the potential benefit of lorlatinib in preventing CNS progression.

Conclusion

The above sets out above my initial views on all of your appeal points.

In respect of your points which I am not minded to refer on you are entitled to submit further clarification and/or evidence to me within the next 10 working days, and I will then give a final decision on the points to put before an appeal panel. For the points I am already content to refer on, an oral appeal will be held which will be held remotely.

Once I have made my final decision, and where there is more than one appellant, each appellant will receive the valid appeal points of the other appellants and their redacted appeal letter. This is to enable appellants to avoid duplication at the hearing where there are overlapping appeal points. If the appeal letter and/or responses to scrutiny contain confidential information please ensure you have provided a version with this information redacted by 12 June 2023.

Ordinarily appeals are conducted on the basis of the appellants' written appeal letters, and the material generated during the appraisal process. Use of additional written material is discouraged, and the panel cannot receive any new evidence. If, exceptionally, you feel there is written material that will not be before the panel that you would wish to rely on you must let the NICE Appeal team know by return of letter, indicating what the material is, why it is desirable to submit it, and when it will be available, by no later than 9 June 2023. Please note that the appeal panel cannot accept papers that are tabled late or ad hoc, as this affects the preparation of the panel and other parties for the appeal.

Yours sincerely

Dr Mark Chakravarty

Lead Non-Executive Director for Appeals & Vice Chairman

National Institute for Health and Care Excellence