Input from manufacturer on the 2nd draft assessment "CPRETOMANID AS PART OF A COMBINATION REGIMEN WITH BEDAQUILINE AND LINEZOLID, IN ADULTS FOR THE TREATMENT OF PULMONARY EXTENSIVELY DRUG RESISTANT (XDR), OR TREATMENT-INTOLERANT OR NONRESPONSIVE MULTIDRUG-RESISTANT (MDR) TUBERCULOSIS (TB)"

Project ID: PTJA14

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 Assessment of pretomanid as part of a combination regimen with bedaquiline and linezolid, in adults for the treatment of pulmonary extensively drug resistant (XDR), or treatment-intolerant or nonresponsive multidrug-resistant (MDR) tuberculosis (TB) was open to review by the manufacturer [Mylan] between **29/06/2020 and 03/07/2020**.

Comments received from:

Market Authorisation Holder
Mylan

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 [Mylan]

Page	Line	Comment	Character of comment[i]	Reply from author
8	10	*For patients with MDR-TB or XDR-TB, long treatment regimens are recommended with at least 4effective medicinal products depending on strains susceptibility (4).* A wording which would better introduce into the treatment situation would be the following: Long MDR-TB treatment regimens last 18 months or more depending on the patient response to therapy and comprising 4 and often 7 or more antibiotics (including injectables) with partly severe toxicities, such as hearing loss and kidney damage (4).	3	This comment is outside of the scope of the factual accuracy check.
8	13/14	It´s necessary to be more precise here. Pretomanid is a nitroimidazooxazine, delamanid is a nitroimidazooxazole. Please compare: https://www.ema.europa.eu/en/medicines/human/orphan-designations/eu307513 and https://www.ema.europa.eu/en/medicines/human/orphan-designations/eu307524 Furthermore, there are other differences between the products. Pretomanid requires only 1 daily tablet and is given in the pre-defined 6 months BPaL regimen (intervention is described in the MAH submission dossier and the EUnetHTA REA version 0.2). It is reserved for adults with highly resistant forms of TB TI/NR MDR-TB and XDR-TB) and does not fit into the WHO groups. Delamanid requires 4 daily tablets over 24 weeks and is indicated for use as part of an appropriate combination regimen for pulmonary multi-drug resistant tuberculosis (MDR-TB) in adult patients when an effective treatment regimen cannot otherwise be composed for reasons of resistance or tolerability. Treatment with an appropriate combination regimen should continue after	1	Information that both products are from the same class (according to CHMP) is factual and is not a judgement regarding potential similarity or differences between the two products.

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		completion of the 24-week delamanid treatment period according to WHO guidelines. In the WHO guidelines, delamanid is classified in group C. It requires a minimum of three additional antibiotics. And the baseline regimen has normally a duration of 18 to 20 months or even longer. https://www.ema.europa.eu/en/documents/product-information/deltyba-epar-product-information_en.pdf https://www.who.int/tb/publications/2019/consolidated-guidelines-drug-resistant-TB-treatment/en/		
8	Table, Comparison	*"Treatments authorised in MDR-TB…"* The systematic literature search identified not only studies in the broader indication MDR-TB, but also in a population which provides higher comparability to the target population mainly suffering from XDR-TB (MAH submission dossier, table 15). Furthermore, data with treatment regimens including bedaquiline and linezolid were available which allow better comparability with the BPaL regimen (MAH submission dossier, table 20) than other (and older) treatment regimens. Especially the study published from Olayanju et al. 2018 provides the best comparability regarding population and intervention. It should be acknowledged that this situation allows a focussed approach.	2	This comment is outside of the scope of the factual accuracy check.
9	10-13	We address concerns about the SLR search methodology in our comments to page 20 in this comment form. However, as a broader note, we worry that the assessment team did not fully appreciate the paucity of rigorous research available regarding XDR-TB. This is a condition which is comparatively rare, especially in high-income countries, and has only been defined recently (in the past 13 years). Moreover, only 3 new MDR-TB treatments (including pretomanid) have been approved in that timeframe.	3	Considerations on medical need and the place in the treatment pathway fall within the scope of appraisal that will be conducted by each country at national level.

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		There is literally no comparator regimen that is approved by any regulatory authority in the world for XDR-TB, and WHO guidelines make little distinction between MDR-TB and XDR-TB treatments despite the additional complexity of XDR-TB treatment (https://www.who.int/tb/publications/2019/consolidated-guidelines-drug-resistant-TB-treatment/en/). It was therefore not a surprise to us to discover that there were comparatively few prior studies on XDR-TB (or TI/NR MDR-TB) to which Nix-TB could be compared to. Indeed, the lack of a standard-of-care comparator regimen was a driving reason why the Nix TB trial was single-armed, and why the FDA and EMA both approved the drug despite this factor.		
10	14	*"Moreover"* Was the intent to say "Additionally"?	3	A medical editing of the assessment report was performed in parallel of this factual accuracy check.
10	47	Two of the 109 patients had their treatment extended by 3 months, not just one as the statement currently reads. See Nix-TB Clinical Study Report, dated 29 October 2019, Section 11.0 Efficacy Evaluation on pg. 111. for confirmation.	2	The assessment report was modified accordingly.
12	10-12	*On an indicative basis, in recent publications in XDR-TB patients, favourable outcomes (cured/treatment completed) ranged from an average of 40% to 70% depending on 11 treatment regimen and patients characteristics (6, 7).* For completeness, the other identified publications about clinical trials in XDR-TB should be cited as well: Pym et al. 2016, Tang et al. 2015, Lee et al. 12, Wang et al. 2018.	3	The authors consider appropriate the reference to the WHO rapid communication 2019 for the lower bound of 40% and to the recent publication of Olayanju in 2018 for the higher bound of 70%.
12	16-19	It may be worth additionally noting that the ongoing ZeNIX trial is taking place in Georgia, Moldova, and Russia in addition to South Africa (https://clinicaltrials.gov/ct2/show/NCT03086486).	2	No results from ongoing ZeNix study were available for this assessment therefore this study is not detailed in the report.

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12	19-20	This sample size is larger than the entire XDR-TB treatment cohort in Western Europe. An assessment of the incidence data for the years 2017 and 2018 published in the WHO's global tuberculosis database https://www.who.int/tb/country/data/download/en/ (accessed 22 October 2019 and provided in the MAH submission dossier in section 2.2 Target population, Table 8, pages 24 and 25), indicates that a total of about 219 cases of XDR-TB were reported in the EU countries including UK. Thereof, 181 XDR-TB cases were reported in Eastern Europe, the EU-region with highest disease burden, and only 38 XDR-TB cases in Western Europe.	2	This comment is outside of the scope of the factual accuracy check.
12	20-21	In the Nix-TB study, performance between HIV and non-HIV co-infected patients was closely matched. The results were consistent regardless of HIV status [Conradie et al.2020]. This is also visible in the Nix-TB clinical study report from 29 October 2019, Efficacy evaluation, page 156, Figure 11-14 Primary Endpoint Subgroup Analyses. And in the safety evaluation, the proportion of HIV-positive and negative patients were comparable for the different TEAE classifications with only very few exceptions where slightly more patients without co-infection had an advantage regarding tolerability as summarized in the Nix-TB clinical study report from 29 October 2019, Safety evaluation, page 253.	2	This comment is outside of the scope of the factual accuracy check. Authoring team's statement on co-infected patients rate in the study is only factual.
12	23-26	The real clinical efficacy of the regimen could only be investigated in naive patients. However, treatment with bedaquiline and linezolid has led to rates of favorable outcomes of 51% to 66% [Collaborative Group for the Meta-Analysis of Individual Patient Data et al. 2018; Olayanju et al. 2018]. Treatment typically required 24 months to complete, where both drugs were used as "add-ons" to regimens consisting of a median total of 8 oral and injectable drugs [Olayanju et al.	2	This comment is outside of the scope of the factual accuracy check.

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		2018].		
12	27	The reviewers are correct that 16 patients had negative baseline cultures. However, they qualified for inclusion based on a positive culture or molecular test within 3 months prior to, or at, screening. The sensitivity analysis presented in the Clinical Study Report, referenced elsewhere in the summary (e.g. section 3.3.2), evaluated efficacy specifically removing these 16 patients. The overall favorable rate was the same (90%) when these patients were excluded from the analysis, so the overall conclusions on efficacy of the trial are correct. This sensitivity analysis may be found in the CSR of Oct 29, 2019, Section 11.4.1.1.1, in the table 11-30 pasted below:	1	This comment is outside of the scope of the factual accuracy check. The sensitivity analysis is described in the report.

<table>
<tr><th>Page</th><th>Line</th><th>Comment</th><th>Character of comment[i]</th><th>Reply from author</th></tr>
<tr><td></td><td></td><td>
Table 11-30 Analysis of the Primary Endpoint Excluding Patients Wh
Culture Positive During the Baseline Period (MITT Analy
<table>
<tr><th></th><th>Total</th><th>XDR</th></tr>
<tr><td>Total enrolled</td><td>109</td><td>71</td></tr>
<tr><td>N not positive at baseline</td><td>16</td><td>9</td></tr>
<tr><td>N in analysis</td><td>93</td><td>62</td></tr>
<tr><td>Unassessable</td><td>2</td><td>1</td></tr>
<tr><td>Total Assessable</td><td>91</td><td>61</td></tr>
<tr><td>Favorable</td><td>82 (90%)</td><td>54 (89%)</td></tr>
<tr><td>Unfavorable</td><td>9 (10%)</td><td>7 (11%)</td></tr>
<tr><td>95% CI for Favorable</td><td>82% to 95%</td><td>78% to 95%</td></tr>
</table>
Abbreviations: CI, confidence interval; MDR, multidrug-resistant; MITT, modified intent-to
of patients; NR, nonresponsive; TI, treatment-intolerant; XDR, extensively drug-resistant
Note: Where baseline period is Screening through Week 4, but they were eligible based on d
Mycobacterium tuberculosis by culture or molecular test within 3 months prior to Screen
Source: Table 4.1
</td><td></td><td></td></tr>
<tr><td>12</td><td>32-36</td><td>As noted in the Nix-TB clinical study report, resistance tests to Rif, INH, a FQ, and an injectable in liquid culture were systematically conducted on isolates from cultures of the patients' sputum.

It is not clear why the assessors are concerned with resistance to any other drugs; these are not part of the definition of XDR-TB or TI/NR MDR-TB.</td><td>1</td><td>This comment is outside of the scope of the factual accuracy check.</td></tr>
<tr><td>12</td><td>39-40</td><td>In the CSR, 47 patients had the opportunity to be followed to the final 24-month endpoint after completion of therapy, and their information is include below. This is highly supportive of long-term efficacy, although the follow up of the remaining patients is</td><td>1</td><td>This comment is outside of the scope of the factual accuracy check.</td></tr>
</table>

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<tr><td></td><td></td><td>ongoing.

As the review notes, final results of Nix-TB are expected in Q2 2021. However, given the favorable results of NIX-TB and the lack of existing approved treatment for XDR-TB, it was thought in the best interests of patients to accelerate the filing timeline.

Table 11-33 Number of Patients Enrolled and Expected to Have 24-M
<table><tr><th></th><th>Total</th><th>XDR</th></tr><tr><td>Total enrolled</td><td>109</td><td>71</td></tr><tr><td>N expected (% total enrolled)</td><td>47</td><td>40</td></tr><tr><td>Favorable</td><td>41 (87%)</td><td>34 (85%)</td></tr><tr><td>Unfavorable</td><td>6 (13%)</td><td>6 (15%)</td></tr><tr><td>95% CI for Favorable</td><td>74% to 95%</td><td>70% to 94%</td></tr></table>Source: Section 12 of the Statistical Report – Efficacy (primary endpoint)

At the time the data were extracted, 47 patients were “expected” to have dat
24-month endpoint.

On the existing evidence, pretomanid received already FDA approval
https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/212862Orig1s000TOC.cfm
and a positive CHMP opinion
https://www.ema.europa.eu/en/medicines/human/summaries-opinion/pretomanid-fgk .</td><td></td><td></td></tr>
<tr><td>12</td><td>40</td><td>• The WHO definition of cure is less stringent than the NIX-TB primary endpoint. The WHO defines a cure as “Treatment completed as recommended by the national policy without</td><td></td><td>The statement that cure defined by WHO guidelines, was not an endpoint specified in Nix-TB is</td></tr>
</table>

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		evidence of failure AND three or more consecutive cultures taken at least 30 days apart are negative after the intensive phase." (citation from World Health Organization. Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis ; 2014) • By contrast, the Nix-TB criteria is more strict than this definition: "*patients were classified as having a favorable outcome at 6 months [i.e. not just at treatment completion] if they had resolution of clinical disease, a negative culture status, and had not already been classified as having had an unfavorable outcome… Culture conversion was defined as at least two consecutive culture-negative samples collected at least 7 days apart."* [Conradie et al. 2020] The NIX cure rate can thus be considered a lower-bound on the WHO-defined cure rate. If the assessors prefer to use the WHO cure criteria rather than the more stringent NIX-TB one, it is easily calculated from the CSR. The Nix trial enrolled 109 patients and 102 (95%) met the criteria of cured or completed treatment. In part for this reason, both the FDA and the CHMP have accepted the NIX-TB results as the basis for their positive opinions. Of note: the FDA uses a different, also more stringent, definition of cure than the WHO. It uses 12- month follow-ups, while the NIX trial used 6- and 24- month horizons. ***US FDA Guidance for Industry Pulmonary Tuberculosis: Developing Drugs for Treatment (https://www.fda.gov/media/87194/download, line 377)*** *The following efficacy endpoints can be used in clinical trials of*		only factual.

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		pulmonary tuberculosis: *A primary clinical efficacy endpoint that is comprised of survival and evaluation of M. tuberculosis on serial sputum culture examinations during treatment and 12 months following completion of treatment*		
12	48	When the Nix-TB trial was designed, there was no validated TB disease-specific utility tool for measuring function or quality of life. The EQ5D5L was chosen because it was a European-derived, very well known, and validated tool (https://euroqol.org/eq-5d-instruments/eq-5d-5l-about/). If the assessors consider that the usage of the questionnaire has *some*, rather than *no,* data value, then there is at least some evidence base to address the concern. More broadly, we note that there is no evidence on adherence, treatment completion, or quality of life for *any* other treatment method for XDR-TB or TI/NR MDR-TB. Given this, we believe that there is strong indicative evidence to believe that the BPaL regimen is an improvement from quality of life standpoint.	2	This comment is outside of the scope of the factual accuracy check. Considerations on the potential added value of this product based on its duration will be part of national appraisals.
15	7	The previous paragraph in the summary notes the usual treatment timeline for MDR TB, i.e. "Shorter regimen of 9–12 months may however be used in patients … in whom resistance to fluoroquinolones and 2 second-line injectable agents has been excluded". We would suggest adding a similar note on the duration of XDR-TB treatment, perhaps "unlike for some MDR-patients for whom shorter treatment courses may be appropriate, the WHO	3	The authors considered that the information regarding longer regimen in MDR-TB patients including patients with additional resistance (XDR-TB) is adequately covered in the report.

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		guidelines indicate longer treatment regimens (usually with a total duration of 18 to 20 months)".		
15	20/21	It´s necessary to be more precise here. Pretomanid is a nitroimidazooxazine, delamanid is a nitroimidazooxazole. Please compare: https://www.ema.europa.eu/en/medicines/human/orphan-designations/eu307513 and https://www.ema.europa.eu/en/medicines/human/orphan-designations/eu307524 Furthermore, there are other differences between the products. Pretomanid requires only 1 daily tablet and is given in the pre-defined 6 months BPaL regimen (intervention is described in the MAH submission dossier and the EUnetHTA REA version 0.2). It is reserved for adults with highly resistant forms of TB TI/NR MDR-TB and XDR-TB) and does not fit into the WHO groups. Delamanid requires 4 daily tablets over 24 weeks and is indicated for use as part of an appropriate combination regimen for pulmonary multi-drug resistant tuberculosis (MDR-TB) in adult patients when an effective treatment regimen cannot otherwise be composed for reasons of resistance or tolerability. Treatment with an appropriate combination regimen should continue after completion of the 24-week delamanid treatment period according to WHO guidelines. In the WHO guidelines, delamanid is classified in group C. It requires a minimum of three additional antibiotics. And the baseline regimen has normally a duration of 18 to 20 months or even longer. https://www.ema.europa.eu/en/documents/product-information/deltyba-epar-product-information_en.pdf https://www.who.int/tb/publications/2019/consolidated-guidelines-drug-resistant-TB-treatment/en/	1	See answer above.

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16	Table 2 (Proprietary name)	The proprietary name will change, and the decision will be published end of July. Could you perhaps change the information in the first line of the table into "under assessment"? We have the rare situation of an MAH transfer after EC approval. Therefore, we hope that you can do this without justifying reference.	2	The proprietary name section has been modified accordingly. Prospective MAH is cited in the table.
16	Table 2, Orphan Designation)	EMA meanwhile confirmed the orphan designation. It was confirmed at 25 Jun 2020. According to the EMA guidelines (https://www.ema.europa.eu/en/medicines/what-we-publish-medicines-when-0), the update was expected 3 July 2020. However, this did not happen until noon. Next possible publication date is 24 July 2020, i.e. after PTJA14 publication.	1	According to the project plan, the report will be finalised on 15/07/2020. At that time, no official documentation will be available to support this modification.
18	Table 4, Comparison	*"Treatments authorised in MDR-TB…"* The treatments listed here are likely the best available comparators, but it is worth noting that there they are not direct comparators. XDR-TB and TI/NR MDR-TB are a subset of broader MDR-TB, but a uniquely challenging one with that is relatively ill-studied. Due to the outcomes in the literature search, we were able to focus on the narrower pretomanid indication spectrum (i.e. XDR-TB and TI/NR MDR-TB). (MAH submission dossier, table 15). In particular, data from Bedaquiline- and linezolid-based regimens is available (in particular, Olayanju et al. 2018), which allows for a direct comparison (MAH submission dossier, table 20) rather than having to rely on data from other, older, treatment regimens. It should be acknowledged that this situation allows a focussed approach.	2	The relevant comparators were defined in the project plan, during the scoping phase and based on the feedback from EUnetHTA Partners (PICO survey).
20	11-14	The NICE guidelines (https://www.nice.org.uk/process/pmg20/chapter/identifying-the-evidence-literature-searching-and-evidence-submission#sources	1	The assessment report states factually that other databases could have been searched as

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		), state that: "For reviews of the effectiveness of pharmacological interventions the following should be prioritised for searching:the Cochrane Central Register of Controlled Trials (CENTRAL), the Cochrane Database of Systematic Reviews (CDSR), Embase, MEDLINE, the Medicines and Healthcare products Regulatory Agency (MHRA) – for drug safety information." Nevertheless, as outlined in the MAH submission dossier section 5.1 page 48, a "hand search" procedure was used to search for conferences of interest in the following conferences websites: • The 50th Union World Conference on Lung Health 2019 • European Respiratory Society (ERS) International Congress 2019 • CHEST Congress 2019 • Conference on retroviruses and Opportunistic Infections (CROI) 2019 • 10th International Aids Society (IAS) Conference 2019		tuberculosis is a disease with high incidence outside Europe or USA.
20	13-18	The committee's suggestion is that Mylan could have run the search further back than 10 years. However, it would have been impossible to do this any greater than 13, given that XDR-TB was only identified in 2006: *World TB Report, 2007:* https://apps.who.int/iris/bitstream/handle/10665/43629/9789241563141_eng.pdf?sequence=1 *The identification of extensively drug-resistant tuberculosis (XDR-TB) during 2006 has prompted many countries to review the quality of their TB control strategy, and to take the necessary steps to strengthen basic TB control.*	1	The authors underlined in assessment the report that a 10-year search is common practice, but without justification in the submission dossier, it is arbitrary. For a future submission dossier, the MAH is invited to further justify the cut-off chosen for the SLR.

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		Of course, even once XDR-TB was identified, it takes time for practice to emerge. For instance, the WHO's 2006 *Guidelines for the programmatic management of drug-resistant tuberculosis* (http://www.stoptb.org/assets/documents/resources/publications/technical/tb_guidelines.pdf) do not even mention the term. Any study that thus started in 2006 or earlier (and likely would have been actually published in 2008+) would not have include XDR-TB as a subject or criterion. As another concern with using longer timeframes: early definitions of XDR-TB may have differed than current ones. For instance, as the WHO noted in footnote 6 of *The Global MDR-TB & XDR-TB Response Plan 2007–2008* (https://apps.who.int/iris/bitstream/handle/10665/69676/WHO_HTM_TB_2007.387_eng.pdf?sequence=1), *"XDR-TB was initially defined [in a March 2006 article from by the WHO and CDC] as MDR-TB with further resistance to three or more of the six main classes of second-line anti-TB drugs (aminoglycosides, polypeptides, fluoroquinolones, thioamides, cycloserine and para-aminosalicylic acid".* Compare this to the later-developed definition (from the same Response Plan) as: *"XDR-TB is defined as resistance to at least rifampicin and isoniazid (which is the definition of MDR-TB), in addition to any fluoroquinolone, and to at least one of the three injectable drugs used in anti-TB treatment: capreomycin, kanamycin and amikacin"* Lastly, it is worth noting that the WHO guidelines changed		

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		recently (https://www.who.int/tb/publications/2018/MDR_RR-TB-TaskForce-FAQs-Updated-June2019.pdf?ua=1) to recommend bedaquiline as a preferred agent for MDR-TB (and implicitly XDR-TB), after first discussing it for use in 2013 (https://www.who.int/tb/challenges/mdr/Report_EGM_BDQ_2013.pdf?ua=1). Given how much MDR-TB and XDR-TB treatment has changed since the introduction of bedaquiline in 2012 (https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2012/204384Orig1s000ltr.pdf), it was thought prudent to avoid confounding the results (and biasing in favor of pretomanid) by including studies considering older, less-effective, non-bedaquiline based treatments. For these reasons we suggest that in addition to being standard practice, a 10-year timeframe is eminently reasonable for an XDR-TB literature search.		
20	18-19	Nice guidelines (https://www.nice.org.uk/process/pmg20/chapter/identifying-the-evidence-literature-searching-and-evidence-submission#sources) explicitly state that "Searches should be limited to studies reported in English." Moreover, this did not appear to be a discussion point in other recent EUnetHTA assessments https://eunethta.eu/rapid-reas/ which also restricted the searches to English publications.	1	This point was not highlighted as a major limit. Indeed, the authors underlined in the assessment report that search is limited to publications in english without justification, but it is generally considered to be the main language of scientific publication.
20	28-30	According to the Cochrane handbook (https://training.cochrane.org/handbook/current/chapter-04) "searches should aim for high sensitivity" and "avoid using too many different search concepts but a wide variety of search terms should be combined with OR." This principle was followed with the intent of maximizing sensitivity, including publications mentioning any relevant term describing pathology, treatments, or clinical study number. Any different use of the Boolean	1	This comment is outside of the scope of the factual accuracy check.

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		operators would have resulted in a *more* restricted identification of studies and thus lower sensitivity; this would have been at cross-purposes to the recommendation later that "this search was generally too specific in the choice of terms".		
20	30-33	The terms delivering no results are the identification number of trials and 4 highly specific terms (Treatment-intolerant multi-drug resistant tuberculosis, TI MDR-TB, Treatment intolerant multi-drug resistant tuberculosis, Nonresponsive multi-drug resistant tuberculosis, for reference see the MAH submission dossier section 7.4) included to increase the sensitivity of the search. Corresponding alternative spelling which produced results were included in the search (NR TB-MDR, Non-responsive multi-drug resistant tuberculosis, for reference see the MAH submission dossier section 7.4). In consideration of the large number of search terms combined with OR, the search was limited to abstract to increase precision; it was considered very unlikely that a paper mentioning XDR-TB or TI/NR MDR TB in the main body but not the title or abstract would be relevant.	1	This comment is outside of the scope of the factual accuracy check.
20	33-37	Relevant MeSH terms ("tuberculosis, multidrug resistant," and "extensively drug-resistant tuberculosis") and Emtree terms ("extensively drug resistant tuberculosis," and "multidrug resistant tuberculosis") exist, but 21 relevant disease terms (including "extensively drug-resistant tuberculosis" and "extensively drug-resistant tuberculosis") have been included in title and abstract search (see MAH submission dossier, 7.4). Moreover, a manual reference check of all included publications at the full-text stage was conducted. For reference see MAH submission dossier, section 5.1, page 48, first sentence. This did not identify any additional relevant study.	2	This comment is outside of the scope of the factual accuracy check.

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20	38-40	The NICE guidelines (https://www.nice.org.uk/process/pmg20/chapter/identifying-the-evidence-literature-searching-and-evidence-submission#sources) state that "Search filters should… be used with caution". Its logic is that "there is often limited evidence on the performance of individual filters" beyond a limited basic set (e.g. dates, language, and a few others). Selection of appropriate type of studies, publications and document types was instead performed manually in phase of abstract screening – effectively a post-hoc filtration.	1	This comment is outside of the scope of the factual accuracy check.
20	40-42	As reported in the Cochrane Handbook (https://training.cochrane.org/handbook/current/chapter-11), "in general, combining randomized with observational studies in a network meta-analysis is not recommended." As such we focused the search on prospective clinical trials and retrospective observational studies, and other study types were excluded from the evidence.	2	This comment is outside of the scope of the factual accuracy check.
20	43-46	As noted above, this critique is at odds with the substance of many of the authoring team's specifically-listed complaints. To have included any further filters (e.g. by document type, or exclusion criteria) would have resulted in a lower-sensitivity search. We have addressed the specific concerns that the search was too specific (e.g. too narrow in dates or missing certain potential keywords).	2	This comment is outside of the scope of the factual accuracy check.
21	18-20	As reported in the Cochrane Handbook (https://training.cochrane.org/handbook/current/chapter-11), "in general, combining randomized with observational studies in a network meta-analysis is not recommended." As such we focused the search on prospective clinical trials and retrospective observational studies, and other study types were excluded from the evidence.	2	This comment is outside of the scope of the factual accuracy check.

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		Furthermore, given the fact that no other drugs were launched for the narrow indication including only the most resistant forms of TB, there is no real paucity of data. The systematic literature search identified not only studies in the broader indication MDR-TB, but also in a population which provides higher comparability to the target population mainly suffering from XDR-TB (MAH submission dossier, table 15). Furthermore, data with treatment regimens including bedaquiline and linezolid were available which allow better comparability with the BPaL regimen (MAH submission dossier, table 20) than other (and older) treatment regimens. Especially the study published from Olayanju et al. 2018 provides the best comparability regarding population and intervention. It should be acknowledged that this situation allows a focussed approach. Indeed, it is regrettable that the ideal comparator - Olayanju et al 2018 represents already a subset of this population- and the indirect comparison with the NixTB data is currently not available for this assessment to guarantee confidentiality of a submitted publication manuscript.		
26	Table 6, Concomitant Treatments	*Strong CYP 3A4 inhibitors or inducers were prohibited* Current wording omits the word "strong". For verification, please see the Nix-TB Protocol, Version 5, dated 16 FEB 2018, Exclusion #17 on page 56.	2	The assessment report was modified accordingly.
30	4	Two of the 109 patients had their treatment extended by 3 months, not just one as the statement currently reads. See Nix-TB Clinical Study Report, dated 29 October 2019, Section 11.0 Efficacy Evaluation on pg. 111. for confirmation.	2	The assessment report was modified accordingly.
30	29	*Strong CYP 3A4 inhibitors or inducers were prohibited* Current wording omits the word "strong". For verification, please see the Nix-TB Protocol, Version 5, dated 16 FEB 2018, Exclusion	2	The assessment report was modified accordingly.

Page	Line	Comment	Character of comment[i]	Reply from author
		#17 on page 56.		
33	1	This statement implicitly suggests that the early stop of the trial is evidence of potential bias, i.e. the stopping criteria were sufficiently subjective to allow investigators latitude in targeting certain results. As stated by the FDA (https://www.fda.gov/media/127592/download), there were objective criteria, agreed upon with regulators, for why the trial's final size was 109 patients: *The trial was originally planned with a sample size of 200 patients assigned to B-L-Pa. Enrollment was initiated in April 2015 and stopped in November 2017, with a final sample size of 109 patients. The applicant stopped enrollment due to the observed efficacy results and enrolled patients in an ongoing randomized Study NC-007 comparing doses and durations of linezolid in B-L-Pa regimens. Per agreement with the FDA, the clinical trial report submitted in the NDA summarizes the evidence for efficacy from the first 45 patients who completed the 6-month follow-up after the treatment period or who died or relapsed.* Additionally, the trial's design success criteria for its primary endpoint was 50% treatment success. The sample pool of 109 patients was able to demonstrate with 95% CI a favorable result for this endpoint. Continuing further enrolment would not have changed this result.	1	The assessment report states in a factual way that the inclusions in the Nix-TB study were stopped after the inclusion of 109 patients, to facilitate the enrolment in the ZeNix study, as explained by the MAH in the submission dossier. Timing of analyses was impacted by the early stop of inclusions as formal sample size calculations have not been performed.
33	3	A characterisation as "only interim data" is incorrect. The Nix-TB clinical trial report from 20 October 2019 is the final primary endpoint report.	1	Data are final for the primary endpoint however final data of 24-month follow-up are still awaited. In the CSR itself it is stated " This current CTR presents the results

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				from an interim analysis of all patients enrolled who completed the primary endpoint assessment".
36	27	When the Nix-TB Trial was designed, there were no formally validated TB symptom questionnaires or validated tools that quantified the impact of TB on function or quality of life. The TB Symptom Profile questionnaire was modified from the questionnaire used by Janssen in their Phase 2 trial of bedaquiline. Both the FDA and the CHMP acknowledged the changes in scores on this symptom profile as supporting improvement from the treatment regimen (see https://www.fda.gov/media/127592/download; table 8-10 on page 26; CHMP report forthcoming)	1	This comment is outside of the scope of the factual accuracy check.
36	35	When the Nix-TB trial was designed there was no validated TB disease-specific utility tool for measuring function or quality of life. The EQ5D5L was chosen because it was a European-derived, very well known, and validated tool (https://euroqol.org/eq-5d-instruments/eq-5d-5l-about/). There are still challenges with QoL assessment in clinical trials. However, generic instruments, which include the EQ5D are well known and widely used and have been well validated across cultures [Haraldstad et al. 2019]. We are confused as to what the reviewers would suggest regarding the timing of the data collection; is there a different set of times than at the beginning, 2 months in, and end of treatment, that they would have preferred? Given the above, we are surprised that the reviewers chose to state that the EQ5D5L data was "not suitable" rather than "less useful than ideal". It would have been helpful had the reviewers then reviewed the EQ5D5L data in some fashion, rather than	1	This comment is outside of the scope of the factual accuracy check.

Page	Line	Comment	Character of comment[i]	Reply from author
		disregarding it entirely.		
38	51	It would be helpful to state what criteria the asessors are using to state the characterisation is lacking. As also summarized in the EUnetHTA REA version 0.2, in the Nix-TB trial, 6 patients (5.5%, common) experienced QT prolongation. In the entire Nix-TB trial, no subject was reported to have a treatment emergent QTcF exceeding 480 ms. One subject was reported to have a change from baseline of QTcF exceeding 60 ms.	2	This statement is taken from the SmPC.
41	38	Two of the 109 patients had their treatment extended by 3 months, not just one as the statement currently reads. See Nix-TB Clinical Study Report, dated 29 October 2019, Section 11.0 Efficacy Evaluation on pg. 111. for confirmation.	2	The assessment report was modified accordingly.
41	6/7	It´s necessary to be more precise here. Pretomanid is a nitroimidazooxazine, delamanid is a nitroimidazooxazole. Please compare: https://www.ema.europa.eu/en/medicines/human/orphan-designations/eu307513 and https://www.ema.europa.eu/en/medicines/human/orphan-designations/eu307524 Furthermore, there are other differences between the products. Pretomanid requires only 1 daily tablet and is given in the pre-defined 6 months BPaL regimen (intervention is described in the MAH submission dossier and the EUnetHTA REA version 0.2). It is reserved for adults with highly resistant forms of TB TI/NR MDR-TB and XDR-TB) and does not fit into the WHO groups. Delamanid requires 4 daily tablets over 24 weeks and is indicated for use as part of an appropriate combination regimen for pulmonary multi-drug resistant tuberculosis (MDR-TB) in adult patients when an effective treatment regimen cannot otherwise be composed for reasons of resistance or tolerability. Treatment		See answer above.

Page	Line	Comment	Character of comment[i]	Reply from author
		with an appropriate combination regimen should continue after completion of the 24-week delamanid treatment period according to WHO guidelines. In the WHO guidelines, delamanid is classified in group C. It requires a minimum of three additional antibiotics. And the baseline regimen has normally a duration of 18 to 20 months or even longer. https://www.ema.europa.eu/en/documents/product-information/deltyba-epar-product-information_en.pdf https://www.who.int/tb/publications/2019/consolidated-guidelines-drug-resistant-TB-treatment/en/		
41	24-25	*However, this study pool with 24 comparators was not used by the MAH to conduct indirect comparisons.* However, this study pool with 24 comparators was not used by the MAH to conduct indirect comparisons because an indirect comparison with the most suitable comparator is currently submitted for publication and confidentiality needs to be guaranteed.	3	This comment is outside of the scope of the factual accuracy check.
41	26-27	See comments above. The objections are discussed in detail in the comments to page 20.	2	
43	5-6	There is no standard of care regimen for treatment of XDR-TB. (https://www.who.int/tb/publications/2019/consolidated-guidelines-drug-resistant-TB-treatment/en/) Prior to the approval of pretomanid, no product or regimen existed in either Europe or the US that is approved for treatment of XDR-TB. For this reason, the proposed comparison would be impossible.	1	This comment is outside of the scope of the factual accuracy check.
43	19-22	It may be worth noting that the ongoing ZeNIX trial is taking place in Georgia, Moldova, and Russia in addition to South Africa (https://clinicaltrials.gov/ct2/show/NCT03086486).	2	See answer above.
43	22	This sample size is larger than the entire annual XDR-TB	2	This comment is outside of the

Page	Line	Comment	Character of comment[i]	Reply from author
		treatment cohort in Western Europe. Data from the WHO's global tuberculosis database https://www.who.int/tb/country/data/download/en/ (accessed 22 October 2019 and provided in the MAH submission dossier in section 2.2 Target population, Table 8, pages 24 and 25), indicates that there are only 38 XDR-TB cases in Western Europe..		scope of the factual accuracy check.
43	23-24	In the Nix-TB study, performance between HIV and non-HIV co-infected patients was closely matched. The results were consistent regardless of HIV status [Conradie et al.2020]. This is also visible in the Nix-TB clinical study report from 29 October 2019, Efficacy evaluation, page 156, Figure 11-14 Primary Endpoint Subgroup Analyses. And in the safety evaluation, the proportion of HIV-positive and negative patients were comparable for the different TEAE classifications with only very few exceptions where slightly more patients without co-infection had an advantage regarding tolerability as summarized in the Nix-TB clinical study report from 29 October 2019, Safety evaluation, page 253.	1	This comment is outside of the scope of the factual accuracy check.
52	Table A5, Rationale	It´s necessary to be more precise here. Pretomanid is a nitroimidazooxazine, delamanid is a nitroimidazooxazole. Please compare: https://www.ema.europa.eu/en/medicines/human/orphan-designations/eu307513 and https://www.ema.europa.eu/en/medicines/human/orphan-designations/eu307524 Furthermore, there are other differences between the products. Pretomanid requires only 1 daily tablet and is given in the pre-defined 6 months BPaL regimen (intervention is described in the	1	See answer above.

Page	Line	Comment	Character of comment[i]	Reply from author
		MAH submission dossier and the EUnetHTA REA version 0.2). It is reserved for adults with highly resistant forms of TB TI/NR MDR-TB and XDR-TB) and does not fit into the WHO groups. Delamanid requires 4 daily tablets over 24 weeks and is indicated for use as part of an appropriate combination regimen for pulmonary multi-drug resistant tuberculosis (MDR-TB) in adult patients when an effective treatment regimen cannot otherwise be composed for reasons of resistance or tolerability. Treatment with an appropriate combination regimen should continue after completion of the 24-week delamanid treatment period according to WHO guidelines. In the WHO guidelines, delamanid is classified in group C. It requires a minimum of three additional antibiotics. And the baseline regimen has normally a duration of 18 to 20 months or even longer. https://www.ema.europa.eu/en/documents/product-information/deltyba-epar-product-information_en.pdf https://www.who.int/tb/publications/2019/consolidated-guidelines-drug-resistant-TB-treatment/en/		

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

'linguistic'=3

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