Input from manufacturer on the 2nd draft assessment "BAMLANIVIMAB MONOTHERAPY AND BAMLANIVIMAB PLUS ETESEVIMAB COMBINATION FOR THE TREATMENT OF COVID-19

Project ID: PTRCR20

eunethta

EUROPEAN NETWORK FOR HEALTH TECHNOLOGY ASSESSMENT

The objective of this reviewer form is to standardise the process of the factual accuracy check of the rapid relative effectiveness assessments.

The 2nd version of the Rapid Collaborative Reivew of bamlanivimab monotherapy and bamlanivimab plus etesevimab combination for the treatment of covid-19 was open to review by the manufacturer [Eli-Lilly] between **19/05/2021 and 21/05/2021**.

Comments received from:

Market Authorisation Holder
Eli-Lilly

All received comments are formally responded in this combined document, to be published on the EUnetHTA website, name of organisation/institution (or individual names of the reviewers/affiliations) disclosed.

Comments from Market Authorisation Holder [Eli-lilly]

Page	Line	Comment	Character of comment[i]	Reply from author
10	30-39	The wording regarding the revokation of the EUA suggests that the decision to withdraw BAM alone was an FDA decision based on signals of lack of efficacy in new variants. This is not the case. Lilly together with FDA made the decision to revoke the EUA for BAM alone, (see https://investor.lilly.com/news-releases/news-release-details/lilly-requests-revocation-emergency-use-authorization And Eli Lilly Asks FDA to Nix EUA for Bamlanivimab Alone | 2021-04-19 | FDAnews). Supplies of BAM were made available under emergency use conditions, but production of ETE to match BAM supply lagged. Once supply could be confirmed, Lilly sought to have the BAM alone EUA revoked. The the full availability of bamlanivimab and etesevimab together was a deciding factor in the timing of the request for revocation of BAM alone EUA. This request is not due to any new safety concern. This was discussed at the investor calls related to SARS-CoV-2 antibodies (See https://investor.lilly.com/static-files/081a5ef7-f5d6-4acc-b0d2-7ae4daf9e953 slide 22). While the EUA addresses the effect of BAM alone and BAM + ETE on emerging variants. The B.1.1.7 variant remains the dominant variant in the US (and noted on page 6 as the dominant variant in the UK). BAM alone remains effective against this variant.	2	The wording is according listed reference: FDA. News release April 16, 2021. Coronavirus (COVID-19) Update: FDA Revokes EmergencyUse Authorization for Monoclonal Antibody Bamlanivimab. https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-revokes-emergency-use-authorization-monoclonal-antibody-bamlanivimab
15 -16	28 - 32	On pages 15 and 16, reference is made to an endpoint – "medically attended visits through day 29". However, medically attended visits is not an outcome reported in the BLAZE trials. *Analyses related to two clinical outcomes (Time weighted average change from baseline in viral load through day 7 and Percentage of patients with one or more medically attended visits through day 29) were performed by authors of this RCR. These analyses incorporated additional outcome data on the outcome time-*	2	Thank you very much, change was made to be in line with the rest of the document: "Proportion of patients with COVID-19–related hospitalizations or emergency department visits at day 29"

Page	Line	Comment	Character of comment[i]	Reply from author
		weighted average change from baseline in viral load that was provided by Eli-Lily.		
16	6- 8	*Certainty of evidence related to two clinical outcomes ("Symptom score at day 11 7 and day 22"" and "Percentage of patients with one or more medically attended visits through day 29") 8 was performed by the authors of this RCR.*	2	See above: "Proportion of patients with COVID-19–related hospitalizations or emergency department visits at day 29"
11, 12	Tables 1.2 and 1.3	We would recommend changing Tables 1.2 and 1.3 to Tables 3 and 4 respectively from the recently updated FDA Fact Sheet	2	In EU, at time of publication of EUnetHTA rapid review, the EMA Rolling Review is still ongoing. Under Article 5(3) the EMA has issued an advice on the use of bamlanivimab monotherapy and bamlanivimab plus etesevimab combination treatment in European Member States. Because no new announcement found related to bamlanivimab monotherapy in EU by EMA, authors of this rapid review found relevant to provide text related to bamlanivimab monotherapy and new SARS-CoV-2 variants, for HTA comunity. As already stated in the current document, when Marketing Authorisation is granted in EU, this Rapid Collaborative Review needs to be read with caution as the indication used in this report may be different from the indication approved by EMA. The authors of this report reserve the right to edit the report at a later point in time if necessary. Table and text on bamlanivimab plus etesevimab combination related to new SARS-CoV-2 variants are in line with the recently updated FDA Fact Sheet, May 2021.
22-25	Table 4.1a	We were unable to verify the analyses included in Table 4.1a and unable to locate the reference provided. The table includes results that appear to be an indirect comparison for which methodological	1	The MAH was asked to check for factual accuracy of the document. This comment is not related to a factual inaccuracy and is, therefore, outside the scope of a fact check.

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		details are missing. We were not determine what dosages of BAM or BAM +ETE have been used in the analyses and there is not discussion within the report of the limitations the indirect comparison. The BLAZE 1 study is a platform trial design common to many treatments for COVID-19 and includes both phase II and phase III arms. The designs were lead by FDA guidance pertaining to endpoints and definitions of the patient at high risk as of May 2020. The RCTs were not powered to conduct direct comparisons between BAM and BAM+ETE. All comparisons are limited to placebo comparisons. The goal of the Lilly SARS-CoV-2 antibody program has always focused on a combination of BAM + ETE for treatment of patients with mild-moderate COVID 19.		
34 - 37	6	As several of the statements included in SECTION 6 report datapoints and statistical values, we recommend the inclusion of references. The statements related to the comparison of BAM vs BAM+ETE are not based on RCT evidence, but an indirect comparison Our comments on the appropriateness of this indirect comparison are noted above.	1	The MAH was asked to check for factual accuracy of the document. This comment is not related to a factual inaccuracy and is, therefore, outside the scope of a fact check.

[i] Character of comment
- 'major'=1
- minor'= 2

'linguistic'=3