**APPEAL AGAINST THE FINAL DRAFT GUIDANCE FOR THERAPEUTICS FOR PEOPLE WITH COVID-19**

**EXECUTIVE SUMMARY**

AstraZeneca appeals the Final Draft Guidance (FDG) on therapeutics for people with COVID-19 on the following grounds:

Ground 1(a)

1.1 The development and use of the framework proposed by the In Vitro Advisory Group as a basis for the recommendations by the Appraisal Committee lacks transparency, was not subject to consultation and is inconsistent

1.2 The ICERs calculated by the Committee and relied upon for its conclusion that Evusheld is not cost effective have not been disclosed

1.3 NICE has considered additional evidence and participated in discussions with the manufacturer of one technology following the second Appraisal Committee Meeting but did not offer such opportunity to AstraZeneca

1.4 The Committee has either failed to consider or has not explained its consideration of Evusheld in the mild COVID-19 population

**INTRODUCTION**

A summary of the information regarding tixagevimab-cilgavimab (Evusheld) is provided here to assist the Appeal Panel. This is not intended to replace the details originally supplied to NICE.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the virus that causes coronavirus disease 2019 (COVID-19). Following emergence of the virus in 2019 it spread rapidly across the globe resulting in the declaration of a pandemic by the World Health Organisation on 11 March 2020. There have been more than 680 million cases worldwide and more than 6.8 million deaths, as well as substantial economic and social consequences due to the disease and efforts to contain it.

The proportion of infections which have resulted in severe COVID-19 disease have varied over the course of the pandemic as a result of changes in factors including: better ascertainment of cases; increased population immunity (due to previous SARS-CoV-2 infection and vaccination); improved treatment; the likelihood that more fragile people have died in earlier waves of infection; and potential changes in SARS-CoV-2 variants.

The final scope for the current multiple technology appraisal (MTA) was to appraise the clinical and cost-effectiveness of interventions (monoclonal antibodies [including Evusheld], antivirals and immunomodulators) for treating (i) people with mild COVID-19 at high-risk of progressing to severe COVID-19 and (ii) people with severe COVID-19. Accelerated timelines were set for the appraisal, resulting in a modified procedure and substantial challenges in an assessment that was already highly complex. The appraisal was principally based on an Assessment Report prepared by an Expert Advisory Group (EAG) Sheffield School of Health and Related Research (ScHARR) in circumstances where inadequate time was permitted for a detailed review. Manufacturers of the technologies considered in the MTA were permitted to provide only a short targeted submission and no economic model.

Evusheld comprises separate vials of two monoclonal antibodies (tixagevimab and cilgavimab) administered by sequential intramuscular injections. It is indicated for the treatment of COVID-19 in adults who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19.

**PROCEDURAL HISTORY OF THE APPRAISAL**

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| **Date** | **Event** |
| 19 April 2022 | Final scope issued |
| 30 June 2022 | Assessment Report prepared by Sheffield School of Health and Related Research (ScHARR)  |
| 29 July 2022 | Comments on the Assessment Report by AstraZeneca |
| 1 August 2022 | Invitation to participate in appraisal |
| 26th August 2022 | AstraZeneca targeted submission (no economic model permitted and only limited content) |
| 3 October 2022 | Updated Assessment Report prepared by ScHARR |
| 18 October 2022 | Appraisal Committee Meeting 1 |
| 16 November 2022 | Appraisal Consultation Document issued for consultation |
| 7 December 2022 | AstraZeneca submits response to consultation on ACD |
| 24 January 2023 | Appraisal Committee Meeting 2 |
| 31 January 2023 | Committee meeting outcome shared with stakeholders |
| 13 February 2023 | Update to committee meeting outcome shared with stakeholder |
| 14 February 2023 | Final Draft Guidance issued to consultees |
| 7 March 2023 | Deadline for appeal |

**GROUNDS OF APPEAL**

1. **GROUND 1a: IN MAKING THE ASSESSMENT THAT PRECEDED THE RECOMMENDATION, NICE HAS FAILED TO ACT FAIRLY**
	1. **The development and use of the framework proposed by the In Vitro Advisory Group as a basis for the recommendations by the Appraisal Committee lacks transparency, was not subject to consultation and is inconsistent**

Paragraph 3.14 of the FDG notes that

“In vitro (laboratory) evidence may provide additional information on whether there is a realistic clinical possibility that a treatment retains efficacy against currently circulating variants”.

Following consultation on the Appraisal Consultation Document (ACD), NICE therefore commissioned an ‘in vitro expert advisory group’ made up of experts in infectious disease, virology, vaccine epidemiology, immunology and pharmacology to develop a decision framework to consider vitro neutralisation data with clinical outcomes. This framework was disclosed to consultees only two working days before the second meeting of the Appraisal Committee; it was not published or subject to external validation or consultation in the context of this appraisal. However, the framework was, nevertheless used by committee as a basis for reaching conclusions on the clinical-effectiveness of therapies for people with COVID-19. The development and use of the IVAG framework in the context of this appraisal is procedurally unfair including for the following reasons:

1. The IVAG framework was introduced very shortly before the second meeting of the Appraisal Committee and was relied upon by the Committee for the purposes of preparing the FDG, without consultation or any input from stakeholders either in terms of its content or the way in which it should be used in this appraisal. Such an approach is inconsistent with any acceptable standards of decision-making or with a fair procedure.
2. NICE’s Manual addresses arrangements following consultation at paragraph 5.7.57:

“When stakeholders submit comments that lead to a substantial revision of the committee's previous decision, involving a significant change in the recommendations, discussions or the evidence base, NICE and the chair of the committee will decide whether it is necessary to repeat the draft guidance consultation. …. NICE will distribute the committee papers with the second draft guidance, together with consultation comments and any new evidence not circulated with the previous draft guidance”.

The requirement for a second consultation is even greater where NICE itself has chosen to develop new evidence or a new method for assessment which changes the approach of the Committee and is central to the outcome, rather than this emerging during initial consultation. However, there is no indication that NICE even considered a second consultation or, if this was considered, the reasons of NICE and the Committee chair for deciding not to proceed with this have not been disclosed.

1. The need for effective consultation before the Committee used the IVAG framework for the purposes of this appraisal is increased in circumstances where the framework includes elements which are uncertain and unvalidated, such as the following:
* “The gold standard for assessing clinical effectiveness of medicines is through blinded randomised clinical trials (RCTs)” rather than in vitro data (page 10 IVAG framework).
* “There is no consensus on the exact relationship between in vitro neutralisation data and clinical outcomes for COVID-19 (such as reducing hospitalisation rates or mortality)” (page 10 IVAG framework).
* “There is no validated tool for appraising in vitro neutralisation data” and work to standardise aspects of in vitro neutralisation studies has not been completed but is ongoing (page 11 IVAG framework)
* The methods used for in vitro assays are not always described in the studies and different manufacturers of nMAbs assume different degrees of tissue penetration, and/or include a margin of error in their assays (page 12 IVAG framework)
* Interpretation of in vitro neutralisation data may be challenging (page 15 IVAG framework)
1. The way in which the Appraisal Committee has interpreted and applied the IVAG framework in the context of the current appraisal is inconsistent and inadequately explained in the FDG:
* The Committee’s approach to and interpretation of neutralisation data is different in the context of the different monoclonal antibodies considered in this appraisal.
	+ The Committee stated that certain monoclonal antibodies (including Evusheld) “were unlikely to retain sufficient neutralisation activity against most variants circulating at the time of this evaluation” and that “this was the most useful estimate of effect against future variants”. The Committee therefore concluded, without considering real world evidence and conflicting with the IVAG framework, that the clinical effectiveness of Evusheld “is highly uncertain in terms of reducing hospitalisation or mortality rates”
	+ In contrast, the Committee recognised that the in vitro evidence for sotrovimab were particularly uncertain and therefore considered data from the OpenSAFELY database, which suggested that sotrovimab maintained clinical effectiveness during the Omicron wave (which included the BA.5 sub-variant) whereas the in vitro evidence suggested that sotrovimab had reduced neutralisation abilities against BA.5. Overall “the committee considered it was unclear how much reduced neutralising effect impacts clinical efficacy”.
	+ Therefore, the Committee relied solely on neutralisation data to current variants when considering Evusheld and concluded that clinical effectiveness was “highly uncertain”, whereas for sotrovimab the Committee considered real world evidence from clinical practice to suggest that in vitro neutralisation data are not determinative.
* In considering the in vitro neutralisation data for Evusheld, the Committee has disregarded the conflicting assessment of the IVAG framework that “there is no consensus on the exact relationship between in vitro neutralisation data and clinical outcomes for COVID-19 (such as reducing hospitalisation rates or mortality)” (page 10 IVAG framework) . No explanation for this approach is provided in the FDG.
1. The Committee concluded that Evusheld is “unlikely to retain sufficient neutralisation activity against most variants circulating at the time of this evaluation”. The Committee does not explain what is meant by “most variants”, suggesting that a technology must have neutralisation activity against at least 50% of variants (i.e., “most”) in circulation to be considered for a positive recommendation. However, no explanation is provided to justify this figure and it is unclear whether such a conclusion is supported by evidence. It is significant that at the time of the second Appraisal Committee meeting, Evusheld had neutralising activity against 14% of variants in general circulation in the UK and the US FDA has stated that it will consider reintroducing the emergency authorisation of Evusheld in circumstances where the product had neutralising activity against at least 10% of variants.
	1. **The ICERs calculated by the Committee and relied upon for its conclusion that Evusheld is not cost effective have not been disclosed**

The Committee’s conclusions regarding the cost-effectiveness of Evusheld are set out at paragraph 3.28 of the FDG:

“The committee noted substantial uncertainty with the relative treatment effects of casirivimab plus imdevimab, tixagevimab plus cilgavimab and molnupiravir. The committee concluded casirivimab plus imdevimab, tixagevimab plus cilgavimab and molnupiravir all have limited and uncertain clinical effectiveness in terms of reducing hospitalisation or mortality rates and therefore the ICERs were considered very uncertain”.

No other information regarding the most plausible ICERs for Evusheld is presented in the FDG, including whether the Committee concluded that these were above or below the standard threshold used by NICE. It is not therefore possible for AstraZeneca and other stakeholders to understand and test whether the Committee’s conclusions are accurate and/or reasonable or to know what it has to do in order to achieve a positive recommendation by NICE. This is unfair. The statement at paragraph 3.28 of the FDG indicates that the Committee has calculated ICERs for Evusheld and in circumstances where NICE is committed to transparency, relevant information should be disclosed to AstraZeneca and, to the extent possible, to other consultees.

* 1. **NICE has considered additional evidence and participated in discussions with the manufacturer of one technology after the Second Appraisal Committee Meeting but has not offered such opportunity to AstraZeneca**

On 31 January 2023, AstraZeneca was contacted by NICE who communicated the outcome of the appraisal following the second meeting of the Appraisal Committee and indicated that none of the monoclonal antibody products had received a positive recommendation. This position was updated on 13 January 2023, when NICE stated that sotrovimab was now recommended and explained this on the basis of “following further discussion by the Committee”.

The “further discussion by the Committee” is unexplained.

* Paragraph 5.7.65 of NICE’s Manual provides that “when NICE sends the final draft guidance to stakeholders, any further analysis done by the company, NICE or the EAG during development of the final draft guidance will be made available to stakeholders. Comments received on the draft guidance (if produced), together with NICE's responses to them are also provided”.
* Paragraph 5.7.67 states: “In exceptional circumstances NICE may do further analysis. The EAG or Decision Support Unit normally does this further analysis before NICE circulates the final draft guidance…. If further analysis is done, NICE will inform stakeholders. NICE will distribute any such analysis to stakeholders and publish it on the website at the same time as the final draft guidance”.

No further analyses in relation to sotrovimab have been circulated by NICE and no justification provided in relation to the further discussion by the Committee. In circumstances where no such discussions took place in relation to other products, the apparent deviation from NICE’s procedures is procedurally unfair.

* 1. **The Committee has either failed to consider or has not explained its consideration of Evusheld in the mild COVID-19 population**

The Committee concludes, based on its assessment of in vitro neutralisation data, that the clinical effectiveness of Evusheld “is highly uncertain in terms of reducing hospitalisation or mortality rates” (paragraph 3.17 of the FDG).

However, while the IVAG framework notes the challenges of interpretation of neutralisation data and states “there is no consensus on the exact relationship between in vitro neutralisation data and clinical outcomes for COVID-19 (such as reducing hospitalisation rates or mortality)” (page 10 IVAG framework), the Committee has considered no other evidence in relation to the clinical effectiveness of the product. In particular, paragraph 3.19 of the FDG includes no assessment of the data for Evusheld, indicating that such data were not considered by the Committee in reaching its conclusions.

**THE DETERMINATION OF THIS APPEAL**

AstraZeneca requests that this appeal should be determined at an oral hearing.

**REQUESTED OUTCOME FOLLOWING APPEAL**

AstraZeneca requests that the appraisal of Evusheld is returned to the Appraisal Committee for further consideration with the following directions:

1. The current FDG should be converted to an ACD and issued for consultation so that the implications of the IVAG framework and its application in the context of this appraisal can be adequately considered.
2. The responses to consultation on the new ACD (the current FDG) should be taken into account by the Appraisal Committee when considering revisions to the draft guidance.
3. Information regarding the most plausible ICERs for Evusheld, as calculated by the Committee should be disclosed to AstraZeneca.
4. The reasons for the change in the draft guidance for sotrovimab should be explained and any additional analyses by the manufacturer or by NICE disclosed. To the extent that other manufacturers (including AstraZeneca) wish to submit additional evidence and/or analyses, opportunity for this should be incorporated in the process.
5. The Committee should provide its assessment of use of Evusheld in the mild COVID population.