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Committee for Medicinal Products for Human use (CHMP)
EMA/R/0000293774

Assessment report on the annual renewal of the conditional marketing authorisation

Procedure no.: EMA/R/0000293774

Invented name: Deltyba

International non-proprietary name: delamanid

Marketing authorisation holder (MAH): Otsuka Novel Products GmbH

Note

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

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Status of this report and steps taken for the assessment			
Current step	**Description**	**Planned date**	**Actual Date**
☐	Start	15 September 2025	15 September 2025
☐	CHMP&PRAC Rapporteur JAR	14 October 2025	14 October 2025
☐	CHMP&PRAC comments	20 October 2025	20 October 2025
☐	Updated CHMP&PRAC Rapporteur JAR	23 October 2025	23 October 2025
☐	PRAC outcome	30 October 2025	30 October 2025
☐	CHMP outcome - RSI	13 November 2025	13 November 2025
☐	Submission of responses	18 November 2025	18 November 2025
☐	Restart	19 November 2025	19 November 2025
☐	CHMP and PRAC Rapporteurs' joint assessment report	26 November 2025	26 November 2025
☐	PRAC outcome	27 November 2025	27 November 2025
☐	CHMP and PRAC members comments	01 December 2025	01 December 2025
☐	Updated CHMP and PRAC Rapporteurs joint assessment report	04 December 2025	04 December 2025
☒	Opinion	11 December 2025	11 December 2025

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List of Abbreviations

B	bedaquiline
BID	twice daily
C	clofazimine
CTCAE	Common Terminology Criteria for Adverse Events
D	delamanid
DST	drug susceptibility testing
endTB	Evaluating Newly Approved Drugs for Multidrug-resistant Tuberculosis
FQ	fluoroquinolone
GDG	Guideline Development Group
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HR	hazard ratio
IPD	Individual Patient Data
ITT	intention-to-treat
L	linezolid
Lfx	levofloxacin
LTFU	lost/loss to follow-up
M	moxifloxacin
MAH	Marketing Authorisation Holder
MDR	multidrug-resistant
MDR-TB	multidrug-resistant tuberculosis - infection with a strain of Mycobacterium tuberculosis with resistance to at least isoniazid and rifampicin
MDR/RR-TB	multidrug-resistant/rifampicin-resistant tuberculosis
MGIT	Mycobacteria Growth Indicator Tube
mITT	modified intention-to-treat
MSF	Médecins Sans Frontières
Mtb	Mycobacterium tuberculosis
OBR	optimised background treatment regimen
Pa	pretomanid
PP	per-protocol
QD	once daily
QTcF	QT interval using Fridericia's formula
RD	risk difference
RMP	Risk Management Plan
RR	rifampicin-resistant
RR-TB	rifampicin-resistant TB
SAP	statistical analysis plan
SCC	sputum culture conversion
SD	standard deviation
SE	standard error
SmPC	Summary of Product Characteristics
SOB	Specific Obligation
SoC	Standard of Care
TB	tuberculosis
WHO	World Health Organization
XDR	extensively multidrug-resistant

1. Background information on the renewal

The European Commission issued on 28 April 2014 a conditional marketing authorisation (MA) for Deltyba. This implied that, pursuant to Article 14-a of Regulation (EC) No 726/2004 and Article 5 of Commission Regulation (EC) No 507/2006, the marketing authorisation holder (MAH) has to complete ongoing studies, or to conduct new studies, as listed in Annex II.E of the MA, the so-called Specific Obligations (SOBs). These data form the basis of the renewal of the conditional MA.

Deltyba was designated as an orphan medicinal product EU/3/07/524 on 1 February 2008.

A conditional MA is valid for one year and may be renewed annually upon request by the MAH. Therefore, pursuant to Article 14-a of Regulation (EC) No 726/2004 and Article 6(2) of Commission Regulation (EC) No 507/2006, the MAH Otsuka Novel Products GmbH, submitted to the Agency on 27 August 2025 an application for renewal of the conditional MA for Deltyba. The expiry date of the MA is 30 April 2026.

The period covered by this annual renewal is 28 April 2024 to 27 April 2025. Cut-off on 20 June 2025 for updates on some specific activities associated to the Life Cycle Management and cut-off on 27 April 2025 for updates on safety and post-marketing experience/pharmacovigilance assessment.

The application contained a justification in support of the possible granting of a marketing authorisation not subject to specific obligations.

2. Overall conclusions and benefit-risk balance

2.1. Specific Obligations (SOBs)

Compliance of SOB data submitted

During the period covered by this annual renewal, data on the SOBs have been submitted that overall are compliant in terms of adherence to deadlines and are compliant in terms of acceptability of data submitted.

The MAH did submit the results of the endTB study, including a critical discussion of the publicly available data with a focus on the evaluation of delamanid, showing that delamanid can be used in the fixed 9-month BDLLfxZ combination regimen in patients with pulmonary RR-tuberculosis. The two other delamanid-containing shortened regimens from the endTB study (DCLLfxZ and DCMZ) are not recommended due to a disbalance in failure and recurrence and amplification of drug resistance. In addition, the results from the BEAT-TB study have been submitted and discussed, supporting delamanid use in a 6-month BDLLfxC regimen in patients with pulmonary RR-tuberculosis. This supports the use of delamanid in different combination treatment regimens as per the approved indication.

These data have been submitted before the due date (Q3 2026) agreed upon during the previous renewal procedure.

As part of this annual renewal the CHMP is of the opinion that the following obligation has been fulfilled, and therefore recommends its deletion from the Annex II:

In order to further investigate the use of delamanid in different combination treatment regimens as per approved indication as well as safety, the MAH should submit the publicly available data of the endTB (Evaluating Newly approved Drugs for multidrug-resistant TB) study, a randomised, controlled Phase III trial in adults and adolescents with multi-drug resistant tuberculosis conducted by Médecins Sans Frontières, with an analysis based on the agreed statistical analysis plan and publicly available results from the BEAT-TB study conducted by Wits Health Consortium.

The last SOB has been fulfilled and the data available concerning this product is considered comprehensive; therefore, there are no remaining Specific Obligations.

2.2. Benefit-risk Balance

During the period covered by this annual renewal, new data have emerged. These data are considered to have an impact on the benefit-risk of Deltyba in the approved indication.

Favourable effects

In study **242-07-204** (204)**,** a 3-month randomised, placebo-controlled phase 2 study conducted with delamanid 100 mg twice daily + OBR or 200 mg twice daily + OBR or placebo + OBR, a higher proportion of subjects with pulmonary tuberculosis caused by organisms that were at least resistant to rifampicin and isoniazid achieved sputum culture conversion (SCC) compared to the placebo group: in 45%, 42% and 30% in those treated with 100 mg bid, 200 mg bid and placebo, respectively; for patients with XDR-TB these figures were 4/24 (17%), 5/18 (28%) and 2/27 (7%) showing that the magnitude of the difference vs. placebo in the MITT population varied by dose group, MDR-TB vs. XDR-TB, presence of cavitation, region and whether the analyses were based on MGIT or solid culture media results.

Two follow-up studies to study 242-07-204 were conducted: Study **242-07-208** (208), a non-controlled, open-label extension of study 204 that evaluated delamanid 100 mg and/or 200 mg twice daily in combination with OBR for an additional 6 months in those patients who completed study 204, and study **242-10-116** (116), an observational study of patients who were randomised in study 204204 (with or without participating in study 208), which captured all relevant data from the microbiological assessments and clinical monitoring of these patients until the end of their treatment or until 24 months after the date of randomisation in study 204, whichever came first.

The confirmatory trial **242-09-213** conducted to compare the addition of delamanid or placebo to OBR for 6 months followed by 12 to 18 months of the background regimen alone, could not confirm the benefit of adding delamanid to OBR. The possible reasons why delamanid was not superior to placebo in trial 213 include changes in patient overall management and the fact that moxifloxacin was allowed as part of the OBR.

Additional data was required to confirm the positive benefit-risk balance of delamanid and to better characterise the patient population that will likely benefit from treatment with delamanid. The MAH did provide and discuss the publicly available data from the **endTB** study, a randomised, controlled phase 3 study in adults and adolescents with fluoroquinolone-susceptible RR-TB, conducted by Médecins Sans Frontières. This study evaluated the efficacy and safety of new, shorter (39 weeks) combination regimens versus the then recommended WHO standard of care (SoC) (mostly individualised regimens of ≥18 months' duration). It enrolled participants in parallel across 5 experimental arms and 1 SoC control arm. Three of the five experimental study arms contained delamanid.

Non-inferiority to standard therapy was established for two of the three delamanid-containing regimens (BDLLfxZ and DCMZ). In the mITT analysis 85.2 % of the 122 patients in the BDLLfxZ group had a favourable outcome at week 73 (Difference from standard therapy was 4.6% [95% CI, -4.9 to 14.1]) and 83.2% of the 107 patients in the DCMZ group (Difference from standard therapy was 2.5% [95% CI, -7.5 to 12.5]. The DCLLfxZ regimen was not non-inferior, 78.8% of the 118 patients had a favourable outcome. Differences in risk from standard therapy was: -1.9% (95% CI, -12.1 to 8.4). Week 104 data confirmed these results.

The MAH did provide and discuss the publicly available data from the **BEAT-TB** South-Africa study, an open label, randomised controlled trial in patients with rifampicin-resistant, pulmonary tuberculosis,

conducted by Wits Health Consortium. In the BEAT-TB study, the 6 month BDLLfxC regimen (from which either Lfx or C could be dropped based on FQ-susceptibility results) showed non-inferiority compared to those receiving SoC (9-12-month all-oral regimens with linezolid for patients with MDR/RR-TB and 18-20 month all-oral regimens for patients with pre-XDR-TB) in its proportion of participants with favourable outcome at week 76 (86.1% in the study arm versus 86.0% in the control). Slightly higher levels of failure or recurrence were observed in the BDLLfxC group (8.4%) than in the control group (7.0%).

The shortening of the treatment duration and the reduction in pill burden in the endTB and BEAT-TB shortened regimens are desirable effects.

Uncertainties and limitations about favourable effects

In study **242-07-204**, the comparison between delamanid and placebo was restricted to 8 weeks only. The magnitude of the difference vs. placebo in the MITT population varied by dose group, MDR-TB vs. XDR-TB, presence of cavitation, region and whether the analyses were based on MGIT or solid culture media results. The results by geographical region/site mostly reflected the local rates of XDR-TB.

The open-label data from the follow-up studies **242-07-208** and **242-07-116** reflected patient decisions to continue with open-label treatment, investigator decisions to change the dose and willingness of patients to be followed up for final outcomes. Data from follow-up studies 208/116 did not address the essential deficiencies of study 204 and the available data could not confirm the appropriateness of the MAH's proposed dose regimen for delamanid.

Study **242-09-213** the confirmatory trial conducted to compare the addition of delamanid or placebo to OBR for 6 months followed by 12 to 18 months of the background regimen alone used a dose regimen of 100 mg BID for 8 weeks followed by 200 mg QD for 4 months. Delamanid was demonstrated not to be superior to placebo for the pre-specified primary efficacy endpoint (distribution of time to SCC using MGIT during the intensive 6-month treatment phase) although there was a 6-day difference (51 vs. 57 days). In the low-risk sub-group (HIV negative and no/unilateral lung cavitation) there was a 13-day difference favouring delamanid for the primary endpoint that just reached significance. Therefore, it could not be concluded that the slightly faster time to SCC observed over the first 8 weeks in the delamanid group is a clinically significant benefit to patients and its effect on the risk of transmission rates is likely marginal overall.
Further sub-group analyses indicated that the benefit in the low-risk patients was in the MDR-TB sub-population and was not found in the Pre-XDR or XDR patients.

The possible reasons why delamanid was not superior to placebo for the primary endpoint or for other endpoints up to the end of the trial include changes in patient overall management and the fact that moxifloxacin was allowed as part of the OBR.

In view of the expected futility of the initially proposed study 242-14-253, exploring the relationship between different doses with respect to 2 months SCC and longer-term outcome, it was agreed that this study was no longer requested. Instead, the MAH further evaluated the PK/PD of delamanid using the HFS-TB model in order to contribute to the evaluation of the dose of delamanid. Due to methodological issues, no conclusions could be drawn from these study results. Using a PK-PD model analysis, the dose of 100 mg BID was chosen over the 200 mg BID dose, based on an increased risk for QT interval prolongation with the 200 mg BID dose.

In the **endTB** study, in eligible MDR/RR-TB patients with confirmed drug susceptibility to fluoroquinolones, one of the delamanid-containing shortened treatment regimens (DCLLfxZ) did not show non-inferiority to the control and two of them (DCLLfxZ and DCMZ) were associated with higher rates of treatment failure/relapse and acquired drug resistance than the control arm. At week 104,

levels of failure or recurrence were 2.5% for SoC, 1.6% for BDLLfxZ, 11.0% for DCLLfxZ and 11.2% for DCMZ. Amplification of drug resistance was shown in 0.0% for SoC and BDLLfxZ, 4.0% for DCLLfxZ and 6.7% for DCMZ. Therefore, not all delamanid-containing regimens allowed shortening of the treatment duration.

In the **BEAT-TB** study, among patients with pre-XDR-TB, the outcomes appeared worse than among those who were fluoroquinolone susceptible. This reduction in the proportion with successful treatment outcomes was numerically greater in the BDLLfxC arm than in the control arm (14.3% vs 3.3%); however, the evidence from the BEAT-TB trial is insufficient to draw definitive conclusions due to the small sample when stratified by fluoroquinolone resistance and related imprecision. This is in line with trial 213 having better results in the MDR-TB subpopulation than in the (pre-)XDR-TB population.

The endTB and BEAT-TB studies further justify the use of delamanid in combination treatment regimens, especially in the MDR/RR-TB patient population.

A population PK modelling and simulation analysis was performed to support the dosing recommendation in the paediatric population. The efficacy in adolescents, children and infants with a body weight of at least 10 kg is expected to be the same as in adults, based on similarity in exposure. Data in children with a body weight of less than 10 kg were too limited to determine doses for that patient population, and have, therefore, not been included in the target population.

Unfavourable effects

Delamanid is associated with prolongation of the QTc interval that is driven predominantly but not wholly by plasma levels of a major metabolite DM-6705. The MAH will further continue to analyse and discuss the risks of QT interval prolongation in upcoming PSURs.

In the context of the PSUSA procedure EMEA/H/C/PSUSA/00010213/202304, in view of available data on nightmares from clinical trial PHOENIx (study 242-201-00004) including in some cases a close temporal relationship and a positive de-challenge, the PRAC considered a causal relationship between delamanid and 'Nightmare' to be at least a reasonable possibility, which was addressed by updating the Deltyba product information accordingly.

There were no new safety issues related to delamanid use in the EndTB or BEAT-TB study.

Uncertainties and limitations about unfavourable effects

The potential for delamanid to be associated with an increased risk of hepatotoxicity is uncertain and requires further monitoring; liver disorders will therefore be further closely monitored in the upcoming PSURs.

The frequency, type and severity of adverse reactions in adolescents, children and infants with a body weight of at least 10 kg are expected to be the same as in adults, but requires further follow-up in the PSURs.

Uncertainties remain about antimicrobial resistance, which are also addressed through close monitoring in the PSURs.

In particular, the ongoing PHOENIx clinical study (expected to conclude in 2027), in which delamanid is administered as monotherapy for the preventive treatment of MDR-TB in high-risk household contacts (i.e. with HIV or non-HIV immunosuppression, latent TB infection, and young children below the age of 5 years) (Kendall MA et al., 2025), provides valuable insights into the drug's safety profile. Safety information of this study is reported in the PSURs. Based on these study results, the SmPC was updated twice: 2021 and 2023.

Benefit-risk assessment and discussion

Importance of favourable and unfavourable effects

In Study 204 the efficacy in terms of sputum culture conversion of the two investigated doses (100 mg BID and 200 mg BID) was superior to placebo, but the duration of comparison was too short. The results of the open label and optional follow-on studies (208/116) could not address the deficiencies of study 204.

Additional data from study 213 have failed to show a consistent benefit for delamanid (total 200 mg/day) over placebo when they were compared for 6 months. The factors driving this lack of benefit remain unclear but may reflect in part the use of moxifloxacin in the OBR in study 213.

The endTB and BEAT-TB investigated shortened delamanid containing regimens versus the then recommended standard of care. Non-inferiority in the proportion of patients with a favourable outcome at week 73 or week 76 was the primary objective. Increase in failure to culture convert, culture reversion or recurrence with treatment shortening should be limited or absent. The amplification of resistance should be taken into account as well.

The main safety issue observed with delamanid relates to QT-prolongation, which will continue to be monitored in future PSURs. In addition, uncertainties still remain regarding delamanid's hepatotoxic potential, antimicrobial resistance and use in children (i.e. recently authorised paediatric formulation in 2021). Safety information will be further monitored in the upcoming PSURs.

Balance of benefits and risks

MDR-TB is a public health problem for which only limited treatment options are available.

At the time of initial approval, the CHMP considered that the benefit-risk balance of Deltyba could be deemed favourable for a limited indication only. Thus, use was restricted to adult patients with pulmonary MDR-TB when an effective treatment regimen cannot otherwise be composed for reasons of resistance or tolerability. The additional data from study 213 did not change this conclusion. These data indicated that adding delamanid to OBR likely had no clinically important benefit for the total trial population. In the easiest to treat subset there was evidence of a faster response to treatment in the delamanid group but this did not appear to easily translate in a tangible benefit to patients. The possible reasons why delamanid was not superior to placebo for the primary endpoint or for other endpoints up to the end of the trial include changes in patient overall management and the fact that moxifloxacin was allowed as part of the OBR.

Additional data was required, in the form of specific obligations, to confirm the positive benefit-risk balance of delamanid and to better characterise the patient population that will likely benefit from treatment with delamanid. Two studies were designed, to address these specific obligations: the endTB study, and the BEAT-TB study.

In the endTB study, the shortened (9-month), all-oral BDLLfxZ regimen was non-inferior to the SoC control group both in the mITT and the PP population at 73 and 104 weeks and may be effectively used instead of the longer (≥ 18 months) regimens. The shortened DCMZ regimen was also non-inferior to the control in the mITT population, but had a higher incidence of failure and recurrence and showed amplification of drug resistance. The DCLLfxZ regimen was not non-inferior to the control in the mITT population, had a higher incidence of failure and recurrence and showed amplification of drug resistance. Therefore, only the shortened BDLLfxZ regimen is recommended for the treatment of fluoroquinolone-susceptible, rifampicin-resistant, pulmonary tuberculosis; i.e. MDR/RR-TB.

In the BEAT-TB study, the 6-month BDLLfxC regimen was non-inferior to the SoC. The differences in failure or recurrence were negligible. Among patients with pre-XDR-TB, the outcomes appeared worse than among those who were fluoroquinolone susceptible.

The endTB and BEAT-TB study justify the use of delamanid in combination treatment regimens in the treatment of pulmonary MDR-TB. Data from study 213, endTB and BEAT-TB study point in the direction of a larger benefit in the fluoroquinolone-susceptible subpopulation.

Therefore, the data collected as part of the specific obligation for Deltyba during the period covered by this annual renewal confirmed its positive benefit-risk balance in the approved indication i.e. for use as part of an appropriate combination regimen for pulmonary multi-drug resistant tuberculosis (MDR-TB) in adults, adolescents, children and infants with a body weight of at least 10 kg when an effective treatment regimen cannot otherwise be composed for reasons of resistance or tolerability.

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

As requested in SOB 002, as amended in R/076, the MAH did provide and discuss the publicly available data from the endTB study in patients with rifampicin-resistant, fluoroquinolone-susceptible pulmonary tuberculosis, conducted by Médecins Sans Frontières. The endTB study evaluated the efficacy and safety of new, shorter (39 weeks), all oral combination regimens for the treatment of MDR-TB. It enrolled participants in parallel across 5 experimental arms and 1 WHO recommended standard of care control arm, mostly individualised regimens of ≥18 months' duration. Three of the five experimental study arms contained Deltyba (BDLLfxZ, DCLLfxZ, and DCMZ).

In the **endTB study**, in eligible MDR/RR-TB patients with confirmed drug susceptibility to fluoroquinolones, one of the delamanid-containing shortened treatment regimens (DCLLfxZ) did not show non-inferiority to the control and two of them (DCLLfxZ and DCMZ) were associated with higher rates of treatment failure/relapse and acquired drug resistance than the control arm.

Thus, one of the delamanid-containing fixed regimens (BDLLfxZ) showed a shortening of the duration of treatment compared to the recommended standard of care. The large majority (90%) of patients in this standard of care control arm were not administered delamanid. Therefore, this study further supports the use of delamanid in the treatment of MDR-TB. The two other shortened regimens in the endTB study not including delamanid showed numerically more favourable outcomes. Therefore, it is proposed not to change the indication of delamanid, being a last line treatment option in pulmonary MDR-TB.

The MAH did provide and discuss the publicly available data from the **BEAT-TB** South-Africa study, an open label, randomised controlled trial in patients with rifampicin-resistant, pulmonary tuberculosis, conducted by Wits Health Consortium. In this study, the 6-month BDLLfxC regimen was non-inferior to the 9-month or longer (> 18 months – if FQ resistance was identified) individualised WHO recommended SoC regimens, in all patients with MDR/RR-TB at week 76. Either levofloxacin (if FQ-resistant, i.e. pre-XDR-TB) or clofazimine (if FQ-susceptible) could be dropped from the regimen.

There were no new safety findings regarding delamanid from the studies in SOB 002.

The provided data confirm the efficacy and safety of the use of delamanid in different combination regimens in patients with RR or MDR pulmonary tuberculosis.

3. Recommendations

☒ Based on the review of the available information on the status of the fulfilment of Specific Obligations, the benefit-risk balance for Deltyba in its approved indication (please refer to the Summary of Product Characteristics) continues to be favourable and all specific obligations have been fulfilled, and therefore the granting of a marketing authorisation no longer subject to specific obligations is recommended, subject to the conditions and obligations as detailed in this assessment report.

Amendments to the marketing authorisation

In view of new data submitted as part of the renewal application, amendments to Annexes I and II and to the Risk Management Plan are recommended.

Updates to the Product Information were made in line with the SmPC guideline and the latest QRD template (version 11).

The following obligation has been fulfilled, and therefore it is recommended that it be deleted from the Annex II.E to the opinion:

Description	Due date
In order to further investigate the use of delamanid in different combination treatment regimens as per approved indication as well as safety, the MAH should submit the publicly available data of the endTB (Evaluating Newly approved Drugs for multidrug-resistant TB) study, a randomised, controlled Phase III trial in adults and adolescents with multi-drug resistant tuberculosis conducted by Médecins Sans Frontières, with an analysis based on the agreed statistical analysis plan and publicly available results from the BEAT-TB study conducted by Wits Health Consortium.	Q3 2026

See Attachment 1 for all agreed changes to the Product Information.

Conditions of the marketing authorisation

Not applicable.

PSUR cycle

Based on fulfilment of SOB 002, and given

(I) Uncertainties about antimicrobial resistance, the closely monitored safety issue of liver disorders and the recently authorised paediatric formulation (2021).

(II) The ongoing PHOENIx clinical study where delamanid is administered as a single drug for preventive treatment of MDR-TB (Kendall MA et al., 2025). Safety information of this study is reported in the PSURs and gives important insights on the safety profile of the drug (e.g. based on these study results, the SmPC was updated twice: 2021 and 2023). Study completion is estimated Jan 2027.

the CHMP is of the opinion that the already existing entry in the EURD list for delamanid needs to be amended as follows:

The frequency of submission should be changed from 6-monthly to 1-yearly.

One further 6-monthly PSUR with DLP 27/10/2025 should be submitted by 05/01/2026, as per the EURD list.

A final 6-monthly PSUR with DLP 27/04/2026 will then be submitted by 06/07/2026.

The list of Union reference dates (EURD) should be updated accordingly.

4. EPAR changes

The table in the "Steps after" module of the EPAR will be updated as follows:

Scope

Renewal of marketing authorisation

Summary

The CHMP, having reviewed the available information on the status of the fulfilment of Specific Obligations and having confirmed the positive benefit risk balance, is of the opinion that the quality, safety and efficacy of this medicinal product continue to be adequately and sufficiently demonstrated. Furthermore, the CHMP considered that, as all Specific Obligations have been fulfilled, there are no remaining grounds for the marketing authorisations to remain conditional and therefore recommends the granting of a marketing authorisation no longer subject to Specific Obligations for Deltyba.

Annex: Rapporteurs' assessment comments on the renewal

PRAC input:

In this annual renewal,	**Yes**	**No**
- RMP submitted (If yes is ticked, discussion should be included in the Risk management plan section of the Annex)	☒	☐
- Outstanding SOB is a non-interventional PASS study (If yes is ticked, the relevant discussion should be included in the sub-section Outstanding Specific Obligations – status report for period covered of the Annex)	☐	☒
- There are issues originating from a parallel/recent PSUR or signal assessment to be flagged to the CHMP rapporteur (If yes is ticked, the relevant discussion should be included in the Clinical safety section of the Annex)	☐	☒
- PhV inspections have been conducted/are ongoing with an impact on the MA under annual Re-Assessment (If yes is ticked, the relevant discussion should be included in the Pharmacovigilance inspections section of the Annex)	☐	☒

5. Specific Obligations

5.1. Specific Obligations adopted with the initial marketing authorisation

Full list of SOBs as adopted with the initial marketing authorisation

Number	Description	Status
SOB 001	Complete confirmatory trial (242-09-213) examining delamanid added to OBR in licensed indication: Phase 3 trial comparing delamanid 100 mg BID for 2 months + 200 mg QD for 4 months plus OBR for 18-24 months versus OBR for 18-24 months with placebo for the first 6 months.	Fulfilled
SOB 002	A further study (242-14-253) exploring the relationship between different doses with respect to 2 months SCC and longer term outcome: to perform a controlled study of the efficacy, safety and PK of delamanid 100 mg twice daily for 2 months followed by delamanid 200 mg in a single daily dose for 4 months or delamanid 400 mg single daily dose for 6 months in adult patients with pulmonary MDR-TB, based on a CHMP-agreed protocol.	Replaced with new SOB 002 and 003

Since the granting of the conditional MA, the MAH has submitted the following SOBs:

The MAH has submitted the final study report for **242-09-213** addressing **SOB 001**. This study was assessed in a variation before the 2017 renewal procedure. Study 242-09-213 was a randomised, double blind and placebo-controlled study that commenced in September 2011. The final CSR dated 7 June 2017 provided unblinded data covering the entire 30-month trial period including final mortality rates.

The primary objective was to evaluate the efficacy of delamanid administered orally as 100 mg BID for 2 months (total dose 200 mg) followed by 200 mg QD for 4 months in combination with an OBR versus placebo with OBR for 6 months. The OBR was selected for each patient based on WHO's Guidelines for the programmatic management of drug-resistant TB in conjunction with national TB programme guidelines in each country.
No difference between treatment groups was seen in the proportion of patients with SCC by 6 months. For the primary efficacy endpoint, time to SCC, a favourable trend was seen for the delamanid group although the difference failed to reach statistical significance ($p = 0.0562$). A difference of 6 days faster median time to SCC for delamanid over placebo was observed.

See variation EMEA/H/C/002552/II/0021 for the full assessment and discussion.

With the submission of the final study report for study 213, SOB 001 was considered fulfilled.

In view of the expected futility of the initially proposed study 242-14-253, it was agreed that this study was no longer requested in order to fulfil SOB 002. It was however considered that further data should be generated to better characterise the patient population that will likely benefit from treatment with delamanid. In addition, the safety profile of delamanid, in particular the potential for QT prolongation and cardiac adverse events when used in combination with other anti-TB drugs affecting QT times, and the potential for hepatotoxicity should be further evaluated before a final MA can be considered. The proposed new SOB 002 study would not contribute to the evaluation of the dose of delamanid. To this end, an additional SOB 003 was agreed. The MAH was requested to further evaluate the PK/PD of

delamanid using the HFS-TB model. These data should allow further evaluation of the adequacy of the dose of delamanid and could also be useful for considerations regarding the susceptibility cut-off points.

Number	Description
New SOB 002	In order to further investigate the use of delamanid in different combination treatment regimens as well as safety, the MAH should submit the results of the endTB (Evaluating Newly approved Drugs for multidrug-resistant TB) study, a randomized, controlled Phase III trial in adults and adolescents with multi-drug-resistant tuberculosis conducted by Médecins Sans Frontières, including an additional analysis of the data with a focus on the evaluation of delamanid based on an agreed statistical analysis plan.
New SOB 003	In order to further characterise the PK/PD relationship of delamanid, the MAH should conduct and submit the results of an *in vitro* study using the HFS-TB model. (Fulfilled)

As agreed in the **new SOB 002**, in order to further investigate the use of delamanid in different combination treatment regimens as well as safety, the MAH should submit the results of the endTB (Evaluating Newly approved Drugs for multidrug-resistant TB) study. This is a randomised, controlled Phase III trial in adults and adolescents with multi-drug-resistant tuberculosis conducted by Médecins Sans Frontières/the endTB consortium. The MAH should perform an additional statistical analysis with a focus on the evaluation of delamanid. This statistical analysis plan, based on individual patient data, has been agreed to by the CHMP within procedure EMEA/H/C/002552/R/0052.

The endTB study was completed in June 2023. Study results have been disclosed during "The Union" Conference on 15 Nov 2023. However, as the MAH did not have access to the Individual Patient Data (IPD) needed for the delamanid specific analysis as set out in the statistical analysis plan (SAP), SOB 002 could not be fulfilled as initially planned. Hence while SOB 002 still concerns the data from the endTB study, a modification of the SOB was proposed in the previous renewal procedure to base the endTB study analysis on the publicly available data instead of the IPD. Furthermore, to consolidate the data package of SOB 002, submission of the results of the BEAT-TB study results was also requested.

In the meantime, a preprint of the study results of the endTB study was available and these results provide reassurance that the benefit-risk of delamanid remains positive in the authorised indication.

The endTB study evaluates the efficacy and safety of new, shorter (39 weeks) combination regimens for the treatment of MDR-TB. It enrolled participants in parallel across 5 experimental arms and 1 standard of care (SoC) control arm. Three of the five experimental study arms contain Deltyba (BDLLfxZ, DCLLfxZ, and DCMZ). One of those, the BDLLfxZ regimen (containing bedaquiline, delamanid, linezolid, levofloxacin and pyrazinamide), was non-inferior to the control group in both mITT and PP populations. DCMZ was non-inferior to the control in the mITT and not non-inferior in the PP populations and DCLLfxZ was not non-inferior to the control in both mITT and PP.

The agreed SAP from SOB 002 outlines the comparisons in a hierarchical fashion starting with the pooled test followed by parallel testing of the BDLLfxZ and DCLLfxZ arms. The unadjusted pooled analysis demonstrates non-inferiority in the mITT set, but it is borderline in the PP set and might depend on the method used to calculate the confidence intervals. The main contributor for the pooled analysis missing the non-inferiority margin in the PP set, seems to be the huge leap in the control arm going from ITT to PP (from 119 to 74 patients, from 80.7% to 95.7%). Availability of IPD or additional publicly available data might clarify this further.

The IPD from the endTB trial have been shared by MSF with the WHO. In the WHO rapid communication in 2024, the WHO Guideline Development group concluded that in eligible MDR/RR-TB patients with confirmed drug susceptibility to fluoroquinolones, the 9-month BDLLfxZ all-oral regimen may be effectively and safely used instead of the longer (≥18 months) regimens. The review

suggested against using DCLLfxZ and DCMZ regimens that were associated with high rates of treatment failure/relapse and acquired drug resistance.
More details on the WHO analyses and corresponding results were expected in the first quarter of 2025 by the upcoming update of the WHO consolidated guidelines '2025 WHO consolidated guidelines on the treatment of TB, drug-resistant TB and patient care and support'. It was decided to await the publication of those data that might bring more details on the endTB study.

In the same WHO rapid communication, the 6-month BDLLfxC regimen was recommended in place of 9-month or longer (> 18 months) regimens, in all patients with MDR/RR-TB with or without fluoroquinolone resistance who have not had previous exposure to bedaquiline, delamanid, and linezolid (defined as > 1-month exposure). This was based on data from the BEAT-TB South-Africa clinical trial, an open label, randomised controlled trial to establish the efficacy and safety of 6 months of bedaquiline (B), delamanid (D), and linezolid (L), with levofloxacin (Lfx) and clofazimine (C) compared to the current South African Standard of Care. The BEAT-TB study results could further justify the use of delamanid in combination treatment regimens and support the endTB trial analysis. The BEAT-TB South Africa study data were not publicly disclosed at the time of the previous renewal procedure.

It was therefore decided to postpone the deadline of SOB 002 to Q3 2026 for a submission alongside the annual renewal 2026.

In conclusion: in order to further investigate the use of delamanid in different combination treatment regimens as per approved indication as well as safety, the MAH should submit the results of the endTB study including a critical discussion of the publicly available data with a focus on the evaluation of delamanid i.e. including as possible an analysis based on the agreed statistical analysis plan and with an additional discussion when deviating from it.
In addition, publicly available results from the BEAT-TB study conducted by Wits Health Consortium should be submitted and discussed as these could further support the efficacy of delamanid in the approved indication.

Number	**Description**	**Due date**
SOB 002	In order to further investigate the use of delamanid in different combination treatment regimens as per approved indication as well as safety, the MAH should submit the publicly available data of the endTB (Evaluating Newly approved Drugs for multidrug-resistant TB) study, a randomised, controlled Phase III trial in adults and adolescents with multi-drug resistant tuberculosis conducted by Médecins Sans Frontières, with an analysis based on the agreed statistical analysis plan and publicly available results from the BEAT-TB study conducted by Wits Health Consortium.	Q3 2026

Regarding the **new SOB 003**, the revised HFS-TB study report together with a non-clinical overview including responses to the questions raised by the Rapporteurs on occasion of the 2019 annual renewal was submitted to the EMA on 02 Jul 2020 (procedure EMEA/H/C/002552/II/0045). This variation procedure was completed in 2021 (EMEA/H/C/002552/II/0045 procedure amendment on 16/9/2021). SOB 003 is therefore fulfilled.

5.2. Outstanding Specific Obligations – status report for period covered

SOB 002: In order to further investigate the use of delamanid in different combination treatment regimens as per approved indication as well as safety, the MAH should submit the publicly available data of the endTB (Evaluating Newly approved Drugs for multidrug-resistant TB) study, a randomised, controlled Phase III trial in adults and adolescents with multi-drug resistant tuberculosis conducted by Médecins Sans Frontières, with an analysis based on the agreed statistical analysis plan and publicly available results from the BEAT-TB study conducted by Wits Health Consortium.

endTB study

Methods

EndTB was a Phase 3, multi-country, open-label, randomised, controlled non-inferiority study to compare standard therapy for treatment of FQ-susceptible, RR-TB with five 9-month oral regimens including various combinations of bedaquiline, delamanid, linezolid, levofloxacin or moxifloxacin, clofazimine, and pyrazinamide.

The endTB trial was an RCT that was led by Partners In Health (PIH), Médecins Sans Frontières (MSF), and Interactive Research and Development (IRD).

Study Participants

Adults and adolescents (≥ 15 years old) with fluoroquinolone-susceptible, pulmonary rifampin-resistant tuberculosis that was confirmed by WHO-endorsed rapid tests were enrolled at 12 sites in Georgia, India, Kazakhstan, Lesotho, Pakistan, Peru, and South Africa.
Inclusion in the trial was irrespective of human immunodeficiency virus (HIV) serostatus and CD4 lymphocyte count.

The trial excluded persons with the following conditions at baseline: pregnancy; elevated liver enzymes; uncorrectable electrolyte disorders; a QT interval corrected according to Fridericia's formula (QTcF) of at least 450 msec; resistance or previous exposure for 30 days or more to bedaquiline, delamanid, clofazimine, or linezolid; and at least 15 days of treatment with any second-line antituberculosis drug during the current episode of tuberculosis.

Treatments

Multidrug treatment regimens for fluoroquinolone-susceptible, rifampin-resistant tuberculosis.

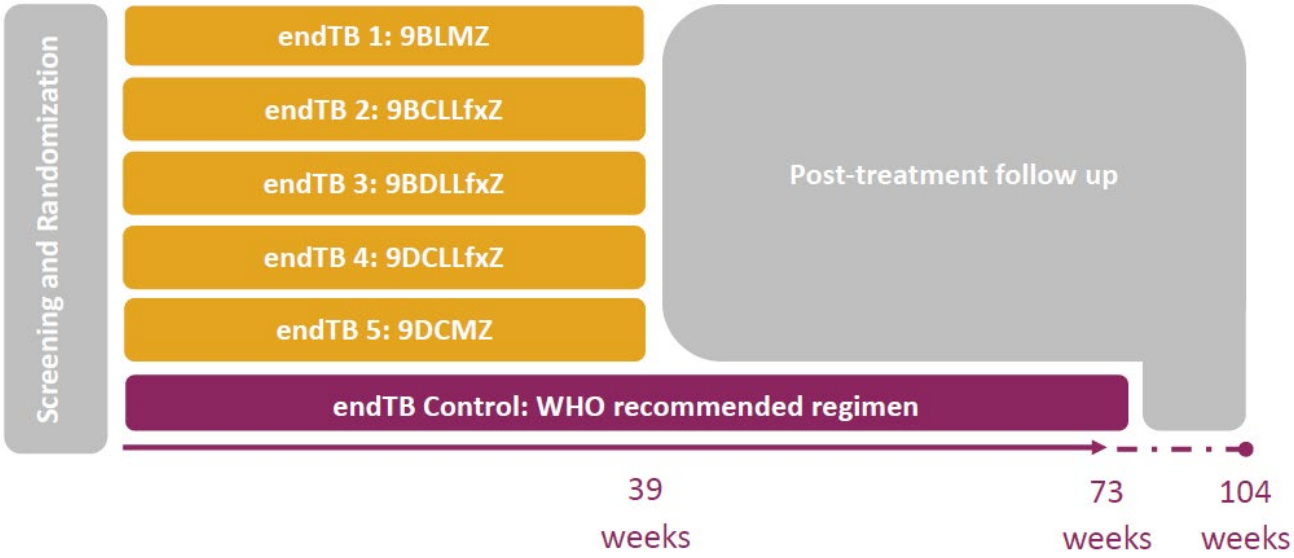

Figure 1. EndTB Study Design

Five Experimental regimens contained bedaquiline (B) and/or delamanid (D) and up to 4 companion drugs (clofazimine (C), linezolid (L), levofloxacin (Lfx), moxifloxacin (M), and pyrazinamide (Z)) and were delivered for 39 weeks (~9 months). The regimen combinations were BLMZ, BCLLfxZ, BDLLfxZ, DCLLfxZ, and DCMZ.

Table 1. Treatment regimens in the endTB study

Trial regimens	Bedaquiline	Delamanid	Clofazimine	Linezolid	Fluoroquinolone	Pyrazinamide
9BLMZ	B			L	M	Z
9BCLLfxZ	B		C	L	Lfx	Z
9BDLLfxZ	B	D		L	Lfx	Z
9DCLLfxZ		D	C	L	Lfx	Z
9DCMZ		D	C		M	Z
Control	Standard of care for the treatment of rifampin-resistant and fluoroquinolone-susceptible tuberculosis. Composed according to latest World Health Organization guidelines, as they evolved during the trial. This group included mostly participants treated with the 18-month conventional regimen.					

Dosing of experimental regimens will be oral and weight based. Delamanid dosing was 100 mg BID.

Standard-of-care control-arm

Standard-therapy regimens reflected the WHO guidelines that were in effect while the study was being conducted. Therefore, duration could vary and would be approximately 86 weeks for the conventional regimen and 39-52 weeks for the standardised shorter regimen. These regimens were expected to be mostly individualised regimens of 18 to 24 months' duration. WHO recommendations endorsed the use of the new drugs bedaquiline and delamanid as well as the repurposed drugs linezolid and clofazimine,

among others. In experimental regimens containing linezolid, the linezolid dose was decreased at ≤ Week 16 if necessary to reduce toxicity.

Note that during the trial enrolment period, the WHO guidelines changed twice.

Patient follow-up was 104 weeks (2 years) post randomisation.

Objectives

Primary: To assess whether the efficacy of experimental regimens at 73 weeks is non-inferior to that of the control.

Secondary objectives included comparison of the efficacy of experimental regimens to that of the control at 104 and 39 weeks and comparison of the safety (deaths, Grade 3 or higher AEs, SAEs, QTc prolongation) among others.

Outcomes/endpoints

The **primary efficacy outcome** is the proportion of participants with **favourable** outcome at **week 73**.

A favourable outcome at week 73 was defined as the absence of an unfavourable outcome and either two consecutive negative cultures (including one between weeks 65 and 73) or favourable bacteriologic, radiologic, and clinical evolution. Unfavourable outcomes included death (from any cause), the replacement or addition of one drug in the experimental regimens or two drugs in the standard-therapy regimen, or the initiation of new treatment for rifampin-resistant tuberculosis.

Rationale for the timing of the primary endpoint evaluation: The greatest risk of recurrence due to relapse is in the period immediately following treatment completion. The recommended minimal follow-up in TB trials is 6 months. endTB has, therefore, elected to follow all participants on experimental regimens for at least 6 months (26 weeks) after completion of the regimen to evaluate potential relapse. Participants may take as long as 47 weeks to complete 39 weeks of treatment. The 73-week endpoint permits 6-month evaluation of those participants who require the full 47 weeks.

Secondary outcome measures

Favourable outcomes at Week 39 and Week 104 were secondary endpoints.

Safety endpoints were Grade 3 or higher AEs, SAEs, death, discontinuation of at least 1 trial drug because of AEs, and adverse events of special interest (AESIs; defined as hepatotoxic events, haematologic toxic events, optic neuritis, peripheral neuropathy, and QTcF prolongation) of ≥Grade 3 by Week 73.

Sample size

750 subject planned, 754 subjects included

Randomisation

Bayesian adaptive randomisation based on efficacy endpoints.

Note that randomisation was ultimately relatively balanced because the experimental regimens performed similarly to standard therapy in the interim analyses used to adjust probabilities.

Statistical methods

In light of the potential benefits without an improvement in efficacy (shortening treatment, all-oral regimen, reduce toxicity, enhance adherence and completion) a non-inferiority design was selected for the endTB trial.

The expected 70% favourable outcome at 73 weeks in the control arm was derived from existing data about the current conventional regimen and the enhanced standard afforded by the control in endTB. The expected 73-week response in the experimental arm is 72%, based on prior study outcomes.

A sufficient sample size was selected to assure 80% power to detect if more than half (3 of 5) of the regimens are non-inferior. Sample size increases to detect 5 non-inferior regimens were not justifiable.

Sample size

The sample size was determined with the assumption that favourable outcomes at Week 73 would be seen in 75% of patients in the experimental regimen groups and in 70% of patients in the standard-therapy group, that relapse would occur in 10% of patients, that 11% of patients would be ineligible for inclusion in the mITT, and an additional 10% would be ineligible for inclusion in the PP. A sample size of 750 was calculated to provide a statistical power of 80% to determine non-inferiority (at a 1-sided type I error rate of 2.5%) of 3 experimental regimens in the mITT and 2 in the PP.

Non-inferiority margin

The non-inferiority margin was set at -12% because the standard therapy was expected to perform better than other reference standards. Slightly worse efficacy of the experimental regimens was considered an acceptable trade-off for the benefits of the shortened treatment duration and reduction of the pill burden. Also, other recent trials of TB treatments had used 12% non-inferiority margins.

Analysis populations

The safety population will include all enrolled participants who had received at least one dose of study treatment (exposed).

The first efficacy population was the modified intention-to-treat population (mITT) population. The mITT population included participants from the safety population who had a pre-randomisation culture positive for Mycobacterium tuberculosis but excluded participants with baseline phenotypic resistance to bedaquiline, clofazimine, delamanid, any fluoroquinolone, or linezolid as well as patients without post-baseline data.

A secondary efficacy population is the per-protocol (PP) population. The PP population included participants from the mITT population who received for less than 7 days a prohibited concomitant medication or a trial drug that was not prescribed according to the protocol and completed protocol-consistent course of treatment (at least 80% of expected doses taken within 120% of the regimen duration) or did not complete the course of treatment because of treatment failure or death.

Primary Endpoint Analyses

The efficacy analysis relied on the absolute between-group difference in the percentages of participants with a favourable outcome at week 73 between each of the 5 experimental arms versus control. To sequence regimen comparisons, a hierarchical testing approach was used. Testing was to continue until a comparison did not establish non-inferiority.

Non-inferiority in the mITT population was to be established if the lower bound of the 95% confidence interval around the difference exceeded -12 percentage points.

PP analyses provided complementary information but were not used for formal testing of non-inferiority.

The primary analysis was unadjusted.

Secondary analyses explored confounding according to prespecified covariates.

Results

From publication of the endTB study results

Participant flow

1542 persons underwent screening and 754 underwent randomisation. Nine participants were excluded from the safety population (which now included 745 participants) and 46 from the modified intention-to-treat population (699 participants). The per-protocol population included 562 participants.

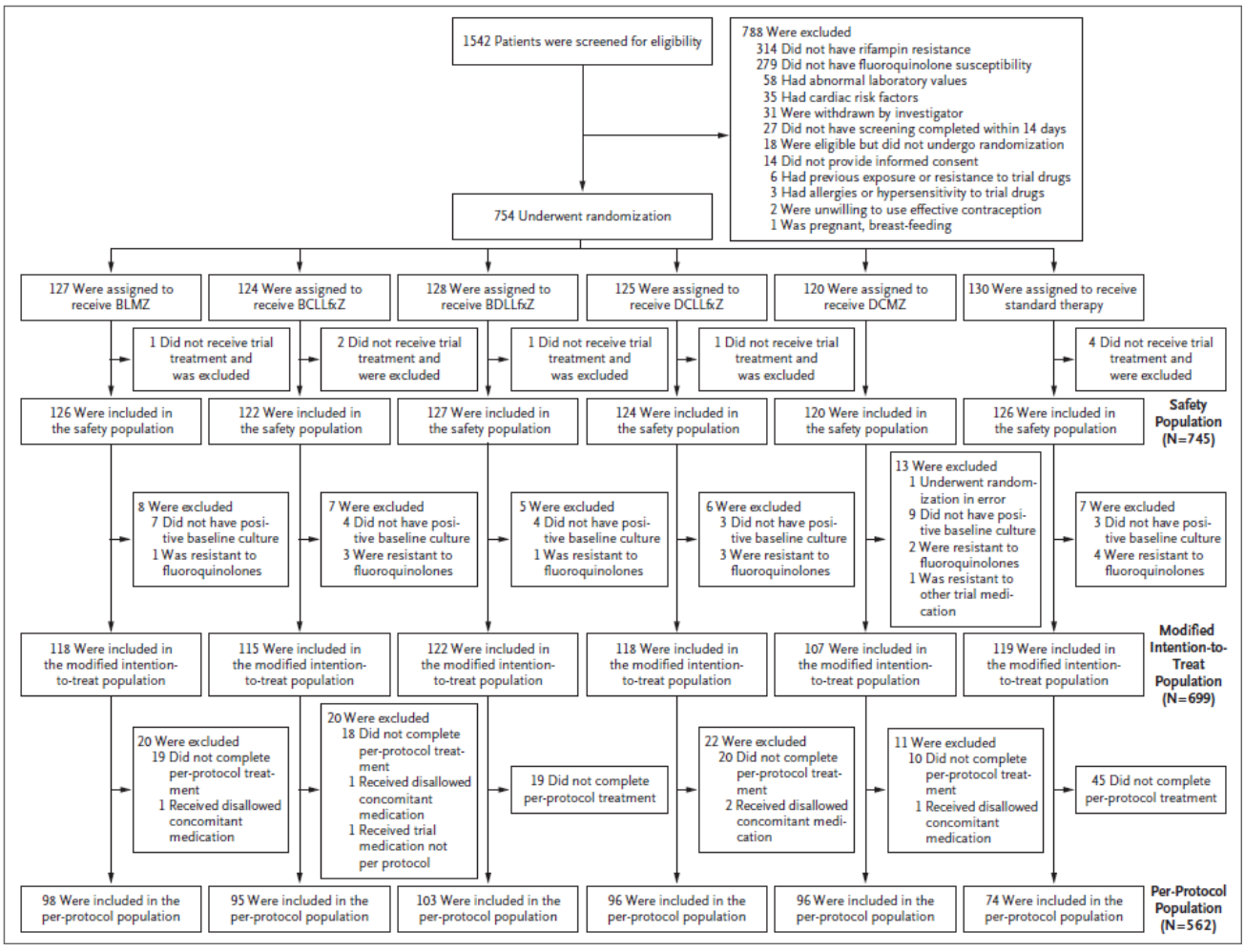

Figure 2. Trial Groups and Analysis Populations

Note: In the experimental arm, study treatment discontinuation is defined as permanent discontinuation of two or more investigational drugs, or addition or replacement of one or more investigational drugs. In the control arm, study treatment discontinuation is defined as addition or replacement of two or more drugs. Discontinuation of a single investigational drug in the experimental arm or two or more investigational drugs in the control arm (without replacement) is not considered to

be study treatment discontinuation. Modification of dose or frequency or temporary suspension of one or more investigational drugs is also not considered to be study treatment discontinuation.

Recruitment

The endTB clinical trial started in 2017 and randomised and followed 754 participants over 7 years and across 12 sites in seven countries: Georgia, India, Kazakhstan, Lesotho, Pakistan, Peru and South Africa.

Baseline data

Table 2. Baseline Characteristics of the Participants (mITT Population)*

Characteristic	BLMZ (N=118)	BCLLfxZ (N=115)	BDLLfxZ (N=122)	DCLLfxZ (N=118)	DCMZ (N=107)	Standard Therapy (N=119)	Total (N=699)
Female sex — no. (%)	41 (34.7)	37 (32.2)	55 (45.1)	38 (32.2)	45 (42.1)	48 (40.3)	264 (37.8)
Age — yr							
Median (IQR)	31 (25–41)	38 (26–50)	32 (22–45)	30 (22–41)	32 (24–46)	31 (22–42)	32 (23–44)
Range	15–69	15–70	15–70	15–69	15–71	15–70	15–71
Country — no. (%)							
Georgia	2 (1.7)	2 (1.7)	1 (0.8)	3 (2.5)	1 (0.9)	3 (2.5)	12 (1.7)
India	8 (6.8)	4 (3.5)	3 (2.5)	3 (2.5)	1 (0.9)	4 (3.4)	23 (3.3)
Kazakhstan	30 (25.4)	35 (30.4)	33 (27.0)	22 (18.6)	24 (22.4)	23 (19.3)	167 (23.9)
Lesotho	14 (11.9)	11 (9.6)	15 (12.3)	11 (9.3)	14 (13.1)	12 (10.1)	77 (11.0)
Pakistan	18 (15.3)	16 (13.9)	13 (10.7)	11 (9.3)	16 (15.0)	18 (15.1)	92 (13.2)
Peru	38 (32.2)	39 (33.9)	49 (40.2)	54 (45.8)	45 (42.1)	51 (42.9)	276 (39.5)
South Africa	8 (6.8)	8 (7.0)	8 (6.6)	14 (11.9)	6 (5.6)	8 (6.7)	52 (7.4)
Median body-mass index (IQR)†	19.9 (17.5–22.1)	20.0 (18.4–23.6)	20.9 (18.8–22.8)	20.6 (18.1–23.6)	19.9 (17.9–22.2)	20.8 (17.6–23.0)	20.4 (18.0–22.8)
ECOG performance-status score — no. (%)‡							
0	42 (35.6)	35 (30.4)	51 (41.8)	47 (39.8)	35 (32.7)	43 (36.1)	253 (36.2)
1	55 (46.6)	62 (53.9)	53 (43.4)	54 (45.8)	53 (49.5)	63 (52.9)	340 (48.6)
2	17 (14.4)	15 (13.0)	12 (9.8)	16 (13.6)	17 (15.9)	11 (9.2)	88 (12.6)
3	4 (3.4)	3 (2.6)	6 (4.9)	1 (0.8)	2 (1.9)	2 (1.7)	18 (2.6)
HIV infection — no. (%)	15 (12.7)	14 (12.2)	17 (13.9)	18 (15.3)	15 (14.0)	19 (16.0)	98 (14.0)
Median CD4 count among participants with HIV infection (IQR) — cells per mm³§	170.5 (41.0–505.0)	190 (85.0–377.0)	314.5 (157.0–478.5)	328.5 (170.5–579.5)	404.0 (143.0–643.0)	269.0 (83.0–443.0)	296.0 (118.0–497.0)
Antiretroviral treatment among participants with HIV infection — no./total no. (%)	12/15 (80.0)	9/14 (64.3)	10/17 (58.8)	14/18 (77.8)	11/15 (73.3)	12/19 (63.2)	68/98 (69.4)
Hepatitis B infection, with hepatitis B surface antigen — no. (%)	3 (2.5)	3 (2.6)	0	2 (1.7)	4 (3.7)	4 (3.4)	16 (2.3)
Hepatitis C infection — no. (%)	5 (4.2)	5 (4.3)	3 (2.5)	4 (3.4)	3 (2.8)	6 (5.0)	26 (3.7)
Diabetes — no. (%)¶	19 (16.1)	19 (16.5)	20 (16.4)	16 (13.6)	16 (15.0)	15 (12.6)	105 (15.0)

Peripheral-blood smear result — no. (%)							
Negative or scanty	20 (16.9)	19 (16.5)	31 (25.4)	24 (20.3)	18 (16.8)	19 (16.0)	131 (18.7)
1 to 2+	57 (48.3)	59 (51.3)	58 (47.5)	49 (41.5)	43 (40.2)	52 (43.7)	318 (45.5)
3+	41 (34.7)	37 (32.2)	33 (27.0)	45 (38.1)	46 (43.0)	48 (40.3)	250 (35.8)
Cavitation — no. (%)‖	68 (57.6)	69 (60.0)	73 (59.8)	53 (44.9)	61 (57.0)	75 (63.0)	399 (57.1)
Extent of tuberculosis — no. (%)**							
Limited	21 (17.8)	14 (12.2)	18 (14.8)	23 (19.5)	20 (18.7)	18 (15.1)	114 (16.3)
Moderate	70 (59.3)	77 (67.0)	77 (63.1)	67 (56.8)	64 (59.8)	71 (59.7)	426 (60.9)
Extensive	27 (22.9)	24 (20.9)	26 (21.3)	25 (21.2)	23 (21.5)	29 (24.4)	154 (22.0)
Previous exposure to tuberculosis treatment — no. (%)††							
None	76 (64.4)	67 (58.3)	78 (63.9)	80 (67.8)	72 (67.3)	74 (62.2)	447 (63.9)
First-line drugs only	20 (16.9)	23 (20.0)	27 (22.1)	25 (21.2)	23 (21.5)	31 (26.1)	149 (21.3)
Other drugs	15 (12.7)	19 (16.5)	15 (12.3)	7 (5.9)	11 (10.3)	11 (9.2)	78 (11.2)
Pyrazinamide resistance — no. (%)‡‡	57 (48.3)	63 (54.8)	66 (54.1)	66 (55.9)	66 (61.7)	59 (49.6)	377 (53.9)
Resistance to second-line injectable medication — no. (%)§§	14 (11.9)	18 (15.7)	15 (12.3)	13 (11.0)	14 (13.1)	16 (13.4)	90 (12.9)

In the mITT population, 264 participants (37.8%) were women. The median age was 32 years, and 25 participants (3.6%) were younger than 18 years of age; 98 participants (14.0%) were living with HIV infection, 568 participants (81.3%) had sputum smear results graded 1+ or higher, and 57.1% of the participants had cavitation on chest radiography.
Modest variability in severity of tuberculosis and previous treatment of tuberculosis was observed among the groups; expected differences in coexisting conditions (e.g., HIV infection, diabetes, and hepatitis C infection) occurred according to country.

Standard-therapy regimens consisted of at least five drugs at the start of the treatment course in 118 of 119 participants in the standard therapy group (99.2%). Most participants (114; 95.8%) were assigned to individualised 18-to-24- month regimens, and 97 participants (81.5%) received treatment in accordance with the WHO 2022 recommendations, and 22 participants (18.5%) started on regimens that conformed with WHO 2016 Guidance and do not conform to 2022 Guidance. Twelve patients (10.1%) in the control arm had a regimen including delamanid at initiation of treatment.

Numbers analysed

The individual patient data are not available.

Table 3. Primary Efficacy End Points at Week 73 (mITT Population)*

Outcome	BLMZ (N=118)	BCLLfxZ (N=115)	BDLLfxZ (N=122)	DCLLfxZ (N=118)	DCMZ (N=107)	Standard Therapy (N=119)	Total (N=699)
Favorable†							
Participants with favorable outcome — no. (%)	105 (89.0)	104 (90.4)	104 (85.2)	93 (78.8)	89 (83.2)	96 (80.7)	591 (84.5)
Difference from standard therapy (95% CI) — percentage points	8.3 (–0.8 to 17.4)	9.8 (0.9 to 18.7)	4.6 (–4.9 to 14.1)	–1.9 (–12.1 to 8.4)	2.5 (–7.5 to 12.5)	—	—
Negative culture results, wk 65 and wk 73 — no. (%)	102 (86.4)	100 (87.0)	102 (83.6)	90 (76.3)	87 (81.3)	91 (76.5)	572 (81.8)
Favorable bacteriologic, clinical, and radiologic evolution — no. (%)‡	3 (2.5)	4 (3.5)	2 (1.6)	3 (2.5)	2 (1.9)	5 (4.2)	19 (2.7)
Unfavorable†							
Participants with unfavorable outcome — no. (%)	13 (11.0)	11 (9.6)	18 (14.8)	25 (21.2)	18 (16.8)	23 (19.3)	108 (15.5)
Death from any cause — no. (%)§	2 (1.7)	1 (0.9)	3 (2.5)	3 (2.5)	2 (1.9)	2 (1.7)	13 (1.9)
Positive culture results — no. (%)¶	1 (0.8)	3 (2.6)	4 (3.3)	12 (10.2)	8 (7.5)	1 (0.8)	29 (4.1)
Recurrence — no. (%)‖	0	0	0	1 (0.8)	2 (1.9)	0	3 (0.4)
Permanent treatment discontinuation due to adverse event — no. (%)	3 (2.5)	3 (2.6)	1 (0.8)	1 (0.8)	1 (0.9)	2 (1.7)	11 (1.6)
Poor treatment adherence or loss to follow-up — no. (%)	3 (2.5)	2 (1.7)	3 (2.5)	3 (2.5)	4 (3.7)	8 (6.7)	23 (3.3)
Withdrawal of consent — no. (%)	1 (0.8)	1 (0.9)	4 (3.3)	3 (2.5)	0	7 (5.9)	16 (2.3)
Other unfavorable outcome — no. (%)**	3 (2.5)	1 (0.9)	3 (2.5)	2 (1.7)	1 (0.9)	3 (2.5)	13 (1.9)

* The widths of the confidence intervals have not been adjusted for multiplicity and should not be used in place of hypothesis testing.
† A favorable outcome at week 73 (the primary efficacy end point) was defined as the absence of an unfavorable outcome and either two consecutive negative cultures (including one between weeks 65 and 73) or favorable bacteriologic, radiologic, and clinical evolution. Unfavorable outcomes included death (from any cause), the replacement or addition of one drug in the experimental regimens or two drugs in the standard-therapy regimen, or the initiation of new treatment for rifampin-resistant tuberculosis (for the full list of unfavorable outcomes, see Section 2.6.2 in the Supplementary Appendix).
‡ This category includes participants without culture results between week 65 and week 73.
§ Thirteen participants in the modified intention-to-treat population died, and one participant in the safety population who was excluded from the modified intention-to-treat population also died. One participant in the modified intention-to-treat population had a positive culture result that was classified as an unfavorable outcome at week 73 and later died.
¶ This category included participants who permanently discontinued treatment because of a positive sputum culture at week 16 or later or who had a positive sputum culture between week 65 and week 73.
‖ Included in this category were participants who had a positive sputum culture or started a new treatment regimen after treatment completion.
** This category comprised participants who were not assessed after treatment completion (6 participants), were deemed by an investigator to have an unfavorable outcome (4 participants), were pregnant or breast-feeding (2 participants), or used a prohibited concomitant medication (1 participant).

Table 4. Primary Efficacy Outcomes at Week 73 (PP Population)*

Outcome	9BLMZ (N = 98)	9BCLLfxZ (N = 95)	9BDLLfxZ (N = 103)	9DCLLfxZ (N = 96)	9DCMZ (N = 96)	Control (N = 74)	Total (N = 562)
Favorable							
Participants - no. (%)	94 (95.9%)	91 (95.8%)	97 (94.2%)	82 (85.4%)	82 (85.4%)	71 (95.9%)	517 (92.0%)
Absolute difference from control (%, 95% CI)	0.0% (-6.0%;5.9%)	-0.2% (-6.2%;5.9%)	-1.8% (-8.1%;4.6%)	-10.5% (-18.9%;-2.2%)	-10.5% (-18.9%;-2.2%)	--	--
Participants with negative culture results, Week 65 and 73 – no. (%)	93 (94.9%)	88 (92.6%)	95 (92.2%)	80 (83.3%)	81 (84.4%)	69 (93.2%)	506 (90.0%)
Participants with favorable bacteriological, clinical and radiological evolution^^ – no. (%)	1 (1.0%)	3 (3.2%)	2 (1.9%)	2 (2.1%)	1 (1.0%)	2 (2.7%)	11 (2.0%)
Unfavorable							
Participants – no. (%)	4 (4.1%)	4 (4.2%)	6 (5.8%)	14 (14.6%)	14 (14.6%)	3 (4.1%)	45 (8.0%)
Death, all cause – no. (%)££	2 (2.0%)	0 (0.0%)	3 (2.9%)	3 (3.1%)	2 (2.1%)	2 (2.7%)	12 (2.1%)
Participants with positive culture results** – no. (%)	1 (1.0%)	3 (3.2%)	1 (1.0%)	10 (10.4%)	8 (8.3%)	1 (1.4%)	24 (4.3%)
Participants with recurrence§§ – no. (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (2.1%)	0 (0.0%)	2 (0.4%)
Participants with permanent treatment discontinuation due to adverse event – no. (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Participants with poor treatment adherence/lost to follow-up – no. (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.0%)	0 (0.0%)	1 (0.2%)
Participants who withdrew consent – no. (%)	0 (0.0%)	0 (0.0%)	1 (1.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)
Participants with other unfavorable outcome## – no. (%)	1 (1.0%)	1 (1.1%)	1 (1.0%)	1 (1.0%)	1 (1.0%)	0 (0.0%)	5 (0.9%)

*A protocol-consistent course of treatment was 80% of expected doses taken within 120% of the intended regimen duration. Participants who received more than 7 days of either a prohibited concomitant medication or a study drug not prescribed according to protocol were also excluded from the per-protocol population.

^^participants without culture results between Week 65 and Week 73;

ff12 PP participants experienced death as a treatment outcome, 1 participant in the safety population who was excluded from the mITT population also experienced death. 1 participant in the mITT population was assigned positive culture result as unfavourable outcome at 73 weeks and later died; 1 death occurred in a participant in the mITT population, who was excluded from PP population. Exclusion occurred because the participant did not complete a protocol-consistent course of treatment. Death occurred after treatment was stopped and was not the reason for receiving less than 80% of doses.
**participants who permanently discontinued treatment because of a positive sputum culture at Week 16 or later, or who had a positive sputum culture between Week 65 and Week 73;
§§participants who, after treatment completion, had a positive sputum culture or started a new treatment regimen;
##participants with other unfavourable outcome: not assessable after completing treatment (n=5).

Outcomes and estimation

In the primary, unadjusted outcome analysis of the standard-therapy group, favourable outcomes occurred in 80.7% (95% confidence interval [CI], 72.4 to 87.3) of the participants in the mITT population and in 95.9% (95% CI, 88.6 to 99.2) of the participants in the PP population. A hierarchically tested comparison revealed that four of the experimental regimens (BCLLfxZ [endTB2], BLMZ [endTB1], BDLLfxZ [endTB3], DCMZ [endTB5]) were non-inferior to standard therapy in the mITT population. Differences in risk from standard therapy were:

BCLLfxZ [endTB2]: 9.8% (95% CI, 0.9 to 18.7)

BLMZ [endTB1]: 8.3% (95% CI, -0.8 to 17.4)

BDLLfxZ [endTB3]: 4.6% (95% CI, -4.9 to 14.1)

DCMZ [endTB5]: 2.5% (95% CI, -7.5 to 12.5)

The DCLLfxZ [endTB4] regimen was not non-inferior in the modified intention-to-treat population. Differences in risk from standard therapy was: -1.9% (95%CI, -12.1 to 8.4). Per-protocol analyses supported these findings, except for DCMZ which was not non-inferior in this population. Per-protocol analyses provided complementary information but were not used for formal testing of a non-inferiority comparison.
Thus, non-inferiority to standard therapy was established for 2 of the 3 delamanid-containing regimens based on the mITT.

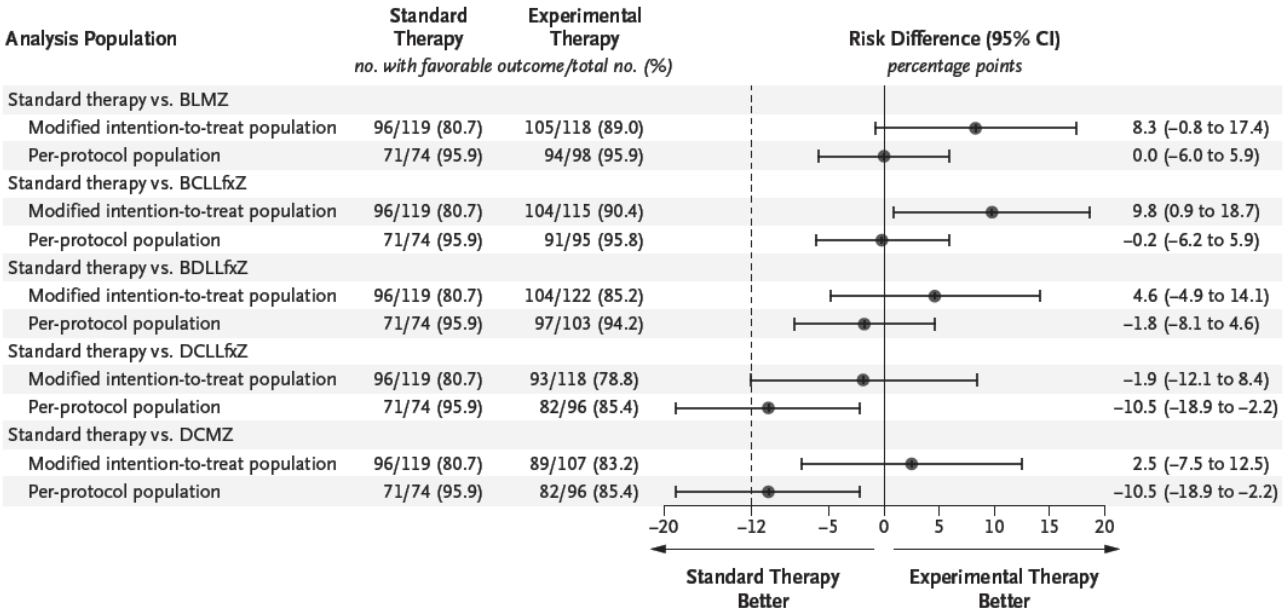

Figure 3. Primary Efficacy Analysis at Week 73, mITT and PP population

Among the participants in the mITT population, unfavourable outcomes due to positive culture occurred in 4.1% of all the participants, in 8 participants (7.5%) in the DCMZ group, and in 12 participants (10.2%) in the DCLLfxZ group (Table 3). Loss to follow-up and withdrawal of consent occurred in a larger percentage of the participants in the standard-therapy group than in any of the experimental regimen groups. (poor treatment adherence/LTFU: control 6.7%, experimental arms 1.7% to 3.7%; withdrawal of consent: control 5.9%, experimental arms 0% to 3.3%; see Table 3). Overall, recurrence occurred in 3 participants (0.4%), i.e. 1 in the DCLLfxZ group and 2 in the DCMZ group.

Ancillary analyses

Efficacy outcomes were similar for secondary end points, at week 39 and week 104, in adjusted analyses, and in sensitivity analyses (Figure 4, Figure 5, Figure 6).

Prespecified adjusted analyses supported the primary results. The adjusted risk difference (aRD) for 9BDLLfxZ in the mITT population was 3.9% (95%CI, -5.8 to 13.6), in the PP population this was -2.9%

(95%CI, -10.2 to 4.4). Relative to the control in the mITT population, 9DCMZ had an aRD of 1.9% (95%CI, -8.4 to 12.3) and in the PP population aRD of -10.8% (95%CI, -19.3 to -2.2).

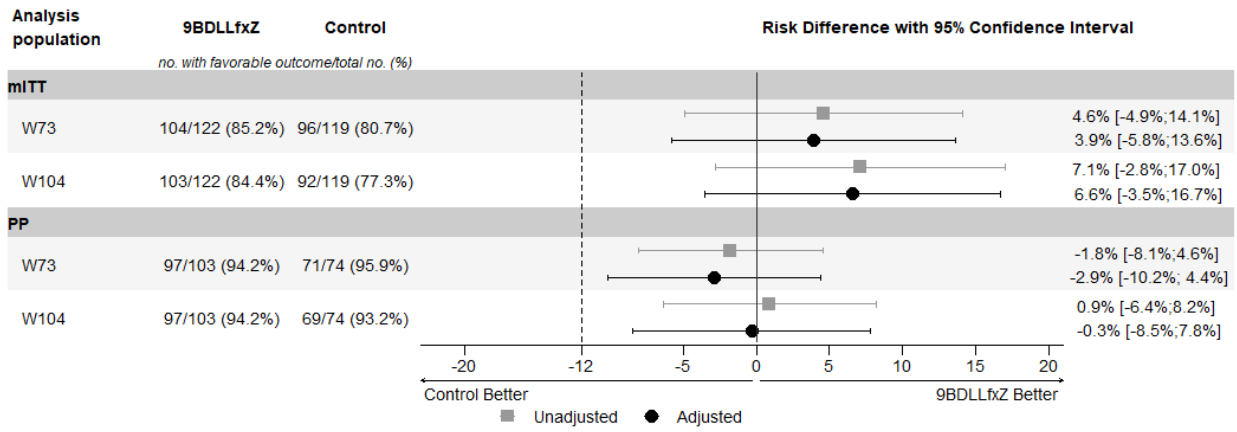

Figure 4. Primary and Secondary efficacy analyses of endTB Trial Regimen 9BDLLfxZ vs Control at Week 73 and Week 104

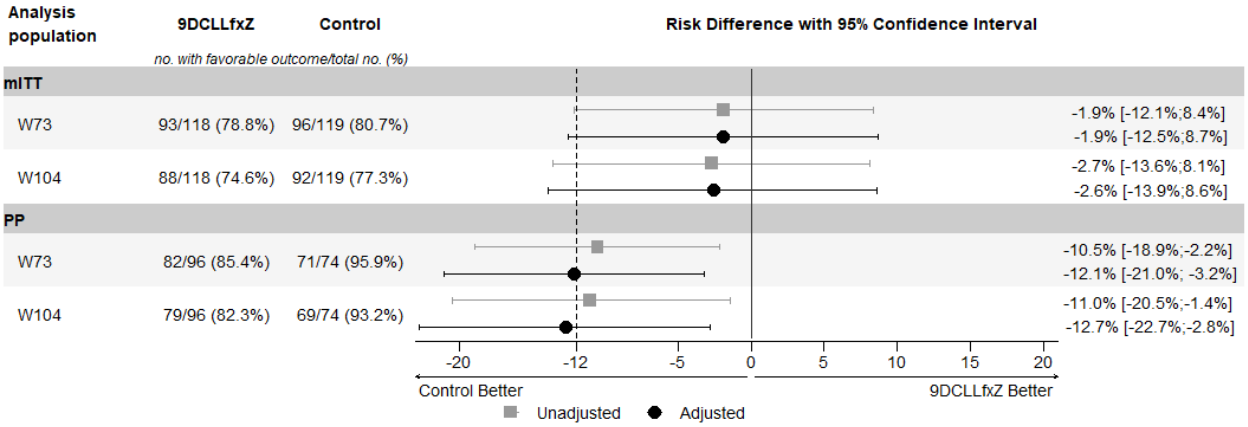

Figure 5. Primary and Secondary efficacy analyses of endTB Trial Regimen 9DCLLfxZ vs Control at Week 73 and Week 104

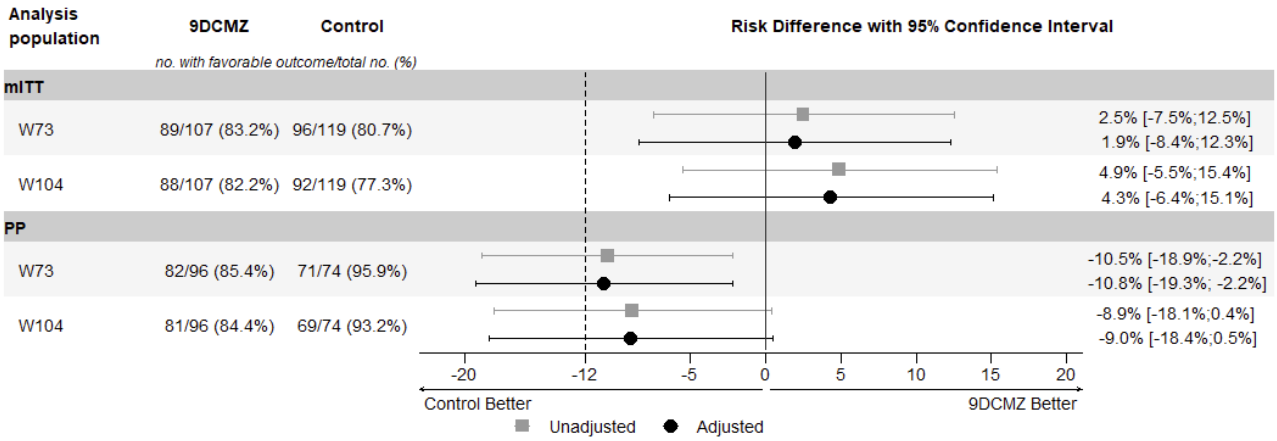

Figure 6. Primary and Secondary efficacy analyses of endTB Trial Regimen 9DCMZ vs Control at Week 73 and Week 104

Note: Confidence intervals widths have not been adjusted for multiplicity and the intervals should not be used in place of hypothesis testing for secondary outcomes (Week 104). They are only presented for precision purposes.

Data-driven backwards selection among pre-specified covariates resulted in mITT (modified-intention-to-treat) model at weeks 73 and 104 adjusted for: hepatitis C, extent of disease; and PP (per-protocol) analyses at weeks 73 and 104 adjusted for: Age, BMI.

Overall, treatment effects at week 73 did not differ substantially in subgroup analyses in the mITT population. Possible exceptions were noted for subgroups defined according to country, previous exposure to second-line antituberculosis drugs, cavitation, HIV infection, and low body-mass index.

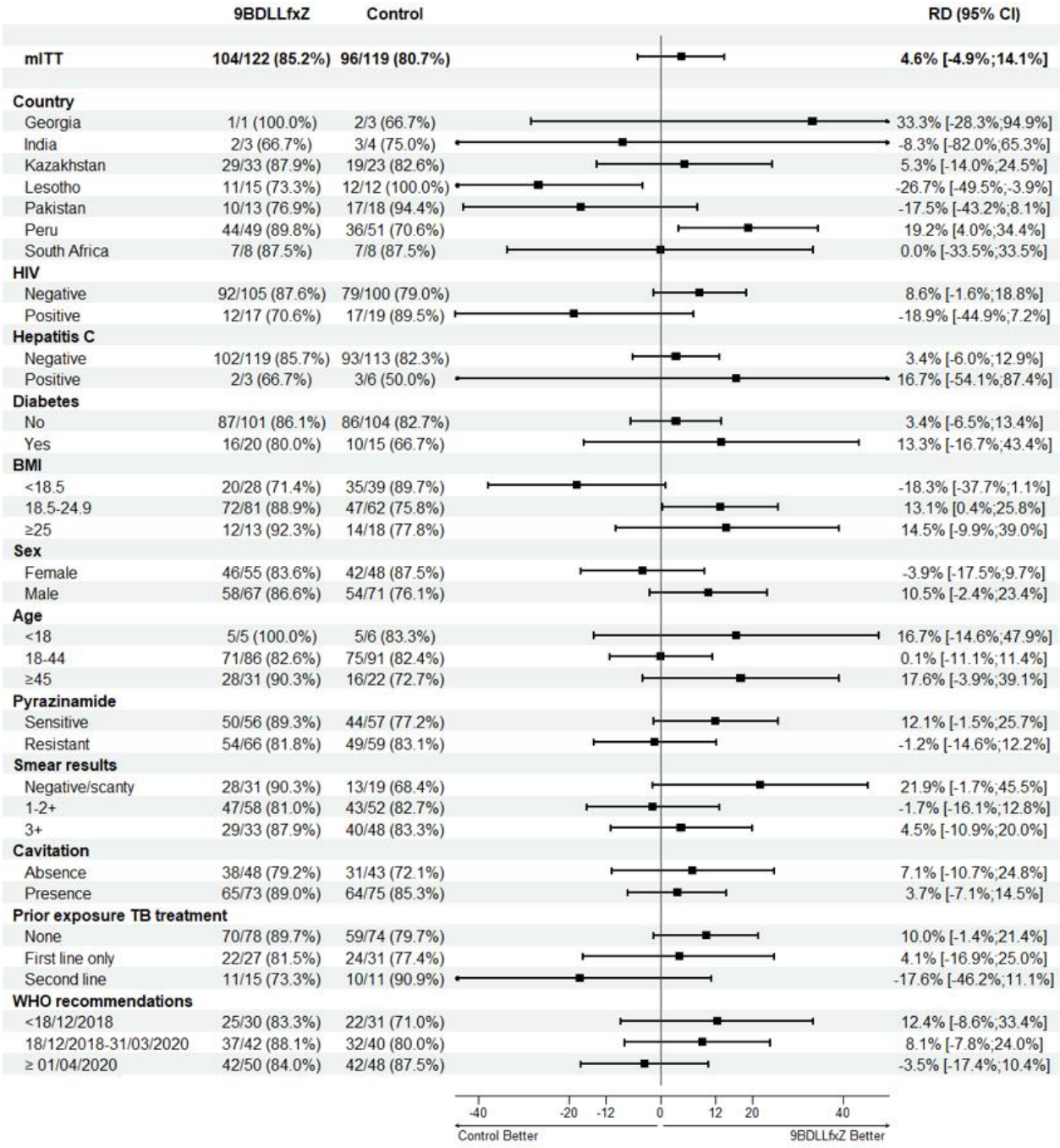

Figure 7. Subgroup Analysis of Efficacy of endTB Trial Regimen 9BDLLfxZ vs Control at Week 73 (mITT Population)

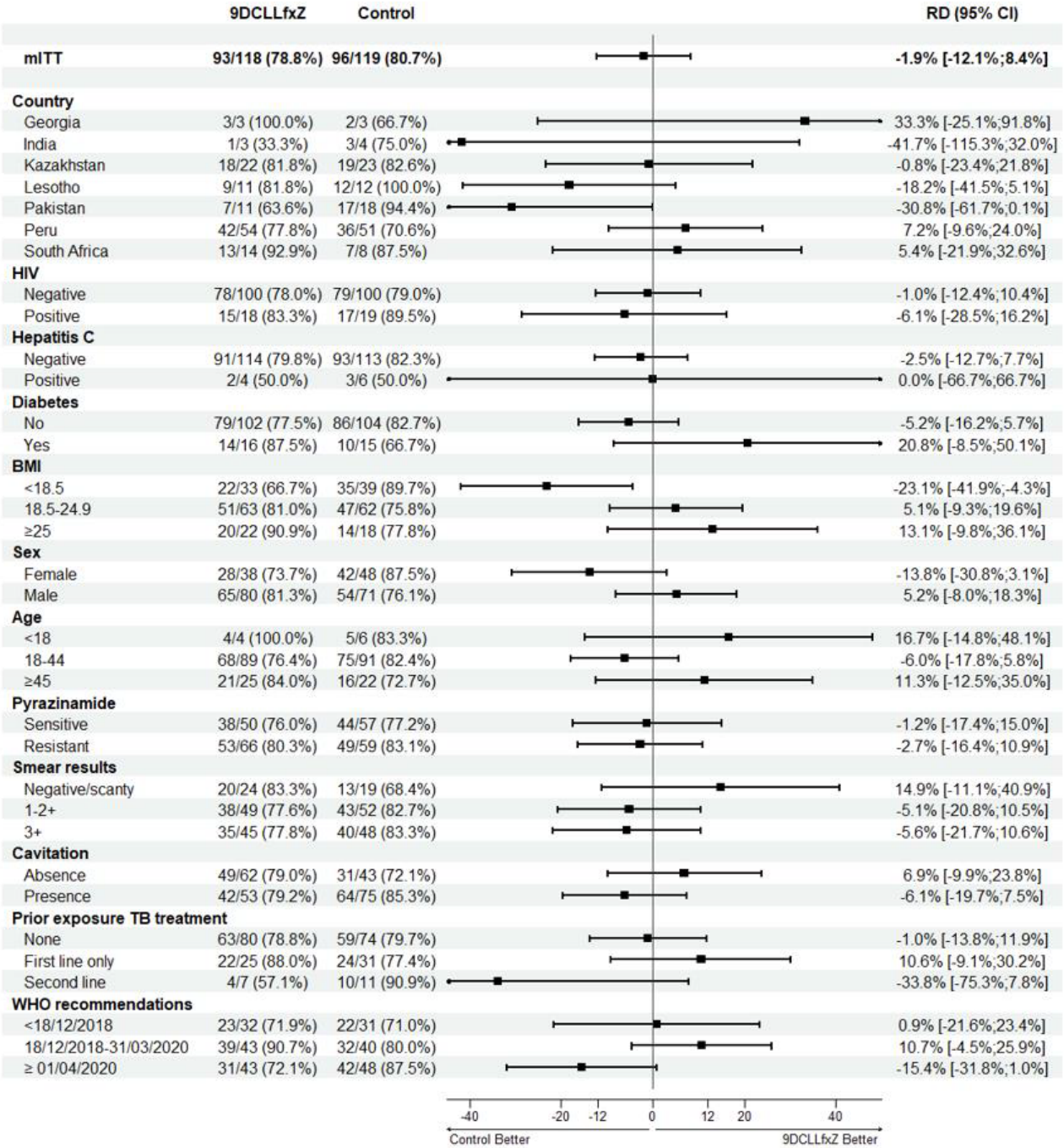

Figure 8. Subgroup Analysis of Efficacy of endTB Trial Regimen 9DCLLfxZ vs Control at Week 73 (mITT Population)

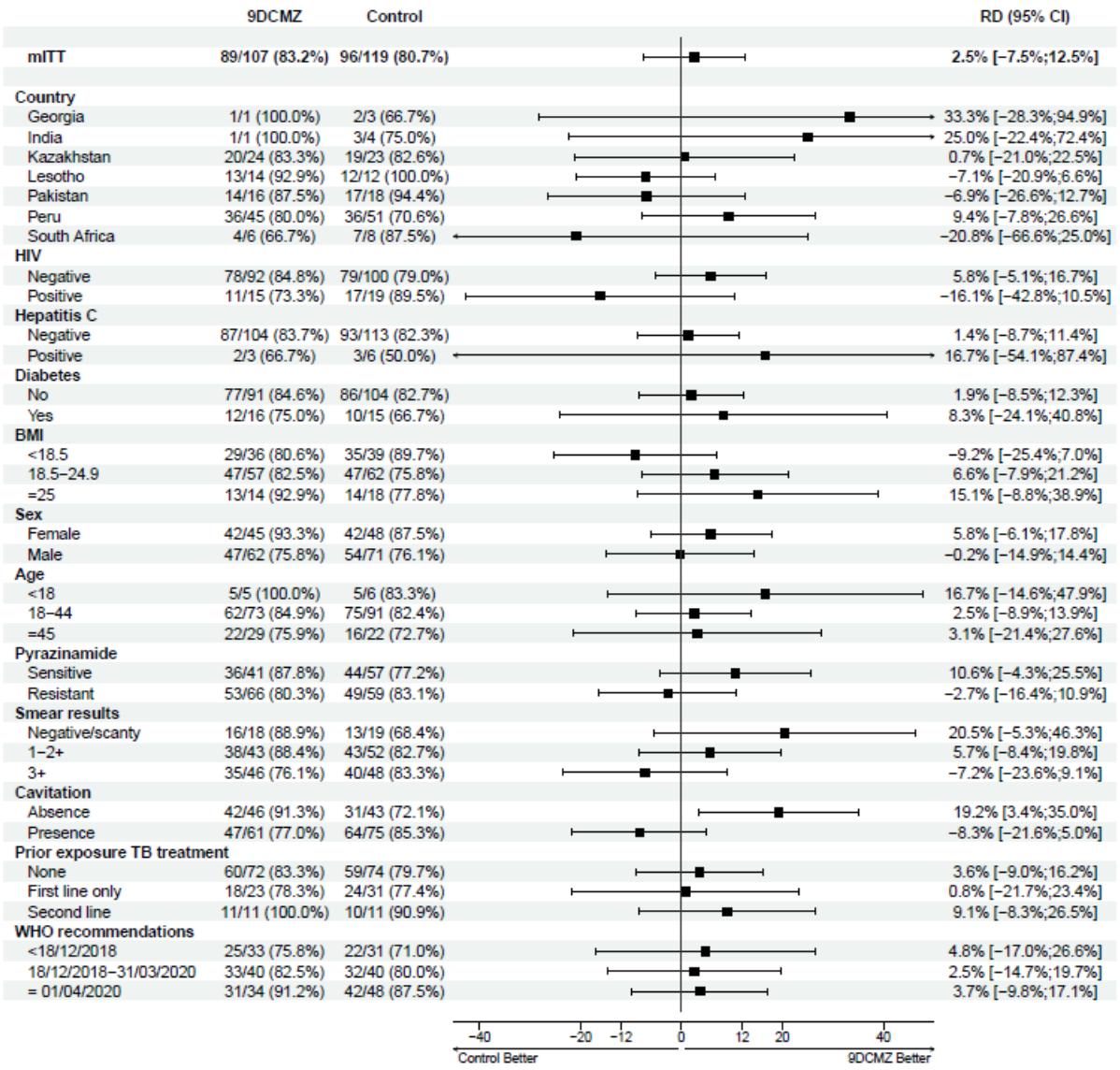

Figure 9. Subgroup Analysis of Efficacy of endTB Trial Regimen 9DCMZ vs Control at Week 73 (mITT Population)

Table 5 shows results of the post-hoc sensitivity analysis of the stricter regimen-change rule as applied to the longer regimen in the control arm. Considering as unfavourable any change of ≥1 drug (instead of the pre-specified ≥2 drugs) in longer regimens in the control arm results in poorer observed performance of the control arm: % favourable outcome declines from 80.7% to 68.1% in the mITT population. The primary results are supported for endTB regimens 9BLMZ, 9BCLLfxZ, 9BDLLfxZ, and 9DCMZ. Using this approach, the performance of endTB regimen 9DCLLfxZ improves relative to the control (RD: 10.7%; 95% CI: -0.4%;21.9%).

Table 5. Post-hoc sensitivity analysis of efficacy of endTB Trial Regimens at 73 Weeks (mITT population): reclassification of W73 treatment outcome of participants in control arm with longer regimen with addition or

change of one or more investigational drug in their regimen as unfavourable outcome (as in experimental arms)

Population	W73 treatment outcome	9BLMZ	9BCLLfxZ	9BDLLfxZ	9DCLLfxZ	9DCMZ	Control	Total
mITT reclassifying outcomes « favorable" to "Unfavorable" in participants from control arm, longer regimen with addition or replacement of one drug	Total in population	118 (100.0%)	115 (100.0%)	122 (100.0%)	118 (100.0%)	107 (100.0%)	119 (100.0%)	699 (100.0%)
	Total Favorable	105 (89.0%)	104 (90.4%)	104 (85.2%)	93 (78.8%)	89 (83.2%)	81 (68.1%)	576 (82.4%)
	95% CI	[81.9%;94.0%]	[83.5%;95.1%]	[77.7%;91.0%]	[70.3%;85.8%]	[74.7%;89.7%]	[58.9%;76.3%]	[79.4%;85.2%]
	Difference from	20.9%	22.4%	17.2%	10.7%	15.1%	-	
	95% CI of the	[10.8%;31.0%]	[12.4%;32.3%]	[6.7%;27.7%]	[-0.4%;21.9%]	[4.1%;26.1%]		

Note: Confidence intervals widths have not been adjusted for multiplicity and the intervals should not be used in place of hypothesis testing. They are only presented for precision purposes.

Rapporteur comment

Replacement of ≥2 drugs in the SoC treatment arm is considered an inherent part of the way these patients are treated. If one would allow a change of more than one drug in the experimental arm, in the end it might not be the experimental regimen anymore that is being investigated.
This analysis is noted.

Delamanid-specific analysis

Given that analyses according to the CHMP agreed delamanid-specific SAP could not be performed, a post hoc delamanid-specific analysis based on publicly available data of the endTB study has been performed. The intention was to conduct the analysis wherever possible in line with the originally planned delamanid-specific analysis as specified in the SAP agreed between Rapporteurs and MAH.

Comparison of Statistical Approaches (CHMP Agreed Statistical Analysis Plan versus endTB Consortium Statistical Analysis Plan versus Post Hoc Analysis)

A comparison of post hoc analyses performed by the MAH, versus statistical methodology employed by the endTB consortium at the one hand and versus the CHMP agreed delamanid-specific SAP on the other hand, are summarised and discussed by the MAH in section 3.2.4 of the Clinical Overview Addendum.

Rapporteur assessment

The most important difference between the initial delamanid-specific SAP and the analyses in endTB are:

- Patients receiving delamanid in the control arm were to be excluded (as having the same treatment in the control would make the results 'more similar', which could be in favour of the experimental treatment in a non-inferiority trial). Overall, 12 patients (10%) in the control arm were administered delamanid; it is conceivable that exclusion of one tenth of all patients from the control arm might have had a relevant impact on study results and interpretation.
- Some differences in exact endpoint-definitions. Where the most important difference seems to be sustained sputum conversion up till week 73 rather than the endTB definition of 'negative sputum at weeks 65 and 73'
- A specific adjusted analysis was defined as primary analyses. The analysis deviates from the adjusted analysis performed in endTB.
- To account for multiplicity, a stepwise testing procedure was set out to test (1) non-inferiority of endTB3 + endTB4, (2) non-inferiority of endTB3 and endTB4 separately, and (3) non-inferiority of endTB5; all using a 1-sided alpha of 0.025.

- The mITT2 and PP2 analysis sets were considered as co-primary for the purpose of establishing the non-inferiority of delamanid compared to control.
  Hence, at each step of the above, both the mITT2- and PP2-analysis must be significant to formally continue to the next. This is mentioned differently by the MAH in the clinical overview addendum.
- Differences in mITT and PP-definitions. There was a difference for analysis set mITT2 that was to be used for primary analysis. It differed from the mITT defined by the endTB consortium by including patients without post-baseline data while assigning them an unfavourable treatment outcome at Week 39. According to the patient flow chart in the publication there was no randomised and treated patient not having post-baseline visits. Therefore, it is assumed that the mITT as used in the endTB publication was comparable to the mITT2 as per CHMP agreed delamanid-specific SAP for all 5 experimental arms.
- Regarding safety analyses, analysis between the pooled delamanid experimental arms and control arm excluding delamanid-treated patients were included

The CHMP agreed delamanid-specific SAP defined a stepwise testing procedure on the mITT ie, to test (1) non-inferiority of endTB3 + endTB4, (2) non-inferiority of endTB3 and endTB4 separately, and (3) non-inferiority of endTB5. This stepwise testing, using a 1-sided alpha of 0.025, was maintained.

It was decided to use 2 analytic approaches that were considered to most closely follow the CHMP agreed delamanid-specific SAP for endTB as much as possible i.e., a meta-analytic approach combining published results and a crude pooled analysis using the published number of patients with favourable outcome.

Methods: The MAH present their analyses in section 3.2.3 of the Clinical Overview Addendum.

Results

Using the meta-analytic approach, the results for the first step of the stepwise test procedure, the difference in proportion of patients with favourable outcome at Week 73 between the pooled delamanid arms endTB3 + endTB4 and control arm was 1.6%, with a 95% CI of −5.4 to 8.6% based on the mITT and the reported unadjusted analysis results. Applying the non-inferiority margin of −12% as used in the endTB study, the combined treatment arms endTB3 + endTB4 could be concluded to be non-inferior to standard of care.

Table 6. Difference in Proportion of Patients with Favourable Outcome at Week 73, Based on Unadjusted Analyses, MAH's Analysis; endTB, mITT

Treatment arms/groups	Proportions	Tau²	95% CI
Del3	85.25		[78.95 ; 91.54]
Del4	78.81		[71.44 ; 86.19]
SoC	80.67		[73.58 ; 87.77]
Diff.: Del3 - SoC	4.57		[−4.91 ; 14.06]
Diff.: Del4 - SoC	−1.86		[−12.09 ; 8.37]
Diff.: Del3 + Del4 - SoC - fixed effect model	1.60		[−5.35 ; 8.56]
Diff.: Del3 + Del4 - SoC - random effect model	1.60	0.00	[−5.35 ; 8.56]
Diff.: Del3 + Del4 - SoC - Del3 + Del4 pooled	1.41		[−7.18 ; 10.01]

CI = confidence interval; Del3 = BDLLfxZ (endTB3); Del4 = DCLLfxZ (endTB4); Diff = difference; mITT = modified intention-to-treat; SoC = standard of care
Source data: Programmed Table 1.1.

Non-inferiority was also shown when applying a crude pooled analysis while using the observed published number of favourable patients in the combined endTB3 + endTB4 arms versus standard of care. The pooled difference in this analysis was 1.4% (95% CI -7.2, 10%).

Of note, the mITT was defined as the primary analysis.

When applying the stepwise procedure defined in the CHMP agreed delamanid-specific SAP and using the results tabulated above, it could be concluded that:

1) endTB3 + endTB4: Non-inferiority was demonstrated using the pooled (meta) analysis

2) endTB3 and endTB4 separately: non-inferiority was demonstrated for endTB3 but not for endT4. This means that at this step, the stepwise testing procedure was to be stopped.

3) endTB5: Non-inferiority of endTB5 versus standard of care could not be investigated, because the stepwise procedure was stopped after Step 2.

Using the meta-analytic approach as described above for the PP population, the difference of pooled endTB3 + endTB4 arms versus control in proportion of patients with favourable outcome at Week 73 was estimated as −5.0% using the fixed model and as −5.7% using the random model. The lower limit of the 95% CI was above the non-inferiority margin of −12% using the fixed analysis model but not using the random effect model, and also not when applying a simple pooled analysis.

Table 7. Difference in Proportion of Patients with Favourable Outcome at Week 73, Based on Unadjusted Analyses, MAH's Analysis; endTB, PP

Treatment arms/groups	Proportions	τ^2	95% CI
Del3	94.17		[89.65 ; 98.70]
Del4	85.42		[78.36 ; 92.48]
SoC	95.95		[91.45 ; 100.00]
Diff.: Del3 - SoC	−1.77		[−8.15 ; 4.60]
Diff.: Del4 - SoC	−10.53		[−18.90 ; -2.16]
Diff.: Del3 + Del4 - SoC - fixed effect model	−4.99		[−10.06 ; 0.08]
Diff.: Del3 + Del4 - SoC - random effect model	−5.71	23.94	[−14.25 ; 2.83]
Diff.: Del3 + Del4 - SoC - Del3 + Del4 pooled	−6.00		[−12.13 ; 0.14]

CI = confidence interval; Del3 = BDLLfxZ (endTB3); Del4 = DCLLfxZ (endTB4); Diff = difference; PP = per-protocol; SoC = standard of care

Analyses using the PP are of exploratory nature.

Discussion of Post Hoc Analyses Performed for endTB Data by the MAH

Based on the mITT, the endTB3 regimen (BDLLfxZ) could be concluded to be non-inferior to control at Week 73 according to results from the endTB consortium as well as the post hoc analyses performed by the MAH. Neither the endTB consortium nor the MAH concluded non-inferiority of the endTB4 regimen (DCLLfxZ) versus control.
The endTB5 regimen (DCMZ) was found to be non-inferior to control by the endTB consortium, while analyses performed by the MAH did not conclude on this regimen, as summarised above.

Non-inferiority of endTB3 + endTB4 could be concluded based on the mITT, but not based on the PP. The outcome for the pooled analyses endTB3 + endTB4 reflects the poor outcome for the endTB4 regimen.

Rapporteur assessment

The CHMP has requested to perform analyses on available/published data that align as close as possible with those planned. In practice, this mainly means replacing adjusted with unadjusted analyses, not excluding patients receiving Delamanid from the control arm and going with endpoint- and mITT- and PP-definitions as used in endTB.

The MAH presented their analyses in section 3.2.3 of the Clinical Overview Addendum. Two analysis-methods are employed: using the crude numbers (pooled over treatment arms if the aimed effect requires it) and a meta-analytic approach where both a fixed-effects and a random-effects model is fitted to the results from the separate arms (which can be adjusted or unadjusted). Such meta-analytic models however don't take into account that both outcomes are correlated (they share the same control arm). Only assessing the (pooled if required) crude numbers is the more honest approach. Also note that in the endTB-analyses, the difference in estimated effect between unadjusted and adjusted models was small, both in point estimate and width of the confidence intervals.

Looking at the unadjusted pooled (endTB3 + endTB4) analyses of the MAH, the pooled analysis shows non-inferiority in the mITT-analysis. It does not for PP (LL 95% CI -12.13). (Note that with Farrington-Manning, which is a standard approach in non-inferiority setting, the LL would be -11.84).

The MAH states that 'Analyses using the PP are of exploratory nature, both according to Guglielmetti et and according to the CHMP agreed delamanid-specific SAP for endTB.' However, that is not the case. In the Delamanid specific SAP, it is explicitly stated in section 5.4 that '*mITT2 and PP2 analysis sets will be considered as co-primary for the purpose of establishing the non-inferiority of delamanid compared to control*'.

While PP-analysis may play an important role in non-inferiority trials, in this specific setting, there are two reasons not to put much weight on the PP-analyses. Firstly, with the very different lengths of treatment, 'per protocol' (at least 80% of the intended treatment in 120% of the intended time window) has a very different meaning in both arms, artificially in favour of the control arm. Secondly, the reduction in number of patients between mITT and PP is very large for the control arm (38% vs less than 20% in the experimental arms), indicating that the selection effect of PP may be much bigger in the control arm compared to the experimental arms. This is confirmed by the proportion of positive outcomes shooting up from 80.7% to 95.9%.

Although PP analyses are typically of particular relevance in non-inferiority trials, due to the differences in treatment duration, the mITT is more relevant for clinical practice.

If it is agreed to focus on mITT, the hierarchical procedure indeed stops at step 2, where endTB3 shows non-inferiority, but endTB4 does not.

The PP analyses do show, however, that BLMZ, BCLLfxZ and BDLLfxZ attain a similar level of efficacy in the per protocol population as the SoC control arm, with the advantage of being shorter treatment regimens and an increased treatment adherence.

Post hoc analyses related to Delamanid use in the Control Arm

Exclusion of patients taking delamanid from the control arm was not possible as IPD from endTB were not available, and the endTB consortium did not use this approach.

In 3 countries, i.e., India, Peru, and South Africa, delamanid was not administered as part of the standard of care regimens in the control arm, providing 4, 51 and 8 patients respectively.

The proportion of patients in the control arm with favourable outcome was higher (89.3%; 95% CI 81.2%; 97.4%) in countries using delamanid and lower (73% [95% CI 62.1%; 84.0%]) in countries not using delamanid as standard of care treatment.

In the post hoc non-inferiority testing in countries where delamanid was not part of the SoC control arm, all 3 delamanid- containing treatment arms are non-inferior to the control standard of care treatment.

In the post hoc non-inferiority testing in countries where delamanid is part of the standard of care treatment (Georgia, Kazakhstan, Lesotho, Pakistan), non-inferiority testing stopped in the first step as non-inferiority could not be concluded for the combined endTB3 + endTB4 arms.

Subgroup analyses of the favourable outcome rate for Peru showed that all 3 delamanid-containing regimens performed better than control, with 95% CI lower bounds above -12% i.e., RD 21.5% (95% CI 6.3%, 36.8%) for endTB3 (BDLLfxZ), 24.3% (95% CI 9.9%, 38.7%) for endTB4 (DCLLfxZ), and 19.2% (95% CI 4.0%, 34.4%) for endTB5 (DCMZ) (Guglielmetti et al, supplemental materials)

Rapporteur assessment/comment:

According to the MAH, these results suggest that delamanid contributed to the positive and higher than expected favourable outcome rate in the control arm. 'Showing non-inferiority' in the countries where Delamanid is not part of the SoC and not showing it (with considerable negative point estimates) in the other countries, is not in line with 'with same/similar treatments in experimental and control, results will tend to be more similar – which may be an advantage in a non-inferiority trial'. It may, however, be driven by the exceptionally bad result in the control arm for Peru (70.6% versus 80.7% overall and 89.3% in countries including – in most cases modest number of – Delamanid in SoC), to which other factors might have contributed, e.g. a large portion (23.5 %) of the participants in the control group in Peru were administered 2nd line injectables and hence were treated according to the earlier WHO guidelines. As the IPD are not available, this cannot be investigated any further.

EndTB analysis performed by the WHO

This analysis is reported in the **WHO 2025 consolidated guidelines on tuberculosis**

Slightly modified analyses were performed by the study team and used for assessment as reflected in the WHO 2025 consolidated guidelines on tuberculosis Module 4: Treatment and care.

For the WHO endTB outcome analyses, IPD from endTB were made available.

For the WHO review, the efficacy analyses used the week 104 endpoint.

Statistical analyses were based on the WHO outcome definitions listed in Annex 2 of the WHO guideline. The endTB outcome definitions were similar to the WHO outcome definitions, except for the LTFU. Patients who were originally classified as being LTFU based on the endTB protocol and statistical analysis plans (and thus assigned an unfavourable outcome) were reclassified as "sustained treatment success" if all of the following conditions were met:

- the participant had completed treatment;
- the participant had been assigned an unfavourable outcome at week 104 based on the endTB protocol solely because of missed visits, LTFU, or withdrawal of consent; and
- the participant had at least one negative culture and no positive cultures after treatment completion.

Overall, assignment of favourable and unfavourable outcomes agreed between endTB consortium and WHO, apart from 7/699 (1%) judged by WHO as having sustained treatment success where endTB had declared unfavourable outcome. This number included 4 patients being LTFU and 3 patients with other reasons. All 4 patients being LTFU and reclassified by WHO as having sustained treatment success were from delamanid-containing arms (endTB4 n = 2; n = 1 each in endTB3 and endTB5).

The WHO applied a new method of determining the magnitude of health effects from clinical studies as basis for decision thresholds. A triangulation approach was used to develop outcome-specific decision thresholds (DTs) for judging the magnitude of the effects for the following health outcomes: death,

sustained treatment success, treatment failure or recurrence, LTFU, AEs and amplification of drug resistance. These outcomes are deemed critical or important for decision-making based on a prioritisation survey of the WHO's GDG and were compared statistically based on estimated 95% CIs between experimental and control arms by absolute effects (RDs) and relative effects (risk ratios). Certainty of evidence for the estimated effect was judged through the number of thresholds. The GDG used the empirical evidence from the GRADE-THRESHOLD trial to calculate suggested utility-adjusted absolute effect thresholds for the different health outcomes. Thresholds for "trivial or no effect", "small effect", "moderate effect", and "large effect" were calculated for health outcomes of: death; sustained treatment success; and treatment failure or recurrence, LTFU, AEs and amplification (acquisition) of drug resistance. As an example, "trivial or no effect" for sustained treatment success was defined as ≤ 15 treatment successes per 1000 people and a "large effect" as ≥ 69 treatment successes per 1000 people. For all quantitative decision threshold values by health outcome and effect level see the WHO consolidated guidelines on tuberculosis.

Figures were created to visually depict absolute effects and 95% CIs from the evidence of the study in relation to the decision thresholds for each health outcome, in order to facilitate the GDG's deliberations.

WHO analyses

The low number of assignments that differed between endTB consortium and WHO are considered to not have a relevant impact on the interpretation of data as assessed by the WHO, relative to assessments by the endTB consortium. (Table 8)

Table 8. Comparison of Main Efficacy Outcome at Week 104 as Assessed by the endTB Consortium and WHO; mITT population

	Treatment		Control	
	WHO	endTB	WHO	endTB
	Sustained treatment success	Favourable treatment outcome	Sustained treatment success	Favourable treatment outcome
Patients with event/ patients (%)				
endTB3	104/122 (85.2)	103/122 (84.4)	92/119 (77.0)	92/119 (77.3)
endTB4	90/118 (76.3)	88/118 (74.6)	92/119 (77.0)	92/119 (77.3)
endTB5	92/107 (84.6)	88/107 (82.2)	92/119 (77.0)	92/119 (77.3)

The WHO risk analysis comparing relative and absolute risks for sustained treatment effect between experimental arms and control at Week 104 based on the mITT result in the following:

- endTB3: 85.2%; control: 77.3%;

  relative risk 1.10 (95% CI 0.98, 1.25)
  absolute RD/effect: 79 more [from 19 fewer to 177 more] per 1000 patients achieve sustained treatment success (large effect)

- endTB4: 76.3%; control: 77.3%;

  Relative risk: 0.99 (95% CI 0.86, 1.13)
  absolute RD/effect: 10 fewer [from 118 fewer to 97 more] per 1000 patients achieve sustained treatment success (trivial or no effect)

- endTB5: 82.2%; control: 77.3%

relative risk: 1.06 (95% CI 0.93, 1.21)
absolute RD/effect: 49 more [from 55 fewer to 154 more] per 1000 patients achieve sustained treatment success (moderate effect)

In the following, the other health related outcomes (failure and recurrence, death, LTFU, AEs, SAEs, amplification of drug resistance) are discussed.

BDLLfxZ (endTB 3) regimen

Patients with MDR/RR-TB receiving the BDLLfxZ regimen (*n*=122 for failure and recurrence, death, and LTFU; *n*=127 for AEs and *n*=128 for amplification of drug resistance) compared with those receiving the currently recommended longer WHO regimens (*n*=119 for failure and recurrence, death and LTFU; *n*=126 for AEs and *n*=130 for amplification of drug resistance) experienced:

- lower levels of failure or recurrence: 1.6% versus 2.5%; RD=9 fewer per 1000 (95% CI: from 45 fewer to 27 more per 1000); (trivial or no effect)
- lower levels of death: 2.5% versus 3.4%; RD=9 fewer per 1000 (95% CI: from 52 fewer to 33 more per 1000); (trivial or no effect)
- lower levels of LTFU: 10.7% versus 16.8%; RD=62 fewer per 1000 (95% CI: from 148 fewer to 25 more per 1000); (moderate effect)
- lower levels of people with at least one Grade 3 to 5 AEs: 63.0% versus 65.1%; RD=21 fewer per 1000 (95% CI: from 139 fewer to 97 more per 1000); (trivial or no effect)
- lower levels of people with at least one serious AE: 15.7% versus 19.0%; RD=33 fewer per 1000 (95% CI: from 126 fewer to 60 more per 1000); (small effect) and
- similar levels of amplified resistance: 0.0% versus 0.0%; RD=0 fewer per 1000 (95% CI: from 29 fewer to 29 more per 1000). (trivial or no effect)

The GDG considered that for endTB3 (BDLLfxZ) compared with control, the desirable effects were: trivial or no effect for outcomes of death and failure/recurrence, moderate for LTFU, trivial or no effect for SAEs, small for AEs, and trivial or no effect for amplification of drug resistance.
Shortening of the treatment duration and reduction in pill burden were considered as desirable effects. The GDG did not consider treatment success as a separate outcome, because treatment success is mathematically the complement of the 3 unfavourable outcomes of failure, death, and LTFU and thus, is not considered to carry additional or independent information.

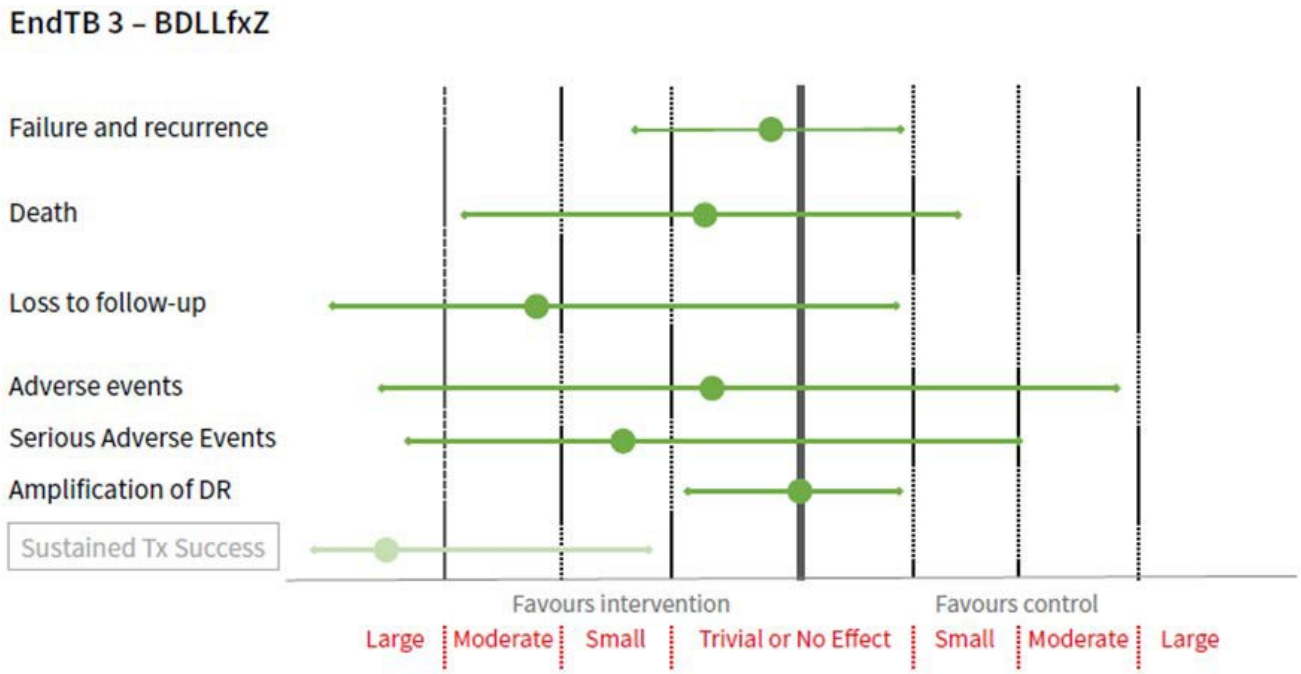

Figure 10. WHO Summary of Research Evidence from endTB3 (BDLLfxZ) versus Standard of Care

The GDG judged the benefits of BLLfxCZ to be small and the undesirable effects to be trivial compared with WHO-recommended longer regimens. The certainty of evidence was judged to be very low overall, with probably no important uncertainty in the values that people place on the outcomes.

Hence, the GDG determined that the balance of health effects probably favours the BDLLfxZ regimen.

WHO suggests using the 9-month all-oral regimens BDLLfxZ over currently recommended longer (> 18 months) regimens in patients with MDR/RR-TB and in whom resistance to FQs has been excluded, as a conditional recommendation, with a very low certainty of evidence (primarily due to imprecision in the effect estimates).

DCLLfxZ (endTB4) regimen

Patients with MDR/RR-TB receiving the DCLLfxZ regimen (n=118 for death, failure and recurrence and LTFU; n=124 for AEs and n=125 for amplification of drug-resistance) compared with those receiving the currently recommended longer WHO regimens (n=119 for death, failure and recurrence and LTFU and n=126 for AEs; and n=130 for amplification of drug resistance) experienced:

- lower levels of death: 2.5% versus 3.4%; RD=8 fewer per 1000 (95% CI: from 51 fewer to 35 more per 1000); (trivial or no effect)
- lower levels of LTFU: 10.2% versus 16.8%; RD=66 fewer per 1000 (95% CI: from 153 fewer to 20 more per 1000); (moderate effect)
- lower levels of Grade 3 to 5 AEs: 62.9% versus 65.1%; RD=22 fewer per 1000 (95% CI: from 141 fewer to 97 more per 1000); (trivial or no effect)
- lower levels of people with at least one serious AE: 15.3% versus 19.0%; RD=37 fewer per 1000 (95% CI: from 131 fewer to 56 more per 1000); (small effect)
- **higher levels of failure or recurrence**: 11.0% versus 2.5%; RD=85 more per 1000 (95% CI: from 22 more to 148 more per 1000); and (moderate effect)

• **higher levels of amplified resistance**: 4.0% versus 0%; RD=40 more per 1000 (95% CI: from 9 more to 87 more per 1000). (small effect)

The GDG considered that for endTB4 (DCLLfxZ) compared with control, the desirable effects were trivial or no effect for the outcome of death, moderate for LTFU, trivial or no effect for all AEs, and small for SAEs. Additionally, the GDG considered the shortening of the treatment duration and the reduction in pill burden as a desirable effect. Undesirable effects were considered to be moderate for the outcome of failure/ recurrence and small for amplification of drug resistance. The GDG did not consider treatment success as a separate outcome, as explained above.
The GDG judged the benefits of DCLLfxZ to be small and the undesirable effects to be moderate compared with WHO-recommended longer regimens. The certainty of evidence was judged to be very low overall, with probably no important uncertainty in the values that people place on the outcomes. Hence, the GDG determined that the balance of health effects probably favours the WHO-recommended longer regimens.

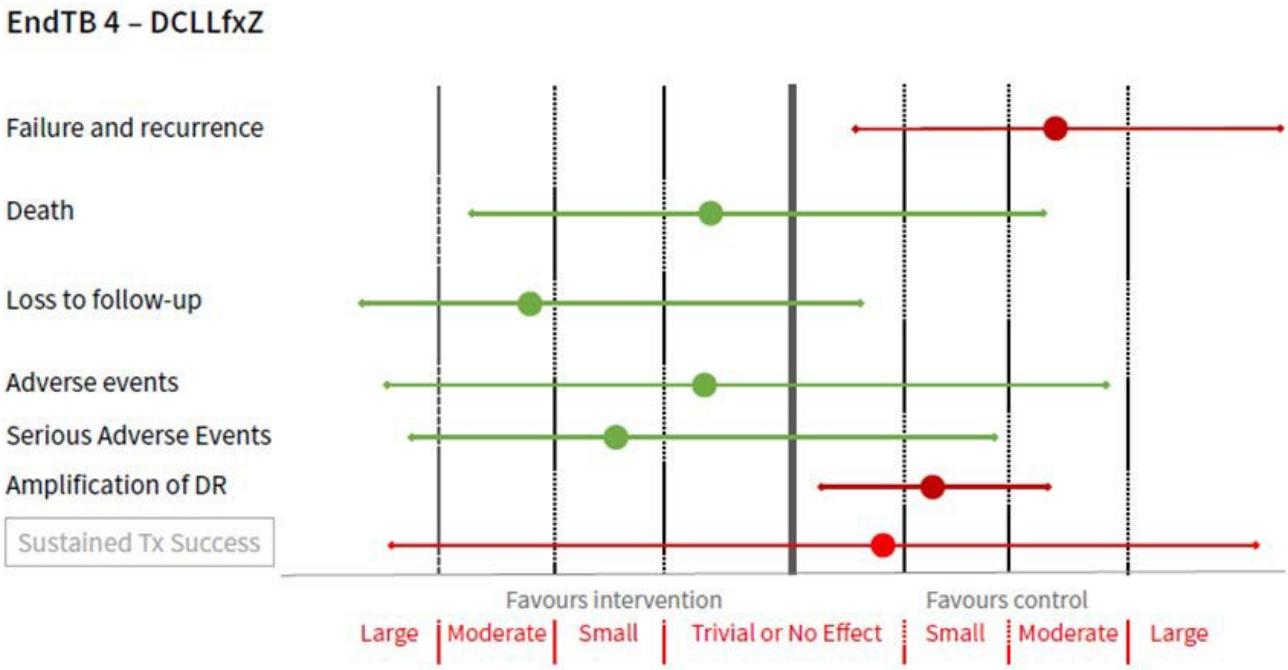

Figure 11. WHO Summary of Research Evidence from endTB4 (DCLLfxZ) versus Standard of Care

DCMZ (endTB5) regimen

Patients with MDR/RR-TB receiving the DCMZ regimen (*n*=107 for death, failure and recurrence and LTFU; *n*=120 for AEs and for amplification of drug resistance) compared with those receiving the currently recommended longer WHO regimens (*n*=119 for death, failure and recurrence and LTFU and *n*=126 for AEs; and *n*=130 for amplification of drug resistance) experienced:

• lower levels of death: 2.8% versus 3.4%; RD=5 fewer per 1000 (95% CI: from 50 fewer to 41 more per 1000); (trivial or no effect)

• lower levels of LTFU: 3.7% versus 16.8%; RD=131 fewer per 1000 (95% CI: from 207 fewer to 54 fewer per 1000); (large effect)

• lower levels of people with at least one Grade 3 to 5 AEs: 60.0% versus 65.1%; RD=51 fewer per 1000 (95% CI: from 172 fewer to 70 more per 1000); (small effect)

• lower levels of people with at least one serious AE: 17.5% versus 19.0%; RD=15 fewer per 1000 (95% CI: from 112 fewer to 81 more per 1000); (trivial or no effect)

• **higher levels of failure or recurrence**: 11.2%% versus 2.5%; RD=87 more per 1000 (95% CI: from 21 more to 153 more per 1000); and (moderate effect)

• **higher levels of amplified resistance**: 6.7% versus 0%; RD=67 more per 1000 (95% CI: from 32 more to 119 more per 1000). (moderate effect)

The GDG considered that for endTB5 (DCMZ) compared with control, the desirable effects were trivial or no effect for death, large for the outcome of LTFU, small for all AEs, and trivial or no effect for SAEs. Additionally, the GDG considered the shortening of the treatment duration and the reduction in pill burden as a desirable effect. Undesirable effects were considered to be moderate for the outcome of failure/ recurrence and moderate for amplification of drug resistance. The GDG did not consider treatment success as a separate outcome, as explained above for endTB3 versus control.

The GDG judged the benefits of DCMZ to be moderate and the undesirable effects to be moderate compared with WHO-recommended longer regimens. The certainty of evidence was judged to be very low overall, with probably no important uncertainty in the values that people place on the outcomes. Within the category of moderate effects, the undesirable effects were considered of greater weight and had higher certainty associated with them – in particular for the amplification of drug resistance. The trial data suggest that drug resistance includes losing FQ in almost all patients who failed treatment. Hence, the GDG determined that the balance of health effects probably favours the WHO-recommended longer regimens.

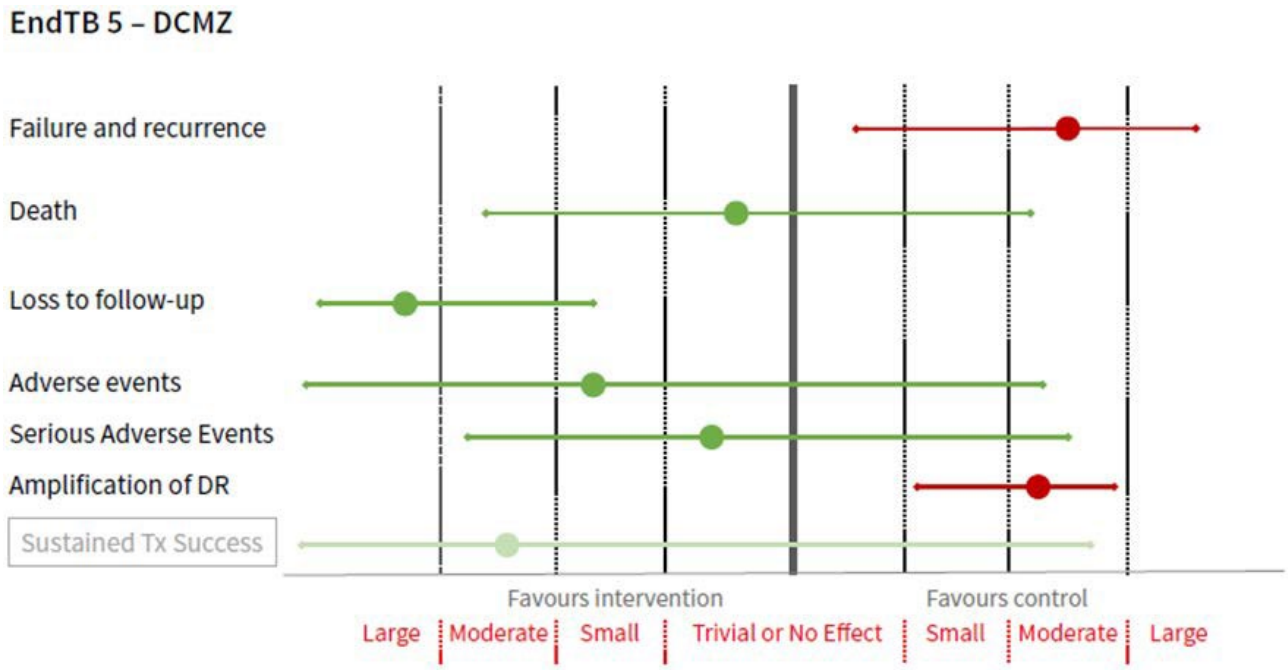

Figure 12. WHO Summary of Research Evidence from endTB5 (DCMZ) verus Standard of Care

BLMZ appeared preferable in terms of the balance of health effects compared with both BLLfxCZ and BDLLfxZ.

BLLfxCZ, compared with BDLLfxZ, was deemed to have a similar but slightly preferable balance of health effects.

Adverse events

In the endTB study, 745 patients were included in the safety population. The number of treated patients (ie, those that received at least 1 dose of study drug) by experimental regimen was as follows: BLMZ (endTB1) n = 126 patients, BCLLfxZ (endTB2) n = 122, BDLLfxZ (endTB3) n = 127, DCLLfxZ (endTB4) n = 124, and DCMZ (endTB5) n = 120. In the control group, most patients (73.1%) received a 5-drug regimen, 20.2% a 6-drug regimen, 5.9% received a 7-drug regimen, and 1 patient received a 4-drug regimen. Overall, 10.1% of patients in the control group received a delamanid-containing regimen.

For all AE analyses, the differences in exposure between experimental arms and control arm (of about factor 2 in duration) need to be considered. All things being equal, a higher incidence of AEs may generally be expected with longer exposure duration, meaning that the comparison between experimental arms and control arm is somewhat biased.

Table 9. Safety Analysis at Week 73 (Safety Population)

Adverse Events	BLMZ (N=126)	BCLLfxZ (N=122)	BDLLfxZ (N=127)	DCLLfxZ (N=124)	DCMZ (N=120)	Standard Therapy (N=126)	Total (N=745)
Any adverse event — no. (%)	126 (100)	122 (100)	127 (100)	124 (100)	120 (100)	125 (99.2)	744 (99.9)
Grade 3 or higher adverse events							
≥1 event — no. (%)	69 (54.8)	68 (55.7)	78 (61.4)	75 (60.5)	72 (60.0)	79 (62.7)	441 (59.2)
No. of events related to trial drug or drugs/total no. of events (%)†	49/136 (36.0)	57/166 (34.3)	56/144 (38.9)	58/148 (39.2)	37/148 (25.0)	56/163 (34.4)	313/901 (34.7)
Serious adverse events							
≥1 event — no. (%)	18 (14.3)	16 (13.1)	20 (15.7)	18 (14.5)	20 (16.7)	21 (16.7)	113 (15.2)
No. of events related to trial drug or drugs/total no. of events (%)†	7/26 (26.9)	11/29 (37.9)	11/30 (36.7)	11/26 (42.3)	6/31 (19.4)	8/32 (25.0)	54/174 (31.0)
Death from any cause — no. (%)	3 (2.4)	1 (0.8)	3 (2.4)	4 (3.2)	2 (1.7)	2 (1.6)	15 (2.0)
Adverse events of special interest							
≥1 event — no. (%)	35 (27.8)	33 (27.0)	25 (19.7)	33 (26.6)	26 (21.7)	26 (20.6)	178 (23.9)
Any grade 3 or 4 increase in ALT or AST — no. (%)	23 (18.3)	17 (13.9)	8 (6.3)	18 (14.5)	12 (10.0)	9 (7.1)	87 (11.7)
Any grade 3 or 4 leukopenia, anemia, or thrombocytopenia — no. (%)	11 (8.7)	9 (7.4)	10 (7.9)	13 (10.5)	9 (7.5)	13 (10.3)	65 (8.7)
Any grade 3 or 4 peripheral neuropathy — no. (%)	4 (3.2)	5 (4.1)	9 (7.1)	3 (2.4)	3 (2.5)	6 (4.8)	30 (4.0)
Any grade 3 or 4 optic neuritis — no. (%)	0	1 (0.8)	0	1 (0.8)	0	2 (1.6)	4 (0.5)
Any grade 3 or 4 QT corrected interval prolonged — no. (%)‡	0	4 (3.3)	0	0	5 (4.2)	0	9 (1.2)
Permanent discontinuation of any drug due to adverse event — no. (%)	26 (20.6)	32 (26.2)	35 (27.6)	29 (23.4)	19 (15.8)	51 (40.5)	192 (25.8)

The percentage of participants who had at least one grade 3 or higher adverse event ranged from 54.8% (in the BLMZ group) to 61.4% (in the BDLLfxZ group) and was 62.7% in the standard therapy group. There were no relevant differences in AE incidences between the groups. The incidence of serious adverse events was similar across the groups, ranging from 13.1% in the BCLLfxZ group to 16.7% in the DCMZ and standard-therapy groups.

Table 10. Number (%) of participants with adverse events (AEs) by Week 73 (Safety Population)

Adverse events (AEs)	9BLMZ (N = 126)	9BCLLfxZ (N = 122)	9BDLLfxZ (N = 127)	9DCLLfxZ (N = 124)	9DCMZ (N = 120)	Control (N = 126)	Total (N = 745)
Grade 3 or higher AE – no. (%)	69 (54.8%)	68 (55.7%)	78 (61.4%)	75 (60.5%)	72 (60.0%)	79 (62.7%)	441 (59.2%)
Risk difference from control (95% CI)	-7.9 (-20.1;4.2)	-7.0 (-19.2;5.2)	-1.3 (-13.2;10.7)	-2.2 (-14.3;9.8)	-2.7 (-14.9;9.5)	-	
Serious adverse events	18 (14.3%)	16 (13.1%)	20 (15.8%)	18 (14.5%)	20 (16.7%)	21 (16.7%)	113 (15.2%)
Risk difference from control (95% CI)	-2.4 (-11.3;6.5)	-3.6 (-12.4;5.3)	-0.9 (-10.0;8.2)	-2.2 (-11.1;6.8)	0.0 (-9.3;9.3)	-	
Death from any cause	3 (2.4%)	1 (0.8%)	3 (2.4%)	4 (3.2%)	2 (1.7%)	2 (1.6%)	15 (2.0%)
Risk difference from control (95% CI)	0.8 (-2.6;4.2)	-0.8 (-3.5;1.9)	0.8 (-2.7;4.2)	1.6 (-2.2;5.4)	0.1 (-3.1;3.2)	-	
Participants with at least one AESI	35 (27.8%)	33 (27.1%)	25 (19.7%)	33 (26.6%)	26 (21.7%)	26 (20.6%)	178 (23.9%)
Risk difference from control (95% CI)	7.1 (-3.4;17.7)	6.4 (-4.2;17.0)	-0.9 (-10.8;8.9)	6.0 (-4.5;16.5)	1.0 (-9.2;11.2)	-	

Among all grade 3 or higher adverse events and serious adverse events, 313 of 901 (34.7%) and 54 of 174 (31.0%), respectively, were classified by the investigator as related to trial drugs.

At least one adverse event of special interest (AESI) was reported in 23.9% of all the participants; the most commonly occurring AESI, hepatotoxic events, which were defined by any grade 3 or 4 increase in levels of ALT or AST, occurred in 7.1% of the participants in the standard-therapy group and ranged from 6.3% (in the BDLLfxZ group) to 18.3% (in the BLMZ group) in the experimental groups. Hematologic toxic events, defined as any grade 3 or 4 leukopenia, anaemia, or thrombocytopenia, occurred in 10.3% of the participants in the standard-therapy group and ranged from 7.4% (in the BCLLfxZ group) to 10.5% (in the DCLLfxZ group) in the experimental groups. Peripheral neuropathy occurred in 4.8% of the participants in the standard-therapy group and ranged from 2.4% (in the DCLLfxZ group) to 7.1% (in the BDLLfxZ group) in the experimental groups.

QTcF prolongation ≥ Grade 3, defined as an increase of > 60 ms from baseline or > 500 ms together with signs/symptoms of serious arrhythmia, occurred only in the experimental groups DCMZ (4.2%) and BCLLfxZ (3.3%). There were no events leading to death, and all patients recovered. Absolute QTcF of > 500 ms were infrequent and occurred only in groups containing clofazimine and a second drug known to prolong QT, ie, bedaquiline or moxifloxacin. [Clinical overview]

Serious adverse event/deaths/other significant events

Deaths

Overall, death from any cause occurred in 15 participants (2.0%) by week 73 (Table 9) and in 18 participants (2.4%) by week 104; the incidence was similar across the groups. No deaths were considered by the investigators to be related to trial drugs. The most common causes of death were disease progression (5 participants) and sepsis (3 participants).
Of the death events reported through Week 104, 10 were reported in regimens including delamanid use.

Safety in special populations

During the study, 10 women became pregnant, including 5 receiving delamanid-containing regimens. In all cases, exposure occurred during the first trimester. Four of the women receiving delamanid-containing regimens remained on study treatment while 1 discontinued treatment prematurely. No AEs or adverse outcomes in the mothers or newborns were reported.

Discontinuation due to adverse events

Permanent discontinuation of any drug due to AEs occurred in 40.5% of participants in the control and in between 15.8% (9DCMZ) and 27.6% (9BDLLfxZ) in the experimental groups. The most frequently stopped drugs due to AEs were pyrazinamide (108 [14.5%] participants at median 92 [IQR: 57.5-184.5] days post randomisation) and linezolid (66 [8.9%] participants at median 164 [IQR: 112-225] days post randomisation). AEs leading to discontinuation of delamanid occurred in 1.1% of patients.

Table 11. Frequency of endTB trial Participants experiencing Adverse Events Leading to (and Time to) Permanent Discontinuation of at Least One Study Drug bu Treatment Group by Week 73 (Safety Population)

Adverse events (AEs)	9BLMZ (n = 126)	9BCLLfxZ (n = 122)	9BDLLfxZ (n = 127)	9DCLLfxZ (n = 124)	9DCMZ (n = 120)	Control (n = 126)	Total (N = 745)
Participants with at least one AE leading to permanent discontinuation ≥1 drug	26 (20.6%)	32 (26.2%)	35 (27.6%)	29 (23.4%)	19 (15.8%)	51 (40.5%)	192 (25.8%)
Days to drug discontinuation, median [IQR]	101 [82-225]	134 [76-217]	127 [61-197]	134 [77-178]	103 [41-217]	160.0 [60-315]	133.5 [65.5-217.5]
- **Pyrazinamide**	**22 (17.5%)**	**23 (18.9%)**	**21 (16.5%)**	**16 (12.9%)**	**15 (12.5%)**	**11 (8.7%)**	**108 (14.5%)**
Days to drug discontinuation, median [IQR]	101 [82-226]	112 [72-199]	103 [61-181]	85 [47-172.5]	63 [41-164]	58 [38-145]	92 [57.5-184.5]
- **Linezolid**	**7 (5.6%)**	**10 (8.2%)**	**15 (11.8%)**	**15 (12.1%)**	**-**	**19 (15.1%)**	**66 (8.9%)**
Days to drug discontinuation, median [IQR]	131 [73-184]	208.5 [112-239]	145 [69-201]	134 [78-195]	-	195 [141-319]	164 [112-225]
- **Clofazimine**	**-**	**5 (4.1%)**	**-**	**5 (4.0%)**	**5 (4.2%)**	**7 (5.6%)**	**22 (3.0%)**
Days to drug discontinuation, median [IQR]	-	192 [163-259]	-	168 [49-273]	103 [50-242]	366.0 [284-440]	250.5 [103-315]
- **Levofloxacin**	**-**	**4 (3.3%)**	**1 (0.8%)**	**5 (4.0%)**	**1 (0.8%)**	**12 (9.5%)**	**23 (3.1%)**
Days to drug discontinuation, median [IQR]	-	232.5 [155-287.5]	69 [69-69]	178 [49-273]	83 [83-83]	245 [164.5-439]	213 [83-323]
- **Bedaquiline**	**4 (3.2%)**	**3 (2.5%)**	**1 (0.8%)**	**-**	**-**	**6 (4.8%)**	**14 (1.9%)**
Days to drug discontinuation, median [IQR]	123.5 [72-190.5]	210 [97-323]	69 [69-69]	-	-	427 [169-440]	189.5 [91-414]
- **Moxifloxacin**	**5 (4.0%)**	**-**	**-**	**-**	**5 (4.2%)**	**1 (0.8%)**	**11 (1.5%)**
Days to drug discontinuation, median [IQR]	112 [90-156]	-	-	-	103 [50-261]	23 [23-23]	103 [50-225]
- **Delamanid**	**-**	**-**	**1 (0.8%)**	**4 (3.2%)**	**3 (2.5%)**	**0 (0.0%)**	**8 (1.1%)**
Days to drug discontinuation, median [IQR]	-	-	69 [69-69]	161 [40-290]	50 [41-103]	-	59.5 [45.0-188]

Discussion

The delamanid containing experimental regimens are discussed in more detail below.

BDLLfxZ (endTB3)

In the analyses performed by the endTB consortium endTB3 (BDLLfxZ) was demonstrated to be non-inferior to standard therapy (RD 4.6%; 95% CI –4.9, 14.1) based on the mITT. The PP analysis was in line with the mITT analysis. Non-inferiority was demonstrated for BDLLfxZ alone versus control (mITT, PP) by the meta-analytic approach used by the MAH.

There were no relevant differences in AEs incidences between endTB3 and SoC. Permanent discontinuation of any drug due to AEs occurred in 40.5% of participants in the control group and in 27.6% in the 9BDLLfxZ group.

These findings are supported also by the recommendations of the updated WHO guidelines. For the WHO review, the efficacy analyses used the week 104 endpoint. The endTB outcome definitions were similar to the WHO outcome definitions, except for the LTFU. The low number of assignments that

differed between endTB consortium and WHO are considered to not have a relevant impact on the interpretation of data as assessed by the WHO, relative to assessments by the endTB consortium.
The WHO GDG considered that for endTB3 (BDLLfxZ) compared with control, the desirable effects were: trivial or no effect for outcomes of death and failure/recurrence, moderate for LTFU, trivial or no effect for SAEs, small for AEs, and trivial or no effect for amplification of drug resistance.
Shortening of the treatment duration and reduction in pill burden were considered as desirable effects.
The GDG judged the benefits of BLLfxCZ to be small and the undesirable effects to be trivial compared with WHO-recommended longer regimens.
WHO suggests using the 9-month all-oral regimens BDLLfxZ over currently recommended longer (> 18 months) regimens in patients with MDR/RR-TB and in whom resistance to FQs has been excluded, as a conditional recommendation, with a very low certainty of evidence (primarily due to imprecision in the effect estimates).

DCLLfxZ (endTB4)

In the analyses performed by the endTB consortium non-inferiority of endTB4 (DCLLfxZ) to standard therapy was not established based on the mITT or the PP. Likewise, the analyses performed by the MAH using a meta-analytic approach did not show non-inferiority for endTB4 (mITT, PP) although the non-inferiority margin was only narrowly missed based on the mITT (RD −1.86; 95% CI −12.09, 8.37).

There are several aspects that might potentially explain this finding. The control arm achieved an unexpectedly high favourable outcome rate in endTB, and this might have contributed to the failure to show non-inferiority of endTB4 versus control. Patients in the control arm of endTB were allowed 2 changes of regimen while only 1 change of regimen was allowed in the experimental arms. A post hoc sensitivity analysis where all patients with > 1 change of regimen were assessed as having an unfavourable outcome was performed. This sensitivity analysis resulted in a significant decline in the favourable outcome rate in the control group from 80.7% to 68.1%. Also the endTB4 regimen achieved non-inferiority versus control in this sensitivity analysis (RD 10.7%; 95% CI −0.4; 21.9%).

In the delamanid specific SAP, exclusion of delamanid treated patients from the control arm was foreseen. Based on the subgroup analyses of the favourable outcome rate for Peru – the largest subgroup without delamanid administration in the control group -, it is hypothesised by the MAH that the favourable outcome rate of the control arm might have been lower than reported by excluding delamanid treated patients from the control arm. This might have increased the chance to show non-inferiority of the experimental delamanid-containing regimens (endTB3, endTB4, endTB5) versus control.

Rapporteur comment:

Other factors might, however, have an effect in this subgroup analysis, e.g. a large portion (23.5 %) of the participants in the control group in Peru were administered 2nd line injectables and hence were treated according to the earlier WHO guidelines. As the IPD are not available, this cannot be investigated any further.

The low treatment effect in the endTB4 arm is currently insufficiently explained. The reason for this unexpectedly low treatment effect of endTB4 is not certain and could be toxicity related, though it is only incompletely explained. Another contributing factor might be the unfavourable outcomes due to positive culture or recurrence for endTB4 (DCLLfxZ) with 10.2% positive culture events and 0.8% (1 patient) recurrence. In comparison, positive culture events occurred in 0.8%-2.6% across the other experimental groups and control. Recurrence was only noted with DCLLfxZ and DCMZ.

The findings by endTB consortium and MAH are reflected by the WHO recommendations against using endTB4 (DCLLfxZ). The GDG considered that for endTB4 (DCLLfxZ) compared with control, the desirable effects were trivial or no effect for the outcome of death, moderate for LTFU, trivial or no effect for all AEs, and small for SAEs. Additionally, the GDG considered the shortening of the treatment duration and the reduction in pill burden as a desirable effect. Undesirable effects were considered to be moderate for the outcome of failure/ recurrence and small for amplification of drug resistance. The GDG judged the benefits of DCLLfxZ to be small and the undesirable effects to be moderate compared with WHO-recommended longer regimens. Hence, the GDG determined that the balance of health effects probably favours the WHO-recommended longer regimens.

DCMZ (endTB5)

EndTB5 is a bedaquiline and linezolid-sparing regimen and a promising regimen in particular for patients with bedaquiline-resistant TB. Also, linezolid is associated with considerable toxicity, and a linezolid-sparing regimen should be advantageous from the safety perspective.

The endTB consortium concluded that DCMZ (endTB5) was non-inferior to standard therapy (RD 2.5%; 95% CI -7.5, 12.5) based on the mITT but not based on the PP. Non-inferiority of endTB5 versus control could not be tested by the MAH using a meta-analytic approach, because the hierarchical testing procedure stopped prior to testing endTB5.

Unfavourable outcomes due to positive culture or recurrence were more frequent in endTB5 and endTB4. In endTB5 (DCMZ), there were 7.5% positive culture events and 1.9% (2 patients) with recurrence. In comparison, positive culture events occurred in 0.8% to 2.6% across the other experimental groups and control. Recurrence was only noted with endTB4 and endTB5.

Guglielmetti et al concluded that overall, there were no relevant differences in AE incidences between the groups. It is notable that DCMZ was the only delamanid-containing regimen with QTcF prolongation ≥Grade 3, defined as ∆QTc > 60 ms from baseline or QTc > 500 ms, and this arm had a higher incidence of such events (4.2%) than the only other arm with QTcF prolongation ≥Grade 3 (endTB2, BCLLfxZ: 3.3%). One death in this arm was judged as being drug-related in this arm by the MAH (but not by the investigator), the event was "death (unknown cause)".

The WHO suggests against using the DCMZ regimen compared with currently recommended longer regimens in patients with FQ-susceptible RR-TB. The WHO GDG considered that for endTB5 (DCMZ) compared with control, the desirable effects were trivial or no effect for death, large for the outcome of LTFU, small for all AEs, and trivial or no effect for SAEs. Additionally, the GDG considered the shortening of the treatment duration and the reduction in pill burden as a desirable effect. Undesirable effects were considered to be moderate for the outcome of failure/ recurrence and moderate for amplification of drug resistance. The GDG judged the benefits of DCMZ to be moderate and the undesirable effects to be moderate compared with WHO-recommended longer regimens. Within the category of moderate effects, the undesirable effects were considered of greater weight and had higher certainty associated with them – in particular for the amplification of drug resistance. The trial data suggest that drug resistance includes losing FQ in almost all patients who failed treatment. Hence, the GDG determined that the balance of health effects probably favours the WHO-recommended longer regimens.

Regarding the use in special populations, WHO stated that, while paediatric patients < 14 years were excluded from the study, data were available from 10 patients aged 15 to 18 years (n = 5 on BDLLfxZ). All medicines in the regimens have been used in children and have well-documented safety and efficacy profiles and sufficient pharmacokinetics/pharmacodynamics data. The WHO therefore found it appropriate to extrapolate efficacy from adults in the endTB study to children and adolescents.

HIV positive patients were included in the endTB study. The WHO concluded that, if suppressive antiretroviral therapy is given, similar efficacy should be expected as in HIV negative patients. However, Subgroup Analysis of Efficacy of endTB Trial Regimen 9BDLLfxZ (Figure 7) showed lower efficacy in HIV positive patients (12/17; 70.6%) versus HIV negative patients (102/119; 85.7%). It should be noted that the confidence intervals were wide for the HIV positive group.

During the study, 5 women receiving delamanid-containing regimens became pregnant. In all cases, exposure occurred during the first trimester. Four of the women receiving delamanid-containing regimens remained on study treatment while 1 discontinued treatment prematurely. No AEs or adverse outcomes in the mothers or newborns were reported.

Rapporteur assessment/comment:

Efficacy

The endTB study investigated 5 novel, all-oral 9-month regimens for pulmonary, fluoroquinolone susceptible, RR-TB. Three of the 5 experimental regimens did contain delamanid (BDLLfxZ, DCLLfxZ and DCMZ).
The study tested the non-inferiority of these regimens to the standard of care reflecting the WHO guidelines that were in effect while the study was being conducted, mostly individualised regimens of 18 to 24 months' duration. 10% of patients in the control arm were administered delamanid. The primary efficacy outcome was the proportion of participants with favourable outcome at week 73 analysed in the ITT population. This was compared to SoC with a 12% non-inferiority margin.

The population in the endTB study was heterogeneous, representing four continents, a range of severity of tuberculosis, and substantial burdens of important coexisting conditions, all of which contributed to the generalisability of the trial results to the broader population of people affected by rifampin-resistant tuberculosis.

The experimental regimens BDLLfxZ produced favourable outcomes in more than 85% of participants at week 73; which is similar to trial results with the regimen of bedaquiline, pretomanid, linezolid, and moxifloxacin (BPaLM) (89%).

Non-inferiority versus SoC was shown for 2 of the 3 delamanid containing shortened regimens BDLLfxZ and DCMZ in the mITT population. The DCLLfxZ regimen was not non-inferior in the mITT population.

The PP analyses do show, BDLLfxZ attained a similar level of efficacy in the per protocol population as the SoC control arm, with the advantage of being shorter treatment regimens and an increased treatment adherence.

In the mITT population, unfavourable outcomes due to positive culture occurred in 4.1% of all the participants, in 8 participants (7.5%) in the DCMZ group, and in 12 participants (10.2%) in the DCLLfxZ group. Recurrence occurred in 3 participants (0.4%), i.e. 1 in the DCLLfxZ group and 2 in the DCMZ group. Loss to follow-up and withdrawal of consent occurred in a larger percentage of the participants in the standard-therapy group than in any of the experimental regimen groups. The DCLLfxZ and DCMZ regimens showed higher levels of amplified resistance than the SoC control arm.

At week 104, non-inferiority was shown versus SoC for BDLLfxZ and DCMZ in the mITT population, but not for DCLLfxZ.

Subgroup analysis of efficacy of the 9BDLLfxZ regimen showed lower efficacy in HIV positive patients (12/17; 70.6%) versus HIV negative patients (102/119; 85.7%). It should be noted that the confidence intervals were wide for the HIV positive group.

Safety

The EndTB trial was not designed or powered for statistical comparison of safety outcomes, nor was it intended to evaluate the safety aspects of single drugs to the regimen. Additionally, due to non-availability of IPD from endTB, patients taking delamanid as part of their standard regimen could not be excluded from the control arm in this study (10% of the patients), hence further impeding a coherent safety assessment. Despite these shortcomings, the following safety-related aspects were noted:

Death from any cause occurred in 15 patients (2.0% of the safety population) by Week 73 and in 18 patients (2.4%) by Week 104, with **comparable incidences across the groups. No deaths were considered to be study drug related by investigators.** Of the death events reported through Week 104, **10 were reported in regimens including delamanid**; these included (Acute) Respiratory failure (n=4; including n=1 co-reporting Acute abdomen), Sepsis (n=2), Disease progression (n=1), Pancreatic carcinoma (n=1) and Death of unknown cause (n=2).

There were **no relevant differences in AE incidences** between the groups. The percentage of participants who had **at least one grade 3 or higher adverse event** ranged from 54.8% (in the BLMZ group) to 61.4% (in the BDLLfxZ group) and was 62.7% in the standard-therapy group. The **incidence of serious adverse events was similar** across the groups, ranging from 13.1% in the BCLLfxZ group to 16.7% in the DCMZ and standard-therapy groups. **Among all grade 3 or higher adverse events and serious adverse events, approximately one third were classified by the investigator as related to trial drugs.**

Important identified risk of QT prolongation: **QTcF prolongation ≥ Grade 3** occurred only in the experimental groups DCMZ (4.2%) and BCLLfxZ (3.3%). There were no events leading to death, and all patients recovered. As regards the delamanid-containing DCMZ-group, in addition to delamanid, clofazimine and moxifloxacin are also drugs known to cause QT interval prolongation.

Important potential risk of Liver disorders: The **most frequent AESI were hepatotoxic events** (defined as any Grade 3/4 increase in ALT or AST), occurring in 7.1% of patients in the standard therapy group, versus 6.3% (BDLLfxZ) to 18.3% (BLMZ) in experimental groups. There were minor differences across experimental groups, with 13.9% to 18.3% of events in groups not containing delamanid, 6.3% to 14.5% in groups containing delamanid, versus 7.1% in the control group. The most frequent PTs in the delamanid-containing regimens were ALT, AST, Conjugated bilirubin, and Transaminases increased. **Hepatic events showed no trend to increase in delamanid-containing regimens.** Notably, the authors of the publication discuss the possible hepatotoxic potential of pyrazinamide, bedaquiline, fluoroquinolones and linezolid, and take into account comorbidities. A possible hepatotoxic potential of delamanid is, however, not considered.

In conclusion, the data from the endTB study do not alter the known safety profile of delamanid.

Balance of benefits and risk

A balance of favourable and unfavourable effects of the BDLLfxZ arm versus control was performed by the WHO and is visualised in Figure 10. WHO suggests using the 9-month all-oral regimens BDLLfxZ over currently recommended longer (> 18 months) regimens in patients with MDR/RR-TB and in whom resistance to FQs has been excluded, as a conditional recommendation, with a very low certainty of evidence (primarily due to imprecision in the effect estimates).

A balance of favourable and unfavourable effects of the DCLLfxZ arm versus control was performed by the WHO and is visualised in Figure 11. The benefits of DCLLfxZ were judged to be small and the undesirable effects (higher levels of failure or recurrence and higher levels of amplified resistance) to be moderate compared with WHO-recommended longer regimens. Hence, the balance of health effects probably favours the WHO-recommended longer regimens.

A balance of favourable and unfavourable effects of the DCMZ arm versus control was performed by the WHO and is visualised in Figure 12. The benefits of DCMZ were judged to be moderate and the undesirable effects (higher levels of failure or recurrence and higher levels of amplified resistance) to be moderate compared with WHO-recommended longer regimens. Within the category of moderate effects, the undesirable effects were considered of greater weight and had higher certainty associated with them – in particular for the amplification of drug resistance. The trial data suggest that drug resistance includes losing FQ in almost all patients who failed treatment. Hence, the balance of health effects probably favours the WHO-recommended longer regimens.

BEAT-TB study South-Africa

Methods

BEAT-TB South Africa was a Phase 3, open-label, multicentre, pragmatic, randomised controlled-strategy and non-inferiority trial in patients with pulmonary RR-TB. A preprint of study data is available.

The study was led by the University of the Witwatersrand.

Study Participants

Patients aged ≥ 6 years with pulmonary TB resistant to at least rifampicin by genotypic or phenotypic DST were eligible. Pregnant and breastfeeding women were allowed to be included.

Treatments

Experimental treatment comprised 5 drugs i.e., bedaquiline, linezolid, delamanid, levofloxacin and clofazimine (BDLLfxC), administered for 6 months. Upon receipt of the FQ DST result, either levofloxacin (if FQ-resistant) or clofazimine (if FQ-susceptible) was dropped from the regimen (i.e., discontinued or not initiated, depending on when DST results became available).
The regimen could be given for 6 months or extended to 9 months if there was no clinical or bacteriological improvement.

Control was the standard treatment for RR-TB used in South-Africa at the time of enrolment, i.e., a 9-month, all-oral regimen with 2 months linezolid or a longer individualised regimen if resistance to FQs was identified.

No changes to medication dosing were allowed unless the weight category of patients changed. If patients experienced an adverse reaction to linezolid, the drug could be stopped temporarily or permanently. After the adverse reaction improved to Grade 1 or baseline level, linezolid was resumed at the initial dose of 600 mg. There was no provision for dose reduction following linezolid-related adverse reactions.

Objectives

The study was designed to compare the safety and efficacy of a novel 6-month regimen, BDLLfxC, for the treatment of MDR/RR-TB or pre-XDR-TB with either a 9-month oral regimen (linezolid containing) or a longer individualised regimen.

Outcomes/endpoints

The primary efficacy endpoint was a successful end of treatment (based on WHO programmatic definitions) followed by a successful end of follow-up outcome.
A successful treatment outcome measured at the end of treatment was defined as either "Cured" ie, adequate treatment adherence (≥ 80% of doses taken) as per protocol without evidence of failure and last 2 negative sputum specimens at the end of treatment (≥ 14 days apart) being negative or "Treatment Completed" ie, adequate treatment adherence (as above) without evidence of failure but without evidence that ≥ consecutive cultures taken ≥ 14 days apart were negative.
A successful end of follow-up outcome measured at 76 weeks after treatment initiation was defined as either "Cured" ie, culture negative at the end of follow-up or "Culture negative" when patient was last seen (if the patient was lost before the end of follow-up and provided they had a successful treatment outcome at the last available study visit).

The primary efficacy analysis was based on the intention-to-treat (ITT), including all randomised participants.

Sample size

A total 403 patients were randomised.

Randomisation

Patients were randomised to study treatment or control; randomisation was stratified by site and HIV status using blocked randomisation with blocks of varying sizes.

Statistical methods

The RD between patients with successful outcome at the end of treatment and follow-up at 76 weeks after randomisation between control and study treatment groups was calculated stratified by HIV and site using Cochran-Mantel-Haenszel weights. Non-inferiority was to be concluded if the upper bound of the 95% CI was below the 10% margin of non-inferiority.

Results

Participant flow

A total of 403 patients were randomised. One of 403 patient was randomised in error and did not start treatment. The other 402 patients formed the primary analysis set.

Conduct of the study

Scheduled visits took place every 2 weeks for the initial 8 weeks, followed by visits every 4 weeks until treatment completion. Post-treatment visits occurred monthly for the first 3 months and subsequently every 3 months. All patients were monitored for 76 weeks.

Baseline data

Median age was 35.0 years, 30 (7%) patients were < 18 years of age. Half of the patients (51%) were HIV positive. Body mass index (BMI) was less than 18.5 kg/m² among 167 (41%) participants. Baseline characteristics were well balanced between strategies. A total of 170 patients (42%) were female, including 9 females (6%) who were pregnant.

The distribution of patients by regimen within control treatment and study treatment is shown in Table 12. This table includes all drugs taken up to 10 days after randomisation; it does not include drugs taken prior to randomisation that were stopped on or before randomisation. Thus, 21 patients in the control arm (21/200; 10.5%) and all 202 patients in the study treatment arm received a delamanid-containing regimen. In the study treatment arm, 71.8% received a BDLLfxC regimen, 20.8% received BDLLfx, and 6.9% received BDLC.

Table 12. Summary of Drugs in Initial Regimen at Randomisation; BEAT-TB

Regimen, N(%)	Control Strategy	Study Strategy
Total	**200**	**202**
Bedaquiline, Delamanid, Linezolid, Levofloxacin, Clofazimine	0	145 (71.8%)
Bedaquiline, Delamanid, Linezolid, Levofloxacin	0	42 (20.8%)
Bedaquiline, Delamanid, Linezolid, Clofazimine	0	14 (6.9%)
Bedaquiline, Delamanid, Clofazimine, Ethambutol, Linezolid, Levofloxacin, Pyrazinamide, Rifafour	0	1 (0.5%)
Bedaquiline, Clofazimine, Ethambutol, Isoniazid, Linezolid, Levofloxacin, Pyrazinamide	168 (84.0%)	0
Bedaquiline, Delamanid, Linezolid, Clofazimine, Terizidone	16 (8.0%)	0
Bedaquiline, Linezolid, Levofloxacin, Clofazimine, Terizidone	8 (4.0%)	0
Bedaquiline, Delamanid, Linezolid, Clofazimine, PAS	5 (2.5%)	0
Bedaquiline, Clofazimine, Ethambutol, Linezolid, Levofloxacin, Pyrazinamide	2 (1.0%)	0
Bedaquiline, Ethambutol, Isoniazid, Linezolid, Levofloxacin, Pyrazinamide	1 (0.5%)	0

Outcomes and estimation

Of the 402 patients the primary analysis set, 172/200 (86.0%) in the control arm and 174/202 (86.1%) in the study treatment arm had successful outcomes at both end of treatment and at 76 weeks (Table 13), with an adjusted RD of −0.2% (95% CI −6.9%, 6.5%), demonstrating non-inferiority (p = 0.0014). The unadjusted difference was −0.1% (95% CI -6.9%, 6.6%; p = 0.0017) and also supported non-inferiority of study treatment versus control.

Table 13. Summary of Week 76 Primary Efficacy Outcome; BEAT-TB, ITT

Primary Outcome	Control Strategy	Study Strategy	Total
Total randomized (ITT population)	**200**	**202**	**402**
Successful outcome at end of treatment and follow-up			
Total	**172 (86.0%)**	**174 (86.1%)**	**346 (86.1%)**
Cured at end of treatment, and end of follow-up	162 (81.0%)	160 (79.2%)	322 (80.1%)
Cured at end of treatment, culture negative when last seen	10 (5.0%)	14 (6.9%)	24 (6.0%)
Unsuccessful end of treatment outcome			
Total	**22 (11.0%)**	**14 (6.9%)**	**36 (9.0%)**
Treatment failed	10 (5.0%)	7 (3.5%)	17 (4.2%)
Lost to follow-up on treatment	4 (2.0%)	2 (1.0%)	6 (1.5%)
Died while on treatment	7 (3.5%)	4 (2.0%)	11 (2.7%)
Not Evaluated (Participant withdrew consent)	1 (0.5%)	1 (<0.5%)	2 (<0.5%)
Unsuccessful end of follow-up			
Total	**6 (3.0%)**	**14 (6.9%)**	**20 (5.0%)**
Recurrence after cure at end of treatment	4 (2.0%)	10 (5.0%)	14 (3.5%)
Died after cure at end of treatment	2 (1.0%)	4 (2.0%)	6 (1.5%)

All 30 paediatric patients had successful outcomes at both end of treatment and at 76 weeks.

In the BEAT-TB trial, the regimen was prolonged for three patients because of late culture conversion.

There was no evidence that treatment effects varied according to age, sex, HIV status, sputum-smear status, cavitation on chest x-ray, or fluoroquinolone resistance although our study was not powered to rule out differences across any subgroups.

Seventeen participants experienced treatment failure (failure to culture convert or culture reversion): 10 participants (5.0%) in the control strategy and seven participants (3.5%) in the study strategy. Five participants in the control strategy and three in the study strategy had resistance to bedaquiline at the time of failure. Fourteen participants experienced a recurrence: 4 (2.0%) from the control strategy and 10 (5.0%) from the study strategy. Two participants in the study strategy exhibited resistance to bedaquiline at the time of relapse. However, as this was a pragmatic study employing standard laboratory testing, resistance data for some participants was missing.

Ancillary analyses

BEAT-TB analysis performed by the WHO

This analysis is reported in the **WHO 2025 consolidated guidelines on tuberculosis**

Participants with MDR/RR-TB (with or without quinolone resistance) receiving the BDLLfxC regimen (n=202) compared to participants receiving WHO-recommended SoC regimens used in the BEAT-TB trial (n=200) experienced:

- higher levels of failure or recurrence: 8.4% vs 7.0%; RD=14 more per 1000, 95% CI: 38 fewer to 66 more per 1000); (trivial or no effect)
- lower levels of death: 5.0% vs 5.0%; RD= 0.5 fewer per 1000 (95% CI: from 43 fewer to 42 more per 1000); (trivial or no effect)
- lower levels of LTFU: 1.0% vs 2.0%; RD= 10 fewer per 1000 (95% CI: from 34 fewer to 14 more per 1000); (trivial or no effect)
- lower levels of grade 3–5 AEs: 34% vs 38%; RD=38 fewer per 1000 (95% CI: 132 fewer to 55 more per 1000); (small effect) and
- lower levels of amplified resistance: 2.5% vs 3.0%; RD=5 fewer per 1000 (95% CI: 37 fewer to 27 more per 1000). (trivial or no effect)

The GDG judged the benefits of BDLLfxC to be small and the undesirable effects to be trivial compared with WHO-recommended SoC regimens. The overall certainty of evidence was very low, primarily due to imprecision in the effect estimates. Additionally, the GDG considered the shortening of the treatment duration and the reduction in pill burden as a desirable effect. Based on this, the panel determined that the balance of health effects probably favours BDLLfxC regimen.

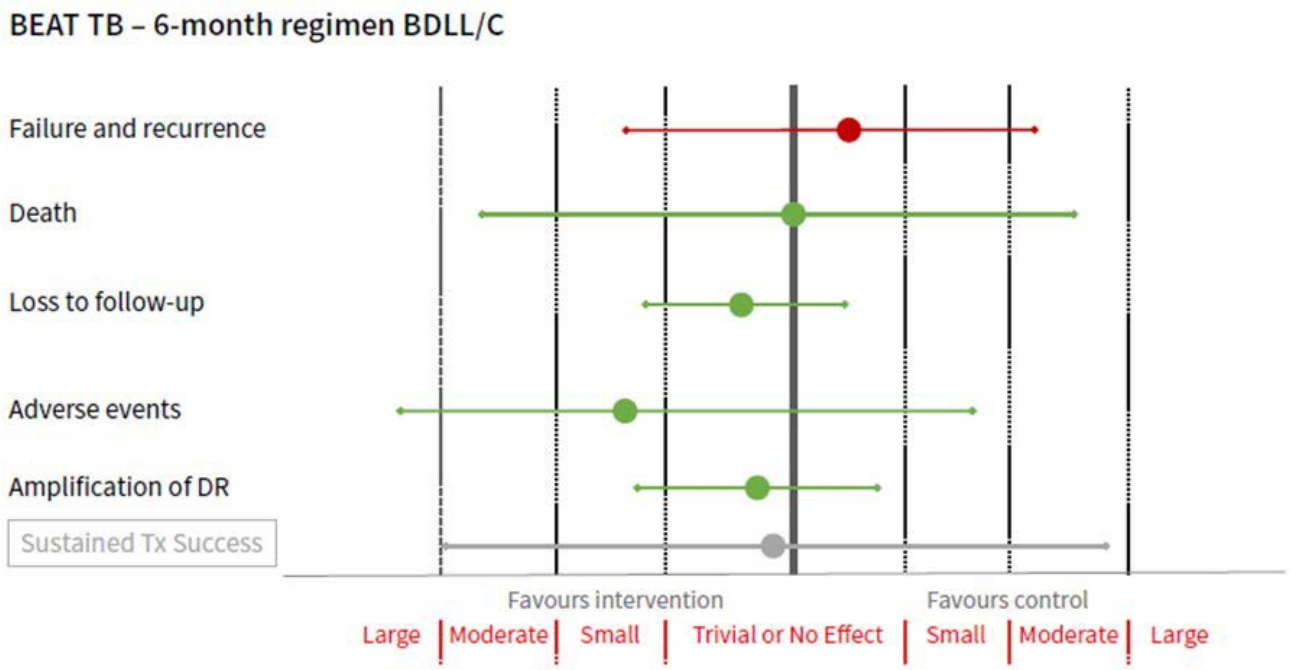

Figure 13. WHO Summary of Research Evidence from BDLLfx/C versus Standard of Care

In BEAT-TB, 202 PLHIV were enrolled, with 105 randomised to the study arm. The median CD4+ in this group was 168 (95% CI: 85.0, 299). No major effect of HIV status on the efficacy of the intervention regimen vs the control was observed (risk difference 2.1% (95% CI: –7.9%, +12.2%). Thus, the recommendation for the BDLLfxC regimen applies to all people, regardless of HIV status or degree of immunosuppression and appeared preferable to the comparator. [WHO 2025]

In the BEAT-TB trial among patients with pre-XDR-TB, the outcomes also appeared worse than among those who were fluoroquinolone susceptible. This reduction in the proportion with successful treatment outcomes was numerically greater in the BDLLfxC arm than in the control arm (14.3% vs 3.3%); however, this difference was within the range of statistical uncertainty and the GDG judged that this should not affect the recommendation or remarks. The rate of acquisition of resistance to bedaquiline was similar between the two groups (11% in BDLLfxC and 9.1% in control). The evidence from the BEAT-TB trial is insufficient to draw definitive conclusions due to the small sample when stratified by fluoroquinolone resistance and related imprecision. Nonetheless, clinicians should remain vigilant and closely monitor the treatment response in this group of patients and promptly take relevant actions (extending the duration of treatment or changing the regimen). [WHO 2025]

There was no exclusion based on BMI. Eighty-five (42%) patients randomised to BDLLfxC had a BMI below 18.5 g/m². No major effect of a low BMI was noted on the efficacy of the BDLLfxC versus the control (RD –4.1% (95% CI: –16.5%, 8.3%), but the evidence is too uncertain to draw specific conclusions. [WHO 2025]

Adverse events

AEs of ≥Grade 3 occurred in 37.0% of patients in the control arm and 31.2% in the study treatment arm (Table 14). For the most frequent AEs of ≥Grade 3 see Table 15.

Table 14. Overall Safety Summary; BEAT-TB

	Control Strategy	Study Strategy	Total	RD (95% CI)
Randomised and starting treatment	**200**	**202**	**402**	
Grade 3-5 AEs	76 (38.0%)	69 (34.2%)	145 (36.1%)	3.8% (-5.5%, 13.2%)
Grade 3-5 AEs during treatment	74 (37.0%)	63 (31.2%)	137 (34.1%)	5.8% (-3.4%, 15.1%)
Grade 3-5 AEs during treatment, at least possibly related	56 (28.0%)	52 (25.7%)	108 (26.9%)	2.3% (-6.4%, 10.9%)
SAEs	44 (22.0%)	45 (22.3%)	89 (22.1%)	-0.3% (-8.4%, 7.8%)
SAEs during treatment	42 (21.0%)	38 (18.8%)	80 (19.9%)	2.2% (-5.6%, 10.0%)
Notable Events (NEs)	31 (15.5%)	36 (17.8%)	67 (16.7%)	-2.3% (-9.6%, 5.0%)
Death at any time	10 (5.0%)	10 (5.0%)	20 (5.0%)	0.0% (-4.2%, 4.3%)
Death during treatment	8 (4.0%)	6 (3.0%)	14 (3.5%)	1.0% (-2.6%, 4.6%)
Death after treatment	2 (1.0%)	4 (2.0%)	6 (1.5%)	-1.0% (-3.3%, 1.4%)
Anaemia leading to treatment discontinuation	8 (4.0%)	10 (5.0%)	18 (4.5%)	-1.0% (-5.0%, 3.1%)
Anaemia leading to blood transfusion	11 (5.5%)	20 (9.9%)	31 (7.7%)	-4.4% (-9.6%, 0.8%)
Grade 3-5 liver abnormality	9 (4.5%)	4 (2.0%)	13 (3.2%)	2.5% (-0.9%, 6.0%)
Perihperal neuropathy leading to treatment discontinuation	7 (3.5%)	10 (5.0%)	17 (4.2%)	-1.5% (-5.4%, 2.5%)
Optic neuropathy leading to treatment discontinuation	2 (1.0%)	7 (3.5%)	9 (2.2%)	-2.5% (-5.3%, 0.4%)
QTcF ≥ 480ms	19 (9.5%)	12 (5.9%)	31 (7.7%)	3.6% (-1.7%, 8.8%)
QTcF ≥ 500ms	7 (3.5%)	5 (2.5%)	12 (3.0%)	1.0% (-2.3%, 4.4%)

Table 15. AEs of Greater than or Equal to Grade 3 that Occurred in Greater than or Equal to 3 Patients Overall; BEAT-TB

	Control Strategy	Study Strategy	Total
Total randomized	**200**	**202**	**402**
No Grade 3-5 AE	**124 (62.0%)**	**133 (65.8%)**	**257 (63.9%)**
Any Grade 3-5 AE	**76 (38.0%)**	**69 (34.2%)**	**145 (36.1%)**
Anaemia	29 (14.5%)	33 (16.3%)	62 (15.4%)
Neuropathy peripheral	12 (6.0%)	16 (7.9%)	28 (7.0%)
Alanine aminotransferase increased	9 (4.5%)	4 (2.0%)	13 (3.2%)
Electrocardiogram QT prolonged	7 (3.5%)	6 (3.0%)	13 (3.2%)
Optic neuritis	2 (1.0%)	5 (2.5%)	7 (1.7%)
Dyspnoea	2 (1.0%)	3 (1.5%)	5 (1.2%)
Treatment failure	4 (2.0%)	1 (0.5%)	5 (1.2%)
Hepatotoxicity	2 (1.0%)	1 (0.5%)	3 (0.7%)
Not yet coded	2 (1.0%)	1 (0.5%)	3 (0.7%)
Pneumonia	1 (0.5%)	2 (1.0%)	3 (0.7%)

Nine (4.5%) liver-related AEs of ≥ Grade 3 occurred in the control arm, versus 4 (2.0%) in the study treatment arm. It is surmised that liver-related AEs for this analysis were ALT elevations reported as AE. It should be noted that only ALT was routinely (monthly) assessed. More detailed assessments of liver parameters were only performed in case of ALT > 3 times the upper limit of normal. This approach may have underestimated hepatic events.
Hepatic AEs of ≥ Grade 3 were ALT increased (control: 9 [4.5%]; treatment: 4 [2.0%]), hepatotoxicity (2 [1.0%] versus 1 [0.5%]), and acute hepatitis B, drug-induced liver injury, and hepatic failure in 1 patient each (0.5%) in the control arm, versus none of the patients in the treatment group. Thus, as far as a conclusion can be drawn based on the low event numbers, clinical hepatic AEs seemed to be rare, although there seemed to be a trend for slightly more frequent AEs in the control arm.

Asymptomatic QTcF prolongation ≥500 ms occurred in 3.5% of participants in the control group versus 2.5% in the treatment group, QTcF prolongation ≥480 ms occurred in 9.3% in the control versus 5.9% of participants in the treatment group.

Drug-related AEs of ≥ Grade 3 and drug-related occurred in 28.0% of patients in the control arm and 25.7% of patients in the treatment arm. The most frequent related AEs of ≥ Grade 3 were anaemia,

attributed to linezolid (control: 14.5%; treatment: 16.3%). Most cases of anaemia occurred within the first 8 weeks of treatment. Anaemia was managed primarily by temporarily interrupting linezolid for a few days. Other manifestations of linezolid-related myelosuppression, such as thrombocytopenia and neutropenia, were rare.

Serious adverse event/deaths/other significant events

SAEs occurred in 22.0% versus 22.3% of patients in the 2 groups.
Twenty patients died through follow-up, 5.0% of patients in each group. Information on the potential relatedness of deaths could not be identified in the publication including supplements, most likely related to the underlying and concomitant diseases.

Safety in special populations

Of 9 women pregnant at baseline and 1 additional becoming pregnant during the trial (6 in the control group, 4 in the study treatment group), all women delivered singleton live births, including 9 full term and 1 premature delivery.

Of the 30 paediatric patients with confirmed RR-TB (17 in the control group versus 13 in the study treatment group), 7 (24%) had FQ-resistance. One adolescent patient had resistance to bedaquiline and clofazimine at baseline and was subsequently switched to an individualised rescue regimen. There were 5 AEs related to linezolid, 3 of which were ≥ Grade 3 (2 cases of anaemia, 1 case of peripheral neuropathy, 2 cases of optic neuritis).
Delamanid was discontinued in one participant due to neuropsychiatric adverse reactions. This was a child in the control group that developed neuropsychiatric adverse reactions, attributed to delamanid; the event led to treatment discontinuation. The patient experienced mixed visual and auditory hallucinations (serious), insomnia, and neuropsychiatric adverse reaction. Event onset was 8 days after start of delamanid treatment; the event was reported as recovered/resolved upon delamanid withdrawal.
Events of visual and auditory hallucinations and insomnia were judged as being delamanid related. The patient also used terizidone concomitantly which is known to cause psychiatric and central nervous system disorders as most important adverse reactions. Information on this patient was retrieved and discussed in the delamanid PSUR no.16 (period 28 Apr 2023 through 27 Oct 2023).

Discussion

The 6-month experimental regimen of BDLLfxC demonstrated non-inferior efficacy to the South African standard of care TB regimen used as control. Safety profiles were comparable between the groups. Thus, BEAT-TB showed that with the new regimen, significant shortening of treatment duration is possible without loss of efficacy compared to the standard longer regimen. Findings provide also evidence for an effective regimen for children aged < 14 years and pregnant women, offering more therapeutic options for all individuals with RR-TB.

BEAT-TB was performed in a single country, which may limit generalisability of the results.

An important limitation of the study was missing data. BEAT-TB was a pragmatic trial conducted within the South African National TB Programme. The TB diagnosis was primarily established using the Xpert system, followed by DST conducted using line-probe assays, which did not yield a result in 20% of cases. In case of unknown FQ resistance, patients assigned to the experimental arm continued treatment with all 5 drugs, while control patients received the standard regimen. Even though bedaquiline resistance is becoming increasingly challenging in the treatment of MDR-TB, bedaquiline susceptibility testing was done only when FQ resistance was confirmed.

An additional limitation concerns the fact that 17% of patients had negative MGIT results at baseline ie, may not have had TB. However, a sensitivity analysis by MGIT status suggests that patients with confirmed TB at baseline had results similar to that of the overall study population, suggesting that the high rate of MGIT negative results had no relevant impact on the overall study outcome (Conradie et al, supplemental materials)

The results of BEAT-TB informed the update of the WHO guidelines for the treatment of DR-TB. The GDG judged the benefits of BDLLfxC to be small and the undesirable effects to be trivial compared with WHO-recommended SoC regimens. The overall certainty of evidence was very low, primarily due to imprecision in the effect estimates. Additionally, the GDG considered the shortening of the treatment duration and the reduction in pill burden as a desirable effect. Based on this, the panel determined that the balance of health effects probably favours BDLLfxC regimen. The BDLLfxC regimen is suggested over currently recommended 9-month or longer regimens in patients with MDR/RR TB.

Rapporteur assessment/comment:

Efficacy

The BEAT-TB study investigated a novel delamanid-including six-month RR-TB strategy for pulmonary TB containing BDLLfxC. Upon receipt of the FQ DST result, either levofloxacin (if FQ-resistant, i.e. pre-XDR-TB) or clofazimine (if FQ-susceptible) was dropped from the regimen (ie, discontinued or not initiated, depending on when DST results became available). The regimen could be extended to 9 months if there was no clinical or bacteriological improvement.

The study tested the non-inferiority of BDLLfxC to the then-current South African nine-month or a longer individualised regimen if resistance to FQs was identified. The majority of patients in the control arm (84%) were administered the 9-month all oral regimen containing bedaquiline, levofloxacin, linezolid for 2 months, clofazimine, isoniazid, pyrazinamide and ethambutol. Also, in this study 10.5% patients in the control arm were administered delamanid.

The primary effectiveness measure was successful treatment completion at the end of treatment and a successful end-of-follow-up outcome at 76 weeks and analysed in the ITT population. This was compared using an adjusted risk difference with a 10% non-inferiority margin.

403 participants were randomised between August 2019 and October 2022 and 402 analysed.

Non-inferiority was shown between the study arm with 86.1% successful outcome and the control arm with 86.0%. The percentage of patients with a successful outcome was similar to the percentage with a favourable outcome in the bedaquiline containing experimental arms in the endTB study, even though there are differences in the design of the study e.g. with the inclusion of FQ-resistant patients. Ten participants (5.0%) in the control arm and seven participants (3.5%) in the experimental arm experienced failure to culture convert or culture reversion. Eight of those had bedaquiline resistance at the time of failure. In addition, 4 (2.0%) participants from the control arm and 10 (5.0%) from the experimental arm experienced a recurrence.

Among patients with pre-XDR-TB, the outcomes appeared worse than among those who were fluoroquinolone susceptible. This reduction in the proportion with successful treatment outcomes was numerically greater in the BDLLfxC arm than in the control arm (14.3% vs 3.3%); however, the evidence from the BEAT-TB trial is insufficient to draw definitive conclusions due to the small sample when stratified by fluoroquinolone resistance and related imprecision. Nonetheless, clinicians should remain vigilant and closely monitor the treatment response in patients with pre-XDR-TB.

The study was conducted in South-Africa, with half (51%) of the patients being HIV-positive. No major effect of HIV status on the efficacy of the intervention regimen vs the control was observed.

Safety

The BEAT-TB trial was not designed or powered for statistical comparison of safety outcomes, nor was it intended to evaluate the safety aspects of single drugs to the regimen. Additionally, due to non-availability of IPD from BEAT-TB, patients taking delamanid as part of their standard regimen could not be excluded from the control arm in this study (10.5% of the patients), hence further impeding a coherent safety assessment. Despite these shortcomings, the following safety-related aspects were noted:

Twenty participants died during treatment and follow-up, with 10 (5.0%) in each group. Information of relatedness of fatal AEs could not be identified in the publication, nor is it specified in which control regimens the deaths occurred (i.e. delamanid-containing or not).

There was **no significant difference in the risk of developing severe** (Grade 3–5) **AEs** between the control and study groups (28.0% in the control group vs. 25.7% in the study group for events at least possibly related to the drug). Likewise, **the risk of developing SAEs during treatment was comparable between treatment groups** (21.0% in the control group vs. 18.8% in the study group).

Important identified risk of QT prolongation: There was no relevant difference in liver-related AEs of ≥ Grade 3 (control 4.5%; study treatment 2.0%).

Important potential risk of Liver disorders: There are no relevant difference in asymptomatic QTcF prolongation ≥ 500 ms (control 3.5%; study treatment 2.5%) and QTcF prolongation ≥ 480 ms (control 9.5%; study treatment 5.9%).

Of note, one child in the control strategy developed neuropsychiatric adverse reactions, which were attributed to delamanid. Delamanid was discontinued; it is not clear whether the AE improved after stopping the drug.

In conclusion, the data from the BEAT-TB study do not alter the known safety profile of delamanid.

Balance of benefits and risk

A balance of favourable and unfavourable effects of the BDLLfxC arm versus control was performed by the WHO and is visualised in Figure 13:

The benefits of BDLLfxC were judged to be small compared with WHO-recommended SoC regimens.

- lower levels of death: 5.0% vs 5.0%; RD= 0.5 fewer per 1000 (95% CI: from 43 fewer to 42 more per 1000); (trivial or no effect)
- lower levels of LTFU: 1.0% vs 2.0%; RD= 10 fewer per 1000 (95% CI: from 34 fewer to 14 more per 1000); (trivial or no effect)
- lower levels of grade 3–5 AEs: 34% vs 38%; RD=38 fewer per 1000 (95% CI: 132 fewer to 55 more per 1000); (small effect) and
- lower levels of amplified resistance: 2.5% vs 3.0%; RD=5 fewer per 1000 (95% CI: 37 fewer to 27 more per 1000). (trivial or no effect)

The undesirable effects of BDLLfxC were judged to be trivial compared with WHO-recommended SoC regimens:

- higher levels of failure or recurrence: 8.4% vs 7.0%; RD=14 more per 1000, 95% CI: 38 fewer to 66 more per 1000); (trivial or no effect)

Shortening of the treatment duration and the reduction in pill burden were considered as a desirable effect.

The overall certainty of evidence was very low, primarily due to imprecision in the effect estimates. Based on this, the panel determined that the balance of health effects probably favours BDLLfxC regimen.

There is additional uncertainty for the patients with pre-XDR-TB, as the outcomes appeared worse than among those who were fluoroquinolone susceptible, but the sample size after stratification was too small and the imprecision was high to draw definitive conclusions. This reduction in the proportion with successful treatment outcomes was numerically greater in the BDLLfxC arm than in the control arm (14.3% vs 3.3%). Therefore, clinicians should remain vigilant and closely monitor the treatment response in patients with pre-XDR-TB.

Conclusion on SOB 002:

The MAH did submit the results of the endTB study, including a critical discussion of the publicly available data with a focus on the evaluation of delamanid, showing that delamanid can be used in the fixed 9-month BDLLfxZ combination regimen in patients with pulmonary fluoroquinolone-susceptible, RR-tuberculosis. The 2 other delamanid-containing shortened regimens from the endTB study (DCLLfxZ and DCMZ) are not recommended due to a disbalance in failure and recurrence and amplification of drug resistance versus the control arm.

In addition the results from the BEAT-TB study have been submitted and discussed, supporting delamanid use in a 6-month BDLLfxC regimen in patients with pulmonary RR-tuberculosis.

This supports the use of delamanid in different combination treatment regimens as per approved indication.

These data have been submitted before the due date (Q3 2026) agreed upon during the previous renewal procedure.

The Rapporteur is of the opinion that Specific Obligation SOB 002 has been fulfilled, and, therefore, recommends its deletion from the Annex II.

5.3. Overall conclusion on Specific Obligations

During the period covered by this annual renewal, new data regarding SOBs have emerged. The new data emerged are compliant in terms of adherence to deadlines and are compliant in terms of acceptability of data submitted.

During the period covered by this annual renewal, new data regarding the following SOB have emerged. The SOB is considered fulfilled:

In order to further investigate the use of delamanid in different combination treatment regimens as per approved indication as well as safety, the MAH should submit the publicly available data of the endTB (Evaluating Newly approved Drugs for multidrug-resistant TB) study, a randomised, controlled Phase III trial in adults and adolescents with multi-drug resistant tuberculosis conducted by Médecins Sans

Frontières, with an analysis based on the agreed statistical analysis plan and publicly available results from the BEAT-TB study conducted by Wits Health Consortium.

6. Additional scientific data provided relevant for the assessment of the benefit/risk balance

6.1. Clinical efficacy

The MAH selected additional sources of publicly available data to support the use of delamanid in different combination treatment regimens as per approved indication. The individual studies are discussed in this report.

Table 16. Additional Sources of Publicly Available Information Selected by the MAH

Reference	Type of study	Article title	Delamanid-containing regimen
Mok 2022[17]	RCT	9 months of delamanid, linezolid, levofloxacin, and pyrazinamide versus conventional therapy for treatment of fluoroquinolone-sensitive multidrug-resistant tuberculosis (MDR-END): a multicentre, randomised, open-label Phase II/III noninferiority trial in South Korea	DLLfxZ versus standard of care regimens
Patil 2023[26]; Guglielmetti 2025b[19]	RCT	Evaluating newly approved drugs in combination regimens for multidrug-resistant tuberculosis with fluoroquinolone resistance (endTB-Q): study protocol for a multi-country randomised controlled trial Bedaquiline, delamanid, linezolid, and clofazimine for rifampicin-resistant and fluoroquinolone-resistant tuberculosis (endTB-Q): an open-label, multicentre, stratified, non-inferiority, randomised, controlled, phase 3 trial	BDLC versus standard of care
Nasiri 2022[27]	Systematic review/ meta-analysis	Delamanid-containing regimens and multidrug-resistant tuberculosis: A systematic review and meta-analysis	D-containing treatment regimens
Ahmed 2024[28]	Systematic review/ meta-analysis	Efficacy and safety of bedaquiline and delamanid in the treatment of drug-resistant tuberculosis in adults: A systematic review and meta-analysis	B- and/or D-containing treatment regimens
Holmgaard 2023[29]	Systematic review/ meta-analysis	Efficacy and tolerability of concomitant use of bedaquiline and delamanid for multidrug- and extensively drug-resistant tuberculosis: A ystematic review and meta-analysis	B + D-containing regimens
Putra 2023[30]	Systematic review	Favourable outcome of individual regimens containing bedaquiline and delamanid in drug-resistant tuberculosis: A systematic review	B + D-containing regimens
Rehman 2024[31]	Systematic review/ meta-analysis	Efficacy and safety of bedaquiline containing regimens in patients of drug-resistant tuberculosis: An updated systematic review and meta-analysis	B-containing treatment regimens, stratified as B versus B + D-containing regimens

Individual studies

MDR-END (Mok 2022)

Study design

This was a multicentre, randomised, open-label phase 2/3 non-inferiority study, performed in South-Korea, with enrolment between 2016 and 2019. It aimed to compare a new, shorter regimen (9-12 months) DLLfxZ regimen with the conventional regimen (20 to 24 months) recommended by WHO and South Korean guidelines in patients with FQ-sensitive MDR-TB. Treatment duration in the DLLfxZ group was 9 months if sputum culture conversion occurred within 3 months but could be extended to 12 months if SCC occurred after 3 to 6 months of treatment.
Delamanid, linezolid, and bedaquiline could be used in the control group in cases of resistance to second-line injectable drugs or the development of AEs related to the initially chosen drugs.

The study included adult (19 to 85 years) patients with MDR-TB confirmed by phenotypic or genotypic DST or RR-TB by genotypic tests. Patients were excluded if presenting with FQ-resistant MDR-TB; with a history of optic or peripheral neuropathy; or with QT prolongation defined as QTcF > 500 ms.

The primary outcome was the treatment success rate at 24 months in the mITT and the PP (primary consideration for mITT). Treatment success was defined according to the 2014 WHO Guidelines using the results of mycobacterial culture on liquid medium. Patients who were "cured" and "completed treatment" were defined as treatment success. Unfavourable outcomes included treatment failure, relapse, death, LTFU, transfer out, and withdrawal from the trial. Patients who died, were LTFU, transferred out, withdrew, or were reinfected by a different strain of Mtb after the completion of treatment and the achievement of negative culture conversion, and patients who withdrew from the study because of pregnancy were excluded from the primary outcome analysis.

Non-inferiority was to be confirmed if the lower limit of the 97.5% 1-sided CI of the difference between the groups was greater than −10%.

The mITT included randomised patients who were treated at least once with a predefined regimen. The PP included patients from the mITT who completed > 80% of the planned treatment and completed the clinical study according to the protocol.

Study results

A total of 214 patients were randomised into the study (n = 106 control; n = 108 DLLfxZ). The mITT included 168 patients (n = 89 control, n = 79 DLLfxZ). 46 patients were excluded from the mITT, the most frequent reasons being FQ resistance (n = 17) and isoniazid sensitivity (n = 17). The PP included 164 patients (n = 87 control, n = 77 DLLfxZ).

In the mITT, 69% of patients were men; median age was 47 years. 45% of patients had a history of previous TB, 20% had diabetes. None of the patients was HIV positive.

Patient disposition and outcome are summarised for the mITT and PP in Table 17. In the mITT, treatment success after 24 months was achieved in 75% of patients in the DLLfxZ group versus 71% of patients in the control group. The between-group difference in treatment success rate at 24 months was 4.4% (97.5% CI −9.5% to infinity). The most frequent reason for treatment failure was the addition of 2 or more additional drugs because of AEs (n = 4 patients on DLLfxZ; n = 10 patients on control). Based on the predefined non-inferiority margin, non-inferiority was demonstrated by the results for the mITT.

In the PP, treatment success was achieved in 76% (DLLfxZ) versus 72% (control) of patients (between-group difference 3.4%; 97.5% CI −10.5% to infinity).

Thus, non-inferiority was shown for the mITT but could not be demonstrated for the PP.

Table 17. Patient Disposition and Outcome in MDR-END

	Modified intention-to-treat population		Per-protocol population	
	Control group	Shorter-regimen group	Control group	Shorter-regimen group
Disposition of the participants				
Underwent randomisation	106	108	106	108
Included in the population	89 (84%)	79 (73%)	87 (82%)	77 (71%)
Not assessable	4 (4%)	7 (9%)	4 (5%)	7 (9%)
Became pregnant during treatment	0	1 (1%)	0	1 (1%)
Achieved negative culture conversion but were lost to follow-up after treatment completion	4 (4%)	3 (4%)	4 (5%)	3 (4%)
Achieved negative culture conversion but died after treatment completion	0	3 (4%)	0	3 (4%)
Included in the primary outcome analysis	85 (80%)	72 (67%)	83 (78%)	70 (65%)
Outcome				
Treatment success at 24 months after the initiation of treatment	60 (71%)	54 (75%)	60 (72%)	53 (76%)
Difference versus the control group (97·5% one-sided CI)	1 (ref)	4·4% (−9·5% to ∞)*	1 (ref)	3·4% (−10·5% to ∞)*
Unfavourable outcomes at 24 months after the initiation of treatment	25 (29%)	18 (25%)	23 (28%)	17 (24%)
Treatment failure				
Failed to obtain negative conversion of sputum culture	0	1† (1%)	0	1† (1%)
Reversion to positive culture in the continuation phase	1 (1%)	0	1 (1%)	0
Started ≥2 additional drugs because of adverse events	10 (12%)	4 (6%)	9 (11%)	4 (6%)
Relapse after treatment completion	0	1‡ (1%)	0	1‡ (1%)
Died during treatment	2 (2%)	2 (3%)	2 (2%)	2 (3%)
Lost to follow-up during treatment	4 (5%)	1 (1%)	3 (4%)	1 (1%)
Withdrew consent during treatment	5 (6%)	6 (8%)	5 (6%)	6 (9%)
Other investigators' decision	3 (4%)	3 (4%)	3 (4%)	2 (3%)

*97·5% one-sided CI for non-inferiority test. †The minimum inhibitory concentrations (MICs) of delamanid in the *Mycobacterium tuberculosis* strain isolated after 8 months of treatment was 0·00625 µg/mL and for linezolid, it was 0·5 µg/mL. ‡Confirmed to be the same strain as the original *M tuberculosis* based on an analysis of Mycobacterial Interspersed Repetitive Units-Variable Tandem Repeats. The MIC of delamanid in the relapsed strain was 0·00625 µg/mL and for linezolid, it was 0·125 µg/mL.

At the end of treatment, 78% of DLLfxZ patients and 72% of control patients achieved treatment success (p = 0.35) in the mITT. One participant in the DLLfxZ group experienced relapse with the same Mtb strain.

The proportion of patients with drug-related AEs was 75% in the DLLfxZ group versus 63% in the control group. Likewise, incidences of AEs ≥Grade 3, SAEs, or AEs leading to death were numerically slightly higher in the DLLfxZ group.

Table 18. Safety Outcomes in MDR-END

	Control group (n=89)	Shorter-regimen group (n=79)
Participants with at least one adverse event	87 (97·8%)	78 (98·7%)
Participants with at least one adverse event considered possibly, probably, or definitely related to the study drugs	56 (62·9%)	59 (74·7%)
Participants with at least one grade 3 or greater adverse event	26 (29·2%)	29 (36·7%)
Participants with serious adverse events	19 (21·3%)	20 (25·3%)
Death		
Any	2 (2·2%)	5 (6·3%)
Tuberculosis-related	0	0

Cause of death for the 2 patients who died in the control group were hepatitis B virus-related acute liver failure and suicide, respectively. Both patients died during treatment. In the DLLfxZ group, 2 patients died during treatment, with cause of death being sepsis and heart failure, respectively. Three additional patients died after treatment completion; cause of death in 1 patient each was bacterial peritonitis; cryptococcal meningitis and pneumonia; and suicide. The 2 patients who committed suicide had no history of psychiatric illness. The patient who died of cryptococcal meningitis and pneumonia had been treated with prednisolone and ciclosporin for underlying idiopathic thrombocytopenic purpura.

In the DLLfxZ group, no patient had QTcF > 500 ms, but 4 patients had ΔQTcF > 60 ms. Amendment of the regimen because of QT prolongation was not required for any of the patients.

Conclusions

In this study, DLLfxZ demonstrated non-inferiority to the conventional 20- to 24-month regimen in patients with FQ-sensitive MDR-TB (mITT population). In the mITT, treatment success rates after 24 months were higher in the DLLfxZ group (75.0%) than the control group (70.6%), meeting the predefined non-inferiority margin. No difference in safety outcomes was identified between DLLfxZ and control group. The authors concluded that 9-month treatment with DLLfxZ represents a new treatment option for patients with FQ-sensitive MDR-TB.

Rapporteur assessment/comment:

The target population in this study were patients with FQ-susceptible, pulmonary MDR-TB, which is similar to the endTB study.

The treatment in the SoC arm was composed according to 2014 WHO treatment guidelines and included second-line injectable drugs. The observed treatment success at 24 months (104 weeks) in the control group of the MDR-END study (71%) is lower than in the endTB study (77%). Non-inferiority of the shortened DLLfxZ regimen in the MDR-END study might have been 'easier' to achieve than in the endTB study, although other characteristics of the study population might influence favourable outcome rates.

Success rate of the 9-12 month DLLfxZ regimen in the MDR-END study (75%) is in line with that of the 9 month DCLLfxZ arm in the endTB study at week 104 (75%). In the DLLfxZ arm in the MDR-END study, 1 patient failed to achieve SCC and one patient had a relapse after completion.

endTB-Q

Study design

The endTB-Q study was a Phase 3 randomised, controlled, open-label non-inferiority trial to evaluate the efficacy and safety of the BDLC combination for the treatment of **pre-XDR-TB** compared with the individualised WHO-recommended longer standard of care. The study was performed in India, Kazakhstan, Lesotho, Pakistan, Peru, and Vietnam.

Patients were randomised between April 2020, and March 2023. Meanwhile, the study has been completed. Results are available from the peer-reviewed publication.

Patients were randomised (2:1) to experimental treatment or standard of care control; randomisation was stratified by country and baseline extent-of-TB-disease phenotype. Limited disease was defined as negative or scanty smear for *Mtb* irrespective of cavitation or smear 1+ in the absence of cavitation; extensive disease was defined as smear 2+ or 3+ irrespective of cavitation or smear 1+ in the presence of cavitation.

Study participation was planned to last for up to 104 weeks.

The study was performed in patients ≥ 15 years with pulmonary pre-XDR-TB, with intolerance to FQs or with disease caused by *Mtb* resistant to rifampicin and not susceptible to FQs.

Treatment duration in the experimental BDLC arm was based on the patient's extent-of-TB-disease at baseline and treatment response prior to 24 weeks. The regimen was administered for 39 weeks (9-month regimen) in patients with extensive disease and for 24 weeks (6-month regimen) in those with limited disease. Treatment could be extended in patients with limited disease to 9 months when the following criteria applied, i.e. (1) treatment duration assigned as 39 weeks based on screening smear and baseline.

Duration of standard of care regimens is about 78 weeks. The control arm could also include drugs used in the BDLC group and other oral and injected agents for the entire duration of treatment.

The primary efficacy endpoint was the proportion of patients with favourable outcome at Week 73 after randomisation in the mITT and PP.

The primary objective was to assess whether the efficacy of the experimental regimen at 73 weeks was non-inferior to that of the control in the mITT and PP. The non-inferiority margin was 12%.

Study results

The study randomised 324 patients. Of these, 1 patient withdrew consent and 5 patients were not treated, all in the BDLC arm. Overall, 318 patients (213 versus 105) were included in the safety population, 247 patients (163 versus 84) in the mITT, and 233 (157 versus 76) in the PP.

In the mITT, median age was 30.5 years. Eighteen patients (7%) were aged 15 to 18 years. 46% of the patients were female. Infection with HIV, hepatitis B or C virus (HBV and HCV) were present in 2%, 2%, and 5% of patients, respectively. 22% of patients had diabetes. Smear results were negative or scanty for 27% to 28% of patients, +1, +2, and +3 smear results were present in 29% to 30%,

17% to 20%, and 23% to 26% of patients, respectively (given as range across the arms). Sixty-six (66) to 68% of patients had cavitations. Extent of disease was limited in 36 to 38% of patients and extensive in 62% to 64% of patients. Baseline characteristics were well balanced between the treatment groups.

In the BDLC group, 29% of patients were assigned to receive 6 months of treatment and 71% were assigned to receive 9 months, using information on baseline disease extent and treatment response. In the control group, all patients were treated with an individualised regimen comprising 4 to 6 drugs; the majority (85%) received 5 drugs. All control group patients had bedaquiline, clofazimine, and linezolid in the initial regimen; cycloserine (93%) and delamanid (91%) were also frequent. Thus, the core regimen of BDLC plus one or more other drugs was used for 91% of control group patients.

Primary efficacy results are summarised in Table 19; adjusted favourable treatment outcome forest plots for mITT and PP at Week 73 are shown in Figure 14. The favourable outcome rate at Week 73 was 87% in the BDLC arm and 89% in the control arm (mITT). In the PP, 88% and 93% achieved favourable treatment outcomes in the BDLC and control groups, respectively. The adjusted RD in the mITT was 0.2% (95% CI –9.1%, 9.5%); in the PP, it was –3.5% (95% CI–12.8%, 5.9%) Figure 14

(A). Thus, non-inferiority could be concluded for the mITT but not for the PP. Overall non-inferiority was not shown.

Table 19. Primary Efficacy Outcomes at Week 73; endTB-Q

	mITT population		Per-protocol population	
	BDLC group (n=163)	Control group (n=84)	BDLC group (n=157)	Control group (n=76)
Favourable outcome				
Number of participants	141 (87%)	75 (89%)	138 (88%)	71 (93%)
Adjusted absolute difference from the control, % (95% CI)*	0·2% (−9·1 to 9·5)	..	−3·5% (−12·8 to 5·9)	..
Participants with negative culture results, weeks 65 and 73	140 (86%)	74 (88%)	137 (87%)	70 (92%)
Participants with favourable bacteriological, clinical, and radiological evolution†	1 (1%)	1 (1%)	1 (1%)	1 (1%)
Unfavourable outcome				
Number of participants	22 (13%)	9 (11%)	19 (12%)	5 (7%)
All-cause mortality‡	4 (2%)	2 (2%)	4 (3%)	2 (3%)
Participants with treatment failure§	7 (4%)	3 (4%)	7 (4%)	3 (4%)
Participants with relapse¶	8 (5%)	0	8 (5%)	0
Participants with permanent treatment discontinuation due to adverse events	1 (1%)	0	0	0
Participants with poor treatment adherence or loss to follow-up	1 (1%)	0	0	0
Participants who withdrew consent	1 (1%)	4 (5%)	0	0

The mITT population included participants who were randomly assigned, received at least one dose of trial treatment, and had a culture positive for *Mycobacterium tuberculosis* before random assignment (excluding those with baseline phenotypic resistance to BDLC). The per-protocol population included participants from the mITT population who did not receive more than 7 days of a prohibited concomitant medication or a trial drug that was not prescribed according to the protocol and completed a protocol consistent course of treatment (at least 80% of expected doses taken within 120% of the regimen duration and no more than 120% of the expected doses in participants who were to receive 24 weeks of treatment) or those who did not do so because of treatment failure or death. BDLC=bedaquiline, delamanid, linezolid, and clofazimine. mITT=modified intention-to-treat. *Analyses adjusted for country and baseline extent of tuberculosis disease (mITT n=227, with 20 observations dropped because of perfect separation; per-protocol n=214, with 19 observations dropped because of perfect separation). †Participants without culture results between weeks 65 and 73. ‡Six participants in the mITT died (part of the treatment outcome) and three died in the safety population (excluded from the mITT population). §Participants who permanently discontinued treatment because of a positive sputum culture at week 16 or later or who had a positive sputum culture between weeks 65 and 73 or who had a combination of culture results insufficient to establish favourable outcome and unfavourable bacteriological, radiological, or clinical evolution. ¶Participants who, after treatment completion, started a new treatment regimen and had a confirmed relapse (same strain on baseline and after treatment).

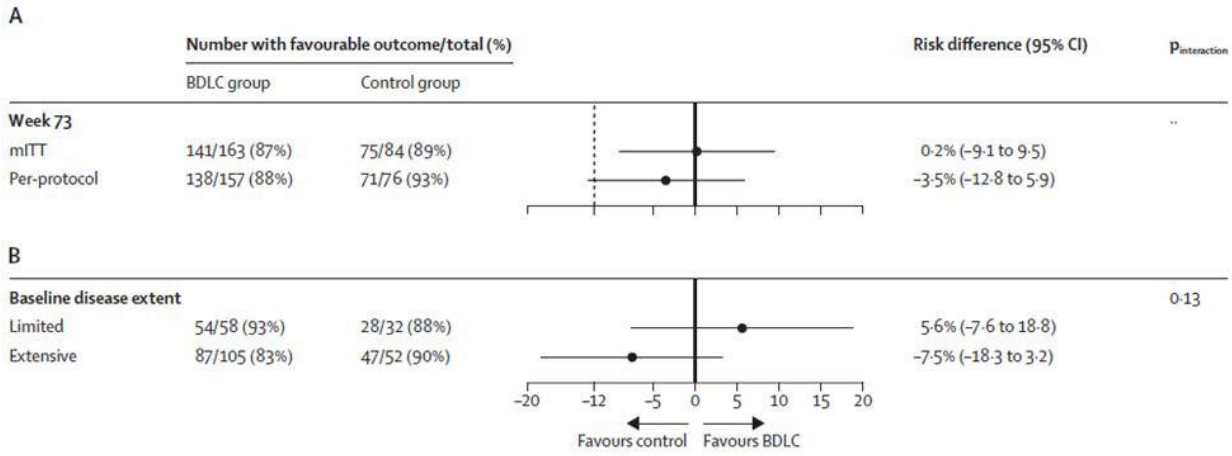

Figure 14. Adjusted Forest Plots for mITT and PP Efficacy at Week 73 (A) and by Baseline Disease extent (B); endTB-Q

The dashed line indicates the non-inferiority margin of −12%. Favourable outcome was defined as 2 consecutive, negative cultures including one between Weeks 65 and 73; or favourable bacteriological, radiological, and clinical evolution) at Week 73 after randomisation.

Results for favourable treatment outcome in the mITT were also assessed by baseline disease extent Figure 14 (B). In patients with limited baseline disease extent, the BDLC regimen did better (favourable outcome rate 93%, versus 88% with control; RD 5.6%, 95% CI −7.6; 18.8%); in patients with extensive baseline disease, the control regimen did better (favourable outcome rate 83%, versus 90% with control RD −7.5%, 95% CI −18.3; 3.2%). This observed difference reflects higher relapse rates among patients with extensive disease in the BDLC group. Overall, efficacy results were similar at Week 104 in the mITT and PP.

Safety results are summarised in Table 20. For any comparison of safety information, the different treatment duration in the 2 arms should be considered.

The BDLC arm showed lower incidences of AEs ≥ Grade 3 (any, related), SAEs (any, related), and permanent discontinuations than the control arm. The overall death rate was somewhat higher in the experimental arm (4% versus 2%) but the overall number of patients who died was low. In each arm, 1 death was judged as being potentially related to study drugs.

Incidences for all AESI categories were lower in the BDLC arm than the control arm. An exception was ≥ Grade 3 increases in ALT or AST, which were despite the much shorter treatment duration more frequent in the experimental BDLC arm than the control arm (6%, versus 4% in the control arm).

Three (1%) patients in the BDLC group versus 4 (4%) in the control group had ≥ Grade 3 to 4 QTc prolongation.

Safety results evaluated at 104 weeks and at 4 weeks after the end of treatment confirmed the general safety profile.

Table 20. Safety Outcomes in endTB-Q at Week 73

	BDLC group (n=213)	Control group (n=105)	Absolute difference (%, 95% CI)*
Participants with any adverse event	213 (100%)	104 (99%)	..
Grade 3 or higher adverse events			
Participants with ≥1 event	145 (68%)	77 (73%)	−6·6 (−15·6 to 2·4)
Number of events	319	182	..
Number of events related to study drugs (% of all events)†	93 (29%)	79 (43%)	..
Serious adverse events			
Participants with ≥1 event	42 (20%)	23 (22%)	−0·9 (−10·6 to 8·9)
Number of events	66	43	..
Number of events related to study drugs (% of all events)†	12 (18%)	11 (26%)	..
Death from any cause	8 (4%)	2 (2%)	1·7 (−2·0 to 5·4)‡
Number of events related to study drugs†	1 (13%)	1 (50%)	..
Adverse event of special interest			
Participants with ≥1 event	73 (34%)	47 (45%)	−10·5 (−21·9 to 1·0)‡
Participants with any grade 3–4 increase in alanine or aspartate aminotransferases	13 (6%)	4 (4%)	..
Participants with any grade 3–4 leukopenia, anaemia, or thrombocytopenia	29 (14%)	22 (21%)	..
Participants with any grade 3–4 peripheral neuropathy	44 (21%)	26 (25%)	..
Participants with any grade 3–4 optic neuritis	2 (1%)	2 (2%)	..
Participants with any grade 3–4 prolonged corrected QT interval§	3 (1%)	4 (4%)	..
Participants with permanent discontinuation of any drug due to an adverse event	30 (14%)	56 (53%)	−39·1 (−49·7 to −28·5)

The safety population included all participants who were randomly assigned and received at least one dose of trial treatment. BDLC=bedaquiline, delamanid, linezolid, and clofazimine. *Analyses adjusted for country and baseline extent of tuberculosis disease. †Related was defined as at least a reasonable possibility to be caused by one or more drugs in the regimen. ‡Analyses adjusted for baseline extent of tuberculosis disease, given the absence of convergence when adjusting for all stratification variables. §QT interval corrected according to the Fridericia formula.

Five patients became pregnant during study participation, including 2 control patients and 3 patients receiving BDLC. All 5 patients were maintained in the study: outcomes were 3 live birth (2 BDLC and 1 control patient), elective termination of pregnancy in 1 BDLC patient, and spontaneous abortion in one control patient.

Conclusions

In the endTB-Q trial BDLC showed non-inferiority to the individualised WHO-recommended longer standard of care in the mITT at week 73 (87% versus. 89%; RD 0.2%, 95 CI −9.1%; 9.5%) but not for the PP. Both treatment strategies produced a high proportion of favourable outcome, especially in patients with limited disease extent at baseline, with BDLC achieving 93% (versus 88% with control; RD 5.6%, 95% CI −7.6; 18.8%). No new safety concerns were identified in endTB-Q. The authors concluded, the findings support the use of a shorter BDLC regimen for patients with pre-XDR-TB with limited disease at baseline; in patients with extensive pre-XDR-TB, longer, reinforced regimens might be required.

Rapporteur assessment/comment:

Participants in the endTB-Q study had pulmonary pre-XDR-TB, with intolerance to FQs or with disease caused by Mtb resistant to rifampicin and not susceptible to FQs. Shortening of treatment regimen with

fixed drug combination BDLC is possible in patients with limited disease at baseline. Higher relapse rates were observed for the BDLC shortened treatment group. The observed difference in patients with baseline disease extent and extensive baseline disease reflects higher relapse rates among patients with extensive disease in the BDLC group.

As the BDLC drug combination is also part of the treatment combination in 91% of the control group, this study does not really contribute to proof of delamanid efficacy per se, but rather investigates in which subpopulation shortening (and simplification) of the treatment regimen is possible.

6.2. Pharmacovigilance inspections

A pharmacovigilance inspection has been conducted by the FAMHP in Otsuka Pharma Scandinavia AB – Belgium. The inspection report was received on 04 December 2024 and no significant findings were identified.

7. Risk management plan

The MAH has submitted an updated RMP within the annual renewal procedure (additions **underlined and bold**, deletions ~~strikethrough~~).

Safety Concerns

Table 1. Summary of the Safety Concerns

Summary of safety concerns	
Important identified risks	QT interval prolongation
Important potential risks	~~Liver disorders~~**None**
Missing information	None

Pharmacovigilance plan

To reflect the fulfilment of SOB 002, the following updates have been implemented (additions **underlined and bold**, deletions ~~strikethrough~~):

Table 2. On-going and planned studies in the post-authorisation pharmacovigilance development plan

~~**Study Status**~~	~~**Summary of objectives**~~	~~**Safety concerns addressed**~~	**Milestones**	**Due dates**
~~**Category 1 –** Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation (key to benefit risk)~~ ~~There are no outstanding imposed mandatory additional pharmacovigilance activities considered key to the Benefit Risk of the product.~~				

~~Study Status~~	~~Summary of objectives~~	~~Safety concerns addressed~~	Milestones	Due dates
~~**Category 2 –** Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances~~				
~~endTB NCT02754765~~	~~In order to further investigate the use of delamanid in different combination treatment regimens as per approved indication as well as safety, the MAH will submit the results of the endTB (Evaluating Newly approved Drugs for multidrug-resistant TB) study, a randomized, controlled Phase III study in adults and adolescents with multi-drug-resistant tuberculosis conducted by Médecins Sans Frontières, including a critical discussion of the publicly available data with a focus on the evaluation of delamanid i.e. including as possible an analysis based on the agreed statistical analysis plan and with an additional discussion when deviating from it.~~	~~The following Safety objectives will be evaluated from EndTB based on the publicly available data:~~ ~~1) To compare, at 104 weeks, the proportion of patients who died of any cause in the experimental arms to that in the control arm~~ ~~2) To compare, at 73 and 104 weeks, the proportion of patients who experience AEs of Grade 3 or higher AEs or SAEs of any grade in the experimental arms to that in the control arm~~ ~~3) To compare, at 73 weeks, the proportion of patients who experience QTc prolongation Grade 3 or higher in the experimental regimens to that in the control arm~~	Final Analysis Report	Q3 2026
~~BEAT-TB NCT04062201~~	~~The publicly available results from the BEAT-TB Study conducted by Wits Health Consortium will be submitted and discussed.~~	~~The following Safety objective will be discussed from BEAT-TB based on the publicly available data:~~ ~~1) The proportion of participants who experience grade 3 or greater adverse events during treatment and up to 30 days following the end of treatment. This includes participants who experienced adverse events grade 3 or higher of QT interval~~	Discussion of results	Q3 2026

~~Study Status~~	~~Summary of objectives~~	~~Safety concerns addressed~~	Milestones	Due dates
		~~prolongation and liver disorders.~~		
~~**Category 3 –** Required additional pharmacovigilance activities~~ ~~There are no required additional pharmacovigilance activities.~~				

There are no ongoing or planned additional pharmacovigilance activities.

Routine pharmacovigilance is sufficient to identify and characterise the risks of the product.

Routine pharmacovigilance is sufficient to monitor the effectiveness of the risk minimisation measures.

Risk minimisation measures

To reflect the fulfilment of SOB 002, the following updates have been implemented (additions **underlined and bold**, deletions ~~strikethrough~~):

Routine risk minimisation activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

Table 3. Summary table of Risk Minimisation Measures

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Important Identified Risks		
QT Interval Prolongation	*Routine risk minimisation measures:* SmPC Sections 4.3, 4.4, 4.5, 4.8 PIL Section 2 and 4 Recommendation for ECG before initiation of treatment and monthly during the full course of treatment with delamanid is included in SmPC Section 4.4. It is further recommended that treatment not be initiated in patients with specific cardiac risk factors unless the possible benefit of delamanid is considered to outweigh the potential risks. Pack Size: Aluminium/Aluminium blister: 48 tablets. Prescription only medicine. *Additional risk minimisation measures:* None	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:* None. *Additional pharmacovigilance activities:* ~~As per the SOB 002, based on the analysis of the publicly available data, the endTB Study (NCT02754765) will provide additional information on delamanid's safety profile when administered in different combination of treatment regimens. The study will assess the proportion of patients in the experimental arms with either QTc interval prolongation of Grade 3 or higher at 73 weeks to that in the control arm as a secondary endpoint. In addition, publicly available results from the BEAT-TB (NCT04062201) Study conducted by Wits Health~~

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
		~~Consortium will be discussed, including QT interval prolongation grade 3 or higher.~~ **None.** None.
Important Potential Risks		
Liver Disorders	~~*Routine risk minimisation measures:*~~ ~~SmPC Section 4.8~~ ~~PL Section 4~~ ~~Pack Size: Aluminium/Aluminium blister: 48 tablets.~~ ~~Prescription only medicine.~~ ~~*Additional risk minimisation measures:*~~ ~~None.~~	~~*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:*~~ ~~None.~~ ~~*Additional pharmacovigilance activities:*~~ ~~As per SOB 002, based on the analysis of the publicly available data, the endTB Study (NCT02754765) will provide additional information on delamanid's safety profile when administered in different combination of treatment regimens. The study will assess the proportion of patients with AEs of Grade 3 or higher AEs or SAEs of any grade in the experimental arms to that in the control arm as a secondary endpoint, including hepatotoxicity.~~ ~~In addition, publicly available results from the BEAT-TB (NCT04062201) Study conducted by Wits Health Consortium will be discussed, including hepatotoxicity grade 3 or higher.~~ **None.**
Missing Information	None	None

The proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication.

Elements for a public summary of the RMP

The elements for a public summary of the RMP require revision following the conclusion of the procedure:

The following section of the public summary of the RMP has been adapted, to reflect the fulfilment of SOB 002 (additions **underlined and bold**, deletions ~~strikethrough~~):

II.C: Post-authorisation Development Plan

II.C.1 Studies which are Conditions of the Marketing Authorisation

~~endTB - Evaluating Newly approved Drugs for multidrug-resistant TB and BEAT-TB - Building Evidence for Advancing New Treatment for Rifampicin Resistant Tuberculosis (RR-TB) Comparing a Short Course of Treatment (Containing Bedaquiline, Delamanid and Linezolid) With the Current South African Standard of Care~~

~~Description: In order to further investigate the use of delamanid in different combination treatment regimens as per approved indication as well as safety, the MAH should submit the publicly available data of the endTB (Evaluating Newly approved Drugs for multidrug-resistant TB) study, a randomised, controlled Phase III trial in adults and adolescents with multi-drug resistant tuberculosis conducted by Médecins Sans Frontières, with an analysis based on the agreed statistical analysis plan and publicly available results from the BEAT-TB study conducted by Wits Health Consortium.~~

~~Due Date: Q3 2026~~

There are no studies which are conditions of the marketing authorisation or specific obligation of Deltyba.

Annexes

The RMP annexes have been updated appropriately.

7.1. Overall conclusion on the RMP

The RMP version 6.1 is acceptable.

8. Changes to the Product Information

Changes to the Product Information, based on the data submitted within the scope of this procedure, are introduced to reflect the fulfilment of SOB 002 and the granting of a marketing authorisation no longer subject to specific obligations. In particular, Annex II.C is revised to remove the requirements for submission of PSURs set out in Article 9 of Regulation (EC) No 507/2006, and Annex II.E is deleted, as no SOBs remain to be fulfilled.

Pursuant to Article 23(3) of Regulation No (EU) 726/2004, Deltyba (Delamanid) is removed from the additional monitoring list as the conditions to the marketing authorisation have been fulfilled. Therefore, the statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information, preceded by an inverted equilateral black triangle, is removed from the summary of product characteristics and the package leaflet.

Updates to the Product Information were also made in line with the SmPC guideline and the latest QRD template (version 11).

See Attachment 1 for all changes resulting from this procedure.

9. Request for Supplementary Information - RSI

The MAH should provide the following supplementary information in response to Day 60 RSI:

9.1. Other concerns

Clinical aspects

SmPC comment

1. The MAH is asked to include a concise summary of the endTB and BEAT-TB study results in section 5.1 of the SmPC.
2. The statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information, preceded by an inverted equilateral black triangle, should be removed from the summary of product characteristics and the package leaflet.

Pharmacovigilance inspections

3. The MAH did not provide an overview of pharmacovigilance inspections conducted during the period covered by this renewal. If no relevant pharmacovigilance inspections have been conducted, the MAH should confirm this. If pharmacovigilance inspections have been conducted, the MAH is requested to provide a history of the inspections (date, inspecting authority, site inspected, type of inspection and if the inspection is product specific, the list of products concerned), as well as an analysis of the impact of the findings overall on the benefit-risk balance of the medicinal product.

Risk Management Plan

4. *Liver disorders* should not be a safety concern, as there is no further evaluation as part of the pharmacovigilance plan (GVP V Rev.2 – Section V.A.1.). Please update the different sections of the RMP accordingly.
5. The risk of Liver disorders remains a safety issue that should be closely monitored and discussed in the PSURs.

10. Assessment of the MAH responses to the RSI

10.1. Other concerns

Clinical aspects

SmPC comment

Question 1

The MAH is asked to include a concise summary of the endTB and BEAT-TB study results in section 5.1 of the SmPC.

Summary of the MAH's response

The MAH acknowledges the Agency request and updated wording in the EU Summary of Product Characteristics (SmPC) section 5.1 as requested.

The following text is included in SmPC section 5.1

end-TB (Evaluating Newly approved Drugs for multidrug resistant TB) study

end-TB was an independent investigator-initiated phase 3, multi-country, open-label, randomised, controlled non-inferiority study in patients aged 15 years and older for treatment of fluoroquinolone-susceptible, rifampicin-resistant (RR)-TB. Five 9 -month oral regimens were evaluated, three of which contained delamanid. In the modified intention-to-treat (mITT) population, 80.7% (95% confidence interval [CI], 72.4 to 87.3) of the 699 participants receiving standard therapy were reported to have a favourable outcome. Based on hierarchical testing, four experimental regimens were found to be non-inferior to standard therapy in the mITT analysis. Non-inferiority to standard therapy was established for two of the three delamanid-containing regimens in the mITT population and for one delamanid containing regimen in the per-protocol population.

BEAT-TB study South-Africa

BEAT-TB was an independent investigator-initiated phase 3, multicentre, open-label, pragmatic, randomised-controlled-strategy and non-inferiority study in patients aged 6 years and older with pulmonary rifampicin-resistant (RR)-TB. Participants were randomised to receive either a novel delamanid-containing six-month regimen, or the then-current South African nine-month, or longer control regimen. In the primary analysis set (n = 402), successful outcomes at both end of treatment and week 76 occurred in 86.0% (172/200) of participants in the control arm and 86.1% (174/202) in the study treatment arm. The study demonstrated non-inferiority of investigational regimen to control.

Assessment of the MAH's response

The MAH updated the SmPC. In section 5.1. of the SmPC, the description of the endTB and BEAT-TB study results should be updated as proposed.

See the comments in the enclosed product information document.

Conclusion

Following circulation of the preliminary response assessment report, the MAH has updated SmPC section 5.1 as proposed.

Issue solved.

Question 2

The statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information, preceded by an inverted equilateral black triangle, should be removed from the summary of product characteristics and the package leaflet.

Summary of the MAH's response

The MAH acknowledges the Agency request pertaining to the additional monitoring and the inverted equilateral black triangle removal and updated the EU SmPC and the package leaflet accordingly.

Assessment of the MAH's response

The MAH has updated the SmPC as requested.

Conclusion

Issue resolved.

Pharmacovigilance inspections

Question 3

The MAH did not provide an overview of pharmacovigilance inspections conducted during the period covered by this renewal. If no relevant pharmacovigilance inspections have been conducted, the MAH should confirm this. If pharmacovigilance inspections have been conducted, the MAH is requested to provide a history of the inspections (date, inspecting authority, site inspected, type of inspection and if the inspection is product specific, the list of products concerned), as well as an analysis of the impact of the findings overall on the benefit-risk balance of the medicinal product.

Summary of the MAH's response

During the reporting period of this renewal (22 June 2024 to 20 June 2025) there was one inspection conducted by the Federal Agency for Medicines and Health Products (FAMHP) from 27 August 2024 to 30 August 2024 (Inspection number PhV/INSP/mmk/2024/005). The site inspected was Otsuka Pharma Scandinavia AB - Belgium (OPSAB).

The inspection was a Routine national Pharmacovigilance (PV) inspection on the PV system and Deltyba was in scope, along with other products (Abilify/Abilify Maintena, Jinarc/Samsca, Rxulti, Inaqovi).

The inspection report was received on 04 December 2024 and no significant findings were identified. Therefore, there is no impact on the overall benefit-risk balance of Deltyba resulting from this inspection.

Assessment of the MAH's response

A pharmacovigilance inspection has been conducted by the FAMHP in Otsuka Pharma Scandinavia AB – Belgium. The inspection report was received on 04 December 2024 and no significant findings were identified.

Conclusion

Issue resolved.

Risk Management Plan

Question 4

Liver disorders should not be a safety concern, as there is no further evaluation as part of the pharmacovigilance plan (GVP V Rev.2 – Section V.A.1.). Please update the different sections of the RMP accordingly.

Summary of the MAH's response

The MAH acknowledges the Agency request to remove Liver disorders as important potential risk from the Risk Management Plan (RMP) safety concerns; modifications have been made to all applicable

sections throughout the EU RMP as requested. The updated RMP version 6.1 is enclosed to the submission of these responses.

Assessment of the MAH's response

The MAH removed Liver disorders from the list of safety concerns in all applicable sections of the RMP v6.1.

Conclusion

Issue resolved.

Question 5

The risk of Liver disorders remains a safety issue that should be closely monitored and discussed in the PSURs.

Summary of the MAH's response

The MAH acknowledges that the risk of Liver disorders remains a safety issue that will continue to be closely monitored and kept being discussed in the Periodic Safety Update Reports (PSURs) as agreed upon in the procedure for PSUR #15 (Procedure No. EMEA/H/C/PSUSA/00010213/202304).

Assessment of the MAH's response

The MAH committed to discuss Liver disorders as a safety issue under close monitoring in next PSURs.

Conclusion

Issue resolved.