EMA/485589/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Procedure No. EMEA/H/C/005167/II/0013

International non-proprietary name: pretomanid

Invented name: Dovprela

Marketing authorisation holder (MAH): Mylan IRE Healthcare Limited

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

Status of this report and steps taken for the assessment			
Current step	**Description**	**Planned date**	**Actual Date**
☐	Start of procedure	30 Jan 2023	30 Jan 2023
☐	CHMP Rapporteur Assessment Report	06 Mar 2023	06 Mar 2023
☐	CHMP members comments	20 Mar 2023	20 Mar 2023
☐	Updated CHMP Rapporteur Assessment Report	23 Mar 2023	23 Mar 2023
☐	Request for Supplementary Information	30 Mar 2023	30 Mar 2023
☐	Submission of Responses	20 Jun 2023	19 Jun 2023
☐	Re-start of procedure	21 Jun 2023	21 Jun 2023
☐	CHMP Rapporteur Assessment Report	05 Jul 2023	10 Jul 2023
☐	CHMP members comments	10 Jul 2023	13 Jul 2023
☐	Updated CHMP Rapporteur Assessment Report	13 Jul 2023	14 Jul 2023
☐	2nd Request for Supplementary Information	30 Mar 2023	30 Mar 2023
☐	Submission of Responses	14 Aug 2023	14 Aug 2023
☐	Re-start of procedure	16 Aug 2023	16 Aug 2023
☐	CHMP Rapporteur Assessment Report	30 Aug 2023	31 Aug 2023
☐	CHMP members comments	04 Sep 2023	N/A
☐	Updated CHMP Rapporteur Assessment Report	07 Sep 2023	N/A
☒	Opinion	14 Sep 2023	14 Sep 2023

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1. Background information on the procedure

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Mylan IRE Healthcare Limited submitted to the European Medicines Agency on 20 December 2022 an application for a variation.

The following changes were proposed:

Variation requested		**Type**	**Annexes affected**
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I, II and IIIB

Update of sections 4.8 and 5.1 of the SmPC in order to update frequency information of several adverse drug reactions (ADRs) as well as to update clinical efficacy information based on final results from study ZeNix (NC007) listed as a specific obligation (SOB/001) in the Annex II. This is a Phase III Partially Blinded, Randomized Trial Assessing the Safety and Efficacy of Various Doses and Treatment Durations of Linezolid plus Bedaquiline and Pretomanid in Participants with Pulmonary Infection of Either Extensively Drug Resistant Tuberculosis (XDRTB), pre-XDR-TB or Treatment Intolerant or Non-Responsive Multi-Drug Resistant Tuberculosis (MDRTB) - ZeNix study. The Annex II and Package Leaflet are updated accordingly. In addition, the MAH took the opportunity to implement editorial changes in the SmPC and to update the list of local representatives in the Package Leaflet.

The requested variation proposed amendments to the Summary of Product Characteristics, Annex II and Package Leaflet.

2. Overall conclusion and impact on the benefit/risk balance

Dovprela (pretomanid) is indicated in combination with bedaquiline and linezolid, in adults, for the treatment of pulmonary XDRTB, or treatment-intolerant or non-responsive MDRTB. Tuberculosis (TB) is rare in the EU, and this product was designated an orphan medicine on 29-Nov-2007.

The MAH proposed to update sections 4.8 and 5.1 of the SmPC to include frequency information of several ADRs as well as to update clinical efficacy information based on results from ZeNix study listed as a specific obligation (SOB/001) in Annex II of the product information (PI). Moreover, the applicant proposed to change the recommended starting dose for linezolid in the pretomanid-based regimen, from 1200 mg to 600 mg daily. Finally, the applicant provided confirmatory and comprehensive data in the context of the Conditional Marketing Authorisation (CMA) that was issued on 31-Jul-2020.

Prior to the approval of pretomanid in combination with bedaquiline and linezolid (B-Pa-L), the treatment of extensively resistant TB required between 6 and 9 medicinal products used for 9-24 months. Predictably, outcomes were not satisfactory, with about half of treated patients failing to be cured. Dovprela received a CMA based on NixTB study, showing cure rates of approximately 90% with 6 months of treatment. Based on this, B-Pa-L is currently the standard therapy for XDR-TB. A SOB including a randomised clinical trial versus previous therapy was not considered feasible as part of the CMA. The applicant was rather asked to replicate the findings for NixTB, and to further explore the optimal linezolid dosing.

ZeNix trial was conducted to evaluate the safety and efficacy of various doses and treatment durations of linezolid, in combination with bedaquiline and pretomanid for 26 weeks in participants with pulmonary infection of either XDR-TB, pre-XDR-TB, or treatment-intolerant or nonresponsive MDR-TB.

ZeNix trial was designed based on Nix-TB trial, in which the B-Pa-L regimen employing a 1200 mg linezolid dose was highly efficacious but not well tolerated. Recruitment, however, was extended

somewhat compared to Nix-TB study, with regards to resistance status, including also patients classified as pre-XDR. Participants in ZeNix study were treated with bedaquiline (200 mg daily for 8 weeks followed by 100 mg daily for 18 weeks), pretomanid (200 mg daily for 26 weeks), and linezolid (randomised to either 1200 mg or 600 mg daily for 26 weeks or 9 weeks in a double-blinded design).

The efficacy of the B-Pa-L regimen, which was demonstrated in NixTB study, from pivotal to approval, was replicated in ZeNix study. Numerically, the 1200 mg linezolid 26-week group had the highest percentage of participants with a favourable outcome at 26 weeks after the end of treatment (93.2%); the 600 mg linezolid 26-week and 1200 mg linezolid 9-week treatment groups followed with 91.1% and 88.9%, respectively. The 600 mg linezolid 9-week group had the numerically lowest percentage of participants with a favourable outcome (84.1%). Overall, ZeNix study confirmed the benefit of the B-Pa-L regimen observed in Nix-TB study for improving outcomes in highly drug-resistant TB.

The efficacy of a linezolid starting dose of 600 mg was similar to that of 1200 mg. However, the uncertainty around the estimate is larger for 600 mg, with only 45 patients receiving this dose. Moreover, the time to culture conversion was somewhat longer when the starting dose was 600 mg rather than 1200 mg. On the other hand, it is notable that also with 600 mg for only 9 weeks, the rate of favourable outcomes was high and meaningful (n=45).

The B-Pa-L regimen is associated with hepatotoxicity (pretomanid, bedaquiline), QT-prolongation (bedaquiline), myelosuppression and peripheral neuropathy (linezolid). Overall, ZeNix study confirmed the known safety profile of the B-Pa-L regimen, with no new emerging safety concerns. The presented data confirmed the benefits assumed at the time of the Conditional Marketing Authorisation.

The 1200 mg 26-week treatment group had the highest percentage of participants with at least 1 treatment emergent adverse event (TEAE) associated with peripheral neuropathy (17 participants [37.8%]), followed by the 600 mg linezolid 26-week and 1200 mg 9-week groups (11 participants each [24.4% and 23.9%, respectively]).

The 600 mg linezolid 9-week treatment group had the lowest percentage of participants with at least 1 TEAE associated with peripheral neuropathy (6 participants [13.3%]). Remaining symptoms of neuropathy at 26 weeks post therapy was seen in 7% of participants in the 1200 mg 26 weeks arm, and in none of the patients in the other treatment arms.

The 600 mg dose of linezolid was associated with fewer required dose modifications, no optic neuropathy cases, and fewer peripheral neuropathy and myelosuppression events. The 1200 mg linezolid dose showed a less favourable safety profile in the 26-week group than in the 9-week group. However, the 600 mg linezolid 26-week and 9-week groups showed less difference in safety outcomes. Hematologic toxicity was uncommon in both 600 mg linezolid arms.

In summary, the 600 mg 26-weeks regimen is clearly superior safety-wise than the 1200 mg 26-week treatment arm. The lower dose arm is numerically similarly efficacious. However, the uncertainty around this estimate is greater than that for 1200 mg.

The MAH claimed that the 600 mg dose has the most favourable benefit/risk balance. The safety profile is clearly better than 1200 mg. Numerically, it yielded similar cure rates as the 1200 mg dose in ZeNix study. Moreover, cure rates remained high although numerically lower when a regimen with a starting dose of 600 mg was given for only 9 weeks. Altogether, if there would be an edge for the higher dose regarding efficacy, this is likely to be no more than minor. It is agreed that this uncertainty is acceptable, given the clearly better safety profile of the lower starting dose.

Balance of benefits and risks

Based on the review of all available data, the CHMP considers that the benefit-risk balance of Dovprela outweigh remains positive.

Scientific grounds for recommending the granting of a marketing authorisation not subject to specific obligations

The MAH provided within this variation their position that comprehensive data are available about the safety and efficacy of Dovprela and supporting the favourable benefit/risk profile of in all approved populations, as the submission of this variation application contains the data outstanding from the last remaining specific obligation (SOB) as follows:

Description	Due date
In order to further evaluate the safety, efficacy and tolerability of linezolid plus bedaquiline and pretomanid after 26 weeks of treatment in participants with either pulmonary XDR-TB, pre-XDR TB, or treatment intolerant or non-responsive MDR-TB, the marketing authorisation holder should complete and submit results from the ongoing study ZeNix – A Phase 3 Partially-blinded, Randomized Trial Assessing the Safety and Efficacy of Various Doses and Treatment Durations of Linezolid Plus Bedaquiline and Pretomanid in Participants With Pulmonary Infection of Either Extensively Drug-resistant Tuberculosis (XDR-TB), Pre-XDR-TB or Treatment Intolerant or Non-responsive Multi-drug Resistant Tuberculosis (MDR-TB)	Final report by Q4 2022

The MAH therefore requested to take the opportunity of the present type II variation to remove the submission of the ZeNix study from the list of specific obligations and to adopt an opinion recommending the granting of a marketing authorisation in accordance with Article 14(1) of Regulation (EC) No 726/2004 ('marketing authorisation not subject to specific obligations').

The clinical safety profile, as well as the efficacy of this product is considered comprehensively characterised and supportive of a positive benefit-risk balance. In conclusion, having reviewed the data submitted by the MAH including the evidence concerning compliance with specific obligations, the CHMP is of the opinion that the risk-benefit balance of Dovprela remains favourable, that all specific obligations laid down in Annex II have been fulfilled and that comprehensive data supports a favourable benefit-risk balance of the above-mentioned medicinal product.

Therefore, following fulfilment of the specific obligations in accordance with Article 14-a(8) of Regulation (EC) No 726/2004 and considering that comprehensive data have now been provided, the CHMP is of the view that the granting of a standard marketing authorisation not subject to specific obligations and valid for five years can be recommended in accordance with Article 14(1) of Regulation (EC) No 726/2004.

The benefit-risk balance of Dovprela remains positive. The proposed changes to the product information are accepted.

3. Recommendations

Based on the review of the submitted data, this application regarding the following change:

Variation approved		Type	Annexes affected
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I, II and IIIB

Update of sections 4.2, 4.4, 4.8 and 5.1 of the SmPC in order to change posology recommendations of

linezolid, update frequency information of several adverse drug reactions as well as to update clinical efficacy information based on final results from ZeNix (NC007) study listed as a specific obligation (SOB/001) in the Annex II. ZeNix study is a phase III partially blinded, randomised trial assessing the safety and efficacy of various doses and treatment durations of linezolid plus bedaquiline and pretomanid in participants with pulmonary infection of either extensively drug resistant tuberculosis (XDR-TB), pre-XDR-TB or treatment intolerant or non-responsive multi-drug resistant tuberculosis (MDR-TB). The Package Leaflet (PL) is updated accordingly.

As a result of this variation, the SmPC, Annex II and PL are also updated to reflect the completion of the specific obligation and the CHMP recommendation to grant a marketing authorisation no longer subject to specific obligations.

In addition, the MAH took the opportunity to implement editorial changes in the SmPC and PL and to update the list of local representatives in the PL.

☒is recommended for approval.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annexes I, II and IIIB are recommended.

As a result of this variation, it is recommended that the following obligation is deleted from the Annex II to the Opinion:

Description	**Due date**
In order to further evaluate the safety, efficacy and tolerability of linezolid plus bedaquiline and pretomanid after 26 weeks of treatment in participants with either pulmonary XDR-TB, pre-XDR TB, or treatment intolerant or non-responsive MDR-TB, the marketing authorisation holder should complete and submit results from the ongoing study ZeNix – A Phase 3 Partially-blinded, Randomized Trial Assessing the Safety and Efficacy of Various Doses and Treatment Durations of Linezolid Plus Bedaquiline and Pretomanid in Participants With Pulmonary Infection of Either Extensively Drug-resistant Tuberculosis (XDR-TB), Pre-XDR-TB or Treatment Intolerant or Non-responsive Multi-drug Resistant Tuberculosis (MDR-TB)	Final report by Q4 2022

4. EPAR changes

The table in Module 8b of the EPAR will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion 'Dovprela-H-C-005167-II-0013'.

Annex: Rapporteur’s assessment comments on the type II variation

5. Introduction

Dovprela (pretomanid) is indicated in combination with bedaquiline and linezolid, in adults, for the treatment of pulmonary XDRTB, or treatment-intolerant or non-responsive MDRTB. Tuberculosis (TB) is rare in the EU, and this product was designated an orphan medicine on 29-Nov-2007. On 31-Jul-2020, the European Commission granted a CMA for Dovprela, including one SOB (i.e., ZeNix study) to fulfil.

This is a Type II variation aiming to update sections 4.8 and 5.1 of the SmPC of Dovprela in order to update frequency information of several ADRs as well as to update clinical efficacy information based on final results from ZeNix (NC007) study listed as a specific obligation (SOB/001) in the Annex II of the product information.

This study was built upon the Nix-TB trial to investigate the safety and efficacy of two doses of linezolid and at different treatment durations (600 mg and 1200 mg for 9 weeks and 26 weeks) along with bedaquiline and pretomanid for 26 weeks in participants with pulmonary infection of either XDR-TB, pre-XDR-TB, or treatment-intolerant or nonresponsive MDR-TB.

No new non-clinical data was provided.

The product information is updated to reflect these new data, including a change in the starting dose of linezolid from 1200 mg/day to 600 mg/day.

6. Clinical Efficacy aspects

6.1. Analysis of data submitted and results

ZeNix study was based on the learnings from the pivotal Nix-TB study presently reflected in the SmPC. It was designed to optimise linezolid dosing with the aim of potentially limiting toxicity while preserving efficacy.

Methods

In this trial, pretomanid was evaluated in phase III partially-blinded, randomised trial assessing the safety and efficacy of various doses and treatment durations of linezolid plus bedaquiline and pretomanid (B-Pa-L) in participants with pulmonary infection of either extensively drug-resistant tuberculosis (XDR-TB), pre-XDR-TB or treatment intolerant or non-responsive multi-drug resistant tuberculosis (MDR-TB).

XDR-TB is defined as tuberculosis with resistance to both rifampicin and isoniazid and to at least one fluoroquinolone and a second-line injectable agent (amikacin, capreomycin or kanamycin). Pre-XDR is defined as tuberculosis resistant to rifampicin and isoniazid together with resistance to either a fluoroquinolone or a second-line injectable agent. MDR-TB is defined as tuberculosis resistant to rifampicin and isoniazid.

This 4-arm study randomised subjects to varying linezolid doses (1200 or 600 mg once daily and varying lengths of linezolid treatment (9 or 26 weeks).

Table 1. Treatment groups

1	Linezolid 1200 mg once daily (QD) for 26 weeks, plus Bedaquiline 200 mg QD for 8 weeks then 100 mg QD for 18 weeks, plus Pretomanid 200 mg QD for 26 weeks
2	Linezolid 1200 mg QD for 9 weeks followed by linezolid placebo for 17 weeks, plus Bedaquiline 200 mg QD for 8 weeks then 100 mg QD for 18 weeks, plus Pretomanid 200 mg QD for 26 weeks
3	Linezolid 600 mg QD for 26 weeks, plus Bedaquiline 200 mg QD for 8 weeks then 100 mg QD for 18 weeks, plus Pretomanid 200 mg QD for 26 weeks
4	Linezolid 600 mg QD for 9 weeks followed by linezolid placebo for 17 weeks, plus Bedaquiline 200 mg QD for 8 weeks then 100 mg QD for 18 weeks, plus Pretomanid 200 mg QD for 26 weeks

The trial was performed at multiple centres located in South Africa, Eastern Europe, and Russia.

Eligible individuals were males and females aged 14 years or older (18 years for sites in Moldova and Russia) with XDR-TB, pre-XDR-TB, or treatment-intolerant or nonresponsive MDR-TB. Key exclusion criteria included any unstable condition likely to impact survival over the study period, including extrapulmonary TB requiring extended treatment, as well as likely resistance to the test drugs. There were also exclusion criteria relating to the risk of QT-prolongation and hepatotoxicity.

The primary efficacy endpoint was the incidence of treatment failure (unfavourable outcome) defined as bacteriologic failure or relapse or clinical failure at 6 months (26 weeks) after the end of therapy. Participants were classified as having a favourable, unfavourable, or un-assessable status at 6 months (26 weeks) after the end of treatment.

No formal statistical pairwise comparisons between the arms were performed. The proportions of assessable participants with a favourable and unfavourable outcome, with 95% and 97.5% confidence intervals (CIs), were presented. For success, the lower bound of the 95% CI (or 97.5% if the Bonferroni adjustment was used) for a favourable outcome was to be above 50%. A 50% treatment success rate was chosen as the target, because it is above the entire range of the historical control for cure of XDR-TB.

The analysis of the primary endpoint using the modified intent-to-treat (MITT) population was considered primary. This excluded subjects on the following grounds:

1. Patients who, having completed treatment, are lost to follow-up or withdrawn from the study, their last status being culture negative and their last positive culture result ("isolated positive culture") followed by at least two negative culture results at different visits (at least 7 days apart, without an intervening positive culture)

2. Women who become pregnant during treatment and stop their allocated treatment.

3. Patients who die during treatment from violent or accidental cause (e.g., road traffic accident). N.B.: This does not include death from suicide, which will be considered an unfavourable outcome.

4. Patients who die during follow-up (after the end of treatment) with no evidence of failure or relapse of their TB, their last status being culture negative and their last positive culture result ("isolated positive culture") followed by at least two negative culture results at different visits (at least 7 days apart), and who have not already been classified as unfavourable.

5. Patients who, after being classified as having culture negative status, are re-infected with a new strain different from that with which they were originally infected. Reinfection will be defined specifically as a patients infected with a strain that is genetically different from the initial strain.

6. Patients who are able to produce sputum at their primary endpoint visit, whose sputum samples are all contaminated or missing, who cannot be brought back for repeat cultures, provided they have not already been classified as unfavourable and provided their last positive culture was followed by at least two negative cultures. N.B.: This does not apply to patients who are unable to produce sputum at 6 months after end of treatment, or to patients who are able to be brought back subsequently and produce negative cultures.

Patients in categories 1-6 above who had already been classified as having unfavourable outcome will not be excluded.

The primary analysis was for the linezolid 1200 mg taken for 26 weeks arm (L1200 26 weeks), with the L1200 9 weeks and L600 26 weeks analysis only being tested if L1200 26 weeks was a success.

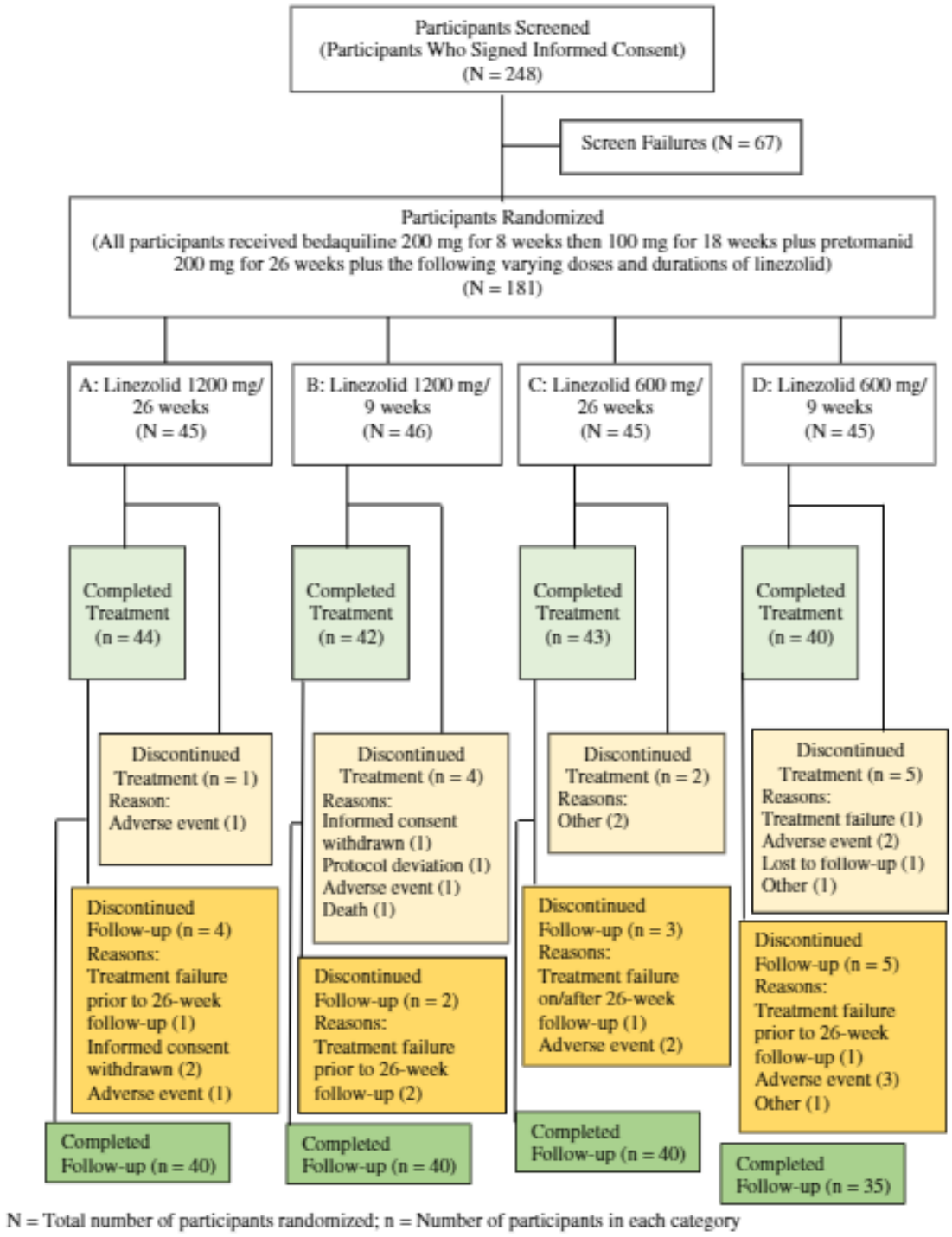
A Bonferroni adjustment was made to compare the L1200 9 weeks and L600 26 weeks arms simultaneously, using $p<0.025$, i.e., used the 97.5% CI. Similarly, the L600 9 weeks arm was only tested if the L600 26 weeks arm was successful.

Secondary endpoints included the proportion of participants classified as favourable at 18 months (78 weeks) after the end of treatment (intent-to-treat (ITT), MITT, and per protocol (PP) populations).

Study subject disposition

A total of 181 subjects were randomised.

Figure 1. Disposition of participants



N = Total number of participants randomized; n = Number of participants in each category

The ITT population consisted of 181 participants randomised to trial treatment.

The MITT population was a subset of the ITT population, consisting of 178 participants who did not have any late screening failures or any predefined withdrawals/exclusions during the trial. The reasons for exclusion from the MITT population (i.e., categorised as un-assessable) were lost to follow-up during the follow-up period and culture negative when last seen (1 participant in the 1200 mg linezolid 26-week group), withdrawal during the follow-up period and culture negative when last seen (1 participant in the 600 mg linezolid 9-week group), and death (violent or accidental, not including suicide) during the treatment period (1 participant in the 1200 mg linezolid 9-week group).

Baseline disease and demographic characteristics

Males represented 67.4% of the subjects included in the trial and the median age of all subjects was 36.0 years. 63.5% of subjects were white. The treatment groups were comparable with respect to demographic characteristics. Seventy-one participants (39.2%) were from Russia, 66 (36.5%) were from South Africa, 34 (18.8%) were from Georgia, and 10 (5.5%) were from Moldova. The proportion of participants from Georgia, Moldova, and Russia was numerically larger in the 1200 mg linezolid 26-week group than in the other 3 treatment groups: 75.6% versus 60.9%, 53.3%, and 64.4% for the 1200 mg linezolid 9-week, 600 mg linezolid 26-week, and 600 mg linezolid 9-week groups, respectively.

The median body mass index (BMI) of all participants was 20.8 kg/m2 (range 17.1 to 31.0 kg/m2), which was similar across treatment groups. At Screening, 36 participants (19.9%) were HIV positive (a stratification factor); 9 HIV-positive participants were randomised to each treatment group.

Table 2. Disease history (All randomised participants)

	Linezolid 1200 mg 26 weeks (N = 45)	Linezolid 1200 mg 9 weeks (N = 46)	Linezolid 600 mg 26 weeks (N = 45)	Linezolid 600 mg 9 weeks (N = 45)	Total (N = 181)
Current TB – n (%)					
MDR-TB (NR)	2 (4.4%)	5 (10.9%)	2 (4.4%)	3 (6.7%)	12 (6.6%)
MDR-TB (TI)	3 (6.7%)	1 (2.2%)	2 (4.4%)	3 (6.7%)	9 (5.0%)
Pre-XDR-TB	19 (42.2%)	22 (47.8%)	22 (48.9%)	22 (48.9%)	85 (47.0%)
XDR-TB	21 (46.7%)	18 (39.1%)	19 (42.2%)	17 (37.8%)	75 (41.4%)
History of TB^ – n (%)					
DS-TB	16 (35.6%)	13 (28.3%)	18 (40.0%)	7 (15.6%)	54 (29.8%)
Mono-resistant TB	0	0	1 (2.2%)	1 (2.2%)	2 (1.1%)
MDR-TB	20 (44.4%)	23 (50.0%)	21 (46.7%)	25 (55.6%)	89 (49.2%)
Pre-XDR-TB	6 (13.3%)	5 (10.9%)	6 (13.3%)	7 (15.6%)	24 (13.3%)
XDR-TB	25 (55.6%)	28 (60.9%)	28 (62.2%)	25 (55.6%)	106 (58.6%)
Screening smear microscopy for AFB* - n (%)					
No AFB seen	23 (51.1%)	24 (52.2%)	23 (51.1%)	20 (44.4%)	90 (49.7%)
Scanty positive	11 (24.4%)	4 (8.7%)	8 (17.8%)	5 (11.1%)	28 (15.5%)
1+	4 (8.9%)	7 (15.2%)	4 (8.9%)	6 (13.3%)	21 (11.6%)
2+	6 (13.3%)	6 (13.0%)	3 (6.7%)	4 (8.9%)	19 (10.5%)
3+	1 (2.2%)	5 (10.9%)	7 (15.6%)	10 (22.2%)	23 (12.7%)
Time to positive at baseline (days)**					
n	30	32	33	36	131
Mean (SD)	14.3 (9.8)	11.3 (6.6)	14.0 (9.7)	12.5 (8.6)	13.0 (8.7)
Median	11.1	9.2	9.9	9.3	10.1
IQR	6.9, 16.8	6.7, 13.7	5.7, 20.3	5.8, 17.7	6.5, 16.8
Min, Max	4.0, 40.5	3.8, 35.2	3.4, 40.7	3.9, 40.3	3.4, 40.7

AFB = acid fast bacilli; DS = drug-sensitive; IQR = interquartile range; Max = maximum; Min = minimum; n = number of participants in each category; N = number of participants randomized; NR = nonresponsive; MDR = multidrug-resistant; MGIT = mycobacteria growth indicator tube; SD = standard deviation; TB = tuberculosis; TI = treatment-intolerant; XDR = extensively drug-resistant.

^One participant could select more than 1 type of TB for history of TB.

*Screening coached spot sputum result.

**Only for participants who were positive at baseline in liquid culture MGIT.

Table 3. Chest X-ray at screening (All randomised participants)

	Linezolid 1200mg 26 weeks (N = 45) n (%)	Linezolid 1200mg 9 weeks (N = 46) n (%)	Linezolid 600mg 26 weeks (N = 45) n (%)	Linezolid 600mg 9 weeks (N = 45) n (%)	Total (N = 181) n (%)
Chest X-Ray					
Normal	2 (4.4%)	2 (4.4%)	1 (2.2%)	2 (4.4%)	7 (3.9%)
Abnormal	43 (95.6%)	44 (95.6%)	44 (97.8%)	43 (95.6%)	174 (96.1%)
Cavities					
None	18 (40.0%)	21 (45.6%)	12 (26.7%)	18 (40.0%)	69 (38.1%)
Unilateral	22 (48.9%)	21 (45.6%)	20 (44.4%)	21 (46.7%)	84 (46.4%)
Bilateral	5 (11.1%)	4 (8.7%)	13 (28.9%)	6 (13.3%)	28 (15.5%)

N = total number of participants randomized; n = number of participants in each category.

Results

The primary efficacy endpoint was the incidence of treatment failure (unfavourable outcome) defined as bacteriologic failure or relapse or clinical failure at 6 months (26 weeks) after the end of therapy. Participants were classified as having a favourable, unfavourable, or un-assessable status at 6 months (26 weeks) after the end of treatment.

Numerically, the 1200 mg linezolid 26-week group had the highest percentage of participants with a favourable outcome at 26 weeks after the end of treatment (93.2%); the 600 mg linezolid 26-week and 1200 mg linezolid 9-week treatment groups followed with 91.1% and 88.9%, respectively.

The 600 mg linezolid 9-week group had the numerically lowest percentage of participants with a favourable outcome (84.1%). The incidences of unfavourable outcomes by both dose and duration was 6.8% for the 1200 mg linezolid 26-week group. The outcome of primary efficacy analysis is presented in the table below.

Table 4. Outcome of primary efficacy analysis

	Linezolid 1 200 mg 26 weeks (N = 45) n (%)	Linezolid 1 200 mg 9 weeks (N = 46) n (%)	Linezolid 600 mg 26 weeks (N = 45) n (%)	Linezolid 600 mg 9 weeks (N = 45) n (%)	Total (N = 181) n (%)
Unassessable	1	1	0	1	3
Total assessable	44	45	45	44	178
Favourable	**41 (93.2%)**	**40 (88.9%)**	**41 (91.1%)**	**37 (84.1%)**	**159 (89.3%)**
Unfavourable	**3 (6.8%)**	**5 (11.1%)**	**4 (8.9%)**	**7 (15.9%)**	**19 (10.7%)**
95% CI for Favourable	81.3% to 98.6%	75.9% to 96.3%	78.8% to 97.5%	69.9% to 93.4%	83.8% to 93.4%
97.5 % CI for Favourable		74.0% to 96.9%	76.9% to 98.0%		

CI = confidence interval; N = total number of participants in the relevant analysis population; n = number of participants in each category. Favourable and unfavourable status as defined in the statistical analysis plan for the modified intent-to-treat population.

Efficacy in the ITT population was, as anticipated given the minor differences from the modified ITT (mITT), roughly similar:

Table 5. Primary efficacy analysis (ITT)

	Linezolid 1200mg 26 weeks (N=45) n (%)	Linezolid 1200mg 9 weeks (N=46) n (%)	Linezolid 600mg 26 weeks (N=45) n (%)	Linezolid 600mg 9 weeks (N=45) n (%)	Total (N=181) n (%)
Unassessable	0	0	0	0	0
Total assessable	45	46	45	45	181
Favourable	**41 (91.1%)**	**40 (87.0%)**	**41 (91.1%)**	**37 (82.2%)**	**159 (87.8%)**
Unfavourable	**4 (8.9%)**	**6 (13.0%)**	**4 (8.9%)**	**8 (17.8%)**	**22 (12.2%)**
95% CI for Favourable	78.8% to 97.5%	73.7% to 95.1%	78.8% to 97.5%	67.9% to 92.0%	82.2% to 92.2%
97.5% CI for Favourable	-	71.8% to 95.8%	76.9% to 98.0%	-	

ITT=Intent-to-treat. Favourable and unfavourable status as defined in the statistical analysis plan for MITT. CI=confidence interval. N=Total number of participants in the relevant analysis population; n=Number of participants in each category.

Results across key subgroups were consistent for the linezolid 26-week regimens (mITT):

Table 6. Linezolid 1200 mg for 26 weeks

Linezolid 1200mg for 26 weeks		n (%)	favourable (95% CI)	proportion favourable (95% CI)
Age	age < 36 years	19 (43%)		90% (67, 99)
	age >=36 years	25 (57%)		96% (80, 100)
Sex	Female	15 (34%)		87% (60, 95)
	Male	29 (66%)		97% (82, 100)
Race	Black	11 (25%)		100% (72, 100)
	White/Other	33 (75%)		91% (76, 98)
Smoking	current	14 (32%)		100% (77, 100)
	former	10 (23%)		100% (69, 100)
	never	20 (46%)		85% (62, 97)
Alcohol	current	8 (18%)		100% (63, 100)
	former	16 (36%)		100% (79, 100)
	never	20 (46%)		85% (62, 97)
HIV	negative	35 (80%)		91% (77, 98)
	positive	9 (20%)		100% (66, 100)
Cavitation	no cavities	18 (41%)		100% (82, 100)
	with cavities	26 (59%)		88% (70, 98)
Baseline TTP	baseline TTP < median	10 (33%)		90% (56, 100)
	baseline TTP ≥ median	20 (67%)		90% (68, 99)
Geographical location	South Africa	11 (25%)		100% (72, 100)
	Georgia, Moldova or Russia	33 (75%)		91% (76, 98)

Table 7. Linezolid 1200 mg for 9 weeks

Linezolid 1200mg for 9 weeks		n (%)	favourable (95% CI)	proportion favourable (95% CI)
Age	age < 36 years	24 (53%)		100% (86, 100)
	age >=36 years	21 (47%)		76% (53, 92)
Sex	Female	16 (36%)		94% (70, 100)
	Male	29 (64%)		86% (68, 96)
Race	Black	18 (40%)		94% (73, 100)
	White/Other	27 (60%)		85% (66, 96)
Smoking	current	21 (47%)		81% (58, 95)
	former	9 (20%)		100% (66, 100)
	never	15 (33%)		93% (68, 100)
Alcohol	current	8 (18%)		62% (24, 92)
	former	25 (56%)		96% (80, 100)
	never	12 (27%)		92% (62, 100)
HIV	negative	37 (82%)		89% (75, 97)
	positive	8 (18%)		88% (47, 100)
Cavitation	no cavities	20 (44%)		100% (83, 100)
	with cavities	25 (56%)		80% (59, 93)
Baseline TTP	baseline TTP < median	17 (53%)		76% (50, 93)
	baseline TTP ≥ median	15 (47%)		93% (68, 100)
Geographical location	South Africa	18 (40%)		94% (73, 100)
	Georgia, Moldova or Russia	27 (60%)		85% (66, 96)

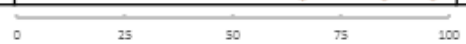


Table 8. Linezolid 600 mg for 26 weeks

Linezolid 600mg for 26 weeks		n (%)	favourable (95% CI)	proportion favourable (95% CI)
Age	age < 36 years	18 (40%)		94% (73, 100)
	age >=36 years	27 (60%)		89% (71, 98)
Sex	Female	14 (31.1%)		93% (66, 100)
	Male	31 (68.9%)		90% (74, 98)
Race	Black	21 (46.7%)		90% (70, 99)
	White/Other	24 (53.3%)		92% (73, 99)
Smoking	current	17 (37.8%)		94% (71, 100)
	former	12 (26.7%)		83% (52, 98)
	never	16 (35.6%)		94% (70, 100)
Alcohol	current	8 (17.8%)		88% (47, 100)
	former	19 (42.2%)		84% (60, 97)
	never	18 (40%)		100% (82, 100)
HIV	negative	36 (80%)		92% (78, 98)
	positive	9 (20%)		89% (52, 100)
Cavitation	no cavities	12 (26.7%)		92% (62, 100)
	with cavities	33 (73.3%)		91% (76, 98)
Baseline TTP	baseline TTP < median	18 (54.5%)		83% (59, 96)
	baseline TTP ≥ median	15 (45.4%)		100% (78, 100)
Geographical location	South Africa	21 (46.7%)		90% (70, 99)
	Georgia, Moldova or Russia	24 (53.3%)		92% (73, 99)

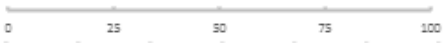
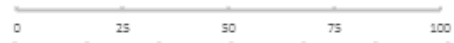


Table 9. Linezolid 600 mg for 9 weeks

Linezolid 600mg for 9 weeks		n (%)	favourable (95% CI)	proportion favourable (95% CI)
Age	age < 36 years	20 (46%)		85% (62, 97)
	age >=36 years	24 (55%)		83% (63, 95)
Sex	Female	14 (32%)		86% (57, 98)
	Male	30 (68%)		83% (65, 94)
Race	Black	16 (36%)		81% (54, 96)
	White/Other	28 (64%)		86% (67, 96)
Smoking	current	12 (27%)		75% (43, 94)
	former	15 (34%)		93% (68, 100)
	never	17 (39%)		83% (57, 96)
Alcohol	current	10 (23%)		80% (44, 98)
	former	23 (52%)		83% (61, 95)
	never	11 (25%)		91% (59, 100)
HIV	negative	35 (80%)		83% (66, 93)
	positive	9 (20%)		89% (52, 100)
Cavitation	no cavities	17 (39%)		100% (80, 100)
	with cavities	27 (61%)		74% (54, 89)
Baseline TTP	baseline TTP < median	19 (54%)		74% (49, 91)
	baseline TTP ≥ median	16 (46%)		88% (62, 98)
Geographical location	South Africa	16 (37%)		81% (54, 96)
	Georgia, Moldova or Russia	28 (64%)		86% (67, 96)



Among subjects with reduced susceptibility to bedaquiline at baseline, outcomes were as follows:

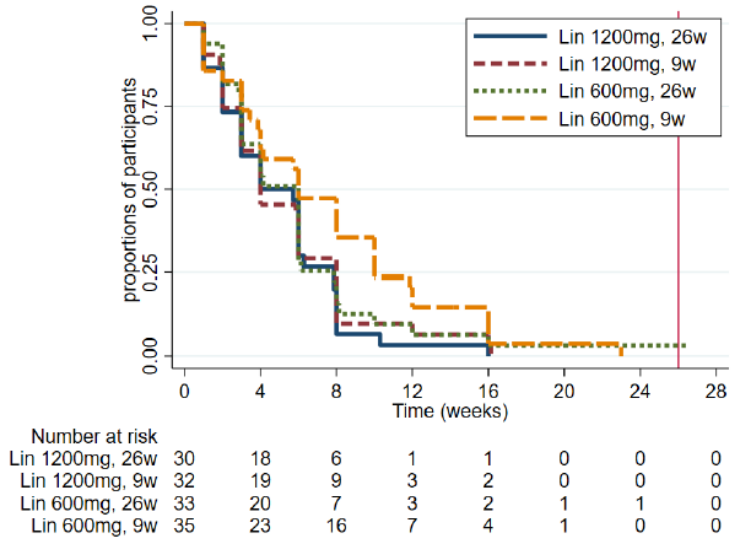
Table 10. Outcome among subjects with reduced susceptibility to bedaquiline at baseline

Participant ID	**Treatment allocation (Linezolid dose/duration)**	Bedaquiline MIC (µg/mL)	Primary endpoint outcome
1001022	1200mg/ 9weeks	4	Unfavourable: Confirmed relapse at 26 weeks follow-up – confirmed by whole genome sequencing and culture results
1004021	1200mg/ 9weeks	4	Favourable
1004036	1200mg/ 9weeks	4	Favourable
1105005	1200mg/ 26weeks	2	Favourable
1105019	1200mg/ 26weeks	2	Favourable
1206003	1200mg/ 26weeks	4	Favourable
1207003	600mg/ 9weeks	2	Favourable
1209001	1200mg/ 9weeks	2	Unfavourable: Confirmed relapse – confirmed by whole genome sequencing and culture results
1209008	1200mg/ 9weeks	4	Unfavourable: Withdrawn (AE) – suicide attempt

MIC = Minimum Inhibitory Concentration

Of the 130 participants who were culture positive at baseline, 125 (96.2%) were culture converted. All participants in the 1200 mg linezolid 26-week treatment group who were positive at baseline were culture converted. Of the 5 participants who did not convert, 1 participant was in the 1200 mg linezolid 9-week group, 2 participants were in the 600 mg linezolid 26-week group, and 2 participants were in the 600 mg linezolid 9-week group. The median time to culture negative status was 4 weeks (interquartile range [IQR] = 2 to 8 weeks) for both, 1200 mg linezolid treatment groups regardless of total duration of linezolid. The 600 mg linezolid 26-week group had a longer median time to culture conversion of 6 weeks (IQR = 3 to 8 weeks). The 600 mg linezolid 9-week group had a median time to culture conversion of 6 weeks. Time to culture conversion in the different treatment groups are presented in the figure below.

Figure 2. Time to culture-negative status (Weeks) for the MITT population



Lin = linezolid; MITT = modified intent-to-treat; w = weeks
Red vertical line indicates week 26.

Favourable outcomes were maintained at follow-up week 78:

Table 11. Secondary endpoint follow-up week 78 efficacy analysis (MITT population)

	Linezolid 1200 mg 26 weeks (N = 45) n (%)	Linezolid 1200 mg 9 weeks (N = 46) n (%)	Linezolid 600 mg 26 weeks (N = 45) n (%)	Linezolid 600 mg 9 weeks (N = 45) n (%)	Total (N = 181) n (%)
Unassessable	2	2	0	1	5
Total assessable	43	44	45	44	176
Favorable	**40 (93.0%)**	**39 (88.6%)**	**40 (88.9%)**	**35 (79.6%)**	**154 (87.5%)**
Unfavorable	**3 (7.0%)**	**5 (11.4%)**	**5 (11.1%)**	**9 (20.4%)**	**22 (12.5%)**
95% CI for Favorable	80.9% to 98.5%	75.4% to 96.2%	75.9% to 96.3%	64.7% to 90.2%	81.7% to 92.0%
97.5% CI for Favorable	-	73.5% to 96.8%	74.0% to 96.9%	-	

CI = confidence interval; MITT = modified intent-to-treat; N = total number of participants in the relevant analysis population; n = number of participants in each category.
Favorable and unfavorable status as defined in the statistical analysis plan for MITT.

6.2. Discussion on efficacy

In ZeNix study, the participants with pulmonary infection of either XDR-TB, pre-XDR-TB, or treatment-intolerant or non-responsive MDR-TB, treatment with various doses and durations of linezolid plus bedaquiline and pretomanid for 26 weeks resulted in all treatment groups meeting the pre-specified

threshold for success of the treatment regimen (the lower bound of the 95% CI, or 97.5% CI as appropriate, for a favourable response being greater than 50%), as measured by the percentage of participants with a favourable outcome at 26 weeks after the end of treatment.

Although the statistical power is limited, the 1200 mg linezolid 26-week group had the numerically highest percentage of participants with a favourable outcome at 26 weeks after the end of treatment (93.2%); the 600 mg linezolid 26-week and 1200 mg linezolid 9-week treatment groups followed with 91.1% and 88.9%, respectively (MITT population). The 600 mg linezolid 9-week group had the lowest percentage of participants with a favourable outcome (84.1%).

The positive outcomes at 26 weeks after the end of treatment were largely maintained at 78 weeks after the end of treatment.

Overall, this study confirms the efficacy of the 26-week B-Pa-L regimen, assumed at the time of the CMA. While the efficacy of a 600 mg linezolid starting dose appears similar to the labelled 1200 mg dose, the evidence for the former dose is limited to 45 patients treated for 26 weeks, supported by another 45 patients treated for 9 weeks. Moreover, time to sputum conversion is somewhat longer with the lower starting dose. It is notable, however, that also for 600 mg/9 weeks, the proportion of patients with a favourable outcome was high and clinically meaningful. Overall, if there is a true advantage of a 1200 mg starting dose, it is anticipated to be minor.

The 9-week treatment duration for linezolid may be associated with a higher failure rate, particularly with the lower starting dose.

7. Clinical Safety aspects

7.1. Analysis of data submitted and results

Extent of exposure

The total safety population of ZeNix comprised 181 patients. Bedaquiline and pretomanid exposure was as follows:

Table 12. Bedaquiline and pretomanid exposure (safety population)

	Linezolid 1200 mg 26 weeks (N = 45)	Linezolid 1200 mg 9 weeks (N = 46)	Linezolid 600 mg 26 weeks (N = 45)	Linezolid 600 mg 9 weeks (N = 45)	Total (N = 181)
Duration bedaquiline including pause (weeks)[5] n (%)**					
<26 weeks (less than allocated)	2 (4.4%)	4 (8.7%)	1 (2.2%)	4 (8.9%)	11 (6.1%)
26 weeks (as expected)	38 (84.4%)	37 (80.4%)	40 (88.9%)	34 (75.6%)	149 (82.3%)
26 to 38 weeks (missed dose/pause extension)	5 (11.1%)	5 (10.9%)**	4 (8.9%)	6 (13.3%)	20 (11.0%)
39 weeks (official treatment extension)	0	0	0	1 (2.2%)	1 (0.6%)
Duration pretomanid including pause (weeks) n (%)					
<26 weeks (less than allocated)	2 (4.4%)	4 (8.7%)	1 (2.2%)	4 (8.9%)	11 (6.1%)
26 weeks (as expected)	38 (84.4%)	37 (80.4%)	40 (88.9%)	34 (75.6%)	149 (82.3%)
26 to 38 weeks (missed dose/pause extension)	5 (11.1%)	5 (10.9%)**	4 (8.9%)	6 (13.3%)	20 (11.0%)
39 weeks (official treatment extension)	0	0	0	1 (2.2%)	1 (0.6%)

N = Total number of participants randomized; n = Number of participants in each category.

Table below summarizes the linezolid exposure for the safety population:

Table 13. Linezolid exposure (safety population)

	Linezolid 1200mg 26 weeks (N = 45)	Linezolid 1200mg 9 weeks (N = 46)	Linezolid 600mg 26 weeks (N = 45)	Linezolid 600mg 9 weeks (N = 45)	Total (N = 181)
Actual duration (days) excluding pause					
Mean (SD)	175.8 (16.4)	60.5 (7.6)	178.4 (23.1)	60.5 (8.7)	118.5 (60.4)
Median	182.0	63.0	182.0	63.0	63.0
IQR	181.0, 182.0	60.0, 63.0	182.0, 182.0	63.0, 63.0	63.0, 182.0
Min, Max	106.0, 183.0	14.0, 64.0	28.0, 187.0	9.0, 63.0	9.0, 187.0
Actual duration (weeks) excluding pause					
Mean (SD)	25.1 (2.3)	8.6 (1.1)	25.5 (3.3)	8.6 (1.2)	16.9 (8.6)
Median	26.0	9.0	26.0	9.0	9.0
IQR	25.9, 26.0	8.6, 9.0	26.0, 26.0	9.0, 9.0	9.0, 26.0
Min, Max	15.1, 26.1	2.0, 9.1	4.0, 26.7	1.3, 9.0	1.3, 26.7
Actual duration (weeks) including pause n (%)					
<9 or <26 weeks (less than allocated)	5 (11.1%)	3 (6.5%)	1 (2.2%)	6 (13.3%)	15 (8.3%)
9 or 26 weeks (as expected)	37 (82.2%)	36 (78.3%)	41 (91.1%)	37 (82.2%)**	151 (83.4%)
9 or 26 weeks to 38 weeks (missed dose/pause extension)	3 (6.7%)	7 (15.2%)	3 (6.7%)	2 (4.4%)	15 (8.3%)
39 weeks (official treatment extension)	0	0	0	0	0
Total exposure to linezolid (mg)					
Mean (SD)	193846.7 (34930.1)	70017.4 (10964.8)	104913.3 (16275.7)	35766.7 (5574.8)	100964.1 (62199.4)
Median	217200.0	75600.0	109200.0	37800.0	75600.0
IQR	153600.0, 218400.0	69600.0, 75600.0	109200.0, 109200.0	37800.0, 37800.0	37800.0, 112200.0
Min, Max	112800.0, 219600.0	16800.0, 76800.0	16800.0, 112200.0	5400.0, 37800.0	5400.0, 219600.0
Average daily exposure to linezolid (mg) (including pauses)					
Mean (SD)	1084.8 (177.1)	1106.5 (165.7)	585.5 (50.3)	583.3 (47.1)	841.5 (285.4)
Median	1200.0	1200.0	600.0	600.0	603.0
IQR	1015.0, 1200.0	1104.0, 1200.0	600.0, 600.0	600.0, 600.0	600.0, 1200.0
Min, Max	619.0, 1230.0	576.0, 1219.0	323.0, 603.0	400.0, 600.0	323.0, 1230.0

IQR = interquartile range; max = maximum; min = minimum; N = total number of participants randomized; n = number of participants in each category; SD = standard deviation

* Participants 1105001 and 1105002 had a gap in linezolid due to drug supply issues and were not considered to have had a formal linezolid pause in those days.

** Participant 1207003 had an official treatment extension to 39 weeks, received 9 weeks of linezolid, and is included in the category "9 or 26 weeks (as expected)"

Regarding linezolid dose interruption, the percentage of participants with at least 1 linezolid pause was greater (by a factor of >2) with increased linezolid dose: 22.2% and 26.1% for the 1200 mg linezolid 26-week and 9-week groups, respectively, versus 6.7% and 8.9% for the 600 mg linezolid 26-week and 9-week groups, respectively. The mean pause duration was also nominally longer in the two 1200 mg groups (15.1 days and 14.1 days for the 26-week and 9-week groups, respectively) than in the 600 mg dose groups (10.7 and 12.0 days for the 26-week and 9-week groups, respectively).

Discontinuations of linezolid (excluding those due to withdrawal of the participant from the trial or death) were only reported in the 26-week treatment groups: 4 participants (8.9%) and 1 participant (2.2%) in the 1200 mg and 600 mg linezolid 26-week groups, respectively.

Adverse effects

Of the 181 participants in ZeNix safety population, 156 participants (86.2%) experienced at least 1 TEAE. Percentages were similar across treatment groups. Any study drug related TEAE was reported from 116 participants (64,1%).

The 1200 mg linezolid 26-week group had the highest percentage of participants who experienced a study drug related TEAE (75.6%). The percentages of drug-related TEAEs in the 1200 mg linezolid 9-week, 600 mg linezolid 26-week, and 600mg linezolid 9-week treatment groups were 63.0%, 60.0%, and 57.8%, respectively.

The 1200 mg linezolid 26-week group had the numerically greatest number of participants with at least 1 TEAE leading to linezolid reduction (9 participants [20.0%]), followed by the 1200 mg linezolid 9-week treatment group (6 participants [13.0%]), the 600 mg linezolid 9-week group (4 participants [8.9%]), and the 600 mg linezolid 26-week group (3 participants [6.7%]) (Table below).

Table 14. Overview of treatment-emergent Adverse Events in study ZeNix (safety population)

TEAE Category	Linezolid 1200mg 26 weeks (N = 45)	Linezolid 1200mg 9 weeks (N = 46)	Linezolid 600mg 26 weeks (N = 45)	Linezolid 600mg 9 weeks (N = 45)	Total (N = 181) n (%)
	n (%)	n (%)	n (%)	n (%)	
Any TEAE	40 (88.9%)	41 (89.1%)	39 (86.7%)	36 (80.0%)	156 (86.2%)
Any grade ≥ 3 TEAE	14 (31.1%)	11 (23.9%)	9 (20.0%)	11 (24.4%)	45 (24.9%)
Any study drug-related TEAE	34 (75.6%)	29 (63.0%)	27 (60.0%)	26 (57.8%)	116 (64.1%)
Any TEAE related to linezolid	29 (64.4%)	27 (58.7%)	24 (53.3%)	22 (48.9%)	102 (56.4%)
Any TEAE related to bedaquiline	26 (57.8%)	25 (54.4%)	22 (48.9%)	24 (53.3%)	97 (53.6%)
Any TEAE related to pretomanid	21 (46.7%)	24 (52.2%)	22 (48.9%)	21 (46.7%)	88 (48.6%)
Any serious TEAE	3 (6.7%)	4 (8.7%)	1 (2.2%)	3 (6.7%)	11 (6.1%)
Any TEAE leading to discontinuation of linezolid	4 (8.9%)	2 (4.4%)	2 (4.4%)	3 (6.7%)	11 (6.1%)
Any TEAE leading to reduction of linezolid	9 (20.0%)	6 (13.0%)	3 (6.7%)	4 (8.9%)	22 (12.2%)
Any TEAE leading to interruption of linezolid	4 (8.9%)	4 (8.7%)	0	0	8 (4.4%)
Any TEAE leading to interruption of full regimen*	5 (11.1%)	5 (10.9%)	3 (6.7%)	6 (13.3%)	19 (10.5%)
Any TEAE leading to bedaquiline/pretomanid discontinuation	1 (2.2%)	2 (4.4%)	1 (2.2%)	3 (6.7%)	7 (3.9%)
Any TEAE leading to study discontinuation	1 (2.2%)	2 (4.4%)	1 (2.2%)	3 (6.7%)	7 (3.9%)
Any TEAE leading to death	0	1 (2.2%)	0	0	1 (0.6%)
Any liver-related TEAE	12 (26.7%)	12 (26.1%)	11 (24.4%)	12 (26.7%)	47 (26.0%)
Any drug related and liver-related TEAE	11 (24.4%)	10 (21.7%)	9 (20.0%)	9 (20.0%)	39 (21.6%)
Any serious liver-related TEAE	0	1 (2.2%)	1 (2.2%)	1 (2.2%)	3 (1.7%)

AE = adverse event; DMID = Division of Microbiology and Infectious Diseases; MedDRA = Medical Dictionary for Regulatory Activities; N = total number of participants in the relevant analysis population; n = number of participants with at least 1 TEAE in each category (participants with multiple AEs in each category are counted only once in each category); TEAE = treatment-emergent adverse event

TEAEs were defined as AEs which started or worsened on or after the first study drug administration up to and including 14 days after the last study drug administration.

TEAEs were coded according to MedDRA v23.0.

TEAE grade was according to DMID. Grade I, II, III, IV TEAEs were defined as TEAEs for which the severity (DMID grade) was indicated as grade 1 (mild), grade 2 (moderate), grade 3 (severe), and grade 4 (potentially life-threatening) respectively.

Liver-related TEAEs were preferred terms under the standardized MedDRA query (v23.0) of hepatic disorder.

*Bedaquiline, pretomanid, and linezolid

The most common TEAEs (preferred terms) related to linezolid overall were peripheral sensory neuropathy (11.0%), neutropenia (7.7%), hepatic enzyme increased (7.2%), hypoesthesia (7.2%), anaemia (6.6%), paraesthesia (5.5%), and nausea (5.0%). The TEAEs were consistent with the known safety profile of linezolid (Table below).

Table 15. Incidence of TEAEs (Preferred Terms) occurring in ≥5% of all participants by System Organ Class and Preferred Term (Safety population)

System Organ Class Preferred Term	Linezolid 1200mg 26 weeks (N=45) n (%)	Linezolid 1200mg 9 weeks (N=46) n (%)	Linezolid 600mg 26 weeks (N=45) n (%)	Linezolid 600mg 9 weeks (N=45) n (%)	Total (N=181) n (%)
Total number of TEAEs	198	202	182	158	740
Number of participants with at least 1 TEAE	40 (88.9%)	41 (89.1%)	39 (86.7%)	36 (80.0%)	156 (86.2%)
Blood and lymphatic system disorders	**12 (26.7%)**	**8 (17.4%)**	**5 (11.1%)**	**7 (15.6%)**	**32 (17.7%)**
Anaemia	7 (15.6%)	3 (6.5%)	1 (2.2%)	3 (6.7%)	14 (7.7%)
Neutropenia	3 (6.7%)	6 (13.0%)	3 (6.7%)	4 (8.9%)	16 (8.8%)
Gastrointestinal disorders	**11 (24.4%)**	**14 (30.4%)**	**10 (22.2%)**	**13 (28.9%)**	**48 (26.5%)**
Diarrhoea	3 (6.7%)	3 (6.5%)	1 (2.2%)	5 (11.1%)	12 (6.6%)
Dyspepsia	4 (8.9%)	3 (6.5%)	1 (2.2%)	1 (2.2%)	9 (5.0%)
Nausea	6 (13.3%)	5 (10.9%)	1 (2.2%)	3 (6.7%)	15 (8.3%)
Vomiting	3 (6.7%)	3 (6.5%)	1 (2.2%)	2 (4.4%)	9 (5.0%)
Infections and infestations	**15 (33.3%)**	**16 (34.8%)**	**14 (31.1%)**	**13 (28.9%)**	**58 (32.0%)**
Upper respiratory tract infection	1 (2.2%)	4 (8.7%)	2 (4.4%)	2 (4.4%)	9 (5.0%)
Investigations	**16 (35.6%)**	**15 (32.6%)**	**12 (26.7%)**	**17 (37.8%)**	**60 (33.2%)**
Hepatic enzyme increased	5 (11.1%)	8 (17.4%)	4 (8.9%)	3 (6.7%)	20 (11.0%)
Transaminases increased	2 (4.4%)	3 (6.5%)	6 (13.3%)	5 (11.1%)	16 (8.8%)
Nervous system disorders	**19 (42.2%)**	**18 (39.1%)**	**12 (26.7%)**	**11 (24.4%)**	**60 (33.2%)**
Headache	4 (8.9%)	5 (10.9%)	1 (2.2%)	3 (6.7%)	13 (7.2%)
Hypoaesthesia	4 (8.9%)	4 (8.7%)	5 (11.1%)	1 (2.2%)	14 (7.7%)
Paraesthesia	2 (4.4%)	3 (6.5%)	3 (6.7%)	3 (6.7%)	11 (6.1%)
Peripheral sensory neuropathy	9 (20.0%)	6 (13.0%)	4 (8.9%)	2 (4.4%)	21 (11.6%)
Skin and subcutaneous tissue disorders	**14 (31.1%)**	**14 (30.4%)**	**12 (26.7%)**	**13 (28.9%)**	**53 (29.3%)**
Dermatitis acneiform	2 (4.4%)	3 (6.5%)	5 (11.1%)	3 (6.7%)	13 (7.2%)
Pruritus	2 (4.4%)	2 (4.4%)	3 (6.7%)	3 (6.7%)	10 (5.5%)
Rash papular	3 (6.7%)	4 (8.7%)	1 (2.2%)	2 (4.4%)	10 (5.5%)
Vascular disorders	**5 (11.1%)**	**1 (2.2%)**	**2 (4.4%)**	**5 (11.1%)**	**13 (7.2%)**
Hypertension	5 (11.1%)	1 (2.2%)	2 (4.4%)	4 (8.9%)	12 (6.6%)

AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; N = total number of participants in the relevant analysis population; n = number of participants with at least 1 TEAE in each category (participants with multiple AEs in each category were counted only once in each category);
TEAE = treatment-emergent adverse event
TEAEs were defined as AEs which started or worsened on or after the first study drug administration up to and including 14 days after the last study drug administration.
TEAEs were coded according to MedDRA v23.0.

Table 16. Incidence of grade 3 and/or grade 4 TEAEs (Preferred Terms) occurring in ≥1% Of participants overall by Preferred Term (Safety population)

System Organ Class Preferred Term	Linezolid 1200mg 26 weeks (N = 45) n (%)	Linezolid 1200mg 9 weeks (N = 46) n (%)	Linezolid 600mg 26 weeks (N = 45) n (%)	Linezolid 600mg 9 weeks (N = 45) n (%)	Total (N = 181) n (%)
Total number of grade 3 or grade 4 TEAEs	17	16	10	19	62
Number of participants with at least one grade 3 or grade 4 TEAE	14 (31.1%)	11 (23.9%)	9 (20.0%)	11 (24.4%)	45 (24.9%)
Blood and lymphatic system disorders	**1 (2.2%)**	**2 (4.4%)**	**1 (2.2%)**	**3 (6.7%)**	**7 (3.9%)**
Neutropenia	0	2 (4.4%)	1 (2.2%)	2 (4.4%)	5 (2.8%)
Hepatobiliary disorders	**1 (2.2%)**	**1 (2.2%)**	**0**	**1 (2.2%)**	**3 (1.7%)**
Drug-induced liver injury	0	1 (2.2%)	0	1 (2.2%)	2 (1.1%)
Investigations	**6 (13.3%)**	**6 (13.0%)**	**5 (11.1%)**	**6 (13.3%)**	**23 (12.7%)**
Blood creatinine phosphokinase increased	1 (2.2%)	0	1 (2.2%)	1 (2.2%)	3 (1.7%)
Hepatic enzyme increased	3 (6.7%)	3 (6.5%)	1 (2.2%)	1 (2.2%)	8 (4.4%)
Lipase increased	2 (4.4%)	0	0	1 (2.2%)	3 (1.7%)
Transaminases increased	1 (2.2%)	2 (4.4%)	3 (6.7%)	3 (6.7%)	9 (5.0%)

Eleven participants (6.1%) overall experienced a total of 15 serious TEAEs.

Table 17. Incidence of serious TEAEs, including death (Safety population)

System Organ Class Preferred Term	Linezolid 1200mg 26 weeks (N = 45) n (%)	Linezolid 1200mg 9 weeks (N = 46) n (%)	Linezolid 600mg 26 weeks (N = 45) n (%)	Linezolid 600mg 9 weeks (N = 45) n (%)	Total (N = 181) n (%)
Total number of serious TEAEs	5	6	1	3	15
Number of participants with at least 1 serious TEAE	3 (6.7%)	4 (8.7%)	1 (2.2%)	3 (6.7%)	11 (6.1%)
Eye disorders	**1 (2.2%)**	**0**	**0**	**0**	**1 (0.6%)**
Optic neuropathy†	1 (2.2%)	0	0	0	1 (0.6%)
Hepatobiliary disorders	**0**	**1 (2.2%)**	**0**	**1 (2.2%)**	**2 (1.1%)**
Drug-induced liver injury	0	1 (2.2%)	0	1 (2.2%)	2 (1.1%)
Infections and infestations	**2 (4.4%)**	**0**	**1 (2.2%)**	**1 (2.2%)**	**4 (2.2%)**
Hepatitis B	0	0	1 (2.2%)	0	1 (0.6%)
Tertiary syphilis	1 (2.2%)	0	0	0	1 (0.6%)
Tuberculosis	0	0	0	1 (2.2%)	1 (0.6%)
Upper respiratory tract infection	1 (2.2%)	0	0	0	1 (0.6%)
Injury, poisoning and procedural complications	**0**	**3 (6.5%)**	**0**	**0**	**3 (1.7%)**
Thermal burn	0	1 (2.2%)	0	0	1 (0.6%)
Toxicity to various agents[¥]	0	1 (2.2%)	0	0	1 (0.6%)
Wound haemorrhage	0	1 (2.2%)	0	0	1 (0.6%)
Nervous system disorders	**1 (2.2%)**	**1 (2.2%)**	**0**	**0**	**2 (1.1%)**
Brain oedema[¥]	0	1 (2.2%)	0	0	1 (0.6%)
Optic neuritis‡	1 (2.2%)	0	0	0	1 (0.6%)
Psychiatric disorders	**0**	**1 (2.2%)**	**0**	**1 (2.2%)**	**2 (1.1%)**
Alcoholic psychosis	0	0	0	1 (2.2%)	1 (0.6%)
Suicide attempt	0	1 (2.2%)	0	0	1 (0.6%)
Respiratory, thoracic and mediastinal disorders	**1 (2.2%)**	**0**	**0**	**0**	**1 (0.6%)**
Pulmonary fibrosis	1 (2.2%)	0	0	0	1 (0.6%)

Deaths

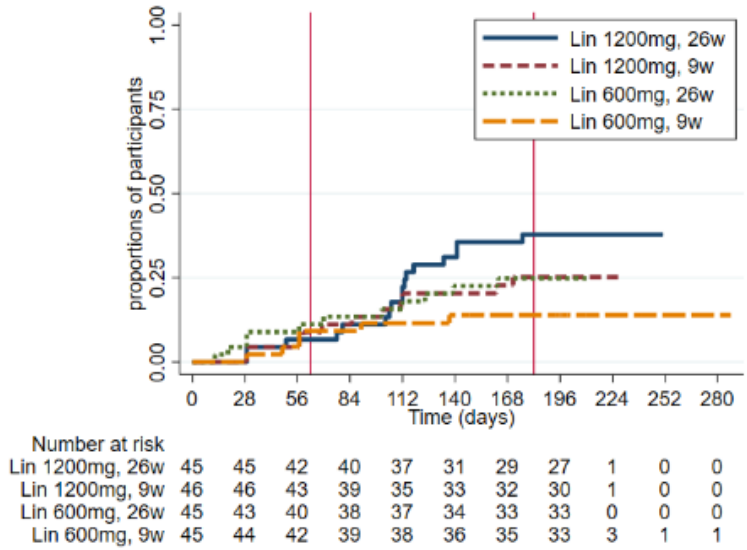
Overall, 1 participant (0.6%) experienced a total of 2 TEAEs leading to death. On Day 95 of trial treatment, the participant experienced the grade 4 serious TEAEs of toxicity to various agents (reported term: exogenous intoxication with methadone) and brain oedema. He was found unconscious in the bathroom by medical staff, and after prolonged resuscitation measures, he expired the same day with multiple organ failure. The investigator reported this death as "Acute heart failure" following an overdose of methadone.

Adverse events of special interest (AESIs)

Hepatotoxicity is a known risk with pretomanid and bedaquiline. Overall, 3 participants (1.7%) experienced a total of 3 serious liver related TEAEs. The 1200 mg linezolid 9-week, 600 mg linezolid 26-week, and 600 mg linezolid 9-week treatment groups each had 1 participant with a serious liver-related TEAE. The serious TEAE of drug-induced liver injury was experienced by 2 participants (1.1%) overall, with 1 participant (2.2%) each in the 1200 mg and 600 mg linezolid 9-week treatment groups. The serious TEAE of hepatitis B was experienced by 1 participant (2.2%) in the 600 mg linezolid 26-week treatment group. this event met the laboratory criteria for a potential Hy's law case.

Peripheral neuropathy is a known adverse effect of long-term use of linezolid. The 1200 mg 26-week treatment group had the highest percentage of participants with at least 1 TEAE associated with peripheral neuropathy (17 participants [37.8%]), followed by the 600 mg linezolid 26-week and 1200 mg 9-week groups (11 participants each [24.4% and 23.9%, respectively]). The 600 mg linezolid 9-week treatment group had the lowest percentage of participants with at least 1 TEAE associated with peripheral neuropathy (6 participants [13.3%]).

Figure 3. Kaplan-Meier curve of time (Days) to first peripheral neuropathy TEAE (Safety population)



All the reported TEAEs were mild (majority of events) or moderate. No grade 3 or grade 4 peripheral neuropathy TEAEs were reported. Longer linezolid treatment duration or higher dose appeared to result in higher incidence of peripheral neuropathy.

With respect to reversibility, it was only in patients allocated to 1200 mg linezolid for 26 weeks that remaining symptoms were reported 26 weeks post therapy.

Table 18. Peripheral neuropathy: Interference with walking or sleeping for participants with a zero score at baseline (Safety population)

	Linezolid 1200mg 26 weeks (N=45) n (%)		Linezolid 1200mg 9 weeks (N=46) n (%)		Linezolid 600mg 26 weeks (N=45) n (%)		Linezolid 600mg 9 weeks (N=45) n (%)		Total (N=181)	
n with zero score at baseline	45		44		44		45		178	
	Maximum post baseline n (%)	At 26 weeks post EOT n (%)	Maximum post baseline n (%)	At 26 weeks post EOT n (%)	Maximum post baseline n (%)	At 26 weeks post EOT n (%)	Maximum post baseline n (%)	At 26 weeks post EOT n (%)	Maximum post baseline n (%)	At 26 weeks post EOT n (%)
None	34 (75.6%)	40 (88.9%)	40 (90.9%)	40 (90.9%)	42 (95.4%)	40 (90.9%)	44 (97.8%)	37 (82.2%)	160 (89.9%)	157 (88.2%)
Minimal	1 (2.2%)	2 (4.4%)	3 (6.8%)	0	1 (2.3%)	0	1 (2.2%)	0	6 (3.4%)	2 (1.1%)
Modest	8 (17.8%)	1 (2.2%)	0	0	1 (2.3%)	0	0	0	9 (5.1%)	1 (0.6%)
Severe	2 (4.4%)	0	1 (2.3%)	0	0	0	0	0	3 (1.7%)	0
N/A	-	2 (4.4%)	-	4 (9.1%)	-	4 (9.1%)	-	8 (17.8%)	-	18 (10.1%)

N=Total number of participants randomised; n=Number of participants in each category. EOT=End Of Treatment, N/A= did not reach 26 weeks post EOT or missing.

Myelosuppression is also a known adverse effect of long-term use of linezolid. The 1200 mg linezolid 26-week group had the highest incidence of TEAEs related to myelosuppression, as identified using the Standardised MedDRA Queries (SMQ) for hematopoietic cytopenias: 28.9% for 1200 mg linezolid 26-week versus 15.6%, 15.2%, and 13.3% for 600 mg linezolid 9-week, 1200 mg linezolid 9-week, and 600 mg linezolid 26-week groups, respectively. The majority (82.4%) of myelosuppression TEAEs were mild or moderate. Overall, myelosuppression appeared to be associated with higher linezolid doses and, for the 1200 mg dose, with longer duration of linezolid treatment.

Four participants (2.2%) had optic neuropathy (another linezolid associated side effect) that reversed; all were in the 1200 mg linezolid 26-week group.

Prolongation of QT interval is a known adverse reaction for bedaquiline. A total of 14 participants (7,7%) reported a TEAE potentially indicative of cardiac rhythm disturbance. The maximum event severity was grade 1(mild). No grade 4 (life-threatening) TEAE potentially indicative of cardiac rhythm disturbance were reported. Integrated analyses of TEAEs, electrocardiogram parameters and pretomanid exposure showed no evidence that pretomanid causes clinically significant changes in QT duration.

7.2. Discussion on safety

The safety outcomes of ZeNix study largely confirmed the safety profile of the B-Pa-L regimen as assessed at the time of CMA. No new safety concerns emerged.

Overall, the B-Pa-L regimen with lower doses and/or shorter durations of linezolid improved safety profiles compared to the 1200 mg 26-week regimen.

The 1200 mg 26-week treatment group had the highest percentage of participants with at least 1 TEAE associated with peripheral neuropathy (17 participants [37.8%]), followed by the 600 mg linezolid 26-week and 1200 mg 9-week groups (11 participants each [24.4% and 23.9%, respectively]). The 600 mg linezolid 9-week treatment group had the lowest percentage of participants with at least 1 TEAE associated with peripheral neuropathy (6 participants [13.3%]). Remaining symptoms of neuropathy at 26 weeks post therapy was seen in 7% of patients in the 1200 mg 26 weeks arm, and in none of the patients in the other treatment arms.

Comparing the 1200 mg and 600 mg linezolid treatment groups matched for duration, the 600 mg groups experienced consistently less peripheral neuropathy and myelosuppression for both durations (26 weeks and 9 weeks).

Comparing the 26-week and 9-week treatment groups matched for dose, the 9-week duration was consistently associated with less peripheral neuropathy and myelosuppression at the 1200 mg linezolid dose, but there was relatively little difference in incidence of myelosuppression at the 600 mg dose. With respect to considering the lower dose 600 mg linezolid 26-week group versus the lower duration 1200 mg linezolid 9-week group, the former appeared to show advantages with respect to lower incidences of linezolid dose modifications, serious TEAEs, TEAEs leading to linezolid interruption, TEAEs leading to linezolid reduction, and laboratory results indicative of myelosuppression. Overall, a lower dose and cumulative exposure to linezolid is associated with a more favourable safety profile.

SmPC section 4.8 has been updated based on the new data.

8. PRAC advice

Not applicable.

9. Changes to the Product Information

As a result of this variation, sections 4.2, 4.4, 4.8 and 5.1 of the SmPC are being updated in order to change posology recommendations of linezolid, include frequency information of several ADRs as well as to update clinical efficacy information based on final results from ZeNix study. The Package Leaflet (PL) is updated accordingly.

Changes are made to the Opinion Annex II conditions as detailed in the recommendations section above.

In addition, the list of local representatives in the PL is being revised.

Editorial changes were also made to the SmPC and PL.

Please refer to Attachment 1 which includes all agreed changes to the Product Information.

10. Request for supplementary information

10.1. Major objections

Not applicable.

10.2. Other concerns

Clinical aspects

1. In its own discussion of benefits and risks (Clinical Overview), the MAH states that: "the totality of the trial data, tend to support the 600 mg linezolid 26-week regimen as having the most favourable risk-benefit ratio among the dosing regimens studied". Still, the applicant does not propose any change to the starting dose of linezolid per SmPC. The better safety profile of a lower dose is recognised; however, it is also noted that uncertainty around the effect estimate is greater than for the 1200 mg starting dose. The applicant is asked to discuss and justify what is the appropriate starting dose of linezolid in the context of the Dovprela-containing regimen.
2. Please provide further justification for shifting the following AEs from Very Common to Common in the 4.8 Tabulated list of adverse reactions: pruritus, musculoskeletal pain, increased gammaglutamyl transferase and increased amylase.
3. Please include headings and numerations for the tables under 5.1.

11. Assessment of the responses to the request for supplementary information

11.1. Major objections

11.2. Other concerns

Clinical aspects

Question 1. In its own discussion of benefits and risks (Clinical Overview), the MAH states that: "the totality of the trial data, tend to support the 600 mg linezolid 26-week regimen as having the most favourable risk-benefit ratio among the dosing regimens studied". Still, the applicant does not propose any change to the starting dose of linezolid per SmPC. The better safety profile of a lower dose is recognised; however, it is also noted that uncertainty around the effect estimate is greater than for the 1200 mg starting dose. The applicant is asked to discuss and justify what is the appropriate starting dose of linezolid in the context of the Dovprela-containing regimen.

Summary of the MAH's response

The Applicant acknowledges the Agency's query on 600 mg and 1200 mg doses of linezolid. The Applicant proposes starting dose of linezolid to be 600 mg and not 1200 mg based on the ZeNix trial results.

In the Nix-TB trial, 90% of the patients with highly drug-resistance tuberculosis (TB) who received bedaquiline, pretomanid, and linezolid (1200 mg) for 26 weeks had a favorable outcome. However, the use of linezolid 1200 mg daily was associated with a high incidence of adverse events.

The ZeNix trial was built upon the Nix-TB trial to investigate the safety and efficacy of two doses of linezolid and at different treatment durations (600 mg and 1200 mg for 9 weeks and 26 weeks) along with bedaquiline and pretomanid for 26 weeks in participants with pulmonary infection of either extensively drug-resistant (XDR)-TB, pre-XDR-TB, or treatment-intolerant or nonresponsive multi-drug resistant (MDR)-TB. Participants in the ZeNix trial were treated with BPaL regimen [bedaquiline (200 mg daily for 8 weeks followed by 100 mg daily for 18 weeks), pretomanid (200 mg daily for 26 weeks), and linezolid (600 mg daily for 26 weeks/9 weeks or 1200 mg for 26 weeks/9 weeks, in a blinded design)].

The primary efficacy endpoint was the incidence of an unfavourable outcome, defined as treatment failure or disease relapse (clinical or bacteriologic) at 26 weeks after completion of treatment.

The ZeNix trial results confirm the benefit of the BPaL regimen observed in the Nix-TB trial for improving outcomes in highly drug-resistant TB and expand this observation to the pre-XDR population. Overall, the efficacy results between 1200 mg and 600 mg 26-week linezolid regimen were similar including the primary and secondary efficacy results. Especially for the primary endpoint favourable outcome, the results were similar between the 600-mg 26-week linezolid regimen [91% (41 of 45) participants] and the 1200-mg 26-week linezolid regimen [93% (41 of 44) participants] (table below) with minor numerical difference. The secondary analyses of the primary efficacy endpoint in the intend-to-treat (ITT) and per-protocol (PP) populations and sensitivity analyses (sensitivity analysis treating all deaths as unfavorable and sensitivity analysis treating all reinfections as unfavourable) were consistent with the primary efficacy analysis.

Table 19: Primary Efficacy Analysis in Modified Intent-to-Treat (MITT) Population

	Bedaquiline–Pretomanid–Linezolid Regimen	
	Linezolid 1200 mg 26 weeks (N = 45)	**Linezolid 600 mg 26 weeks (N = 45)**
Total assessable	44	45
Favorable **Unfavorable**	**41/44 (93.2%)** **3 (6.8%)**	**41/45 (91.1%)** **4 (8.9%)**
95% CI for Favorable	81.3% to 98.6%	78.8% to 97.5%
97.5% CI for Favorable	-	76.9% to 98.0%

CI = confidence interval; MITT = modified intent-to-treat; N = total number of participants in the relevant analysis population; n = number of participants in each category.

Favorable and unfavorable status as defined in the statistical analysis plan for MITT.

Safety:

Overall, the 600 mg linezolid 26-week group, showed a more favourable safety profile than in the 1200 mg linezolid 26-week group. The 600-mg 26-week linezolid regimen showed lower percentage of drug-related TEAEs (60.0%) compared with the 1200-mg 26-week regimen (75.6%). The 600-mg 26-week linezolid regimen had a numerically lower percentage of participants with at least one grade 3 or grade 4 TEAE (20.0%) compared with the 1200-mg 26-week linezolid regimen (31.1%). One (2.2%) participant in the 600-mg 26-week linezolid regimen and 3 (6.7%) participants in the 1200-mg 26-week linezolid regimen,

reported serious TEAEs. A lower percentage of participants in the 600 mg 26-week linezolid regimen required dose modification (reduction, interruption, or discontinuation) of linezolid as compared to participants in 1200-mg 26-week linezolid regimen (13.3% versus 51.1%).

Analyses of TEAEs Related to Peripheral Neuropathy, Myelosuppression and Optic Neuropathy

Prolonged use of linezolid is associated with peripheral neuropathy, myelosuppression and optic neuropathy (WHO consolidate TB guidance 2022 - enclosed in m1- additional data folder). The ZeNix trial revealed that the incidence of these events were all lower/nil in the 600-mg 26-week regimen compared to the 1200-mg 26-week regimen (Conradie F et al, 2022-enclosed in m1 additional data folder). Further, a comparison between 600 mg and 1200 mg linezolid regimens, on the incidences of these events are discussed below.

Peripheral Neuropathy

A search of the database using the standardized MedDRA query (SMQ) of peripheral neuropathy revealed that the 600-mg 26-week linezolid regimen had the lowest percentage of participants (11 of 45 participants [24.4%]) with at least one TEAE associated with peripheral neuropathy as compared to participants with 1200-mg 26-week linezolid regimen (17 of 45 participants [37.8%]) (Table below).

Myelosuppression

A search of the database using the SMQ of myelosuppression revealed that the 600-mg 26-week linezolid regimen had the lowest percentage of participants (6 of 45 participants [13.3%]) with at least one TEAE associated with myelosuppression as compared to participants with 1200-mg 26-week regimen (13 of 45 participants [28.9%]) (Table below).

Optic Neuropathy

A search of the database using the SMQ of optic neuropathy revealed that the 600-mg 26-week regimen had no participants with at least one TEAE associated with optic neuropathy as compared to participants with 1200-mg 26-week regimen (4 of 45 participants [8.9%]) (Table below).

Table 20: Incidence of TEAEs Related to Peripheral Neuropathy, Myelosuppression and Optic Neuropathy in Safety Population

Events		**Bedaquiline–Pretomanid–Linezolid Regimen**	
		Linezolid 1200 mg 26 weeks (N = 45) n (%)	**Linezolid 600 mg 26 weeks (N = 45) n (%)**
Peripheral neuropathy‡	Total number of TEAEs	24	17
	Number of participants with at least 1 TEAE	17 (37.8%)	11 (24.4%)
Myelosuppression§		20	9
		13 (28.9%)	6 (13.3%)
Optic neuropathy§§		4	0
		4 (8.9%)	0

N = Total number of participants in the relevant analysis population; n = Number of participants with at least one TEAE in each category (participants with multiple AEs in each category are counted only once in each category); PT = preferred term; SMQ = standardized MedDRA query; TEAE = treatment-emergent adverse event
TEAEs were coded according to Medical Dictionary for Regulatory Activities (MedDRA) v23.0.
‡All PTs under SMQ (peripheral neuropathy);
§All PTs under SMQ (Hematopoyetic cytopenias);
§§All PTs under SMQ (optic neuropathy)

WHO Recommendation (WHO consolidated guidelines on TB, 2022)

The current World Health Organisation (WHO) consolidated guidelines on TB, were developed based on data from several studies including the ZeNix trial and recommend the use of 600 mg linezolid over 1200 mg linezolid, for 26 weeks as part of the BPaL regimen with or without moxifloxacin in adults with MDR/(Rifampicin resistant) RR-TB or pre-XDR-TB.

Conclusion

Given the similar efficacy across the two doses, 600 mg and 1200 mg of linezolid 26 weeks, the risk-benefit ratio which is largely driven by safety and tolerability, favours the 600 mg linezolid dose. In particular, the 600 mg dose was associated with fewer linezolid dose modifications, fewer incidences of peripheral neuropathy and myelosuppression, with no incidence of optic neuropathy. The 600 mg linezolid regimen also showed to have lesser incidences of TEAEs and SAEs as compared with 1200 mg linezolid.

Based on the above points, the 600 mg linezolid 26-week regimen with most favourable risk-benefit ratio among the dosing regimens studied, concurs with the WHO Guideline Development Group (GDG) panel recommendation of 600-mg 26-week linezolid regimen of linezolid in adult patients with MDR-TB or pre-XDR-TB.

Assessment of the MAH's response

The MAH proposal to use 600 mg linezolid as a starting dose, is agreed. Data are compatible with similar efficacy as with a starting dose of 1200 mg. The uncertainty about any difference in efficacy is agreed to be acceptable, and the safety profile is clearly more favourable with the 600 mg dose compared to the 1200 mg dose.

Conclusion: Issue resolved.

Question 2. Please provide further justification for shifting the following AEs from Very Common to Common in the 4.8 Tabulated list of adverse reactions: pruritus, musculoskeletal pain, increased gammaglutamyl transferase and increased amylase.

Summary of the MAH's response

The updated ADR table submitted in Dec 2022 includes all patients from Nix and ZeNix dosed for 26 weeks with linezolid 1200mg. An increasing denominator decreased the frequency of the following events {pruritus, musculoskeletal pain, increased gamma-glutamyl transferase and increased amylase with observed frequency of ≤ 2%} from very common to common. The current updated ADR table includes all participants from Nix and ZeNix dosed for 26 weeks with linezolid (600 and 1200 mg). Hence in comparison to the revision in December 2022, a few additional preferred terms {headache, abdominal pain, rash} are shifted from "Very Common" to "Common" during the current update. In addition, few preferred terms shifted from "Uncommon" to "Common": oral candidiasis, hypomagnesaemia, dry eye and blood creatinine increase (all new PT`s in the "common" category were observed with a frequency equal or inferior to 2%).

Assessment of the MAH's response

The MAH has provided a justification for the changes in frequencies for pruritus, musculoskeletal pain, increased gammaglutamyl transferase and increased amylase. In addition, the MAH has also moved other reactions, as a result of adding the group receiving 600 mg linezolid to the denominator.

Conclusion: Issue resolved.

Question 3. Please include headings and numerations for the tables under 5.1.

Summary of the MAH's response

The tables under 5.1 have been updated with headings and numerations. For consistency within the document, also a table header was included for the ADR table in 4.8.

Additional revisions in the combined product information were made to address the assessor's comments in the labelling document:

- Section 4.2: Change of the appropriate starting dose of linezolid from 1200 mg to 600 mg

- Section 4.8: Update of the ADR table, taking into account also the 45 patients treated with pretomanid in the group with 600 mg linezolid/26 weeks. Due to the revised starting dose, the MAH is of the opinion that this patient group should be included also in the ADR table.

- Section 5.1: Description of the proportions with XDR, pre-XDR and MDR TB, as well as the demographics for the patients in the ZeNix trial.

The additional revisions are included in track changes and were in addition highlighted.

Assessment of the MAH's response

The proposed changes are substantially agreed. However, there are some remaining formalities with respect to the clarity of the SmPC.

Conclusion: Issue partially resolved.

12. Assessment of the responses to the 2nd request for supplementary information

Question 1. Please address the points raised by the assessors in the product information.

Assessment of the MAH's response

The applicant has appropriately addressed the points that were raised.

Conclusion: Issue resolved.