11 December 2025
EMADOC-1700519818-2703796
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Invented name: Dovprela

International non-proprietary name: Pretomanid

Procedure No. EMA/VR/0000258124

Marketing authorisation holder (MAH) Mylan IRE Healthcare Limited

Note

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

Table of Contents

List of abbreviations

ADR	Adverse drug reaction
AE	Adverse events
AESI	Adverse events of special interest
Am	Amikacin
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
B	Bedaquiline
BPaL	Bedaquiline, Pretomanid, Linezolid
BPaLM	Bedaquiline, Pretomanid, Linezolid, Moxifloxacin
BPaLC	Bedaquiline, Pretomanid, Linezolid, Clofazimine
Cfz	Clofazimine
CI	Confidence interval
Cm	Capreomycin
Cs	Cycloserine
CSR	Clinical study report
D	Delamanid
DSMB	Data and Safety Monitoring Committee Board
DS	Drug susceptible
DST	Drug susceptibility test
e-DISH	Evaluation of Drug-Induced Serious Hepatotoxicity
E	Ethambutol
ECG	Electrocardiogram
EMA	European medicines agency
ERA	Environmental risk assessment
Eto	Ethionamide
EU	European Union
GCP	Good clinical practice
Hh	Isoniazid
HIV	Human Immunodeficiency Virus
ICF	Informed consent form
IMP	Investigational medicinal product
ITT	Intention to treat
Km	Kanamycin
LLN	Lower limit of normal
Lfx	Levofloxacin
LTFU	Loss to follow up
Lzd	Linezolid
MAA	Marketing authorisation application
MAH	Marketing authorisation holder
MedDRA	Medical Dictionary for Regulatory Activities
MDR	Multi-Drug Resistant
Mfx	Moxifloxacin
MGIT	Mycobacteria growth indicator tube
MTB	Mycobacterium tuberculosis
NI	non-inferiority
Pa	Pretomanid (PA-824)

PAS	Para-Amino-salicylate Sodium
PEC	Predicted environmental concentration
PD	Pharmacodynamics
PI	Principal Investigator
PK	Pharmacokinetics
PMT	Project Management Team
PP	Per-protocol
Pto	Prothionamide
QT	Interval between Q and T waves on an ECG
QTcF	QT interval correction using Fridericia's formula
R	Rifampicin
RR-TB	Rifampicin resistant TB
SAC	Scientific Advisory Committee
SAE	Serious Adverse Events
SAP	Statistical analysis plan
SmPC	Summary of Product Characteristics
SoC	Standard of Care
SOC	System Organ Class
TB	Tuberculosis
TdP	Torsades de Pointes
TEAE	Treatment emergent AEs
Trd	Terizidone
US	United States
WHO	World Health Organisation
XDR	Extensively drug resistant
Z	Pyrazinamide

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Mylan IRE Healthcare Limited submitted to the European Medicines Agency on 07 March 2025 an application for a variation.

The following changes were proposed:

Variation requested		**Type**
C.I.6.a	C.I.6.a Addition of a new therapeutic indication or modification of an approved one	Variation type II

Extension of indication to include in combination with bedaquiline, linezolid and moxifloxacin the treatment of adults with pulmonary tuberculosis (TB) due to Mycobacterium tuberculosis resistant to rifampicin, with or without resistance to isoniazid, for DOVPRELA and to update the current regimen, based on final results of the TB-PRACTECAL study; this is a randomised, controlled, open-label, phase II-III trial to evaluate the safety and efficacy of regimens containing bedaquiline and pretomanid for the treatment of adult patients with pulmonary multidrug resistant tuberculosis. As a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. In addition, the MAH took the opportunity to introduce minor editorial changes to the PI.

The requested variation(s) proposed amendments to the Summary of Product Characteristics and Package Leaflet.

Information relating to orphan designation

Dovprela, was designated as an orphan medicinal product EU/3/07/513 on 29 November 2007. Dovprela was designated as an orphan medicinal product in the following indication: Treatment of tuberculosis.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0295/2024 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0295/2024 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the application included a critical report addressing the possible similarity with authorised orphan medicinal products.

Protocol assistance

The MAH did not seek Protocol Assistance at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Filip Josephson Co-Rapporteur: N/A

Timetable	Actual dates
Submission date:	07 March 2025
Start of procedure:	24 March 2025
CHMP Rapporteur Assessment Report	30 Abril 2025
Updated CHMP Rapporteur Assessment Report	15 May 2025
Request for supplementary information (RSI)	22 May 2025
MAH's responses submitted to the CHMP on:	10 October 2025
CHMP Rapporteur preliminary assessment report on the MAH's responses circulated on:	18 November 2025
ETF discussion	26 November 2025
CHMP Rapporteur updated assessment report on the MAH's responses circulated on:	04 December 2025
CHMP opinion:	11 December 2025
The CHMP adopted a report on similarity of Dovprela on	11 December 2025

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

Tuberculosis, an infectious disease caused by *Mycobacterium tuberculosis*, is a significant cause of morbidity and mortality worldwide. During more recent years the burden of TB resistant to first line therapy has increased rapidly and TB resistant to multiple anti-mycobacterial agents is now increasingly reported in all regions of the world. The incidence of RR-TB and MDR-TB (18% in 2021) is highest amongst those previously treated with anti-mycobacterial agents, particularly with suboptimal compliance or treatment duration.

MDR-TB is an orphan disease in EU and US.

State the claimed therapeutic indication

Dovprela (pretomanid) is presently indicated in combination with bedaquiline and linezolid for the treatment of:

- adults with pulmonary TB due to *M. tuberculosis* resistant to all of isoniazid, rifampicin, a fluoroquinolone and a second line injectable antibacterial drug and;

- adults with pulmonary TB due to *M. tuberculosis* resistant to both isoniazid and rifampicin, who are treatment-intolerant or nonresponsive to standard therapy.

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

This application is intended to broaden and update the indication as follows:

- Dovprela is indicated in combination with bedaquiline, linezolid and moxifloxacin for the treatment of adults with pulmonary TB due to *M. tuberculosis* resistant to rifampicin, with or without resistance to isoniazid.

- Dovprela is indicated in combination with bedaquiline and linezolid for the treatment of adults with pulmonary TB due to *M. tuberculosis* resistant to rifampicin and a fluoroquinolone, with or without resistance to isoniazid.

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

Epidemiology and risk factors

In 2017, approximately more than 10 million new cases of tuberculosis were reported and approximately 1.6 million deaths were attributed to TB. Globally in 2023, 79% of people (3.4/4.3 million) diagnosed with bacteriologically confirmed pulmonary TB were tested for rifampicin resistance. Among those tested in 2023, 159,684 people with MDR/RR-TB and 28,982 people with pre-XDR-TB or XDR-TB were detected, giving a combined total of 188,666 (5.5% of those tested).

Clinical presentation

Typical symptoms of pulmonary TB are breathing difficulties, chest pain, cough (including haemoptysis), fever, fatigue and weight loss.

Management

The WHO operational handbook on tuberculosis, 2022 update, recommends a 6-month all-oral regimen (BPaLM) comprising bedaquiline (B), pretomanid (Pa), linezolid (Lzd), and moxifloxacin (Mfx) for most patients with rifampicin-resistant TB.

This is the regimen for which approval is requested by the MAH with the following posology: Pretomanid (200 mg once daily) should be administered only in combination with bedaquiline (400 mg once daily for 2 weeks followed by 200 mg 3 times per week [with at least 48 hours between doses] orally for a total of 26 weeks) and linezolid (600 mg daily orally for up to 26 weeks), with or without moxifloxacin (400 mg once daily for 26 weeks). In case of confirmed pulmonary TB resistant to

rifampicin and a fluoroquinolone, with or without resistance to isoniazid, pretomanid should be combined with bedaquiline and linezolid, and moxifloxacin should be omitted.

2.1.2. About the product

Pretomanid is a chemical entity member of a class of compounds known as nitroimidazooxazines. During early development, pretomanid was referred to as PA-824. The international non-proprietary name and the US adopted name are both pretomanid. Pretomanid was developed as an oral tablet formulation for the treatment of tuberculosis in combination with other antituberculosis agents.

In non-clinical and clinical studies, pretomanid has been found to possess significant anti-tuberculosis activity. Pretomanid demonstrated in vitro activity against both drug-susceptible and drug-resistant *M. tuberculosis* including MDR and XDR strains. Pretomanid also demonstrated activity in animal models of tuberculosis, most notably in mouse models.

2.2. Non-clinical aspects

No new clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Ecotoxicity/environmental risk assessment

The MAH provided a justification for not performing a new ERA for this type II variation to include the addition of moxifloxacin to the current approved regimen of pretomanid. The MAH confirmed that the posology of pretomanid remains unchanged, where the recommended dosage is 200 mg (i.e. one tablet) of pretomanid once daily, for 26-weeks.

The MAH submitted an ERA with the MAA conducted in accordance with EMEA/CHMP/SWP/4447/00 corr. 2 guideline on ERA. The ERA concluded that pretomanid has a measured LogKow < 4.5 and a PEC of 0.0005 µg/l which falls below the action limit of 0.01 µg/l. Therefore, no specific measures are recommended for the environmentally safe use and disposal of pretomanid. In agreement with the guideline on ERA, no additional ERA studies were submitted for pretomanid.

2.2.2. Discussion on non-clinical aspects

Consistent with CHMP guidance EMEA/CHMP/SWP/4447/00 Rev 1 Corr. (01 September 2024) entitled "Guideline on the environmental risk assessment of medicinal products for human use", for applications supporting a type II variation an evaluation of the environmental impact is not required because an increase in environmental exposure to pretomanid is not anticipated.

The posology, pharmaceutical form, presentation, and orphan status designation for pretomanid remains unchanged since the MAA. Therefore, an increase in use of pretomanid is not expected to increase as a result of this application.

2.2.3. Conclusion on the non-clinical aspects

No new non-clinical data have been submitted in this application, which is considered acceptable. An acceptable justification has been provided for not performing a new ERA considering that an increase in environmental exposure to pretomanid is not anticipated.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

2.3.2. Pharmacokinetics

No new pharmacokinetics data from the TB-PRACTECAL study has been submitted.

2.3.3. Discussion on clinical pharmacology

According to the CSR, a sub-study collecting PK/PD information was performed. The MAH explained that PK data is not relevant for this application since there is clinical efficacy and safety data for the intended dose and population.

The MAH provided a discussion on the risk for PK drug interactions between moxifloxacin and the other components in the regimen (i.e. pretomanid, bedaquiline and linezolid) concluding that the risk for clinically relevant PK interactions is low based on elimination routes and known interaction properties of the drugs. This is agreed, and no further information is needed in the product information.

2.3.4. Conclusions on clinical pharmacology

No new pharmacokinetic data is available, which is considered acceptable. The pharmacokinetic interaction risk between moxifloxacin and the other components in the regimen (i.e. pretomanid, bedaquiline and linezolid) is low based on mechanistic knowledge.

2.4. Clinical efficacy

2.4.1. Main study

The pivotal TB-PRACTECAL study was a multi-centre, open label, multi-arm, randomised, controlled, phase II-III trial; evaluating short treatment regimens containing bedaquiline and pretomanid in combination with existing and re-purposed anti-TB drugs for the treatment of microbiologically confirmed pulmonary MDR-TB.

Methods

Study participants

Inclusion Criteria

Patients were required to meet the following inclusion criteria to be considered eligible:

- Male or female subjects aged 15 years or above (aged 18 or above in Uzbekistan and Belarus sites), regardless of HIV status.
- Microbiological test (molecular or phenotypic) confirming presence of *M. tuberculosis* in sputum.
- Resistant to at least rifampicin by either molecular or phenotypic drug susceptibility test.
- Completed ICF.

Exclusion Criteria

- Known allergies, hypersensitivity, or intolerance to any of the study drugs.
- Pregnant, breast-feeding, or unwilling to use appropriate contraceptive measures if of childbearing potential.
- ALT and/or AST and/or bilirubin >3 times the upper limit of normal.
- Taking any medications contraindicated with the medicines in the trial.
- QTcF > 450ms.
- One or more risk factors for QTc prolongation (excluding age and gender) or other uncorrected risk factors for TdP.
- History of cardiac disease, syncopal episodes, symptomatic or significant asymptomatic arrhythmias (except sinus arrhythmia).
- Any baseline laboratory value consistent with Grade 4 toxicity.
- Moribund.
- Known resistance to bedaquiline, pretomanid, linezolid or delamanid.
- Any other condition (social or medical) which, in the opinion of the investigator, would make study participation unsafe.
- Prior use of bedaquiline and/or pretomanid and/or linezolid and/or delamanid for one or more months.
- Patients not eligible to start a new course of MDR-TB/XDR-TB treatment according to local protocol, including but not limited to:
    - currently on MDR-TB treatment for at least 2 weeks (and not failing),
    - unstable physical address,
    - loss to follow-up in previous treatment with no change in circumstance and motivation.

- Tuberculous meningoencephalitis, brain abscesses, osteomyelitis or arthritis.

Treatments

Treatment regimens in Stage 1:

Regimens:

- Regimen 1: bedaquiline + pretomanid + linezolid + moxifloxacin for 24 weeks;
- Regimen 2: bedaquiline + pretomanid + linezolid + clofazimine for 24 weeks;
- Regimen 3: bedaquiline + pretomanid + linezolid for 24 weeks.

Dosages of the included drugs were the same across treatment regimens:

- Bedaquiline 400 mg daily for two weeks followed by 200 mg three times weekly for 22 weeks;
- Pretomanid 200 mg daily for 24 weeks;
- Linezolid 600 mg daily for 16 weeks then 300 mg daily for 8 weeks with dose reduction allowable earlier in case of side effects;
- Moxifloxacin 400 mg daily for 24 weeks (in BPaLM only);
- Clofazimine 100 mg daily (or 50 mg daily if <3 0kg) for 24 weeks (in BPaLC only).

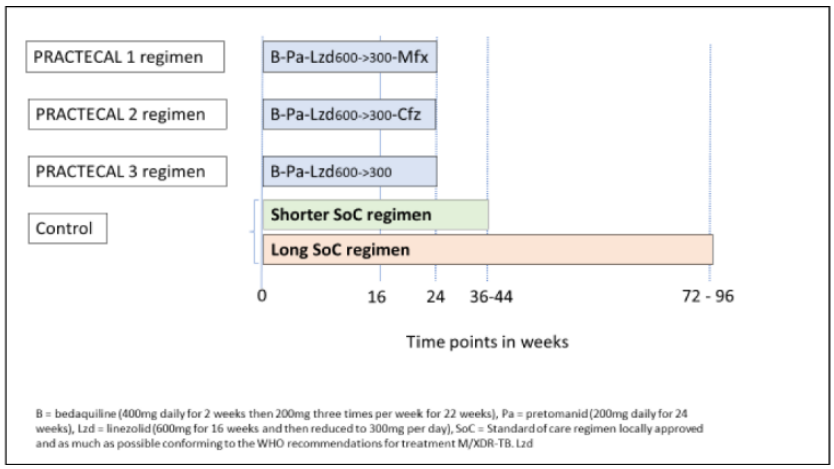


Figure 1: Schema of PRACTECAL regimens (stage 1)

Treatment regimens in Stage 2:

Regimen 1 above (BPaLM) was selected for stage 2, to be compared with standard of care (SoC).

The SoC group received treatment regimens according to local guidelines which were as consistent as possible with WHO guidelines active at the time of randomisation. Investigators were allowed to revise the regimen on receipt of baseline molecular or phenotypic DST.

Throughout the study, investigators could use either an individualised treatment guided by an algorithm or standardised shorter treatments. Individualised treatments included the use of four to seven drugs including a later generation quinolone (moxifloxacin [Mfx] or levofloxacin [Lfx]), a second line injectable (capreomycin [Cm] or kanamycin [Km] or amikacin [Am]), pyrazinamide [Z] and two of

prothionamide [Pto] or ethionamide [Eto], cycloserine [Cs] or terizidone [Trd], linezolid [Lzd] or clofazimine [Cfz].

Other drugs such as ethambutol (E), High dose isoniazid (Hh), bedaquiline [B], delamanid (D), P-aminosalicylic acid (PAS), Imipenem (Imp)/cilastatin (Cin) and meropenem (Mpm) could also be used. Following the 2019 WHO guideline update (or earlier as recommended in South Africa), clinical guidelines recommended all-oral regimens as the preferred option.

A standardised shorter regimen or modified shortened course for RR/MDR-TB patients with no second line drug resistance could be used if approved locally and patients otherwise met criteria as described in the clinical guidelines.

The site-specific SoC regimens were as follows:

1. Uzbekistan: Nukus (Site 01) and Tashkent (Site 04)

a. Fluoroquinolone sensitive RR-TB

From site activation (site 01 activated in January 2017, site 04 activated in December 2018), patients meeting criteria for a standardised shorter regimen, were provided Hh/E/Z/Cm/Mfx/Pto/Cfz for 16-24 weeks and then 20 weeks of E/Z/Mfx/Pto/Cfz.

Km could be used in lieu of Cm when DST showed sensitivity.

In August 2019, site 01 implemented the WHO recommended modified shorter regimen, the second line injectable was replaced with B for 24 weeks and Lfx could be used in lieu of Mfx. In site 04, Km/Cm was replaced by Am in September 2019. Pto was removed from the continuation phase in Nukus at this time and on 11 March 2021 in Tashkent.

A longer regimen for those not meeting criteria the shorter regimen was 80 weeks Z/Cm/Lfx/Pto/Cs/Cfz.

From August (site 01) / September (site 04) 2019, this was replaced with 72-80 weeks of B/Lzd/Lfx/Cfz +/- Cs.

b. Fluoroquinolone resistant RR-TB

Patients were commenced on an individualised regimen. The starting regimen was 96 weeks of Z/Cm/Mfx/B/Lzd/Cfz +/- Pto, Cs, PAS, Imp, D.

In August (site 01)/ September (site 04) 2019, duration was reduced to 72-80 weeks. Starting regimens were updated to B/Lzd/D/Cfz/Cs. Cm/Km was phased out with amikacin only used when no other alternative was available.

2. Belarus (Site 02)

a. Fluoroquinolone sensitive RR-TB

From site activation (December 2017), patients were commenced on 80 weeks of B/Lfx or Mfx /Lzd/Cs/Cfz, +/- Cm/Z.

The use of Cm after August 2019 was discontinued due to implementation of new WHO recommendation.

b. Fluoroquinolone resistant RR-TB

Patients were commenced on an individualised regimen. The starting regimen was 90 weeks of B /Mfx/Lzd/Cfz /Cs/D, +/- Am, Imp + Amoxicillin-Clavulanic acid (Amx/Clv), Pto.

Mfx was prescribed with preserved sensitivity to it.

After August 2019, Cm/Km was phased out with amikacin only used when no other alternative was available.

3. South Africa (Sites 03, 05 and 06)

a. Fluoroquinolone sensitive RR-TB

From site 03 activation (November 2017) patients meeting criteria for a standardised shorter regimen, were provided 16-24 weeks of Hh/E/Z/Cm/Mfx/Eto/Cfz and then 20 weeks E/Z/Mfx/Cfz.

In September 2018, a modified shorter regimen with the second-line injectable agent was replaced with 24 weeks of B and 8 weeks of Lzd was added. Eto was removed from the regimen.

For patients not meeting the criteria for the above shorter regimen, 80 weeks of Z/Cm/Mfx/B/Lzd plus Eto, Trd or PAS was provided.

From June 2019, the duration was reduced to 72-80 weeks. The starting regimen was modified to B/Lfx/Lzd/Cfz/Trd.

b. Fluoroquinolone resistant RR-TB

From site activation, a 96-week individualized regimen was designed.

From June 2019, the duration was reduced to 72-80 weeks. The recommended initial regimen proposed from June 2019 was B/Lzd/D or PAS/Cfz/Trd/Z/Hh or Eto. Cm/Km were phased out in September 2018.

Satellite site 03b was activated in October 2018, site 05 was activated in December 2018 and site 06 was activated in November 2019. Latest SoC was implemented from activation.

Objectives

Primary Objective

Stage 1:

Identify regimens containing bedaquiline and pretomanid for further evaluation based on safety and efficacy outcomes after 8 weeks of treatment.

Stage 2:

Evaluate the safety and efficacy of the investigational regimens containing bedaquiline and pretomanid compared with the SoC at 72 weeks post-randomisation.

Secondary Objectives

Stage 2:

1. To compare the rates of culture conversion between the SoC and investigational arms at specified time periods after randomisation (i.e. 12 weeks, 24 weeks).

2. To compare the frequency of SAEs, grade 3 and higher AEs between the SoC arm and investigational arms.

3. To compare unfavourable outcomes between the SoC arm and investigational arms (including failure, treatment discontinuation, death, loss to follow-up, still on treatment at 108 weeks and recurrence) at specified time periods post randomisation (i.e. 24 weeks, 48 weeks and 108 weeks).

Outcomes/endpoints

All primary and secondary efficacy outcome analyses were based on the mITT-population-exclude-switches" and "PP-population" efficacy populations.

Stage 1 Primary Outcomes

- Efficacy: percentage of patients with culture conversion in liquid media at 8 weeks post randomisation.
- Safety: percentage of patients with treatment discontinuation for any reason and death at 8 weeks post randomisation.

Stage 2 Primary Outcomes

- Percentage of patients with an unfavourable outcome (treatment failure, death, treatment discontinuation, recurrence, loss to follow-up) at 72 weeks post-randomisation.

Stage 1 Secondary Outcomes

- Percentage of patients with grade 3 or higher QT prolongation within 8 weeks post randomisation.
- Percentage of patients experiencing at least one SAE within 8 weeks post randomisation.
- Percentage of patients experiencing at least one new grade 3 or higher AE within 8 weeks post randomisation.

Stage 2 Secondary outcomes

- Percentage of patients with culture conversion at 12 weeks post randomisation.
- Percentage of patients with an unfavourable outcome (i.e. failure, treatment discontinuation, death, loss to follow up) at 24 weeks post randomisation.
- Percentage of patients with an unfavourable outcome (i.e. failure, treatment discontinuation, death, loss to follow up, still on treatment at censure and recurrence) at 108 weeks post randomisation.
- Median time to culture conversion.
- Percentage of patients with an SAE or new grade 3 or higher AE at 72 weeks post randomisation.
- Percentage of patients with an SAE or new grade 3 or higher AE at 108 weeks post randomisation.
- Percentage of patients with an SAE or grade 3 or higher AE at the end of treatment (at 24 weeks in investigational arms and at 36-80+ weeks in SoC arm).
- Mean single QTcF at 24 weeks post randomisation.

Definitions of outcomes:

- Death: Death of a patient from all causes.

- Treatment failure: Treatment failure in the SoC arm will be defined based on DST-adjusted treatment (i.e. the regimen prescribed on receipt of the baseline DST). The date of the first positive culture will be considered the date of treatment failure.

Conventional MDR-TB standard of care regimen

The presence of a positive mycobacterial culture in MGIT liquid media in each of two separate specimens taken at least 2 weeks apart from Week 28 (196 days – 7-day window = 189 days) until the end of treatment.

Shorter MDR-TB standard of care regimen

The presence of a positive mycobacterial culture in MGIT liquid media in each of two separate specimens taken at least 2 weeks apart from Week 16 (112 days – 7-day window = 105 days) until the end of treatment.

Investigational regimens:

The presence of a positive mycobacterial culture in MGIT liquid media in each of two separate specimens taken at least 2 weeks apart from Week 16 (112 days – 7-day window = 105 days) until the end of treatment.

- Lost to follow-up at 108 weeks post-randomisation/date of censor: A patient who has missed his/her appointment after completing treatment and cannot be traced until the end of the expected follow-up period (108 weeks) or date of censor if not followed-up to 108 weeks by design. The date of lost to follow-up is defined as the last visit attended, among those expected for each patient.

- Treatment discontinuation: A decision by an investigator to discontinue treatment:

1) either due to the need to significantly modify the trial regimen for whatever reason,

2) or due to the patient missing some or all drugs regularly,

3) or due to the patient missing all drugs for more than 2 consecutive weeks.

- Still on treatment: A subject who is still taking treatment for M/XDR-TB 108 weeks after starting but was not declared a treatment failure.

- Culture conversion: A subject who had at least one positive mycobacterial culture in MGIT liquid media at baseline (includes samples taken from day 0 (minus 1 day window) to week 4 (plus 3-day window)) and had at least two consecutive negative sputum cultures taken at least 2 weeks apart. The date of the first negative culture was considered the conversion date.

- Recurrence: A subject who has completed treatment without being declared a failure and who has subsequently been diagnosed and requires MDR-TB treatment (for whom there is evidence that the recurrence is due to an MDR or XDR TB strain).

- Re-infection: A subject who has completed treatment without being declared a failure and who has subsequently been diagnosed and requires MDR-TB treatment but for whom there is evidence that the recurrence is due to a different strain to the baseline specimen. If the strain is a DS strain the patient is subsequently non-assessable.

- Relapse: A subject who has completed treatment without being declared a failure and who has subsequently been diagnosed and requires MDR-TB treatment and for whom there is evidence that the recurrence is due to the same strain recorded in the baseline specimen.

- Withdrawals of consent: Withdrawals of consent which occur whilst patients are still on treatment will be classified as early discontinuations. Withdrawals of consent which occur following treatment completion will be classified as losses to follow-up.

- Unfavourable outcome by 108 weeks post-randomisation: A composite outcome comprising death, treatment failure, treatment discontinuation, recurrence by 108 weeks; or loss to follow-up at 108 weeks or date of censor if not followed-up to 108 weeks by design; or still on treatment at 108 weeks.

- Unfavourable outcome at 72 weeks post-randomisation: A composite outcome comprising death, treatment failure, treatment discontinuation and recurrence by 72 weeks (including window of +7 days); or loss to follow-up at 108 weeks or date of censor if not followed-up to 108 weeks by design and where the loss to follow-up occurred by 72 weeks.

- Unfavourable outcome at 48 weeks post-randomisation: A composite outcome comprising death, treatment failure, treatment discontinuation, and recurrence by 48 weeks (including window of +7 days); or loss to follow-up at 108 weeks or date of censor if not followed-up to 108 weeks by design and where the loss to follow-up occurred by 48 weeks.

- Unfavourable outcome at 24 weeks post-randomisation: A composite outcome comprising death, treatment failure, and treatment discontinuation.

Sample size

The analysis of stage 1 was based on test arms only and there was no comparison with the SoC arm. The sample size was based on the number required to detect culture conversion <40% and/or a percentage of treatment discontinuation for any cause and death >45% in an investigational arm.

With 60 participants in an investigational arm evaluable for treatment discontinuation, 29% patients or fewer would have needed to be discontinued, to have 80% power with a one-sided alpha=0.05 to reject the null hypothesis of a true underlying discontinuation rate of 45% (or greater).

Analysis at stage 2 was based on a non-inferiority design to assess efficacy. Sample size calculations were based on this efficacy non-inferiority comparison of the composite primary outcome. In order to allow for both the adaptive nature of the design and the multiple comparisons with three possible arms, an alpha of 1.7% was used.

The underlying assumptions for these power calculations were based on the failure rates seen in patients receiving the control regimen at the time of original protocol writing. An analysis of LTFU over time suggested an additional 10% LTFU rate per 6 months of treatment after the first 6-8 months. These data were also supported by an individual patient data meta-analysis of more than 9000 MDR-TB patients. If assumed that the control and investigational regimens performed the same on all variables included in the composite efficacy other than LTFU, then the likely decrease in LTFU rate expected in the investigational arms due to the shorter length of treatment would lead to the investigational arm performing better overall.

Although the primary outcome was efficacy at 72 weeks, the final sample size allowed for adequate power to assess the secondary outcome of efficacy at 108 weeks.

Therefore, assuming a failure rate of 50% in the control arm and of 45% in the investigational arms, 181 patients per arm was required for a delta of 12% with approximately 85% power and a one sided 98.3% confidence interval (to allow for both the adaptive nature of the design and the multiple comparisons of the three arms).

The delta of 12% was chosen following consultation. The benefits of reducing treatment duration from 9-24 months to 6 months, reduced pill burden, and all oral nature of the investigational regimens had advantages which were considered to outweigh a possible increase in failure rate as reflected in the 12% non-inferiority margin. This delta was also comparable to contemporary ongoing MDR-TB clinical trials such as STREAM, endTB and STAND.

Information available from patients recruited by the end of stage 1 suggested that the number excluded from the mITT population was closer to 10% rather than 5%, and therefore the recruitment target was increased from 181 to *201 per arm in a protocol amendment (protocol version 7.0, dated 13 July 2020).*

Randomisation

Treatment allocation was done using ratios of 1:1:1:1 in stage 1 and 1:1 in stage 2. Randomisation lists were produced by the trial statistician for each stage of the study, stratified by study site. In stage 1, a fixed block size of 8 was used. In stage 2, a varying block size of 4 and 6 was used.

In stage 1, the code for each individual was provided in a secure manner to the sites in separate, opaque sealed envelopes and assigned to individuals in the order in which they were enrolled in the study. The sealed randomisation envelopes looked identical and were kept in a separate room, in a locked cupboard with restricted access. Each envelope had a sequential number and contained the details of the regimen the patient would receive. Delegated personnel were responsible for opening the next sequential envelope, documenting the treatment allocation and assigning the study number. Personnel in charge of the randomisation were not involved in direct patient care.

In stage 2, the same procedure was followed except randomisation personnel used an online, self-service randomisation system to receive the treatment allocation in lieu of envelopes. Randomisation personnel then notified the investigator of the allocation.

Blinding (masking)

TB-PRATECAL was an open-label trial. However, the laboratory personnel and centralised ECG reviewers were blinded to treatment allocation.

Statistical methods

A timeline of important study dates, such as the issuing of the SAP, is provided in the subsection Conduct of the study of this report.

Analysis populations

The protocol stated that the primary analysis would be conducted in a PP population and in an ITT population. However, version 1 of the SAP replaced the ITT population with a mITT population and stated that only the mITT population would be used in the analysis of stage 1.

In version 3 of the SAP, the mITT population for stage 2 was replaced by 'mITT-population-exclude-switches' population.

The analysis populations were defined as follows:

- *mITT:* All patients assigned a randomisation number, dispensed study medication on at least one occasion, and who satisfied the following:
    - Enrolled prior to Version 6.0 of the protocol:
        - A bacterial culture positive for *M. tuberculosis* and resistant to at least rifampicin by a phenotypic drug susceptibility test in a study approved laboratory from samples collected between 28 days before Day 0 and week 4 (28 days + 3-day window = 31 days).
    - Enrolled under Version 6.0 of the protocol or later:
        - A bacterial culture positive for *M. tuberculosis* and resistant to at least rifampicin confirmed by at least two tests (MGIT drug susceptibility test, Gene Xpert, or MTBDRplus) from samples collected between 28 days before Day 0 and week 4 (28 days + 3-day window = 31 days).

        OR

        - A molecular (Gene Xpert, MTBDRplus) or phenotypic drug susceptibility test suggesting rifampicin resistance at screening and subsequent negative bacterial culture for M. tuberculosis, from samples collected between 28 days before Day 0 and week 4 (28 days + 3-day window = 31 days).
- *mITT-population-exclude-switches:* mITT with the exclusion of patients in the SoC arm who were switched to PRACTECAL arm-1 after 18 March 2021, when enrolment to the study was stopped.
- *PP:* mITT with the exclusion of (i) participants not completing a protocol-adherent course of treatment, other than for treatment failure or death; (ii) participants who discontinued treatment early because they violated at least one of the inclusion and exclusion criteria; and (iii) patients who switched from SoC to PRACTECAL arm-1 after enrolment was stopped on 18 March 2021.

  A participant was considered to have completed a protocol-adherent course of treatment if they had taken 80% of doses within 120% of the prescribed duration. A dose was defined as all the study medications at the correct dose for that day.

Efficacy analysis

In stage 1, the primary hypothesis was that at least two regimens containing bedaquiline and pretomanid and other repurposed anti-TB drugs would have culture conversion rates of greater than 40% and discontinuation and death rates of less than 45%.

In stage 2, the primary hypothesis was that regimens containing bedaquiline and pretomanid and other repurposed anti-TB drugs are not inferior to the SoC regimen when evaluated at 72 weeks after starting treatment. As of version 2.0 of the SAP, if non-inferiority of an investigational regimen was demonstrated, p-values for superiority would also be calculated.

The protocol stated that efficacy analyses would be conducted using generalised linear models and that the effects would be reported as adjusted differences in proportions (the adjustment variables were not specified). Version 1 of the SAP clarified that the generalised linear models were adjusted for site and had a binomial outcome with an identity link function. It also explained that risk ratios were calculated using a generalised linear model with a binomial outcome and a log link function (adjusted for site).

Two-sided 96.6% CI were used for the primary endpoint (see *Sample size* below*)*. Two-sided 95% CI were used for secondary endpoints. Secondary endpoints were not adjusted for multiplicity.

Patients who were randomised to BPaLM or SoC in stage 1 were also included in the analysis of stage 2. This inclusion was in line with the protocol.

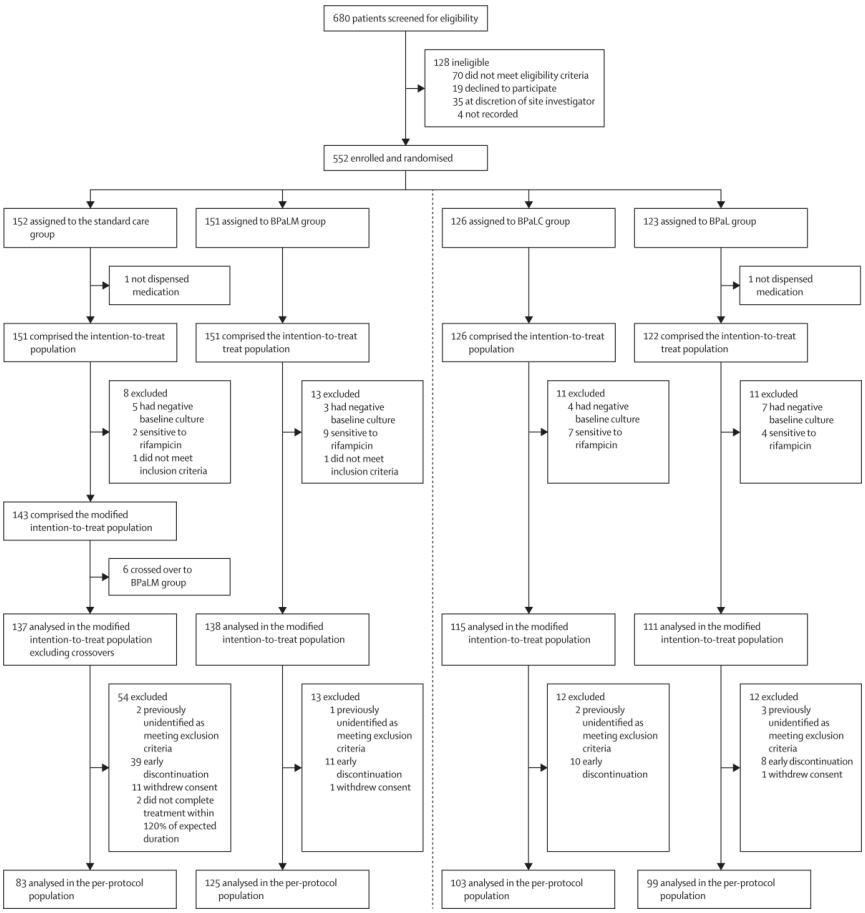
Interim analysis

No interim efficacy analyses were planned. In February 2021, the DSMB for TB-PRACTECAL recommended that further randomisation into the study be terminated. An unplanned interim efficacy analysis was conducted, with database snapshot taken on 19 Aug 2021 (See *Conduct of the study* section below).

Results

Participant flow

Table 1: Participant flow



Recruitment

In stage 1 of the study, 240 patients were enrolled. A total of 552 patients were recruited at the end of stage 2. On the recommendation of the DSMB, the trial was stopped for benefit on 18 March 12021, after an unplanned analysis requested by the board.

302 participants met the criteria for inclusion in stage 2 ITT population (and the safety population): 151 in the SoC group and 151 in the BPaLM group. 275 participants were included in the MITT (137, excluding switches, in the SoC group and 138 in the BPaLM group) and 208 were included in the per-protocol population (83 in the standard care group and 125 in the BPaLM group). Six participants in the SoC group switched to the BPaLM group after enrolment was terminated, and these participants were not included in the primary analysis.

Table 2: Study populations

	STANDARD CARE	BPaLM	BPaLC	BPaL
Total randomised	152	151	126	123
ITT population	151	151	126	122
mITT population	143	138	115	111
Not meeting inclusion criteria	1	1	0	0
Not dispensed any medication	1	0	0	1
Negative baseline culture	5	3	4	7
Rifampicin sensitive	2	9	7	4
mITT-excludes-switches population	137	138	115	111
PP population	83	125	103	99
Not meeting inclusion/exclusion criteria (detected after first dose)	2	1	1	2
Treatment not completed	50	12	10	9
Treatment completed, not within120% of expected duration	2	0	0	0
Switched from standard care to BPaLM	6	0	0	0
Bedaquiline resistant	0	0	1	1

Table 3: Study population by country, mITT excluding switches

	Belarus	South Africa	Uzbekistan
Total number	92	182	227
Standard of care, n (%)	27 (29.4)	49 (26.9)	61 (26.9)
BPaLM, n (%)	26 (28.3)	49 (26.9)	63 (27.8)
BPaLC, n (%)	19 (20.7)	43 (23.6)	53 (23.4)
BPaL, n (%)	20 (21.7)	41 (22.5)	50 (22.0)

Conduct of the study

Table 4: Study timeline

Date	Event
26 November 2015	Protocol version 3.0
30 June 2016	Protocol version 4.0
17 January 2017	First patient randomised
02 March 2017	Protocol version 5.0
16 January 2019	Protocol version 6.1

23 April 2019	Protocol version 6.2
20 November 2019	Statistical analysis plan version 1.0
02 Dec 2019	Stage 1 analysis (planned) – database snapshot taken
13 July 2020	Protocol version 7
14 August 2020	Protocol version 7.1
Nov 2020	Stage 2 commenced
Feb 2021	DSMB recommended stopping randomisation
18 March 2021	Last patient randomised
19 Aug 2021	Interim stage 2 analysis (unplanned) – database snapshot taken
03 September 2021	Statistical analysis plan version 2.0
05 Aug 2022	Follow-up complete
15 September 2022	Protocol version 7.2
	Protocol version 7.3
	Statistical analysis plan version 3.0
17 Jan 2023	Final stage 2 analysis – final database lock

Key protocol amendments

- Revision of inclusion/ exclusion criteria (protocol version 6.0)

There were higher than expected levels of rifampicin susceptibility and culture negativity in the trial cohort. This was often detected some time after the participants had been on treatment. Up to protocol version 6, the participants were discontinued per procedure. However, it transpired that this led to continued treatment with standard care RR-TB regimens according to programmatic care. As a result, and with the emergence of reassuring safety data, inclusion criteria were broadened to allow retention of culture negative participants. Those with discordant rifampicin results were also allowed to continue if an additional molecular test confirmed their RR-TB status.

- Retention of pregnant women (South Africa only, version 6.0)

This was done in response to a changing paradigm of continued inclusion of pregnant women in therapeutic clinical trials. Treatment for RR-TB in pregnancy has little evidence and caring for participants within the trial was considered on balance a reasonable course. Investigators in collaboration with the medical monitor were able to make decisions with the participant on best-interest grounds.

- Re-challenging participants with treatment interruption due to AEs (protocol version 6.0)

The sponsor received advice from the DSMB stating that protocol version 5.0 did not clearly state a procedure for rechallenging study drugs in the event of a treatment emergent AE requiring treatment interruption. At the time, there were significant concerns especially around the risk of hepatoxicity with the pause of another TB trial containing similar regimens.

Protocol version 6 was revised to explicitly allow rechallenge of IMP under the advice and supervision of the medical monitor.

- Stage 2 with only 1 investigational arm (protocol version 7.0/7.1)

Late in 2019, the DSMB highlighted to the sponsor the slower than expected recruitment rate. This coincided with the completion of stage 1. The sponsor PMT proposed to the trial steering committee that only one arm progress to stage 2. During the discussion, the COVID pandemic emerged with new constraints of recruitment. This was agreed to but required a protocol amendment (protocol version 6 and earlier versions had stipulated at least 2 arms would be progressed). On this basis, sites transitioned slowly throughout 2020 in line with the approval of protocol version 7.0/7.1.

- Addition of COVID-19 PCR and serology (protocol version 7.0/7.1)

In response to the COVID-19 pandemic, testing to discern differing presentations of respiratory disease as well as a risk management tool to protect site teams was included in the protocol. Additionally, serology was added to determine if COVID-19 exposure (prior to vaccination being available) caused any confounding in study outcomes.

- Addition of baseline sequencing (protocol version 7.2/7.3)

Transition to genotypic DST, specifically whole genome sequencing, as a gold-standard complementing phenotypic testing commenced during the study period. On this basis, it was considered key to enable sequencing of the baseline isolates.

Key notifications to regulatory authorities, ethics committees and participants

- Alteration of the investigational schedule for COVID disruptions

In March 2020, the COVID outbreak was declared a pandemic by WHO. In collaboration with investigators, early transition to the stage 2 investigational schedule was brought forward pending implementation of protocol versions 7.0/7.1. Investigators were encouraged to complete as much of the investigational schedule as was feasible and safe. Phone visits were done, and bigger drug kits were distributed to ensure continued drug supply. Dedicated deviation reporting was implemented to ensure detection of quality issues directly linked to the pandemic. Regulatory authorities and ethics committees were notified of this action.

- Early termination of randomisation (March 2021)

The DSMB charter stipulated that the DSMB should consider recommending termination of the trial if a difference of at least three standard deviations was reached in the interim analysis of a major endpoint. However, a less stringent p-value was able to be considered if the trial was to be stopped for futility.

The decision to recommend termination of recruitment would be based on statistical considerations, the nature of the condition being studied and the likelihood that the data presented would impact current clinical practice. Due to the non-inferiority design of the trial, stopping the trial for efficacy needed to be based on superiority comparisons.

In February 2021, the DSMB for TB-PRACTECAL recommended that further randomisation into the study be terminated.

The sponsor, in accordance with the Trial Steering Committee's decision and on the advice of the Trial SAC accepted this recommendation and the last patient was randomised on the 18 March 2021 with

552 patients recruited. 75% of the planned sample size for stage 2 of 201 patients per arm had been included at that time point. Regulatory authorities, ethics committees and participants (via an amended informed consent form) were notified of this action.

Protocol deviations

There were a total of 1843 deviations from the protocol. Deviations were grouped depending on the nature of the deviation. Major deviations were uncommon making up 18% of all deviations, no critical deviations were reported. Reported deviations were evenly distributed across arms. According to the MAH, care deviating from the protocol appears to be unlikely to have contributed to the effect estimate.

Deviations around inclusion/exclusion criteria and discontinuation criteria were rare. Wording in the protocol early in the trial led to several participants being recruited outside the eligible 28-day period prior to randomisation. This may have led to higher-than-expected culture negative rates on baseline sputum samples. This was clarified by the sponsor and training was provided. Additionally, 6 participants recruited under protocol version 5 who were culture negative or had unproven rifampicin resistance were not discontinued per protocol due to an impending protocol change (version 6) where this would no longer occur.

Baseline data

Table 5: Demographics of stage 1 population – mITT

All countries	SOC	BPaLM	BPALC	BPAL
Total number (n)		52	52	51
Age (years), mean (range)		35 (18-61)	32 (20-63)	37 (18-62)
Sex – male, n (%)		30 (57.7)	31 (59.6)	29 (56.9)
BMI, mean (range)		20.4 (15.6-31.2)	20.2 (13.2-37.6)	20.57 (13.4-29.8)
HIV positive, n (%)		12 (23.1)	12 (23.1)	10 (19.6)

Table 6: Demographics of the study patients by study arm – mITT population

	STANDARD CARE	BPaLM	BPaLC	BPaL
Total number	143	138	115	111
Belarus, n (%)	29 (20.3)	26 (18.8)	19 (16.5)	20 (18.0)
South Africa, n (%)	49 (34.3)	49 (35.5)	43 (37.4)	41 (36.9)
Uzbekistan, n (%)	65 (45.5)	63 (45.7)	53 (46.1)	50 (45.1)
Age (years), median (range)	37 (18 to 71)	35 (17 to 71)	32 (19 to 67)	34 (15 to 72)
Female, n (%)	54 (37.8)	61 (44.2)	39 (33.9)	54 (48.7)
BMI (kg/m^2), median (IQR)	19.9 (17.5 to 22.8)	19.7 (17.7 to 22.7)	19.4 (17.6 to 22.1)	20.0 (18.1 to 22.5)
HIV positive, n (%)	39 (27.3)	34 (24.6)	31 (27.0)	36 (32.4)
CD4 count (cells/µL), median (IQR)	250 (143 to 445) Missing = 2	330 (223 to 547) Missing = 2	297 (115 to 511) Missing = 1	383 (161 to 550) Missing = 1
Smear positive, n (%)	94 (65.7)	86 (62.3)	79 (68.7)	73 (65.8)
Cavity present, n (%)	90 (62.9)	76 (55.1)	74 (64.4)	68 (61.3)
Fluoroquinolone resistant, n (%)	32 (25.2) Missing = 16	32 (25.8) Missing = 14	22 (20.2) Missing = 6	25 (25.5) Missing = 13
Bedaquiline resistant, n (%)	1 (0.8) Missing = 18	1 (0.9) Missing = 21	2 (1.9) Missing = 8	1 (1.1) Missing = 17
QTcF (ms), mean (SD)	400 (19)	399 (19)	395 (18)	399 (19)
ALT (IU/l), median (IQR)	20 (15 to 28) Missing = 2	19 (14 to 28) Missing = 1	17 (14 to 26) Missing = 1	19 (14 to 29) Missing = 0
Culture positive, n (%)	127 (88.8)	120 (87.0)	107 (93.0)	96 (86.5)
Previous treatment for MDR-TB, n (%)	13 (9.1)	18 (13.0)	12 (10.4)	16 (14.4)

Table 7: Baseline phenotypic DST of the study patients – proportion testing resistant by arm (mITT)

	STANDARD CARE n (%)	BPaLM n (%)	BPaLC n (%)	BPaL n (%)
n	143	138	115	111
Rifampicin	114 (91.2) Missing = 18	105 (87.5) Missing = 18	99 (93.4) Missing = 9	88 (93.6) Missing = 17
Isoniazid	115 (92.0) Missing = 18	106 (88.3) Missing = 18	99 (93.4) Missing = 9	85 (90.4) Missing = 17
Ethambutol	72 (57.6) Missing = 18	72 (60.0) Missing = 18	67 (63.2) Missing = 9	57 (60.6) Missing = 17
Pyrazinamide	82 (65.1) Missing = 17	73 (60.8) Missing = 18	68 (64.2) Missing = 9	60 (63.2) Missing = 16
Streptomycin	103 (82.4) Missing = 18	95 (79.2) Missing = 18	86 (81.1) Missing = 9	75 (79.8) Missing = 17
Kanamycin	29 (23.0) Missing = 17	41 (34.2) Missing = 18	21 (19.8) Missing = 9	26 (27.4) Missing = 16
Capreomycin	11 (8.7) Missing = 17	20 (16.7) Missing = 18	7 (6.6) Missing = 9	12 (12.6) Missing = 16
Moxifloxacin (0.25 or 0.5)	28 (22.2) Missing = 17	23 (19.2) Missing = 18	20 (18.9) Missing = 9	22 (23.2) Missing = 16
Moxifloxacin (1 or 2)	10 (8.0) Missing = 18	7 (5.8) Missing = 18	4 (3.8) Missing = 9	2 (2.1) Missing = 16

Notably, participants with documented rifampicin resistance by molecular testing methods were eligible for inclusion in the mITT population, even in the absence of phenotypic confirmation.

Therefore, approximately 10% of participants without phenotypic DST results were included in the mITT population based on molecular evidence of rifampicin resistance, consistent with the study's predefined criteria.

Table 8: Summary of regiments used in SoC

	Prior to current guideline* n (%)	Current guideline* n (%)
ITT population (n = 151)		
Long regimen	33 (71.7%)	64 (61.0%)
Containing Bdq	30	64
Containing Lzd	30	64
Short regimen	13 (28.3%)	41 (39.0%)

* Current guideline dates: Nukus – 20/08/2019; Tashkent – 07/09/2019; Belarus – 29/08/2019; South Africa – 18/09/2018

Table 9: Summary of regiment components in standard care participants (ITT and who were dispensed at least one dose of the study medication (n = 151))

	Total n (%)	Shorter regimen (36-44 weeks) n (%)	Long regimen (72-80+ weeks) n (%)
Any	151 (100%)	54 (100%)	97 (100%)
Bedaquiline	133 (88.1%)	39 (72.2%)	94 (96.9%)
Linezolid	132 (87.4%)	38 (70.4%)	94 (96.9%)
Moxifloxacin or Levofloxacin	146 (96.7%)	54 (100%)	92 (94.9%)
Cycloserine	76 (50.3%)	3 (5.6%)	73 (75.3%)
Clofazimine	149 (98.7%)	54 (100%)	95 (97.9%)
Delamanid	20 (13.3%)	0 (0%)	20 (20.6%)
Pyrazinamide	93 (61.6%)	54 (100%)	39 (40.2%)
Injectable (Am/Cm/Km)	36 (23.8%)	15 (27.8%)	21 (21.6%)

Outcomes and estimation

There were three major analyses undertaken:

1. Stage 1 analysis (planned) – database snapshot taken on 02 December 2019;

2. Interim stage 2 analysis (unplanned) – database snapshot taken on 19 August 2021;

3. Final stage 2 analysis – final database lock on 17 January 2023.

Stage 1

the BPaLM-regimen achieved highest rate of culture conversion of the tested regimens. Consequently, this regimen was selected for further evaluation in stage 2.

Table 10: Stage 1 primary efficacy outcomes at week 8 (mITT population, stage 1 analysis)

	STANDARD CARE n/N (%)	BPaLM n/N (%)	BPaLC n/N (%)	BPaL n/N (%)
Number with culture conversion in liquid media at 8 weeks post randomization, n/N (%)	N/A	37/48 (77.1%)	33/49 (67.3%)	21/46 (45.7%)
[85% CI]		[66.4, 85.6]	[56.2, 77.2]	[34.4, 57.3]

Stage 2:

As outlined in the section above on *Statistical Methods*, version 3 of the SAP, the mITT population for stage 2 was replaced by an 'mITT-population-exclude-switches' population. This corresponds to the mITT population with the exclusion of patients in the SoC arm who were switched to BPaLM after 18 March 2021, when enrolment to the study was stopped.

Table 2 (Study populations) under the heading of recruitment illustrates that this population includes 137/143 patients from the mITT population of the SoC arm, and 138/138 patients from the mITT population of the BPaLM arm.

Primary endpoint

As outlined below, 88.3% of patients in the BPaLM arm had a favourable outcome, compared to 59.1% in the control arm.

Table 11: Primary outcome (mITT-excludes-switches population) – unfavourable outcomes (death, treatment failure, treatment discontinuation, loss to follow up, and recurrence) at 72 weeks

	STANDARD CARE n (%)	BPaLM n (%)
Number in mITT-excludes-switches population	137	138
Number with no unfavourable outcome	81 (59.1%)	121 (88.3%)
Number with an unfavourable outcome	56 (40.9%)	16 (11.7%)
Number non-assessable	0	1
Unadjusted risk difference (two-sided 96.6% confidence interval)		-29.2% (-39.8% to -18.6%)
Non-inferiority p-value (non-inferiority margin of +12%)		p<0.0001
Superiority p-value		p<0.0001
Adjusted risk difference (two-sided 96.6% confidence interval)		-29.2% (-39.4% to -19.0%)
Unadjusted risk ratio (two-sided 96.6% confidence interval)		0.29 (0.17 to 0.49)
Adjusted risk ratio (two-sided 96.6% confidence interval)		0.28 (0.16 to 0.47)
Deaths	5 (3.7%)	0 (0%)
Early discontinuations	50 (36.5%)	11 (8.0%)
Adherence issues	11	1
Adverse event	23	7
Not meeting inclusion/exclusion criteria (detected after 1st dose)	2	1
Withdrew consent whilst still on treatment	11	1
Other	3	1
Treatment failure	0 (0%)	0 (0%)
Lost to follow-up at 72 weeks	1 (0.7%)	4 (2.9%)
Losses to follow-up	1	1
Withdrew consent	0	3
Recurrence	0 (0%)	1 (0.7%)

The corresponding PP population illustrates how this difference was driven by differences in "early discontinuations".

Table 12: Primary outcome (PP population) – unfavourable outcomes (death, treatment failure, treatment discontinuation, loss to follow up, and recurrence) at 72 weeks

	STANDARD CARE n (%)	BPaLM n (%)
Number in PP population	83	125
Number with no unfavourable outcome	77 (92.8%)	120 (96.0%)
Number with an unfavourable outcome	6 (7.2%)	5 (4.0%)
Number non-assessable	0	0
Unadjusted risk difference (two-sided 96.6% confidence interval)		-3.2% (-10.3% to 3.9%)
Non-inferiority p-value (non-inferiority margin of +12%)		p<0.0001
Superiority p-value		p=0.24
Adjusted risk difference (two-sided 96.6% confidence interval)		-3.3% (-10.5% to 4.0%)
Unadjusted risk ratio (two-sided 96.6% confidence interval)		0.55 (0.16 to 1.93)
Adjusted risk ratio (two-sided 96.6% confidence interval)		0.56 (0.16 to 1.96)

Deaths	5 (6.0%)	0 (0%)
Early discontinuations	0 (0%)	0 (0%)
Treatment failure	0 (0%)	0 (0%)
Lost to follow-up at 72 weeks	1 (1.2%)	4 (3.2%)
Losses to follow-up	1	1
Withdrew consent	0	3
Recurrence	0 (0%)	1 (0.8%)

Selected secondary outcomes

The difference in the proportion of patients meeting the "early discontinuation" component of the endpoint is evident already at 24 weeks when the BPaLM treatment is more or less over.

Table 13: Unfavourable outcomes (death, treatment failure, and treatment discontinuation) at 24 weeks (mITT-excludes-switches population)

	STANDARD CARE n (%)	BPaLM (%)
Number in mITT-excludes-switches population	137	138
Number with no unfavourable outcome	94 (68.6%)	126 (92.0%)
Number with an unfavourable outcome	43 (31.4%)	11 (8.0%)
Number non-assessable	0	1
Unadjusted risk difference (two-sided 95% confidence interval)		-23.4% (-32.4% to -14.4%)
Non-inferiority p-value (non-inferiority margin of +12%)		p<0.0001
Superiority p-value		p<0.0001
Adjusted risk difference (two-sided 95% confidence interval)		-23.4% (-32.2% to -14.7%)
Unadjusted risk ratio (two-sided 95% confidence interval)		0.26 (0.14 to 0.47)
Adjusted risk ratio (two-sided 95% confidence interval)		0.25 (0.14 to 0.46)
Deaths	4 (2.9%)	0 (0%)
Early discontinuations	39 (28.5%)	11 (8.0%)
Adherence issues	6	1
Adverse event	22	7

Not meeting inclusion/exclusion criteria (detected after 1st dose)	2	1
Withdrew consent whilst still on treatment	6	1
Other	3	1
Treatment failure	0 (0%)	0 (0%)

Efficacy estimates were stable at 108 weeks:

Table 14: Unfavourable outcomes (death, treatment failure, treatment discontinuation, loss to follow-up, recurrence, and still on treatment) at 108 weeks (mITT-excludes-switches population)

	STANDARD CARE n (%)	BPaLM n (%)
Number in mITT-excludes-switches population	137	138
Number with no unfavourable outcome	73 (53.3%)	118 (86.1%)
Number with an unfavourable outcome	64 (46.7%)	19 (13.9%)
Number non-assessable	0	1
Unadjusted risk difference (two-sided 95% confidence interval)		-32.8% (-43.0% to -22.7%)
Non-inferiority p-value (non-inferiority margin of +12%)		p<0.0001
Superiority p-value		p<0.0001
Adjusted risk difference (two-sided 95% confidence interval)		-32.8% (-42.6% to -22.9%)
Unadjusted risk ratio (two-sided 95% confidence interval)		0.30 (0.19 to 0.47)
Adjusted risk ratio (two-sided 95% confidence interval)		0.29 (0.19 to 0.46)
Deaths	6 (4.4%)	0 (0%)
Early discontinuations	51 (37.2%)	12 (8.8%)
Adherence issues	11	1
Adverse event	23	7
Not meeting inclusion/exclusion criteria (detected after 1st dose)	2	1
Withdrew consent whilst still on treatment	12	1
Other	3	2
Treatment failure	0 (0%)	0 (0%)
Lost to follow-up at 108 weeks	6 (4.4%)	6 (4.4%)
Losses to follow-up	4	3
Withdrew consent	2	3
Recurrence	1 (0.7%)	1 (0.7%)
Still on treatment at 108 weeks	0 (0%)	0 (0%)

Outcomes in the mITT population

Table 15: Unfavourable outcomes (death, treatment failure, treatment discontinuation, loss to follow-up, and recurrence) at 72 weeks, including patients who switched from SoC to BPaLM within the SoC group (mITT population)

	STANDARD CARE	BPaLM
Number in mITT population	143	138
Number with no unfavourable outcome	85 (59.4%)	121 (88.3%)
Number with an unfavourable outcome	58 (40.6%)	16 (11.7%)
Number non-assessable	0	1
Unadjusted risk difference (two-sided 95% confidence interval)		-28.9% (-38.6% to -19.2%)
Non-inferiority p-value (non-inferiority margin of +12%)		p<0.0001
Superiority p-value		p<0.0001
Unadjusted risk ratio (two-sided 95% confidence interval)		0.29 (0.17 to 0.48)
Deaths	5 (3.5%)	0 (0%)
Early discontinuations	52 (36.4%)	11 (8.0%)
Adherence issues	13	1
Adverse event	23	7
Not meeting inclusion/exclusion criteria (detected after 1st dose)	2	1
Withdrew consent whilst still on treatment	11	1
Other	3	1
Treatment failure	0 (0%)	0 (0%)
Lost to follow-up at 72 weeks	1 (0.7%)	4 (2.9%)
Losses to follow-up	1	1
Withdrew consent	0	3
Recurrence	0 (0%)	1 (0.7%)

Outcomes in patients excluded from the mITT population

As outlined above, six patients in the SoC arm were excluded from the mITT population because of switch to the BPaLM regimen.

Table 16: Line list – Outcomes of participants switched from SoC to BPaLM arm by week 72

Participant	Standard care regimen type	Planned duration (weeks)	Duration of therapy at time of switch (weeks)	Time to culture conversion from day 0 (weeks)	Outcome at week 72
1	Long all-oral	72 weeks	14.9	12	Early discontinued (adherence issues)
2	Long all-oral	72 weeks	10.4	4	Early discontinued (adherence issues)
3	Long all-oral	72 weeks	28	8	No unfavourable outcome
4	Long all-oral	72 weeks	17	12	No unfavourable outcome
5	Long all-oral	72 weeks	15	Baseline culture negative	No unfavourable outcome
6	Long all-oral	72 weeks	14	12	No unfavourable outcome

Culture conversion and recurrence

Table 17: Culture conversion at 12 weeks and 108 weeks (mITT-excludes-switches population)

	STANDARD CARE	BPaLM
Number in mITT-excludes-switches population	137	138
Number with at least one positive mycobacterial culture in MGIT liquid media at baseline	121	120
Number with culture conversion up to 12 weeks	99 (81.8%)	107 (89.2%)
Unadjusted risk difference (two-sided 95% confidence interval)		7.3% (-1.5% to 16.2%)
Adjusted risk difference (two-sided 95% confidence interval)		7.1% (-2.0% to 16.2%)
Unadjusted risk ratio (two-sided 95% confidence interval)		1.09 (0.98 to 1.21)
Adjusted risk ratio (two-sided 95% confidence interval)		1.09 (0.98 to 1.21)
Number with culture conversion up to 108 weeks	106 (87.6%)	113 (94.2%)
Median (IQR) time to culture conversion (days)	56 (28 to 83)	55 (28 to 57)
Unadjusted hazard ratio (two-sided 95% confidence interval)		1.38 (1.05 to 1.81)
Adjusted hazard ratio (two-sided 95% confidence interval)		1.31 (1.00 to 1.72)

Table 18: Recurrence in the mITT population at week 108 excluding switches

	STANDARD CARE	BPaLM	BPaLC	BPaL
Total number in mITT	137	138	115	111
Number of recurrences (%)	1 (0.7%)	1 (0.7%)	5 (4.4%)	4 (3.6%)
Proportion with baseline resistance to component drug	0	0	0	0
Clinical grounds only	1	0	1	0
Clinical and culture proven	0	1	4*	4
New resistance to ≥ 1 component drug	0	0	0	3**

mITT – modified intention to treat
*Culture confirming recurrence was through non-trial samples for one participant.
** 3 participants had isolates which tested resistant to bedaquiline on phenotypic DST; of these participants, 1 also tested resistant to clofazimine

Ancillary analyses

The figure below represents the proportion of patients with unfavourable outcomes.

Table 19: Subgroup analyses (mITT-excludes-switches population) at week 72

	STANDARD CARE n/N (%)	BPaLM n/N (%)	Risk difference (two-sided 96.6% CI)	Interaction p-value
Age (years)				
<18	0/0 (0.0)	0/1 (0.0)	-	
18 to <45	33/100 (33.0)	12/101 (11.9)	-21.1% (-33.2% to -9.0%)	
45 to <65	22/36 (61.1)	3/33 (9.1)	-52.0% (-72.3 to -31.8%)	
≥65	1/1 (100.0)	1/2 (50.0)	-	N/A
Sex				
Female	21/52 (40.4)	7/60 (11.7)	-28.7% (-45.6% to -11.8%)	
Male	35/85 (41.2)	9/77 (11.7)	-29.5% (-43.2% to -15.8%)	p = 0.94
Country				
Belarus	17/27 (63.0)	1/26 (3.9)	-59.1% (-80.4% to -37.9%)	
South Africa	12/49 (24.5)	9/48 (18.8)	-5.7% (-23.4% to 11.9%)	
Uzbekistan	27/61 (44.3)	6/63 (9.5)	-34.7% (-50.3% to -19.1%)	p = 0.0002
HIV status				
Negative	47/99 (47.5)	9/103 (8.7)	-38.7% (-50.9% to -26.6%)	
Positive	9/38 (23.7)	7/34 (20.6)	-3.1% (-23.8% to 17.6%)	p = 0.0017
Smear positivity				
Negative	23/46 (50.0)	9/52 (17.3)	-32.7% (-51.9% to -13.5%)	
Positive	33/91 (36.3)	7/85 (8.2)	-28.0% (-40.4% to -15.6%)	p = 0.67
Cavity present				
Absent	25/51 (49.0)	12/61 (19.7)	-29.3% (-47.7% to -11.0%)	
Present	31/86 (36.1)	4/76 (5.3)	-30.8% (-43.0 to -18.5%)	p = 0.89
Previous TB treatment				
No	32/78 (41.0)	11/83 (13.3)	-27.8% (-42.0% to -13.6%)	
Yes	24/59 (40.7)	5/54 (9.3)	-31.4% (-47.3% to -15.5%)	p = 0.72
Current smoking status				
Not currently smoking	36/91 (39.6)	14/94 (14.9)	-24.7% (-38.0% to -11.2%)	
Currently smoking	20/46 (43.5)	2/43 (4.7)	-38.8% (-55.8% to -21.9%)	p = 0.16
Isoniazid resistance				
Sensitive	2/10 (20.0)	2/14 (14.3)	-5.7% (-39.1% to 27.6%)	
Resistant	46/110 (41.8)	9/105 (8.6)	-33.2% (-44.8% to -21.7%)	p = 0.10
Fluoroquinolone resistance				
Sensitive	38/91 (41.8)	5/91 (5.5)	-36.3% (-48.3% to -24.2%)	
Resistant	11/31 (35.5)	6/32 (18.8)	-16.7% (-40.1% to 6.6%)	p = 0.12
WHO declaring coronavirus a public health emergency of international concern (30th January 2020)				
Pre	37/78 (47.4)	6/74 (8.1)	-39.3% (-53.1% to -25.6%)	
Post	19/59 (32.2)	10/63 (15.9)	-16.3% (-32.5% to 0.0%)	p = 0.022

The following figure was provided to show that the trial was not stopped at a time when the effect estimate was unusually large (a 'random high').

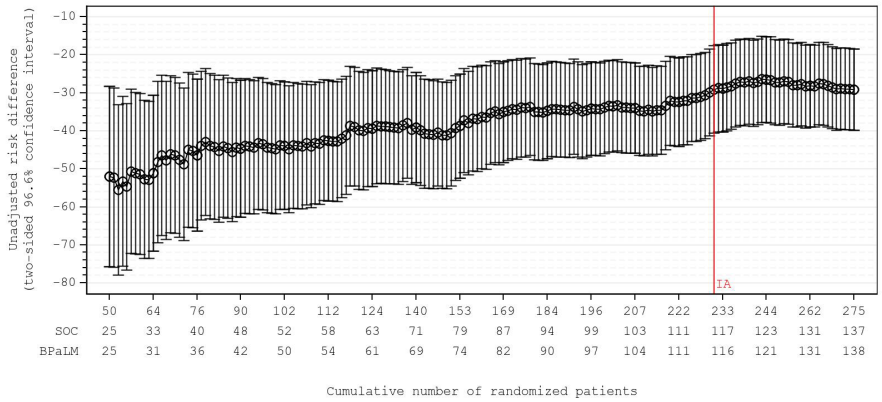


Figure 2: Risk difference of unfavourable outcome at 72 weeks, effect of each additional post-interim subject in mITT population-excludes-switches (unadjusted risk difference)

Unfavourable outcome is the composite outcome of death, treatment failure, treatment discontinuation, loss to follow-up, and recurrence at 72 weeks.

Cumulative number of participants is calculated as the number of participants randomised up to next randomisation date.

When more than one participant randomised at the same date, all participants are added at once.

The Cochran-Mantel-Haenszel method was used instead of generalized linear model adjusted for site, when convergence issues occurred.

Summary of main study

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 20: Summary of efficacy for trial TB-PRACTECAL

Title: TB-PRACTECAL		
Study identifier	NCT02589782	
Design	Randomised, open-label study	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	108 weeks not applicable not applicable
Hypothesis	Non-inferiority	
Treatments groups	BPaLM	24 weeks treatment, 151 randomised
	Standard care	36-96 seeks, 152 randomised
Endpoints and definitions	Primary endpoint	Percentage of patients with an unfavourable outcome (treatment failure, death, treatment discontinuation, recurrence, loss to follow-up) at 72 weeks post-randomisation.
Database lock	17 Jan 2023	

Results and Analysis				
Analysis description	**Primary Analysis**			
Analysis population and time point description	mITT excluding switches, 72 weeks post randomisation			
Percent favourable outcomes	Treatment group	Standard care	BPaLM	Difference
	Number of subjects	137	138	
	Primary endpoint. % with unfavourable outcome	40.9%	11.7%	29.2%
	Two-sided 96.6% CI			-39.8- -18.6%

2.4.2. Discussion on clinical efficacy

Design and conduct of clinical studies

The study had two stages. In stage 1 of the trial, corresponding to a phase-2 trial, patients were randomised to a combination of Pretomanid, Bedaquiline and Linezolid alone or with Moxifloxacin; or with Clofazimine; or to the SoC. Stage 2 of the study included patients in stage 1 that had been randomised to BPaLM or SoC. Further inclusion and randomisation in stage 2 was limited to these two treatment arms.

The primary objective of stage 2 of the trial was to demonstrate the efficacy of BPaLM using a non-inferiority comparison to SoC with a margin of 12%. The primary endpoint was a composite outcome comprising death, treatment failure, treatment discontinuation and recurrence by 72 weeks (including window of +7 days); or LTFU at 108 weeks or date of censor if not followed up to 108 weeks by design and where the LTFU occurred by 72 weeks.

The primary statistical analysis of stage 2 was a between-arm difference in the percentage of patients with an unfavourable outcome at week 72. This difference was calculated using a 'generalised linear model a binomial outcome with an identity link function.', meaning that a linear regression was used. Linear regression is a valid method for estimating the risk difference between two groups, although this is not the standard use of the model.

The model was adjusted for the 6 trial sites, and it was pre-specified in the SAP before the end of stage 1. Notably the NI margin of 12% is not based on any calculations of retention of the effect with a given substitution. Rather, it is pragmatically grounded in what might be considered relevant with respect to clinical equivalence. This margin was recently accepted by the CHMP in the context of the confirmatory STREAM study for bedaquiline.

Overall, the study may be considered a comparative effectiveness study. The anti-mycobacterial efficacy of all treatment components was previously established.

The primary endpoint was adequately prespecified. The protocol and SAP stated that LTFU at week 108 would be counted as an unfavourable outcome, but the analysis presented in the CSR included only LTFU until week 72. Although this is not strictly pre-specified, it is appropriate and acceptable.

The protocol stated that the efficacy analysis in stage 2 would be conducted in both a PP set and an ITT set. However, the ITT set was replaced by a mITT set in version 1 of the SAP. Since this version of the SAP was issued before the end of stage 1, it can be considered pre-specified.

The mITT set included all randomised patients who were dispensed at least one dose of study medication and were confirmed resistant to at least rifampicin. These criteria led to the exclusion of 6% (n=9/152) of patients randomised to SoC and 9% (n=13/151) of patients randomised to BPaLM arm. The analysis of stage 2 was also conducted in an analysis set called 'mITT-population-exclude-switches,' which excluded patients in the SoC arm who received the test treatment (BPaLM) after randomisation had been stopped. This analysis set cannot be considered pre-specified because it was defined after the last patient's last visit (in version 3 of the SAP). However, this is a minor issue because the efficacy results were similar in the mITT-population-exclude-switches set and the pre-specified mITT set (the difference is only 6 patients excluded from the SoC arm analysis population).

The target sample size was initially 181 patients per arm in stage 2. This target number was increased to 201 patients per arm in protocol amendment 7 because the analysis of stage 1 had suggested that the number of patients that would need to be excluded from the mITT set was higher than initially expected. This increase in sample size cannot be considered pre-specified because the protocol amendment was issued 7 months after the analysis of stage 1 and 13 months before the unplanned interim analysis. However, this issue is not further pursued because neither the original sample size nor the updated sample size was reached because the trial was stopped early.

The pre-specified primary analysis of stage 2 included patients who were randomised during stage 1. In fact, only 44 out of 275 patients were randomised during stage 2. The explanation for this is that recruitment into all 4 arms of stage 1 continued long after the primary analysis of stage 1, and recruitment into stage 2 started only 4 months before randomisation was stopped (upon a recommendation from the DSMB).

The decision to continue recruitment into stage 1 after the primary analysis of this stage is not in line with the protocol, and it makes a separate analysis of stage 2 rather uninformative (due to the small sample size in stage 2). This would have been a major limitation if the trial had been needed to establish the efficacy of BPaLM. As explained below however, the trial is only needed to demonstrate that BPaLM is clinically useful. For this purpose, the small sample size of stage 2 is acceptable.

The sponsor used 96.6% CIs and 2-sided significance levels of 3.4% because of "the adaptive nature of the design and the multiple comparisons with three possible arms". However, this approach does not ensure that the type-1 error is controlled at the conventional 5% level (two-sided) in the efficacy analysis of stage 2. This limitation was accepted because the study is not needed to establish the efficacy of BPaLM, as explained below.

In the primary analysis, treatment discontinuation was handled as an unfavourable outcome. Since treatment discontinuation was mainly due to tolerability issues, the primary analysis was a composite endpoint that does not isolate between-arm differences in efficacy. This would have been a major limitation if the trial had been needed to demonstrate the efficacy of BPaLM, but as explained below, the trial is only needed to establish the clinical usefulness of BPaLM. It was not possible to conduct an analysis in which treatment discontinuations were ignored (a treatment-policy strategy) because patients were not followed up after treatment discontinuation.

By design, the duration of SoC was at least 36 weeks and the duration of BPaLM (the test treatment) was only 24 weeks. This difference in treatment duration could have biased the results in favour of BPaLM because patients were classified as having an unfavourable outcome if they prematurely discontinued treatment (a shorter treatment regimen is, in general, easier to complete). However, there is no indication that this was the case, as the results at 24 weeks (when all patients could still be treated) were similar to the primary results at 72 weeks.

Efficacy data and additional analyses

302 participants met the criteria for inclusion in the stage two ITT population (and the safety population): 151 in the SoC group and 151 in the BPaLM group. Of these, 143 (SoC group) and 138 (BPaLM group) were included in the mITT population (shown to be at least rifampicin resistant). Further to that, six participants in the SoC group switched to the BPaLM group after enrolment was terminated, and these participants were not included in the primary analysis.

On the recommendation of the DSMB, the trial was stopped for efficacy on 18 March 2021. At this time approximately 150 patients were randomised to each of the BPaLM and SoC arms, but follow-up continued until all patients completed 72 weeks or withdrew from the trial.

Stopping a trial early for efficacy based on the results of an unplanned interim analysis means that the type-1 error is not controlled. This limitation could not be entirely resolved, but the MAH provided a plot of how the effect estimate (difference in risk) changed as the sample size increased. This plot showed that the effect estimate decreased as the sample size increased, which provided reassurance that the interim analysis was not a 'random high' (a good result just by chance). The lack of proper type-1-error control would have been a major limitation if the trial had been needed to establish the efficacy of BPaLM, but as explained below, the trial is only needed to demonstrate the clinical usefulness of BPaLM. For this purpose, the lack of type-1-error control is acceptable.

Regarding the primary outcome at 72 weeks among the mITT population, 56 (41%) of 137 participants in the SoC group and 16 (12%) of 137 participants in the BPaLM group met criteria for the unfavourable outcome (unadjusted risk difference −29·2 percentage points [96·6% CI −39·8 to −18·6].

The main reason for meeting the unfavourable outcome definition was early discontinuation (50 [89%] of 56 participants with unfavourable outcomes in the SoC group and 11 [69%] of 16 in the BPaLM group), which was mainly attributed to AEs.

Results for the unfavourable outcome at 108 weeks in the mITT population were consistent with those for the primary outcome. Two disease recurrences occurred by 108 weeks: one in the SoC group and one in the BPaLM group. This is indicative of a high cure rate for a treatment duration of 24 weeks.

Culture conversion at week 12 was seen for 81.8% in the control arm and for 89.2% in the BPaLM arm.

Superiority of BPaLM regarding the composite endpoint was seen in key disease-related subgroups such as those smear-positive at baseline, those with pulmonary cavities and those with bacteria that were fluoroquinolone resistant. Similar outcomes were seen in the HIV-positive.

The MAH claimed that the trial also showed the superiority of BPaLM. The test of superiority was not pre-specified, as it was introduced in version 2.0 of the SAP, which was issued after the unplanned interim efficacy that led to early stopping.

The treatment duration in the TB-PRACTECAL trial was 24 weeks. The recommended treatment duration of BPaL/BPaLM is up to 26 weeks. This is a standardisation according to WHO policy and is not anticipated to substantially impact efficacy or safety.

Moreover, the MAH is proposing to broaden the existing indication with BPaL without M for patients with rifampicin, isoniazid and fluoroquinolone resistance, to cover patients with rifampicin- and fluoroquinolone resistance regardless of isoniazid resistance status. This is in line with WHO guidance treating rifampicin-resistance and rifampicin-isoniazid resistance and omits the fluoroquinolone where this is not anticipated to be efficacious. Therefore, this is acceptable.

2.4.3. Conclusions on the clinical efficacy

The efficacy of the BPaLM 24-week regimen for TB patients that have at least resistance to rifampicin has been demonstrated, with 88% of treated patients showing a favourable outcome, 4% lost to follow up and 0.7% showing disease recurrence. The antibacterial efficacy of adding moxifloxacin to the previously approved BPaL regimen has been demonstrated with an incremental culture conversion rate at 8 weeks of 77% versus 46%.

Notably, the WHO operational handbook on tuberculosis, 2022 update, recommends a 6-month all-oral regimen (BPaLM) comprising bedaquiline, pretomanid, linezolid, and moxifloxacin for most patients with rifampicin-resistant TB.

2.5. Clinical safety

Introduction

The safety evaluation is focussed on the comparison of the BPaLM and BPaL regimens considering that the safety profile of the latter is already described in the product information and that a comparison to the SoC arm, that includes many different regimens, may not be useful. For completeness, safety data for the SoC arm are also included in this assessment report.

The safety population in the TB-PRACTECAL study was identical to the efficacy population. In total, 179 participants met the criteria for inclusion in the stage 1 ITT population (60 in the BPaLM group, 60 in the BPaLC group, and 59 in the BPaL group). For the stage 2, 302 participants met the criteria for inclusion in the ITT population (and the safety population): 151 in the SoC group and 151 in the BPaLM group; 126 were included in the BPaLC arm and 122 in the BPaL arm. The safety analysis is based on the ITT population of 550 as two participants that were randomised did not receive study drugs.

A summary of the demographic and baseline characteristics of the TB-PRACTECAL safety population are presented above in the section on efficacy.

Adverse events

For all studies, a TEAE was defined as an AE that started or worsened at or during the time of first study drug administration, or after first study drug administration, up until 14 days after the last study drug administration.

AEs were classified using standard terminology (i.e., SOC and PT) from the verbatim description (investigator term) according to the MedDRA version 20.0.

AEs were reported in the integrated safety database as being related or not related to any of the study drugs within the investigational regimen. AEs with unknown relationship to study regimen/drug were counted as related to study drug. AE intensity was categorised as grades 1, 2, 3, or 4 (mild, moderate, severe, or potentially life-threatening, respectively).

The subject incidence of all TEAEs reported in TB-PRACTECAL by SOC and PT was provided at 108 weeks.

In the SoC group, the most frequently reported primary SOCs were Investigations (142 [94.0%] patients), Gastrointestinal Disorders (113 [74.8%] patients), Metabolism and nutrition disorders (99 [65.5%] patients), Nervous system disorders (83 [54.9%] patients), Blood and lymphatic system disorders (87 [57.6%]) and Skin and Subcutaneous Tissue Disorders (90 [59.6%] patients).

In the BPaLM group, the most frequently reported primary SOCs were Investigations (123 patients [81.4%]), Gastrointestinal Disorders (85 [56.2%] patients), Metabolism and nutrition disorders (123 [81.4%] patients), Nervous system disorders (65 [43.0%] patients), Blood and lymphatic system disorders (71 [47.0%] patients) and Skin and Subcutaneous Tissue Disorders (54 [35.8%] patients).

In the BPaL group, the most frequently reported primary SOCs were Investigations (105 [86.0%] patients), Nervous system disorders (52 [42.6%]), Metabolism and nutrition disorders (105 [86.0%]), Gastrointestinal Disorders (56 [45.9%] patients), and Blood and lymphatic system disorders (60 [49.1%] patients), and Skin and Subcutaneous Tissue Disorders (58 [47.5%] patients).

The most frequent ADRs during treatment with pretomanid in combination with bedaquiline, linezolid and moxifloxacin were transaminases increased and QTc prolongation:

- ADRs of increased transaminases were reported in 58 (38.4%) patients in BPaLM arm, where one patient could have reported more than one PT which were collapsed into category of Increased transaminases. The majority of the events were of grade 1 or grade 2 category, 6 patients had reported grade 3 severity, the outcome in 5 patients was resolved and in one patient outcome was not known.

- 46 (30.5%) patients reported QT prolongation related to study drugs, out of which only 1 patient reported grade 3 severity of QT prolongation. The outcome was resolved.

52 patients reported ADRs of myelosuppression in the BPaLM arm, out of which 27 (18%) patients reported leukopenia, 26 (17.2%) patients reported neutropenia and 21 (14%) patients reported anaemia, one patient could have reported more than one PT. Grade 3 or more severity was observed in 6 patients and outcome was resolved in 4 patients in 2 patients the outcome was not known. In addition, 13 (8.6%) patients reported PTs collapsed to peripheral neuropathy, most of the events were of grade 1 or grade 2 severity and all the events resolved.

Serious adverse event/deaths/other significant events

Serious adverse events

Table 21: Proportion of patients in each arm reporting the PTs for Serious AEs and Severe (grade 3+ events)

	SoC Arm, N=151	BPaLM Arm, N=151	BPaL Arm, N=122

PT	SAEs n(%)	Grade 3 AEs n(%)	SAEs n(%)	Grade 3 AEs n(%)	SAEs n(%)	Grade 3 AEs n(%)
Blood and Lymphatic disorders						
Anaemia	6(4.0%)	7 (4.6%)	1 (0.7%)	5 (3.3%)		1 (0.8%)
Leukopenia		1 (0.7%)				
Neutropenia		3 (2.0%)		3 (2.0%)		1 (0.8%)
Polycythaemia					1 (0.8%)	
Thrombocytopenia	1 (0.7%)				1 (0.8%)	
Ear and labyrinth disorders						
Cerumen impaction				1 (0.7%)		
Deafness/ Hypoacusis	1 (0.7%)			1 (0.7%)		2 (1.7%)
Deafness bilateral	1 (0.7%)					
Gastrointestinal disorders						
Dyspepsia		1 (0.7%)				
Nausea	1 (0.7%)					
Pancreatitis/ Pancreatitis acute	3 (2.0%)		1 (0.7%)			
Pancreatitis chronic				1 (0.7%)		
Vomiting	2 (1.3%)	1 (0.7%)				
General disorders and administration site conditions						
Asthenia	1 (0.7%)					
Cardiac death	1 (0.7%)					
Fatigue	1 (0.7%)					
General physical health deterioration	1 (0.7%)					
Pyrexia		1 (0.7%)		1 (0.7%)		
Sudden death	1 (0.7%)					
Hepatobiliary disorders						
Cholecystitis acute					1 (0.8%)	
Cholelithiasis	1 (0.7%)					
Immune system disorders						
Hypersensitivity			1 (0.7%)		1 (0.8%)	
Immune reconstitution inflammatory syndrome			1 (0.7%)			
Infections and infestations						
Tuberculosis			1 (0.7%)			
COVID-19	2 (1.3%)				1 (0.8%)	
Gastroenteritis	1 (0.7%)					
Herpes zoster		1 (0.7%)				
Immune reconstitution inflammatory syndrome		1 (0.7%)				
Lower respiratory tract infection	1 (0.7%)				1 (0.8%)	
Meningitis					1 (0.8%)	
COVID 19 Pneumonia	1 (0.7%)	1 (0.7%)				

Pneumonia					1 (0.8%)	
Pulmonary tuberculoma	1 (0.7%)					
Salpingo-oophoritis	1 (0.7%)					
Sinusitis	1 (0.7%)					
Nosocomial infection		1 (0.7%)				
Injury, poisoning and procedural complications						
Fall						1 (0.8%)
Head injury						1 (0.8%)
Hip fracture			1 (0.7%)			
Radius fracture	1 (0.7%)					
Road traffic accident	1 (0.7%)					
Stab wound	1 (0.7%)					
Investigations						
ALT increased	1 (0.7%)	4 (2.6%)	1 (0.7%)	2 (1.3%)	1 (0.8%)	1 (0.8%)
AST increased	1 (0.7%)	9 (6.0%)		9 (6.0%)		1 (0.8%)
Blood creatinine increased		1 (0.7%)		1 (0.7%)		
Blood magnesium decreased		1 (0.7%)				
CD4 lymphocytes decreased		2 (1.3%)				
Creatinine renal clearance decreased		7 (4.6%)		5 (3.3%)		3 (2.5%)
Electrocardiogram QT prolonged	6 (4.0%)	8 (5.3%)		1 (0.7%)		
Electrocardiogram ST-T change						1 (0.8%)
Electrocardiogram T wave abnormal	1 (0.7%)					
GGT increased		3 (2.0%)		2 (1.3%)		
Hepatic enzyme increased		3 (2.0%)		3 (2%)		1 (0.8%)
Lipase increased		1 (0.7%)		2 (1.3%)		7 (5.7%)
Lymphocyte count decreased		1 (0.7%)		2 (1.3%)		1 (0.8%)
Transaminases increased	1 (0.7%)	1 (0.7%)		2 (1.3%)	1 (0.8%)	
Weight decreased		1 (0.7%)				
Platelet count decreased					1 (0.8%)	
Metabolism and nutrition disorders						
Diabetes mellitus inadequate			1 (0.7%)			
Hypercalcaemia		1 (0.7%)				
Hyperglycaemia		1 (0.7%)				2 (1.6%)
Hyperkalaemia		1 (0.7%)				
Hypokalaemia	1 (0.7%)	2 (1.3%)				
Obesity						1 (0.8%)
Musculoskeletal and connective tissue disorders						
Arthralgia					1 (0.8%)	
Arthritis		1 (0.7%)				
Costochondritis	1 (0.7%)					

Myalgia				1 (0.7%)		
Vascular disorders						
Embolism venous	1 (0.7%)					
Neoplasms benign, malignant and unspecified (including cysts, polyps)						
Bladder cancer					1 (0.8%)	
Lung neoplasm			1 (0.7%)			
Thyroid cancer					1 (0.8%)	
Nervous system disorders						
Neuropathy peripheral		2 (1.3%)				
Seizure	1 (0.7%)				1 (0.8%)	
Syncope	1 (0.7%)	2 (1.3%)		1 (0.7%)		
Pregnancy, puerperium and perinatal conditions						
Abortion threatened			1 (0.7%)		1 (0.8%)	
Morning sickness			1 (0.7%)			
Psychiatric disorders						
Alcoholism					1 (0.8%)	
Anxiety			1 (0.7%)			
Completed suicide	1 (0.7%)					
Depression		1 (6.7%)				1 (0.8%)
Major depression						1 (0.8%)
Psychotic disorder/ Acute psychosis	1 (0.7%)					
Substance-induced psychotic	1 (0.7%)					
Suicide attempt	1 (0.7%)				1 (0.8%)	
Renal and urinary disorders						
Acute kidney injury	1 (0.7%)	1 (0.7%)	1 (0.7%)			1 (0.8%)
Calculus urinary					1 (0.8%)	
Nephrolithiasis					1 (0.8%)	
Urinary tract infection						1 (0.8%)
Respiratory, thoracic and mediastinal disorders						
Dyspnoea	1 (0.7%)					
Haemoptysis	1 (0.7%)				1 (0.8%)	
Pulmonary tuberculosis			1 (0.7%)			
Skin and subcutaneous tissue disorders						
Dermatitis allergic/Urticaria	1 (0.7%)					
Pruritus		1 (0.7%)				
Cardiac disorders						
Acute myocardial infarction					1 (0.8%)	

N : number of patients in each arm.

n(%) : number of patients reporting serious adverse events and grade 3 events in each arm with percentages.

Few patients in each arm reported more than one event.

Deaths

In total, 13 patients died during the trial until week 108. No patients died in the BPaLM group (see table below).

Table 22: Deaths at week 108 (as treated population)

Study site	Cause of death	On Rx, during F/U, post discontinuation	Treatment related	TB-PRACTECAL Arm
UZ-01	Enterocolitis	Post discontinuation	No	SoC
UZ-01	Seizure	During follow-up	No	BPaL
UZ-01	Not related to study	On treatment	Yes	SoC
SA-03	Pancreatitis acute	Post discontinuation	Yes	SoC
BY-02	Sudden cardiac death	On treatment	Yes	SoC
UZ-04	COVID-19 pneumonia	On treatment	No	SoC
UZ-01	Pneumonia	Post discontinuation	No	BPaLC
SA-03	Chronic obstructive pulmonary disease	During follow-up	No	BPaLC
SA-03	Not related to study	During follow-up	No	SoC
BY-02	Sudden death	On treatment	Yes	SoC
SA-06	Pancreatitis acute	On treatment	Yes	SoC
SA-06	Lower respiratory tract infection	During follow-up	No	BPaL
UZ-04	COVID-19	Post discontinuation	No	SoC

Of the six deaths, four were considered related to treatment of SoC (sudden cardiac death, sudden death, acute pancreatitis, and suicide) and two were not related. Of the four deaths in investigational arms, two each in BPaLC and BPaL arms, all were not related to treatment (Seizure and lower respiratory tract infection in BPaL arm and Pneumonia and chronic obstructive pulmonary disease in BPaLC arm).

Treatment-Emergent AESIs

Information on AESIs by category, treatment arm and characteristics is provided in the below table.

Hepatotoxicity ≥grade 3

A total of 43 patients reported hepatotoxicity ≥grade 3, with 17 in the SoC arm, 13 in the BPaLM arm, and 6 in the BPaL arm. Out of the 43 patients, the AE was possibly related to the treatment drugs in 32 patients. Outcome was resolved in 31 patients, 13 in the SoC arm, 7 in the BPaLM arm, 6 in the BPaLC arm, and 5 in the BPaL arm. Grade 4 hepatoxicity was observed in one patient each in the BPaLM treatment group.

QT prolongation ≥grade 3 and sudden deaths.
A total of 22 patients reported QT prolongation ≥grade 3 and sudden deaths, with 15 in the SoC arm, 2 in the BPaLM arm, 2 in the BPaLC arm, and 3 in the BPaL arm. Out of the 15 patients, the AE was possibly related to the treatment drugs in 19 patients. Outcome was resolved in 16 patients, 15 in the SoC arm, 1 in the BPaLM arm, and 2 in the BPaL arm. Grade 4 QT prolongation was observed in four patients in the SoC arm.

Any grade of pancreatitis
A total of 16 patients reported any grade of pancreatitis, with 5 in the SoC arm, 3 in the BPaLM arm, and 4 in the BPaL arm. Out of the 16 patients, the AE was possibly related to the treatment drugs in 11 patients. Outcome was resolved in 13 patients, 3 in the SoC arm, 3 in the BPaLM arm, and 3 in the BPaL arm. Grade 4 pancreatitis was observed in two patients in the BPaLM arm, 1 in the BPaLC arm, 1 in the BPaL arm and 3 in the SoC arm.

Any grade of seizures and fainting: Vasovagal syncope and Seizure
A total of 9 patients reported any grade of seizures and fainting, with 4 in the SoC arm, 2 in the BPaLM arm, and 1 in the BPaL arm. Out of the 9 patients, the AE was possibly related to the treatment drugs in 4 patients. Outcome was resolved in 8 patients, 4 in the SoC arm, 2 in the BPaLM arm, and 2 in the BPaLC arm. Only one patient in BPaL arm had grade 4 AE. None of the events were associated with any other cardiac event.

Other grade 3 dysrhythmias
A total of 3 patients reported grade 3 dysrhythmias, with 1 in the SoC arm and 2 in the BPaL arm. The AE was possibly related to the treatment drugs in one patient in the BPaL arm. Outcome was resolved in all patients.

Any grade cataract and optic neuritis
Cataract was observed in one patient in the BPaLM group and was assessed as related to the study drug the event resolved. Optic neuritis was not observed in any arm. Grade 4 AEs which are not SAEs, Anaemia, Neutropenia, Depression, and Hypercalcaemia were observed in 7 patients, with 4 in the SoC arm, and 1 in the BPaL.

Myelotoxicity
Events of anaemia, leukopenia and neutropenia were reported with higher numbers in all the groups, other events like, haemoglobin decreased, neutrophil count decreased, platelet count decreased, white blood cell count decreased and thrombocytopenia were reported with lower frequency in single digits. In SoC, events of anaemia, leukopenia and neutropenia were reported with frequency of 59, 63 and 24 events respectively. In BPaLM events of anaemia, leukopenia and neutropenia were reported with frequency of 31, 63 and 46 events respectively. In BPaL events of anaemia, leukopenia and neutropenia were reported with frequency of 20, 43 and 21 events respectively. Out of all the myelotoxicity events, 79.3% resolved in SoC, 87.1% resolved in BPaLM arm, 80% resolved in BPaLC arm and 80.9% resolved in BPaL arm. More than 50% of the events in all arms were grade 1. 20 to 25% were grade 2 in all arms of SoC, BPaLM and BPaL, and 54.3% in BPaLC arm. Grade 3 and 4

events were reported in all arms: SoC (20.8%), BPaLM (14.5%) and BPaLC (8.6%), except in the BPaL arm were grade 3 (6.4%) events were reported but no grade 4 events.

Table 23: Number of participants with AESIs by category, treatment arm and characteristics

AESI Category	BPaLM (151)	BPaL (122)	SoC (151)	Total
Hepatotoxicity ≥grade 3	**13**	**6**	**17**	**43**
Post study discontinuation	1	1	2	6
Serious adverse event	1	2	2	8
Maximum grade 4	1			2
Outcome: resolved	7	5	13	31
Possibly related to study drugs	6	4	16	32
Viral hepatitis	2	1	1	6
Alcohol	8	4	7	23
Other related drugs	4			5
QT prolongation ≥grade 3 & sudden deaths	**2**	**3**	**15**	**22**
Post study discontinuation	1	3	3	7
Serious adverse event	1	2	8	11
Maximum grade 4			4	4
Outcome: resolved	1	2	11	16
Possibly related to study drugs	2		15	19
Electrolytes imbalance			3	4
Alcohol		1	2	3
Hypothyroidism			2	2
Other related drugs		1	2	3
Any grade of pancreatitis	3	4	5	16
Post study discontinuation			1	2
Serious adverse event	1		4	5
Maximum grade 4	2	1	3	7
Outcome: resolved	3	3	3	13
Possibly related to study drugs	2	2	4	11
Clinical manifestation	1		3	5
Alcohol	1	2	1	4
Any grade of seizures and fainting	2	1	4	9
Post study discontinuation	1			1
Serious adverse event		1	2	3
Maximum grade 4		1		1
Outcome: resolved	2		4	8
Possibly related to study drugs	1		2	4
Associated cardiac event				0
Vasovagal syncope	2		2	6
Seizure		1	1	2

Peripheral neuropathy ≥grade 3			**2**	**3**
Post study discontinuation				1
Serious adverse event				0
Maximum grade 4				0
Outcome: resolved				0
Possibly related to study drugs			2	3
HIV+			1	1
Alcohol				1
Diabetes				0
Other related drugs				1
All grade 4 AEs which are not SAEs		**2**	**4**	**7**
Post study discontinuation				0
Outcome: resolved		2	3	6
Possibly related to study drugs		1	2	4
Anaemia			2	2
Neutropenia			1	2
Depression		2		2
Hypercalcaemia			1	1
Other grade 3 dysrhythmias		**2**	**1**	**3**
Post study discontinuation		1	1	2
Serious adverse event		1	1	2
Maximum grade 4				0
Outcome: resolved		2	1	3
Possibly related to study drugs		1		1
Clinical manifestation				0
Any grade cataract	**1**			**1**
Post study discontinuation				0
Serious adverse event				0
Maximum grade 4				0
Outcome: resolved				0
Possibly related to study drugs	1			1
Elderly				0
Any grade optic neuritis				**0**

Laboratory findings

Liver dysfunction

A summary of liver dysfunction AEs is presented in the below table.

Table 24: Summary of all events-both related and unrelated, by arm

	SoC N=151	**BPaLM N=151**	**BPaL N=122**	**Total 550**

Total number of patients who experienced the AEs	93 (61.5%)	71 (47%)	69 (56.5%)	307
Preferred Level Term				
Alanine aminotransferase	69	60	48	244
Aspartate aminotransferase	118	78	80	351
Gamma-glutamyltransferase	6	4	2	14
Hepatic Transaminases	23	13	19	76
Transaminase increased	5	7	6	19

Hepatotoxicity

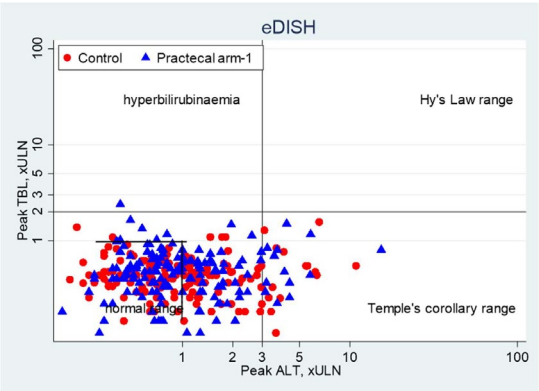
Hepatotoxicity of grade 4 was observed in one patient each in the BPaLM and BPaLC groups. Hepatotoxicity ≥ Grade 3 was observed in 17 patients receiving SoC, 13 patients receiving BPaLM, 7 patients receiving BPaLC, and 6 patients receiving BPaL.

Causality was identified in a total of 32 patients: 16 in those receiving SoC, 6 patients receiving BPaLM, 6 patients receiving BPaLC, and 4 patients receiving BPaL. Grade 4 Hepatoxicity was observed in one patient in the BPaLM group.

Hy's law assessment

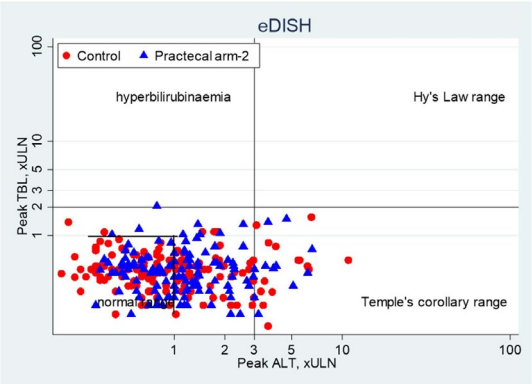
e-DISH plots are presented below. This analysis followed standard regulatory methodology for identifying potential Hy's Law cases.

Figure 3: eDISH tool, as-treated population by week 72, standard of care versus BPaLM



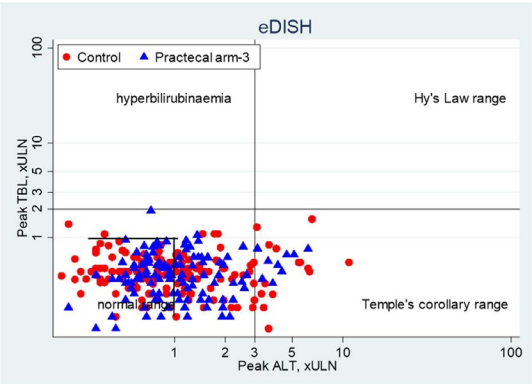
*control – standard of care; Practecal arm-1 – BpaLM

Figure 4: eDISH tool, as-treated population by week 72, standard of care versus BPaLC



*control – standard of care; Practecal arm-2 – BPaLC

Figure 5: eDISH tool, as-treated population by week 72, standard of care versus BPaL



*control – standard of care; Practecal arm-3 – BPaL

Haematology

Table 25: The frequency of nadir haemoglobin test results in TB-PRACTECAL

Hb levels	(LLN to 9.5]	(9.5 to 8.0]	(8.0 to 6.5]	<6.5
Standard care arm	57 (65.5%)	16 (18.4%)	8 (9.2%)	6 (6.9%)
BPaLM	47 (78.3%)	7 (11.7%)	6 (10.0%)	0 (0.0%)
BPaL	37 (78.7%)	7 (14.9%)	3 (6.4%)	0 (0.0%)

88.5% patients out of the 550 had neutrophil levels (LLN to 1.00), 7.1% patients had neutrophil levels (1.0 to 0.75), 3.3% patients had neutrophil count (0.75 to 0.50), and 1.1% patient had count of <0.50. One patient in the SoC arm and 1 patient in the BPaL arm had neutrophil count of <0.50.

74.1% patients out of the 550 had lymphocyte count (LLN to 0.8), 22.7% patients had lymphocyte levels (0.8 to 0.5), 3.1% patients had lymphocyte count (0.5 to 0.2).

93.6% patients out of the 550 had platelet count (LLN to 75], 22.7% patients had platelet levels (75 to 50), 3.1% patients had platelet count (50 to 75).

ECG

QTcF at 24 weeks was 440.9 msec in the SoC arm in 96 patients, 425.1 msec in the BPaLM in 128 patients (RR [max-min]; -17.5 [-22.0 to -12.9]), 436.3 msec in the and 421.8 msec in the BPaL arm in 99 patients (-21.1 [-25.6 to -16.6]).

Treatment emergent increases in QTc

Treatment emergent increases in QTc from baseline of >30 and >60 ms in the SoC, BPaLM and BPaL arms are shown in Table 26.

Table 26: Patients with QTc from baseline to >30 and >60 in SoC, BPaLM and BPaL

Treatment Arms	**SoC**	**BPaLM**	**BPaL**
Number patients per arm*	N=151	N=151	N=122
Patient's data available for each arm	96	128	99
Number of Patients >30	78 (81.3%)	57 (44.6%)	32 (32.3%)
Number of Patients >60	17 (17.8%)	4 (3.1%)	2 (2.0%)
Number of patients with absolute on treatment values 460-499	18 (18.8%)	6 (4.7%)	1 (1.0%)
Number of patients with Absolute on treatment values >500	none	1 (0.8%)	None

*Intent to treat population

Arrythmias

For ventricular dysrhythmias, High Level Terms of supraventricular arrhythmias and ventricular arrhythmias, and PTs like arrhythmia supraventricular and supraventricular tachycardia were considered.

A total of 38 patients reported events related to ventricular dysrhythmias, of whom 22 experienced related AEs. Among these, six patients across all three treatment arms had grade 2 events, while the remaining had grade 1 events; all events resolved.

In the SoC arm, 12 patients reported related events, including supraventricular extrasystoles in four patients, sinus tachycardia in three patients, sinus bradycardia in two patients, and one patient each with supraventricular tachycardia, ventricular arrhythmia, and ventricular extrasystole. All events were resolved in this arm.

In the BPaLM arm, six patients reported related events, including sinus bradycardia in three patients, and one patient each with supraventricular extrasystole, ventricular extrasystole, sinus arrhythmia, and supraventricular arrhythmia. Notably, one patient experienced both sinus bradycardia and supraventricular arrhythmia. All events in this arm were resolved.

In the BPaL arm, four patients reported related events, with one patient each experiencing sinus bradycardia, sinus tachycardia, supraventricular tachycardia, and supraventricular extrasystole; all events resolved also in this arm.

Table 27: Dysrhythmias reported in the study for SoC, BPaLM and BPaL

PT	**Sub No. ****	**Arm**	**Grade**	**Relation**
Arrhythmia supraventricular	-	BPaL	1	NR
	-	BPaLM	1	R
	-	BPaLM	2	NR
	-	BPaLM	1	NR
	-	SoC	1	R
	-	BPaL	2	R

PT	Sub No. **	Arm	Grade	Relation
Bradycardia/ Sinus Bradycardia	-	BPaL	1	NR
	-	BPaL	1	NR
	-	BPaL	1	NR
	-	BPaL	1	R/NR
	-	BPaLM	1	R
	-	BPaLM	1	NR
	-	BPaLM	2	R
	-	BPaLM	1	R
	-	BPaLM	1	NR
	-	SoC	1	NR
	-	SoC	1	R
	-	SoC	1	R
Sinus Arrhythmia	-	BPaLM	2	R
Sinus Tachycardia/ Tachycardia/ Supra Ventricular Tachycardia	-	BPaL	1	R
	-	BPaL	1	R
	-	BPaL	1	NR
	-	BPaLM	1	NR
	-	BPaLM	1	NR
	-	SoC	1	NR
	-	SoC	1	R
	-	SoC	1	R
	-	SoC	1	R
	-	SoC	2	NR/R
Ventricular extrasystoles/ Supraventricular extrasystoles	-	BPaL	1	R
	-	BPaL	1	NR
	-	BPaLM	1	R
	-	BPaLM	2	R
	-	BPaLM	1	NR
	-	SoC	2	R
	-	SoC	1	R
	-	SoC	1	R
	-	SoC	2	R
	-	SoC	1	NR
	-	SoC	1	NR
	-	SoC	2	R

*Two patients, one in SoC (Sinus tachycardia) and one in BPaL arm (Bradycardia/ sinus bradycardia) reported 3 events each of dysrhythmia out which 2 events were not related in both the subjects and 1 event related in both the subjects. In SoC arm subject grade 2 event tachycardia was reported and event resolved. In BPaL arm grade 1 event of bradycardia/sinus bradycardia was reported and the event resolved.

** Subject numbers not included for protection of personal data.

Safety in special populations

Pregnancy

Table 28: Pregnancy and DR-TB treatment outcomes in the as treated safety population

Characteristics	TB-PRACTECAL
Number of pregnant women	16
Median (min-max) days on DR-TB treatment at pregnancy start	329 (104-727)
DR-TB treatment outcome assigned	7
Favourable	7 (100%)

Unfavourable	0
Known pregnancy outcomes	14
Number of live births	10
Number of low-birthweight neonates	0
- *	3
- *	1
* Information not included for protection of personal data	

2.5.1. Discussion on clinical safety

The clinical safety of treatment up to 26 weeks with bedaquiline, pretomanid and linezolid was previously described and is compatible with a positive benefit risk balance for the treatment of pulmonary tuberculosis. The present application concerns the addition of moxifloxacin to this combination.

Hepatotoxicity was dose-limiting in the development of pretomanid. Appropriate monitoring is described in the SmPC.

Linezolid treatment for a longer duration (as for TB) may cause myelosuppression, peripheral- and optic neuropathy, as well as lactic acidosis. QT-prolongation is associated with bedaquiline and the BPaL regimen.

Moxifloxacin is known to cause QT prolongation, and may rarely cause, e.g., hepatotoxicity, severe skin reactions and seizures (see Avelox SmPC).

The safety population to support the addition of moxifloxacin to the previously approved BPaL regimen consists of 151 patients in the SoC group, 122 in the BPaL group and 151 in the BPaLM group. The size of the safety population was large enough to detect very common and common AEs but limited for the purpose of detecting uncommon, rare and very rare AEs.

Imbalances between the BPaL and BPaLM arms with a disadvantage for BPaLM treatment were observed for the PTs oral candidiasis (2.6 % in the BPaLM arm versus 0% in the BPaL arm), vulvovaginal candidiasis (4 versus 2.5%), tremor (7.9 versus 3.3%), nausea (32.5 versus 12.3%), vomiting (24.5 versus 9.8%), dyspepsia (15.9 versus 10.7%), ECG QT prolonged (31.1 versus 23.8%), anaemia (17.2 versus 11.5%), neutropenia (17.2 versus 13.1%), thrombocytopenia (4.6 versus 2.5%) and blood creatinine increased (18.5 versus 13.1%).

Grade 3+ events and SAEs

At 72 weeks, grade ≥3 or SAE were observed in 47.7% of patients in the SoC arm, 22.5% patients in the BPaLM arm and 23.8% patients in the BPaL arm.

Imbalances between BPaLM treatment and BPaL treatment with a disadvantage for BPaLM treatment were observed for hepatic disorders (17 events; 11.2% in the BPaLM arm versus 5 events; 4% in the BPaL arm), as well as cardiac disorders (2 events; 1.32% versus 0 events).

In total, 13 patients died during the trial until week 108. No patients died in the BPaLM group. Two deaths occurred in the BPaLC group (one post discontinuation and one during follow-up), and two in the BPaL group (both during follow-up).

Adverse events of special interest

Treatment emergent AESIs include hepatotoxicity, QTc prolongation, pancreatitis, seizures and fainting.

A total of 43 patients reported hepatotoxicity grade 3, with 17 in the SoC arm (11.3%), 13 in the BPaLM arm (8.6%), and 6 in the BPaL arm (4.9%). Grade 4 hepatoxicity was observed in one patient each in the BPaLM (0.66%) and BPaLC arm (0.79%) each. None of the patients did however fulfil Hy´s law criteria in any of the treatment arms.

The grading system for QT-prolongation (boxes from left to right is grade 1 through 4 is as follows:

Average QTcF 450 - 480 ms	Average QTcF 481 - 500 ms	Average QTcF >= 501 ms without signs/symptoms of serious arrhythmia	Average QTcF >= 501 or >60 ms change from baseline and one of the following: Torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious

A total of 22 patients reported QT prolongation ≥grade 3 and sudden deaths, with 15 in the SoC arm (9.9%), 2 in the BPaLM arm (1.32%), 2 in the BPaLC arm (1.59%), and 3 in the BPaL arm (1.99%). Grade 4 QT prolongation was observed in four patients in the SoC arm (2.65%).

A total of 16 patients reported any grade of pancreatitis, with 5 in the SoC arm (3.3%), 3 in the BPaLM arm (1.99%), 4 in the BPaLC arm (3.2%), and 4 (3.28%) in the BPaL arm.

A total of 9 patients reported any grade of seizures and fainting, with 4 in the SoC arm (2.65%), 2 in the BPaLM arm (1.32%), 2 in the BPaLC arm (1.59%), and 1 in the BPaL arm (0.82%). Out of the 9 patients, the AE was possibly related to the treatment drugs in 4 patients. Only one patient in BPaL arm had a grade 4 AE. None of the events were associated with any other cardiac event.

Cataract was observed in one patient in the BPaLM group and was assessed as related to the study drug the event resolved. Optic neuritis was not observed in any arm.

ADR methodology

Regarding ADR methodology as a basis for the SmPC section 4.8., the MAH based the assessment for this SmPC update on Pretomanid and then applied the AE dataset from TB-PRACTECAL study, where all the subjects who had been treated in BPaLM and BPaL arms of TB-PRACTECAL study (24 weeks) were included in the assessment. Only those AEs that were considered at least possibly related to BPaLM and BPaL regimen as assessed by the investigators, were included. Several ADRs collapsed to one medical concept and frequency was assigned based on the collapsed term's frequency.

The ADR methodology is based on the investigator assessment of possible causality. This is acceptable given the difficulties of isolating AEs with respect to causality to a specific drug, as well as the fact that all components of treatment are well-known with previously described safety profiles.

2.5.2. Conclusions on clinical safety

Overall, the BPaLM regimen is tolerated to the same extent as the previously approved BPaL combination and is generally better tolerated than the SoC comparator.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Update of the Product information

The CHMP adopted a broadening and update of the indications of Dovprela as follows:

> "Dovprela is indicated in combination with bedaquiline, linezolid and moxifloxacin for the treatment of adults with pulmonary TB due to *M. tuberculosis* resistant to rifampicin, with or without resistance to isoniazid.
>
> Dovprela is indicated in combination with bedaquiline and linezolid for the treatment of adults with pulmonary TB due to *M. tuberculosis* resistant to rifampicin and a fluoroquinolone, with or without resistance to isoniazid.
>
> Consideration should be given to official guidance on the appropriate use of antibacterial agents."

As a consequence of this broader and updated indications, sections 4.2, 4.4, 4.8 and of the SmPC have been updated. The Package Leaflet has been updated accordingly.

In addition, the list of local representatives in the PL has been revised.

2.6.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

The MAH has confirmed that the proposed Common Package Leaflet for Dovprela is comparable with the current approved Common Package Leaflet in content, design and layout. It is considered that the added information is similar in content, structure and wording to what is stated in the currently approved package leaflet.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Dovprela (pretomanid) is presently indicated in combination with bedaquiline and linezolid for the treatment of pulmonary tuberculosis resistant to all of isoniazid, rifampicin, a fluoroquinolone and a second line injectable antibacterial drug; and for patients with MDR-TB (resistance to rifampicin and isoniazid) that are intolerant or non-responsive to standard therapy.

The MAH is seeking an extension of indication adding moxifloxacin to this treatment regimen, and to also cover patients with only rifampicin resistance; that is, for patients for whom the standard first line

6 months isoniazid/rifampicin-based regimen is not suitable. Moreover, the MAH is proposing to broaden the existing indication for patients with rifampicin, isoniazid and fluoroquinolone resistance, to cover patients with rifampicin- and fluoroquinolone resistance regardless of isoniazid resistance status.

3.1.2. Available therapies and unmet medical need

Until recently, treatments included the use of four to seven drugs. Presently the WHO recommends a six-month regimen including bedaquiline, pretomanid, linezolid and moxifloxacin for these patients (BPaLM), use for which the MAH is seeking approval in this procedure.

3.1.3. Main clinical studies

TB-PRACTECAL was conducted from 2017-2023 in Belarus, Uzbekistan and South Africa. Patients eligible for inclusion in the trial had pulmonary tuberculosis, were 15 years of age or above, and could be HIV positive or negative. Their mycobacteria were deemed resistant to at least rifampicin by either molecular or phenotypic drug susceptibility testing. Moreover, there should be no known resistance to bedaquiline, pretomanid, delamanid or linezolid.

Apart from rifampicin resistance, mycobacteria were mostly resistant to isoniazid. Resistance to other agents was also common, with approximately 20-30% exhibiting resistance to kanamycin and/or moxifloxacin.

The study primarily compared the BPaLM combination for 24 weeks with WHO SoC treatments not including pretomanid. Longer SoC regimens (>72 weeks) were used by approximately 70% of patients in the control arm; these mostly included bedaquiline, linezolid and/or clofazimine.

The primary objective of stage 2 was to demonstrate the efficacy of BPaLM using a NI comparison to SoC with an NI margin of 12%. This is not based on any calculations of retention of the effect with a given substitution. Rather, it is pragmatically grounded in what might be considered relevant with respect to clinical equivalence.

On the recommendation of the DSMB, the trial was stopped for efficacy on 18 March 2021, after an unplanned analysis, conducted by request of the board.

143 patients in the SoC group and 138 in the BPaLM group were included in the mITT population (rifampicin resistant). Further to that, six participants in the SoC group switched to the BPaLM group after enrolment was terminated, and these participants were not included in the primary analysis.

3.2. Favourable effects

At week 72, 41% of participants in the SoC group and 12% in the BPaLM group met criteria for the unfavourable outcome (unadjusted risk difference −29·2 percentage points [96·6% CI −39·8 to −18·6]. Thus, 88% of patients treated with the BPaLM regimen had a favourable outcome.

The main reason for meeting the unfavourable outcome definition was early discontinuation (89% of 56 participants with unfavourable outcomes in the SoC group and 69% of 16 in the BPaLM group), which was mainly attributed to AEs.

Results for the unfavourable outcome at 108 weeks in the mITT population were consistent with those for the primary outcome. Two disease recurrences had occurred by 108 weeks: one in the SoC group and one in the BPaLM group.

Culture conversion at week 12 was seen for 81.8% in the control arm and for 89.2% in the BPaLM arm.

3.3. Uncertainties and limitations about favourable effects

The study was stopped early for efficacy based on the results of an unplanned interim analysis. This means that the type-1 error is not controlled. This limitation could not be entirely resolved, but the MAH provided a plot of how the effect estimate (difference in risk) changed as the sample size increased. This plot showed that the effect estimate decreased as the sample size increased, which provided reassurance that the interim analysis was not a 'random high' (a good result just by chance).

The MAH claimed that the trial showed the superiority of BPaLM, as well as non-inferiority. The test of superiority was not pre-specified, as it was introduced in version 2.0 of the SAP, which was issued after the unplanned interim efficacy that led to early stopping. This issue was resolved by including only descriptive results in the SmPC.

The primary analysis is a composite of antimycobacterial efficacy and a tolerability endpoint (discontinuations). This is acceptable but represents a measure of "effectiveness" (clinical usefulness) rather than the relative efficacy of the regimens. It was not possible to estimate the efficacy of BPaLM by ignoring treatment discontinuations (a treatment-policy strategy) because patients were not followed up after treatment discontinuation.

3.4. Unfavourable effects

The clinical safety of treatment up to 26 weeks with bedaquiline, pretomanid and linezolid has been previously described and is compatible with a positive B/R for the treatment of tuberculosis. The present application concerns the addition of moxifloxacin to this combination.

Treatment emergent AESIs for the BPaLM regimen include hepatotoxicity, QTc prolongation, pancreatitis, seizures and fainting. A total of 43 patients reported hepatotoxicity ≥grade 3, with 17 in the SoC arm (11.3%), 13 in the BPaLM arm (8.6%), and 6 in the BPaL arm (4.9%). Grade 4 hepatoxicity was observed in one patient each in the BPaLM (0.66%) and BPaLC arms (0.79%).

A total of 22 patients reported QT prolongation ≥grade 3 (>500 ms) and sudden deaths, with 15 in the SoC arm (9.9%), 2 in the BPaLM arm (1.32%), 2 in the BPaLC arm (1.59%), and 3 in the BPaL arm (1.99%). Grade 4 QT prolongation was observed in four patients in the SoC arm (2.65%).

A total of 3 patients reported grade 3 dysrhythmias, with 1 in the SoC arm (0.66%) and 2 in the BPaL arm (1.64%). The AE was possibly related to the treatment drugs in one patient in the BPaL arm. Outcome was resolved in all patients.

Cataract was observed in one patient in the BPaLM group and was assessed as related to the study drug. The event resolved.

No patients died in the BPaLM group.

3.5. Uncertainties and limitations about unfavourable effects

The size of the safety population is large enough to detect very common and common AEs but limited for the purpose of detecting uncommon, rare and very rare AEs.

3.6. Effects Table

Table 29. Effects Table for pretomanid

Effect	Short description	Unit	BPaLM arm	Standard Care arm	Uncertainties / Strength of evidence	References
Favourable Effects						
Proportion with favourable outcome	Primary composite endpoint	%	88.3	59.1	Composite endpoint including both efficacy and tolerability components	Study TB-PRACTECAL
Effect	**Short description**	**Unit**	**BPaLM**	**BPaL**	**Uncertainties / Strength of evidence**	**References**
Unfavourable Effects						
Hepatotoxicity>Grade 3	Week 108	%	8.6	4.9		Study TB-PRACTECAL
QTc prolongation ≥ grade 3 (>500 ms)	Week 108	%	1.32	1.99		Study TB-PRACTECAL

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The efficacy of the BPaLM 24-week regimen in the studied population, with rifampicin-resistant TB (generally accompanied by isoniazid resistance as well as resistance to other agents), was demonstrated with an 88% rate of favourable outcomes. The regimen is obviously better tolerated and adhered to than the previous SoC consisting of 4-7 drugs used for at least 36 weeks. Consequently, the BPaLM regimen has been adopted as standard for such patients by the WHO.

Moreover, the MAH proposed to broaden the existing indication with BPaL without moxifloxacin for patients with rifampicin, isoniazid and fluoroquinolone resistance, to cover patients with rifampicin- and fluoroquinolone resistance regardless of isoniazid resistance status. This is in line with WHO guidance treating rifampicin-resistance and rifampicin-isoniazid resistance and omits the fluoroquinolone where this is not anticipated to be efficacious. This is acceptable.

The regimen has an acceptable safety profile, allowing for high cure rates. Key safety aspects when adding moxifloxacin to the previously approved BPaL regimen include additive hepatotoxicity and QT-prolongation with no signal of concern.

3.7.2. Balance of benefits and risks

The balance of benefits and risk is considered positive.

3.8. Conclusions

The overall B/R of Dovprela is positive in the approved indications.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends, by consensus, the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include in combination with bedaquiline, linezolid and moxifloxacin the treatment of adults with pulmonary tuberculosis (TB) due to Mycobacterium tuberculosis resistant to rifampicin, with or without resistance to isoniazid, for DOVPRELA and to update the current regimen, based on final results of the TB-PRACTECAL study; this is a randomised, controlled, open-label, phase II-III trial to evaluate the safety and efficacy of regimens containing bedaquiline and pretomanid for the treatment of adult patients with pulmonary multidrug resistant tuberculosis. As a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. In addition, the MAH took the opportunity to introduce minor editorial changes to the PI and to update the list of local representatives in the Package Leaflet.

Amendments to the marketing authorisation

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

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Dovprela is not similar to Deltyba within the meaning of Article 3 of Commission Regulation (EC) No. 847/200. See appendix 1.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion 'Dovprela-H-C-005167-EMA/VR/0000258124'.