EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

25 April 2024
EMA/318955/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Invented name: Sirturo

International non-proprietary name: bedaquiline

Procedure No. EMEA/H/C/002614/II/0056

Marketing authorisation holder (MAH): Janssen-Cilag International N.V.

Note

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

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List of abbreviations

AE	adverse event
AESI	adverse event of special interest
AFB	acid-fast bacilli
ALT	alanine aminotransferase
AM	amikacin
AR	assessment report
ART	antiretroviral therapy
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
BDQ	bedaquiline (also known as JNJ-16175328 and TMC207) is a diarylquinoline with in vitro activity against DS-TB and drug-resistant strains to all anti-TB drugs (INH, RMP, EMB, PZA, streptomycin, fluoroquinolones, injectables) either as monoresistance or resistant to several drugs
BMI	body mass index
BPaL	6-month treatment regimen composed of BDQ, PMD, and LZD (WHO 2022c) BPaLC treatment regimen composed of BDQ, PMD, LZD, and CFZ
BPaLM	6-month treatment regimen composed of BDQ, PMD, LZD, and MFX (WHO 2022c)
BR	background regimen (anti-TB medication used during the investigational and background treatment periods, excluding BDQ [or placebo])
C_{avg}	average plasma concentration
CD	cluster of differentiation
CDE	Center for Drug Evaluation
CFZ	clofazimine
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CMA	conditional marketing authorisation
CL/F	apparent total clearance
C_{max}	maximum plasma concentration
CS	cycloserine
C_{trough}	trough concentration
CYP3A4	cytochrome P450 3A4
CV	coefficient of variation
DAIDS	Division of Acquired Immunodeficiency Syndrome
DDI	drug-drug interaction
DLM	delamanid
DS	drug susceptible
DST	drug susceptibility test
EBE	empirical Bayes estimates
EC	European Commission
EC50	half maximal effective concentration
ECG	electrocardiogram
EFV	efavirenz
EMA	European Medicines Agency
EMB	ethambutol
EOT	end of treatment
ETO/ETH	ethionamide
EU	European Union
FDA	Food and Drug Administration

FM	fraction metabolised
FOCE	First-order conditional estimation
GCP	good clinical practice
GMR	geometric mean ratio
GOF	goodness-of-fit
HBV	hepatitis B virus
HIV	human immunodeficiency virus
HR	heart rate
HV	healthy volunteer
IDMC	independent data monitoring committee
ICH	International Council for Harmonisation
IIV	interindividual variability
INH	isoniazid
ITT	intent-to-treat
KM	kanamycin
LC-MS/MS	liquid Chromatography with tandem mass spectrometry
LFX	levofloxacin
LLOQ	lower limit of quantification
LOAEL	lowest-observed-adverse-effect level
LPV	lopinavir
LZD	linezolid
MTB/ M. tuberculosis	Mycobacterium tuberculosis
M2	*N*-monodesmethyl metabolite
MA	marketing authorisation
MAA	marketing authorisation application
MAH	marketing authorisation holder
MDR	multidrug-resistant
MedDRA	Medical Dictionary for Regulatory Activities
MFX	moxifloxacin
MGIT	mycobacteria growth indicator tube
MIC	minimal inhibitory concentration
mITT	modified intent-to-treat
mPP	modified per protocol
N	number of participants
N/A	not applicable
NCA	non-compartmental analyses
NI	noninferiority
NOAEL	no-observed-adverse-effect level
NRTIs	nucleoside reverse transcriptase inhibitors
NVP	nevirapine
OBJ	objective function value
OFL	ofloxacin
PBT	persistent bioaccumulative and toxic
PD	pharmacodynamic(s)
PEC	predicted environmental concentration
PI	product information
PIP	paediatric investigation plan
PMD	pretomanid

PNEC	predicted no effect concentration
PK	pharmacokinetic(s)
PopPK	population PK
PP	per protocol
pre-XDR	pre-extensively drug-resistant
PT	preferred term
PTO	prothionamide
PZA	pyrazinamide
QD	once daily
QRD	Quality Review of Documents
QTcF	QT interval corrected for heart rate using the Fridericia correction
RMP	rifampicin
RR/MDR	rifampicin-resistant or multidrug-resistant
RR	rifampicin-resistant
RSE	relative standard error
RTV	ritonavir
RUV	residual unexplained variability
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SIR	sampling importance resampling
SM	streptomycin
SmPC	Summary of Product Characteristics
SMQ	Standardized MedDRA Query
SOC	standard of care
STREAM	Evaluation of a Standard Treatment Regimen of Anti-tuberculosis Drugs for Patients with Multidrug-resistant Tuberculosis
TB	tuberculosis
tiw	3 times per week
T_{max}	time to reach the maximum plasma concentration
ULN	upper limit of normal
USA	United States of America
Vc/F	apparent volume of distribution of the central compartment
VPC	visual predictive checks
WHO	World Health Organization
XDR	extensively drug-resistant

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Janssen-Cilag International N.V. submitted to the European Medicines Agency on 7 November 2023 an application for a variation.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II, IIIA and IIIB

Extension of indications by removal of the restriction for use of SIRTURO, based on final results from study STREAM Stage 2; this is an multicenter, open-label, parallel-group, randomized, active-controlled study in participants aged 15 years or older with RR/MDR-TB to evaluate an investigational BDQ-containing, all-oral, 40-week regimen of anti-TB drugs (Regimen C) compared to an injectable-containing 40-week control regimen (Regimen B). Submission of the study fulfils SOB 007. As a consequence of the data emerging from the study, sections 2, 4.1, 4.2, 4.4, 4.5, 4.8, 4.9, 5.1, 5.2 and 5.3 of the SmPC are updated. In addition, section E of Annex II has also been updated to reflect fulfilment of the last outstanding Specific Obligation. The Labelling and Package Leaflet are updated in accordance. Version 10.1 of the RMP has also been submitted. Furthermore, the PI is brought in line with the latest QRD template version 10.3. As part of the application, the MAH is requesting the switch from a conditional MA to standard MA.

The variation requested amendments to the Summary of Product Characteristics, Annex II, Labelling and Package Leaflet and to the Risk Management Plan (RMP).

Information relating to orphan designation

Sirturo was designated as an orphan medicinal product EU/3/05/314 on 26th August 2005 in the following indication: Treatment of tuberculosis. The new indication, which is the subject of this application, falls within the above-mentioned orphan designation.

Sirturo was removed from the European Community (EC) register for orphan designated medicinal products on 7 March 2024.

Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0470/2022 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0470/2022 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 orphan medicinal products authorised at the start of the procedure.

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	7 November 2023
Start of procedure	25 November 2023
CHMP Rapporteur Assessment Report	19 January 2024
PRAC Rapporteur Assessment Report	19 January 2024
PRAC members comments	31 January 2024
PRAC Outcome	8 February 2024
CHMP members comments	
Updated CHMP Rapporteur Assessment Report	15 February 2024
Request for supplementary information (RSI)	22 February 2024
PRAC Rapporteur Assessment Report	2 April 2024
PRAC members comments	3 April 2024
CHMP Rapporteur Assessment Report	9 April 2024
PRAC Outcome	11 April 2024
CHMP members comments	15 April 2024
Updated CHMP Rapporteur Assessment Report	19 April 2024
CHMP Opinion	25 April 2024

2. Scientific discussion

2.1. Introduction

Sirturo received initial conditional marketing authorisation (CMA) in the European Union (EU) on 5th March 2014, with a later extension to the paediatric population, for the indication:

"SIRTURO is indicated for use as part of an appropriate combination regimen for pulmonary MDR-TB in adult and paediatric patients (5-<18 years of age and weighing ≥15 kg) when an effective treatment regimen cannot otherwise be composed for reasons of resistance or tolerability. Consideration should be given to official guidance on the appropriate use of antibacterial agents."

The main evidence for the efficacy of bedaquiline in the treatment of M. tuberculosis infection derived from the C208 study, in which patients with MDR- or pre-XDR pulmonary TB were randomised to receive bedaquiline or placebo as add on to an optimised background regimen. This study clearly demonstrated the antimicrobial activity of bedaquiline, with a shorter time to sputum conversion and an increased cure rate. However, the safety database was limited. There was a numerical excess in mortality in the bedaquiline arm, as well as concerns related to QT-prolongation and the impact of an increase in exposure, e.g., due to DDI with antiretrovirals. Thus, the data were deemed non-comprehensive, and a confirmatory Phase 3 study was required as a Specific Obligation, to provide additional efficacy and safety data and in particular to address remaining uncertainties relating to clinical safety. Additional data were also generated to address questions on pharmacokinetics, including drug-drug interactions (DDI).

With this type II variation application, the MAH submits the results from the confirmatory Phase 3 STREAM Stage 2 study, to fulfil the last outstanding Specific Obligation related to the EU Conditional Marketing Authorisation and to support updates to the conditions of Marketing Authorisation (including the switch to a standard marketing authorisation no longer subject to specific obligations), the Risk Management Plan and the Product Information (including the extension of the indication).

Data supporting other proposed changes to the Product Information are provided in the form of four population PK reports (STREAM / M2 metabolite / DDI / QT) and the results from a phase 1 Drug-Drug Interaction (DDI) study with clarithromycin (CYP3A4 inhibitor).

Since removal of the restriction would broaden the indication, an Environmental Risk Assessment has been submitted. The MAH also provided updated safety margins (animal/human ratios) based on human exposure data of BDQ and its major metabolite (M2) from the STREAM Stage 2 study.

The data from preceding Phase 2 trials (TMC207-C208 and TMC207-C209) have been assessed in previous regulatory procedures and are not extensively rediscussed here. Due to differences in the study populations, including extent of TB resistance, and composition and duration of study intervention (including BDQ), efficacy data from the Phase 2 studies and from the Phase 3 study STREAM Stage 2 have not been pooled, but a high-level summary is provided the discussion on clinical efficacy.

2.1.1. Problem statement

Disease or condition

Tuberculosis (TB), an infectious disease caused by *M. 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 rifampicin-resistant TB (RR-TB) and multi-drug resistant TB (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 USA.

Claimed therapeutic indication

The MAH asserts that the results of the Phase 3 study combined with evidence from published data related to BDQ support the switch to a standard marketing authorisation no longer subject to specific obligations and the removal of the current restriction of the indication: namely use "when an effective treatment regimen cannot otherwise be composed for reasons of resistance or tolerability". In addition, as the terminology MDR-TB is subject to changes in definition over time, it is proposed to replace the acronym for "MDR-TB" with the definition of the specific patient population by extent of resistance. The newly proposed indication is:

"*SIRTURO is indicated as part of combination therapy in adult (≥18 years) and paediatric patients (5-<18 years of age and weighing ≥15 kg) with pulmonary TB due to M. tuberculosis resistant to at least RMP and INH. Consideration should be given to official guidance on the appropriate use of antibacterial agents.*"

Other proposed minor updates to the Product Information are supported by new/additional data specifically relating to:

- Elderly and HIV-coinfected special populations.
- Black and African American patients.
- Co-administration with CYP3A4 inducers and inhibitors.
- Longer treatment duration in patients >15 years and older beyond 24 weeks if necessary.

Epidemiology

Globally in 2021, approximately 10.6 million people developed TB disease, with a much higher probability of developing TB disease in people also infected with HIV. In 2021, TB caused an estimated 1.4 million deaths among HIV-negative people and an additional 187,000 deaths among people living with HIV. The burden of disease is notably different between the EU and low- and middle-income countries. Indeed, 8 countries account for two-thirds of the global total of TB cases, namely India (28%), Indonesia (9.2%), China (7.4%), the Philippines (7.0%), Pakistan (5.8%), Nigeria (4.4%), Bangladesh (3.6%), and the Democratic Republic of the Congo (2.9%). An estimated 0.5 million older adolescents aged ≥15 to 19 years and 7.5 million children and adolescents aged <15 years become infected every year.

Roughly 5% of all notified TB cases are caused by *M. tuberculosis* strains that are resistant to at least RMP and INH (multidrug-resistant TB, MDR-TB) and are thus incurable with standard first-line treatment, requiring second-line drugs. Three countries accounted for 42% of global cases of MDR-TB in 2021: India (26%), the Russian Federation (8.5%) and Pakistan (7.9%). An estimated 25,000 to 32,000 children and young adolescents aged <15 years of age develop MDR-TB disease every year.

Management

Recommendations on management of MDR-TB have evolved since Sirturo was first granted Conditional Marketing Authorisation in the EU in 2014 and will continue to evolve in the future. The two most important classes of second-line anti-TB drugs were previously the injectable drugs (i.e., capreomycin and the aminoglycosides amikacin and kanamycin) and the fluoroquinolones. Whereas earlier WHO guidance recommended only conditional/ second-line use of BDQ in longer (≥18 months) regimens for the treatment of MDR-TB, the current WHO recommendation (2021) for the treatment of RR/MDR-TB patients is an all-oral 6-month regimen of BDQ, pretomanid (PMD), linezolid (LZD) and moxifloxacin (MFX) (abbreviated to BPaLM), omitting MFX in case of documented fluoroquinolone resistance. In the meantime, injectable antibiotics have fallen out of favour due to their comparatively problematic safety profiles (most notably the risk of irreversible hearing loss) and cumbersome administrative regimens.

2.1.2. About the product

Bedaquiline (BDQ) is marketed under the tradename Sirturo as 100-mg and 20-mg tablets and is approved in >70 countries/ territories worldwide.

BDQ is a first- and (still) only-in-class diarylquinoline anti-mycobacterial agent used as part of a combination therapy for MDR-TB due to Mycobacterium tuberculosis (M. tuberculosis). Bedaquiline has a unique mechanism of action involving specific inhibition of mycobacterial adenosine 5' triphosphate (ATP) synthase, which minimises the potential for cross-resistance with existing anti-TB drugs. In vitro testing has shown bactericidal activity against drug susceptible (DS), MDR, pre-extensively drug resistant (pre-XDR), and extensively drug resistant (XDR) strains of M. tuberculosis in the range of ≤0.008 to 0.25 µg/mL. Animal models indicate that bedaquiline is a sterilising agent that could significantly reduce the number of drugs and/or treatment duration required.

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

General guidance is available in the form of the 2017 revised CHMP *Addendum to the note for guidance on evaluation of medicinal products indicated for treatment of bacterial infections to specifically address the clinical development of new agents to treat disease due to Mycobacterium Tuberculosis* (EMA/CHMP/EWP/14377/2008 Rev 1).

Whilst the STREAM Stage 2 study was ongoing, the MAH sought informal discussions with EMA and the CHMP Rapporteur's assessment team in September 2017 and again in January 2018 in relation to the EU renewal procedure for Sirturo (EMEA/H/C/002614/R/0024). Specifically, in the face of recruitment difficulties and changes in the treatment landscape rendering two of four study treatment regimens untenable, the MAH sought feedback regarding the switch to a non-inferiority design (non-inferiority margin of 10%) for the STREAM Stage 2 study, with a primary analysis only between Regimens B and C (bedaquiline) and thus a reduced sample size of 200 participants per regimen. Superiority testing was to be a secondary analysis. This was agreed by both EMA and FDA, since the antimicrobial efficacy

of bedaquiline was already established and not in doubt. The study aim was to demonstrate the clinical usefulness of a regimen where oral bedaquiline replaces the injectable aminoglycoside.

In discussions with EMA in 2020 in relation to the EU renewal procedure for Sirturo (EMEA/H/C/002614/R/0045) further modifications to study follow up, specifically curtailment of efficacy data collection beyond Week 96, were agreed.

A summary of all major changes to the study protocol was provided.

Ongoing studies

Ongoing clinical studies with BDQ that do not form part of this submission are summarised below:

Table 1 Overview of Ongoing BDQ Studies in Treatment of RR/MDR-TB

Study Phase	Participants Enrolled	Participants Exposed to BDQ[a]	BDQ Dose	Population	References
2	Cohort 1 (≥12 to <18 years): 15	15	400 mg qd in Weeks 1 and 2; 200 mg tiw in Weeks 3 to 24	Adolescents and children with confirmed or probable MDR-TB	TMC207-C211[b] (Janssen-sponsored)
	Cohort 2 (≥5 to <12 years): 15	15	200 mg qd in Weeks 1 and 2; 100 mg tiw in Weeks 3 to 24		
	Cohort 3 (≥2 to <5 years): 11	11	8 mg/kg qd in Weeks 1 and 2; 4 mg/kg tiw in Weeks 3 to 24		
	Cohort 4 (0 months to <2 years): 0	0	To be determined		
4	118	52	Regimen 1: 400 mg qd for the first 2 weeks, 200 mg tiw (with at least 48 hours between doses) for remaining weeks (ie, 22 weeks or 38 weeks in case BDQ treatment is extended to 40 weeks)	Adults (18-65 years) with microbiologically confirmed pulmonary MDR-TB	TMC207TBC4006[c] (Janssen-collaborative-partner-sponsored)

[a] At the cutoff date (30 June 2023)
[b] At the cutoff date for this document (30 June 2023), Cohorts 1 and 2 were completed and Cohort 3 enrollment is ongoing.
[c] PROSPECT study, a postmarketing commitment for BDQ in China, is sponsored by IATB (Beijing, China) in collaboration with Janssen Research and Development, LLC and Xian Janssen Pharmaceutical Ltd.

2.2. Non-clinical aspects

2.2.1. Introduction

Since the indication would broaden by the proposed removal of the restriction, an Environmental Risk Assessment (ERA) has been prepared and is provided as part of this submission. The MAH also provided updated safety margins (animal/human ratios) based on human exposure data of BDQ and its major metabolite (M2) from the STREAM Stage 2.

No new nonclinical safety pharmacology, toxicology or non-clinical pharmacokinetic data were submitted.

2.2.2. Toxicology

Toxicokinetic data

Safety margins for a 6-month BDQ-containing treatment in human are calculated based on the 39-week (9-month) repeat-dose dog NOAEL (2 mg/kg/day) and the lowest dose of 5 mg/kg/day (LOAEL) in the 26-week (6-month) repeat-dose rat study. The exposures to BDQ and M2 in human at the end of Week 2 in the STREAM Stage 2 study were used as they represent the highest exposure in the clinical regimen and thus provide the most conservative assessment (Table 1). Of note: the exposure measures from STREAM Stage 2 on Week 2 were comparable to those observed in the Phase 2 TMC207-C208 study on Week 2 (BDQ/M2 $AUC_{0\text{-}24h}$ 43/9.4 µg.h/mL; C_{max} 3,3/0.45 µg/mL).

Safety margins based on the exposures in human at the end of Week 24 (BDQ/M2 $AUC_{0\text{-}24h}$ [$AUC0_{\text{-}168h}$ divided by 7] 23/5.3 µg.h/mL; C_{max} 1.8/0.23 µg.h/mL) are also provided (Table 3).

Table 2: Animal/Human Exposure Ratio at LOAEL/NOAEL in Animals and Based on the Exposure Data in Human After 2 Weeks of Treatment

Species	Study	Dose (mg/kg/day)		BDQ				M2			
				C_{max} (µg/mL)		Animal/Man Ratio		C_{max} (µg/mL)		Animal/Man Ratio	
		M	F	M	F	M	F	M	F	M	F
Rat	26-weeks	5 (LOAEL)		0.7	1.0	0.23	0.32	0.3	0.5	0.91	1.5
Dog	39-weeks	2 (NOAEL)		1.6	1.2	0.52	0.39	0.6	0.7	1.8	2.1
Human	STREAM Stage 2[a]	-		3.1		-	-	0.33		-	-
				$AUC_{0\text{-}24h}$ (µg.h/mL)		Animal/Man Ratio		$AUC_{0\text{-}24h}$ (µg.h/mL)		Animal/Man Ratio	
Rat	26-weeks	5 (LOAEL)		6.6	16.8	0.16	0.40	5.1	8.9	0.70	1.2
Dog	39-weeks	2 (NOAEL)		27.9	21.3	0.66	0.51	11.7	13.3	1.6	1.8
Human	STREAM Stage 2[a]	-		42		-	-	7.3		-	-

[a] Exposure data determined at the end of Week 2 of clinical trial STREAM Stage 2; [b] LOAEL
F = female; M = male

Table 3: Animal/Human Exposure Ratio at LOAEL/NOAEL in Animals and Based on the Exposure Data in Human After 24 Weeks of Treatment

Species	Study	Dose (mg/kg/day)		BDQ				M2			
				C_{max} (µg/mL)		Animal/Man Ratio		C_{max} (µg/mL)		Animal/Man Ratio	
		M	F	M	F	M	F	M	F	M	F
Rat	26-weeks	5 (LOAEL)		0.7	1.0	0.39	0.56	0.3	0.5	1.3	2.2
Dog	39-weeks	2 (NOAEL)		1.6	1.2	0.89	0.67	0.6	0.7	2.6	3.0
Human	STREAM Stage 2[a]	-		1.8		-	-	0.23		-	-
				$AUC_{0\text{-}24h}$ (µg.h/mL)		Animal/Man Ratio		$AUC_{0\text{-}24h}$ (µg.h/mL)		Animal/Man Ratio	
Rat	26-weeks	5 (LOAEL)		6.6	16.8	0.30	0.73	5.1	8.9	0.96	1.7
Dog	39-weeks	2 (NOAEL)		27.9	21.3	1.2	0.92	11.7	13.3	2.2	2.5

Human	STREAM Stage 2[a]		23	-	-	5.3	-	-

[a] Exposure data determined at the end of Week 24 of clinical trial STREAM Stage 2 (AUC_{0-24h} were calculated by dividing AUC_{0-168h} by 7); [b] LOAEL
F = female; M = male

The CHMP noted that exposure margins for a 6-month BDQ-containing treatment in human are calculated based on the exposure to BDQ and M2 at the 39-week (9-month) repeat-dose dog NOAEL (2 mg/kg/day) and at the lowest dose of 5 mg/kg/day (LOAEL) in the 26-week (6-month) repeat-dose rat study using the exposures to BDQ and M2 in human at the end of Week 2 in the STREAM Stage 2 study. The exposure at the end of Week 2 represent the highest exposure in the clinical regimen and thus provide the most conservative assessment. As the exposure at the end of Week 2 in the STREAM Stage 2 study (BDQ/M2 AUC_{0-24h} 42/7.3 µg.h/mL; C_{max} 3.1/0.33 µg/mL) are comparable or slightly lower to those observed in the Phase 2 TMC207-C208 study on Week 2 (BDQ/M2 AUC_{0-24h} 43/9.4 µg.h/mL; C_{max} 3.3/0.45 µg/mL) the exposure margins from the STREAM Stage 2 study are not lower than those based on the Phase 2 study. An update of section 5.3 of the SmPC is thus not considered necessary.

2.2.3. Ecotoxicity/environmental risk assessment

A full ERA, including Phase I and Phase II, tier A and B, was submitted and assessed for the initial marketing authorisation application MAA and subsequent extensions to the MAA. Using an unrefined market penetration factor (Fpen) and a bedaquiline dose of 400mg/day the predicted environmental concentration in surface water ($PEC_{surfacewater}$) was calculated to 2 µg/L. After refining Fpen and $PEC_{surfacewater}$ the risk quotents (ratio $PEC_{surfacewater}$/ $PNEC_{water}$) were below 1 and no risk was identified for any of the compartments. The substance bedaquiline is however classified as a PBT substance.

For this Type II variation, the applicant has provided an ERA with the purpose to determine if there has been a significant increase in the environmental exposure to bedaquiline after the conditional approval 2021 for the treatment of pulmonary MDR-TB in adult and paediatric patients 5 years to less than 18 years of age and weighing at least 15 kg that would justify an update to the previously submitted ERA. The current (2019) and updated (2023) estimates of Fpen and $PEC_{surfacewater}$ were presented.

Current exposure estimate for bedaquiline (2019)

The most current ERA version meeting the requirements of the EMA guideline on environmental risk assessment was submitted in 2019 in support of the conditional marketing authorisation (MA) of Sirturo (bedaquiline) for treatment of pulmonary multi-drug-resistant tuberculosis (MDR-TB) in adult and paediatric patients 5 years to less than 18 years of age and weighing at least 15 kg. The $PEC_{surfacewater}$ was calculated based on a refined Fpen.

Based on WHO 2018 data indicating that the member state with the highest prevalence of MDR in adult patients was Lithuania with a prevalence of 9.0 in 100000 and assuming a 100% market share for Sirturo, the applicant estimated the potential population of adult patients treated for MDR in the EU to 15,201.

To determine the number of potential paediatric patients in the EU, the applicant assumed that the potential population of paediatrics eligible for treatment with bedaquiline was 10% of the adult population (based on WHO Global Tuberculosis report 2018, that reported that Children <15 years represented 10% of overall incidence of MDR in adults) resulting in 16,721 patients (15,201 + (10% x 15,201)).

With a treatment regimen of Sirturo of 400 mg tablet orally, once daily (qd), for the first 2 weeks, followed by 200 mg 3 times per week (tiw) for 22 weeks, the total amount consumed per patient per treatment cycle was calculated to 18,800 mg and the total volume of bedaquiline on the EU market to cover 16,721 patients was calculated to 314356680 mg (18,800 mg x 16721).

The market penetration factor was then calculated as follows:

Fpen = CONai,region/DOSEai X Ni = 0.0000042 (0.00042%)

Where: CONai,region: = Estimated consumption of active substance in geographic region per year (mg/year) = 314356680 mg/year

DOSEai: = Maximum daily dose consumed per patient = 400 mg

Ni: = Inhabitants in geographic area = 512.7 million in EU (2018)

Nd: = Number of days in year = 365 d/year

The $PEC_{surfacewater}$ calculated using the formula in the ERA GL, i.e., DOSEai X Fpen/WASTEWinhab X DILUTION, and the refined Fpen of 0.0000042 is 0.00084 µg/L:

DOSEai = Maximum daily dose consumed per patient = 400 mg

WASTEWinhab = 200 L per inhabitant and day

DILUTION = Dilution factor 10

Upon review of the risk assessment, the EMA concluded in the Public Assessment report (CHMP-Sirturo Assessment Report. EMA/CHMP/598014/2020. 28 January 2021. Procedure No. EMEA/H/C/002614/X/0036/G) that: no risk is identified for any of the compartments (ratio $PEC_{surfacewater}/PNEC_{water}$ is below 1; 0.00084 µg/L / 0.077 µg/L), but since the substance is a PBT, the following wording was included in the package Leaflet:

"This medicine may pose a risk to the environment. Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment."

Assessment of potential increase in environmental exposure (2023)

A similar procedure is followed to determine if there has been a significant change in the environmental exposure to bedaquiline after the conditional marketing authorisation.

The WHO Global tuberculosis report 2022 (WHO 2022 Report) indicates Lithuania is still the member state with the highest prevalence of MDR in adult patients, with a prevalence of 5.4 in 100000 (a decrease compared to 9.0 reported in 2018 that was used in the risk assessment). The potential adult population based on the prevalence of 5.4 is 9060 patients. The WHO 2022 Report also suggests that children <15 years represents 11% of overall incidence of MDR) (an increase compared to the 10% reported in 2018). The total patient population (adult and paediatric) was thus calculated to 10057 patients (9060 + (11% x 9060)).

The total volume of bedaquiline to support 10057 patients with 18,800 mg per patient and treatment cycle would be 189064080 mg. A refined Fpen of 0.0000029 (0.00029%) is determined according to the formula above using the number of inhabitants in EU 2022, i.e., 446.8 million.

The $PEC_{surfacewater}$ calculated using the formula above and the refined Fpen of 0.0000029 is 0.0006 µg/L which is lower than the value accepted 2021.

Conclusion

The CHMP noted the ERA provided by the MAH, with the purpose to determine if there has been a significant change in the environmental exposure to bedaquiline after the conditional approval 2021 for the treatment of pulmonary MDR-TB in adult and paediatric patients 5 years to less than 18 years of age and weighing at least 15 kg. The most recent estimates of Fpen and $PEC_{surfacewater}$ approved 2021 were presented and compared with estimates updated 2023. The updated estimates were calculated in the same way as the previous calculations using values for the prevalence of MDR-TB and inhabitants in EU reported by WHO 2022. As the updated $PEC_{surfacewater}$ (0.0006 µg/L) was lower than previous estimate (0.00084 µg/L) no risk was identified (ratio $PEC_{surfacewater}/PNEC_{water}$ is below 1; 0.0006 µg/L / 0.077 µg/L). Whereas the calculations for the population of adult patients treated for MDR-TB in the EU could not be followed, the number of adult inhabitants in EU used for the calculations seem to be too low, a potential underestimation is not considered to have any critical impact on the assessment of risk (the ratio $PEC_{surfacewater}/PNEC_{water}$ submitted 2019 and 2023 based on for example a 3-fold underestimation will still be below 1; 0.0025 µg/L and 0.0018 µg/L / 0.077 µg/L, respectively). The CHMP agreed that an ERA update is not necessary and that the current standard wording of Section 6.6 of the SmPC (special precautions for disposal) can be maintained.

2.2.4. Discussion on non-clinical aspects

No new nonclinical safety pharmacology, toxicology or non-clinical pharmacokinetic data were submitted.

Exposure margins

Updated exposure margins (animal/human ratios) based on human exposure data of BDQ and its major metabolite (M2) from the STREAM Stage 2 study were provided. As the exposure at the end of Week 2 in the STREAM Stage 2 study are comparable to or slightly lower than those observed in the Phase 2 TMC207-C208 study on Week 2 the exposure margins from the STREAM Stage 2 study are not lower than reported previously. Update of section 5.3 of the SmPC is thus not considered necessary.

Environmental risk assessment (ERA)

Since the indication would broaden by the proposed removal of the restriction, an ERA with the purpose to determine if there has been a significant change in the environmental exposure to bedaquiline after the conditional approval in 2021 for the treatment of pulmonary MDR-TB in adult and paediatric patients (5 years to less than 18 years of age and weighing at least 15 kg) was provided. The most recent estimates of Fpen and $PEC_{surfacewater}$ approved 2021 and calculated using the prevalence data for both the adult and the complete paediatric (0-18 years of age) population were presented and compared with estimates updated 2023. As the updated $PEC_{surfacewater}$ (0.0006 µg/L) was lower than previous estimate (0.00084 µg/L) no risk was identified (ratio $PEC_{surfacewater}/PNEC_{water}$ is below 1; 0.0006 µg/L / 0.077 µg/L).

2.2.5. Conclusion on the non-clinical aspects

The updated evaluations related to non-clinical aspects are adequate and support the extended indication. There are no objections for approval of the current application for Sirturo from a non-clinical perspective.

The updated data submitted in this application do not lead to a significant increase in environmental exposure further to the use of bedaquiline. Considering the above data, bedaquiline is not expected to

pose a risk to the environment.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The MAH has provided a statement to the effect that the STREAM Stage 2 clinical trial conducted outside the community (Ethiopia, Georgia, India, Moldova, Mongolia, South Africa and Uganda) were carried out in accordance with the ethical standards of Directive 2001/20/EC.

2.3.2. Pharmacokinetics

Clinical Pharmacology Studies includes new PK and PK/PD information from the Phase 3 Study STREAM Stage 2. To enable a collective assessment of the DDI liability when co-administering CYP3A4 perpetrators with BDQ chronically, additional PK information available from a new DDI study with clarithromycin, a strong CYP3A4 inhibitor (Study TMC207NTM1001), as well as a new PopPK analysis focusing on DDIs are incorporated.

Including STREAM Stage 2 and Study TMC207NTM1001, the PK properties of BDQ were studied in 1,009 participants in 13 Phase 1 studies, 4 Phase 2 studies (for the ongoing paediatric Study C211, Cohort 1 [adolescents 12 to <18 years] and Cohort 2 [children, 5 to <12 years] are included), and 1 Phase 3 study, most of which have been summarised in the original submission. Table 4 lists all studies from which data are presented in this summary with the new studies highlighted.

Table 4: List of PK Studies (New or Previously Submitted and Used for Comparisons in This Addendum to the Summary of Clinical Pharmacology Studies)

Study	Population	N	BDQ Dose Regimen	Coadministered Drug(s)
TMC207NTM1001 (**new**; Section 2.2.1.1)	Healthy adults	16	100 mg, single dose	Clarithromycin, 500 mg q12h for 14 days
TMC207-C110 (Mod2.7.2/Original SumClinPharm/Sec2.7.4)	Healthy adults	16	400 mg, single dose	LPV/RTV, 400/100 mg bid for 24 days
TMC207-C117 (Mod2.7.2/Original SumClinPharm/Sec2.7.5)	HIV-infected	16	400 mg, single dose	NVP, 200 mg qd for 2 weeks followed by 200 mg bid for 4 weeks
TMC207-C208 (Stages 1 and 2) (Mod2.7.2/Original SumClinPharm/ Sec2.5.2.1)	MDR-TB (including pre-XDR-TB and XDR-TB)	102 (23+79)	400 mg qd for 2 weeks, followed by 200 mg tiw for 6 weeks (Stage 1) or 22 weeks (Stage 2)	*BR:* KM (or amikacin), ofloxacin (or ciprofloxacin), ethionamide (or PTO), PZA, and terizidone (or EMB)
TMC207-C209 (Mod2.7.2/Original SumClinPharm/ Sec2.5.2.2)	MDR-TB (including pre-XDR-TB and XDR-TB)	233	400 mg qd for 2 weeks, followed by 200 mg tiw for 22 weeks	*BR:* individualized MDR-TB using commonly prescribed antimycobacterial TB drugs
STREAM Stage 2 (TMC207TBC3007) (**new**; Section 2.1.1)	RR/MDR-TB	282[a] (173+109 in Regimens C and D)	400 mg qd for 2 weeks, followed by 200 mg tiw for 26 weeks (Regimen D) or 38 weeks (Regimen C)	*BR (Regimen C):* LFX, CFZ, EMB, and PZA, supplemented by high-dose INH and PTO for the first 16 weeks *BR (Regimen D):* LFX, CFZ, and PZA, supplemented by KM and INH at a higher dose than used in Regimens B and C for the first 8 weeks
Total (all studies)[b]		**1,009[b]**		

BDQ=bedaquiline; bid=twice daily; BR=background regimen; CFZ=clofazimine; EMB=ethambutol; HIV=human immunodeficiency virus; INH=isoniazid; KM=kanamycin; LFX=levofloxacin; LPV=lopinavir; MDR-TB=multidrug-resistant tuberculosis; N=number of participants; NVP=nevirapine; PK=pharmacokinetic(s); PTO=prothionamide; PZA=pyrazinamide; q12h=every 12 hours; qd=once daily; RR/MDR-TB=rifampicin-resistant or multidrug-resistant tuberculosis; RTV=ritonavir; TB=tuberculosis; tiw=3 times per week; XDR-TB=extensively drug-resistant tuberculosis.

[a] Participants in the PK Analysis Set.

[b] Total number of participants from all Phase 1 and 2 studies included in the previous submissions (for Study C211, Cohort 1 [12 to <18 years] and Cohort 2 [5 to <12 years] are included) and new studies added in the current submission.

Source: Mod2.7.2/Original SCP/Sec1.2; Mod5.3.5.1/STREAM Stage 2 CSR; Mod5.3.3.4/TMC207NTM1001 CSR

The CHMP noted the PK analyses performed by the MAH, with different purposes in the dossier.

Two new clinical studies with PK information which were not included in the original submission are presented (STREAM Stage 2 and TMC207NTM1001) in the current procedure. In addition, updated PopPK analyses are provided for several clinical studies included in the original submission.

The PK data from STREAM Stage 2 was used to describe PK in the target population and to perform subgroup analyses to support dosing recommendations in special populations. The PK data from

STREAM Stage 2 was also used to perform exposure-response analyses. The PK data from STREAM Stage 2 was presented (1) as a summary of the underlying PK observations (e.g. as PK observations plotted vs time) and (2) by applying an updated PopPK model based on PK data from studies C208 and C209. The description of PK data in the target population included both bedaquiline (parent) and the metabolite M2.

The clinical DDI study TMC207NTM1001 was used to support new dosing recommendations for interaction scenarios. The updated PopPK analyses of studies TMC207-C110 and TMC207-C117 were also used to support new dosing recommendations for interaction scenarios. In addition, a PK subgroup analysis was performed to provide additional support for new dosing recommendations for interaction scenarios.

Although PK data was used for several reasons as outlined above, the PK is in general considered supportive only, with low impact for the total benefit-risk assessment. The CHMP considered that clinical efficacy and safety data comprising mainly of Studies C208, C209 and STREAM Stage 2 is sufficiently robust to draw the most necessary conclusions to determine the benefit-risk of this procedure. The PK data is used to describe PK and support the benefit-risk assessment in certain subgroups (e.g. dosing recommendations for interaction scenarios).

2.3.2.1. Bioanalysis methods

According to the summary of clinical pharmacology, the plasma samples from STEAM 2 was performed with an updated bioanalysis method compared to the LC-MS/MS method used in the initial application, the current method is named BA10946. The updated method was validated for lithium-heparin plasma samples, transferred to another system and for a lower sample volume.

Table 5 Overview of analytical method BA10946

Laboratory	Year Validated	Matrix, Anticoagulant Stabilizer	Extraction Procedure	Chromatography	Mass Spectrometry Conditions	Remarks
PRA Health Sciences, Assen, Netherlands	2016	Human plasma (lithium-heparin)	Protein precipitation	Acquity UPLC BEH C18 column (1.7 µm, 50 × 2.1 mm) gradient 10 mM ammonium formate pH 4 as mobile phase A and methanol as mobile phase B, flow rate of 0.6 mL/min	MRM mode Bedaquiline: m/z 555.2 → 58.0 *N*-mono-desmethyl bedaquiline (M2): m/z 541.2 → 480.1	Validation to accommodate different LC-MS/MS system and reduced sample volume

BEH=ethylene bridged hybrid; LC-MS/MS=liquid chromatographic-mass spectrometry/mass spectrometry; MRM=multiple reaction monitoring; UPLC=ultra-performance liquid chromatography.

A full validation of BA10946 from PRA health sciences is presented in a report from 2016, but no within-study bioanalysis report was located in the documentation.

The PK-samples from the clarithromycin DDI study were also analysed by PRA health sciences in Assen, the Netherlands. In the within-study bioanalysis report, the method number is called PRA-NL-SML-1702 and reference is made to a pre-study validation report from 2016 which could not be located in the documentation.

The CHMP noted that the bioanalysis of bedaquiline and M2 was performed by the same laboratory in the Netherlands for both STEAM 2 and the clarithromycin DDI study. Given that the methods used

were claimed to be similar to the methods used in the initial submission and that the PK data is of low impact, no further assessment of the bioanalysis methods has been performed in this variation.

2.3.2.2. Population PK analysis

PopPK analyses were applied in several different settings which can be summarised by the following:

- PopPK model development in TB patients (Study C208 and C209)
- Evaluation and application of PopPK model in STREAM Stage 2
- PopPK model development of DDI studies

2.3.2.2.1. PopPK model development in TB patients

Objectives

1. Perform an exploratory graphical analysis of the plasma concentration-time profile of bedaquiline and M2 in healthy volunteers (HVs) and patients with tuberculosis (TB).

2. Expand the previously developed population pharmacokinetic (PK) model for bedaquiline by incorporating a metabolite compartment(s) to describe the observed bedaquiline and M2 PK data.

(a) Quantify population PK parameters, including typical parameter values and random inter-individual and residual variability.

(b) Identify and quantify covariate effects which describe variability in the PK of bedaquiline and M2.

The CHMP considered the objectives for the PopPK model to be acceptable.

Data

The original dataset used to develop population PK model for bedaquiline were expanded by including M2 data. PK data from HVs recruited in studies R207910-CDE102, TMC207-TiDP13-C104, TMC207-TiDP13-C109, TMC207-TiDP13-C110, TMC207-TiDP13-C111, and TMC207-TBC1003 and patients recruited in studies TMC207-TiDP13-C202, TMC207-TiDP13-C208 and TMC207-TiDP13-C209 were included in the analysis dataset (Table 4). The model building dataset consisted of 5222 bedaquiline concentrations and 4717 M2 concentrations from 479 adult subjects (111 HVs and 368 patients with TB) with weight range of 30 kg to 113 kg.

Table 6: Overview of Studies Included in the Population PK Update

Study	Description	Population	$N_{subjects}$	Bedaquiline Dose	Formulation	$N_{samples}$ per subject	Duration of Sampling
R207910-CDE-102	A double-blind randomised placebo controlled, Multiple ascending dose trial in healthy male volunteers	Healthy	18	50,150 or 400 mg QD for 14days	Solution	43	Up to 7 days after the last dose
TMC207-TiDP13-C104	An open-label,1-sequencecross-over trial in 24 healthy male volunteers to investigate DDI between repeated dosing of bedaquiline and the combination isoniazid/pyrazinamide(H/Z)	Healthy	22	400 mg QD for 15 days with co-administration of H/Z 300/2000 mg QD fromday11-15	Solution	12	Up to 24 hours after the last dose
TMC207-TiDP13-C109	An open-label,1-sequencecross-over trial in 16 healthy male volunteers to investigate DDI between repeated dosing of bedaquiline and ketoconazole	Healthy	16	400 mg QD fromday1-14 with co-administration of ketoconazole 400 mg QD fromday12-14	Solution	13	Up to 24 hours after the last dose
TMC207-TiDP13-C110	An open-label, randomized crossover trial to investigate the pharmacokinetic interaction between steady-state lopinavir/ritonavir and single-Dose bedaquiline	Healthy	8	400 mg single dose	Tablet	16	Up to 14 days after dosing

TMC207- TiDP13-C111	An open-label randomized,3-waycrossover trial to determine the relative oral bioavailability of bedaquiline after single dose administration of bedaquiline100 mg as the Phase II clinical trial tablet formulation and as a newly developed tablet formulation, under fed and fasted conditions	Healthy	13	100 mg single dose	Tablet	18	Up to 28 days after dosing
TMC207- TBC1003	A double-blind, randomized, placebo- and positive-controlled, parallel-group trial to evaluate the effect of single-dose bedaquiline on the QT/QTc interval in healthy subjects	Healthy	44	800 mg single dose	Tablet	12	Up to 24 hours after dosing
TMC207- TiDP13-C202*	An open-label randomised trial in 75 treatment-naïve subjects with microscopic sputum smear-positive pulmonary TB	TB patients	45	25,100 or 400 mg QD for 7 days	Solution	12	Up to 24 hours after The last dose
TMC207- TiDP13-C208 Stage1	Exploratory stage of an anti-bacterial activity, safety, and tolerability trial of bedaquiline in subjects with sputum smear-positive pulmonary infection with multi-drug resistant Mycobacterium tuberculosis	MDR-TB patients	22	400 mg QD for the rst 2 weeks,200 mg TIW for The following 6weeks	Tablet	Up to 43	Up to 36 weeks after The last dose
TMC207- TiDP13-C208 Stage2	Proof of efficacy stage of an anti-bacterial activity, safety, and tolerability trial of bedaquiline in subjects with sputum smear-positive pulmonary infection with multi-drug resistant Mycobacterium tuberculosis	MDR-TB patients	78	400 mg QD for the rst 2 weeks,200 mg TIW for The following 22 weeks	Tablet	Up to 33	Up to 36 weeks after The last dose
TMC207- TiDP13-C209	An open-label, safety, tolerability, and efficacy trial in subjects with sputum smear-positive pulmonary infection with multi-drug resistant Mycobacterium tuberculosis	MDR-TB patients	229	400 mg QD for the rst 2 weeks,200 mg TIW for The following 22 weeks	Tablet	Up to 11	Up to 72 hours after The last dose

QD = once daily, TIW = three times a week, MDR-TB = multi-drug resistant *Mycobacterium tuberculosis*, TB = tuberculosis.

*Only bedaquiline concentration-time data were included.

The baseline characteristics of the included subjects are summarised in Table 7.

Table 7: Summary of Baseline Demographics

	Age (years)	Weight (kg)	Albumin (g/L)	BMI (kg/m^2)	BSA (m^2)	Sex	Race	Study	Health Status
N	479	479	479	479	479	Male: 330 (68.89%)	White: 134 (27.97%)	102: 18 (3.76%)	Healthy: 111 (23.17%)
Mean	34.7	61.2	37.9	21.3	1.69	Female: 149 (31.11%)	Black: 149 (31.11%)	104: 22 (4.59%)	Tuberculosis: 368 (76.83%)
SD	12.0	14.3	7.80	3.90	0.223		Hispanic: 41 (8.56%)	109: 15 (3.13%)	
CV %	34.4	23.4	20.6	18.3	13.1		Asian: 99 (20.67%)	110: 8 (1.67%)	
Median	32	59	38	20.742	1.67		Am. Ind.: 56 (11.69%)	111: 4 (0.84%)	
Min	18	30	15	13.149	1.16			202: 43 (8.98%)	
Max	68	113	53	36.808	2.39			208: 98 (20.46%)	
								209: 227 (47.39%)	
								1003: 44 (9.19%)	

N = number of subjects, SD = standard deviation, CV = coefficient of variation, Min = minimum, Max = maximum, Am Ind = American Indian, BMI = body mass index, BSA = body surface area.

A total of 292 observations (127 bedaquiline and 165 M2 observations, 2.9%) were excluded from the model building dataset. The majority of these observations were excluded due to BLQ samples (112 of 292, 38.4%) and duplicate time (110 of 292, 37.7%).

The CHMP noted that the PopPK model was developed on a dataset including 368 TB patients and 111 healthy volunteers, including a total of 5222 bedaquiline concentrations and 4717 M2 concentrations.

It is unclear why the PK data from STREAM Stage 2 was not included in the PopPK dataset. It would have strengthened the analysis. However, the dataset and proposed approach is considered overall acceptable and therefore this limitation is not pursued further.

The CHMP considered the covariates and the distributions to be overall acceptable. These are largely unchanged compared to the initial submission. An important covariate based on the covariate analysis from the initial submission is black race which was a strong predictor for BDQ PK.

Methods

The MAH conducted a graphical analysis to understand and explore the available data. This exploratory analysis was used to assess whether the disposition of M2 appears to be mono or biexponential, the M2 PK is linear across the evaluated dose range, or if there is an impact of potentially relevant covariates.

The model-based analysis was carried out in the software NONMEM 7.4.4 using the FOCE as the estimation method. A prior structural model for bedaquiline was retained with metabolite compartment(s) included to describe the M2 PK. Initially the M2 data was described by a 1-compartment model, with 2-compartment and 3-compartment models explored. For identifiability of the fraction metabolised (FM), volume of distribution of M2 was fixed to the parent.

The prior model for bedaquiline included two demographic covariate effects, black race and HV population on CL/F and sex on Vc/F. The covariates included in the previous model was retained with the influence of continuous and categorical covariates on M2 PK explored. Age, weight, albumin, sex and race were explored on M2 CL and Vc. Continuous covariates were explored using a power function.

A formal covariate analysis was not undertaken, however following development of the base model and graphical assessment of covariate-eta (η) relationships, the covariate model was built according to the following steps:

1. If a visually apparent relationship is identified, covariates will be added to the model in a stepwise forward manner.

2. Covariates will be identified as significant if change in objective function value (OBJ) 7.9 ($p < 0.005$ for 1 degree of freedom).

3. All significant covariates from the univariate analysis was included in a full model. A backwards elimination process was then be performed, where covariates were deleted singly from the full model in a backward elimination process and the OBJ computed from the full model. Covariates that can be deleted from the full model without an associated increase in objective function value (OBJ) 10.8 ($p < 0.001$ for 1 degree of freedom) were sorted by OBJ and the covariate with the smallest OBJ was removed from the model. This process was repeated until no more covariates can be removed from the model.

Model evaluation techniques to assess the quality of model fit include statistical tests, diagnostic plots, and consideration of scientific plausibility.

The OBJ using the likelihood ratio test was used for model selection and evaluation. Generation of acceptable relative standard errors (RSEs) for the parameter estimates was aimed for, using 35%CV for fixed effects and 50%CV for variability parameters as a general guide. RSEs were calculated using the NONMEM covariance step and using sampling importance resampling (SIR).

Diagnostic plots included the standard goodness-of-fit plots and visual predictive checks. Forest plots were generated to evaluate the impact of covariates on model-predicted exposure metrics.

The CHMP noted that the current proposed workflow relies on a previous PopPK model for bedaquiline. The general structure and covariates of the original BDQ PopPK model was kept and the model was expanded to include an additional model for M2 PK. This considered an acceptable strategy.

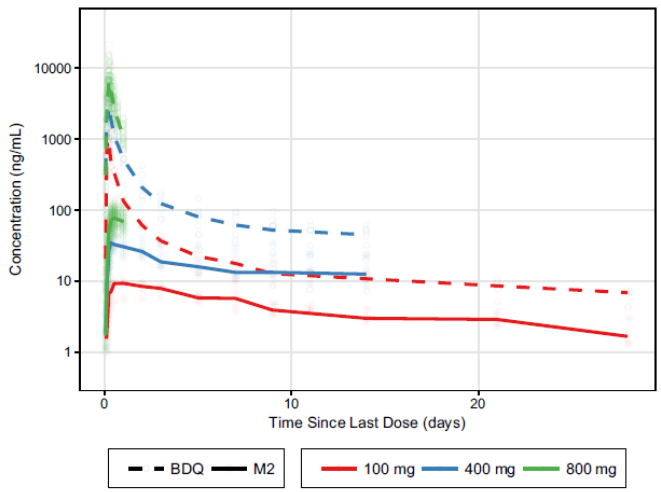
The workflow for development of the M2 PK model included testing of 1-, 2- and 3-compartment models which is considered acceptable. The covariate model development relied on visual assessment of eta vs covariate trends. This is not an optimal strategy since it is sensitive to eta-shrinkage for CL and Vc for the metabolite. The eta-shrinkages were 22% and 33% for M2 CL and Vc, respectively which is too high for relying on this approach. However, this issue is not further pursued given the limited impact of the PopPK model.

The CHMP was of the view that reasonable model evaluation techniques were used.

Results

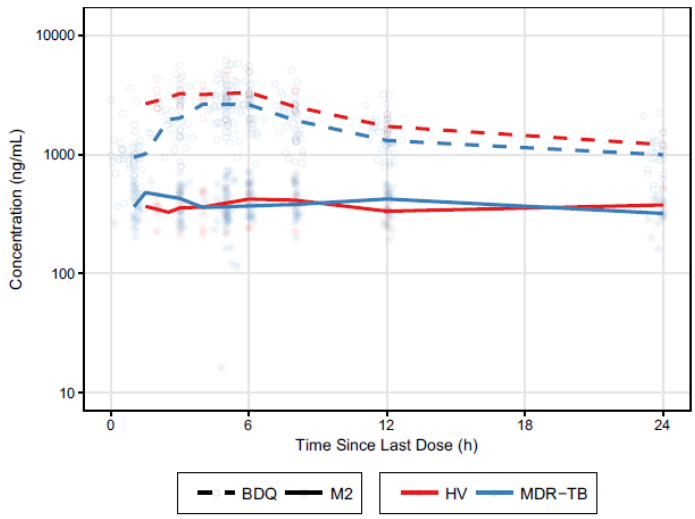
Figure 1 and Figure 2 show median concentration-time profiles of bedaquiline (dashed lines) and M2 (solid lines) in healthy volunteers and patients, respectively.

Figure 1 Concentration-time profiles by dose - single dose (HVs)



Solid and dashed lines show the median of M2 and bedaquiline with symbols representing the observed data. Y-axis on log scale. Data below the LLOQ were excluded. Note: only data from single dose studies were included (i.e., studies TMC207-TiDP13-C110, TMC207-TiDP13-C111and TMC207-TBC1003). BDQ = bedaquiline.

Figure 2 Concentration-time profiles by population (400 mg QD)

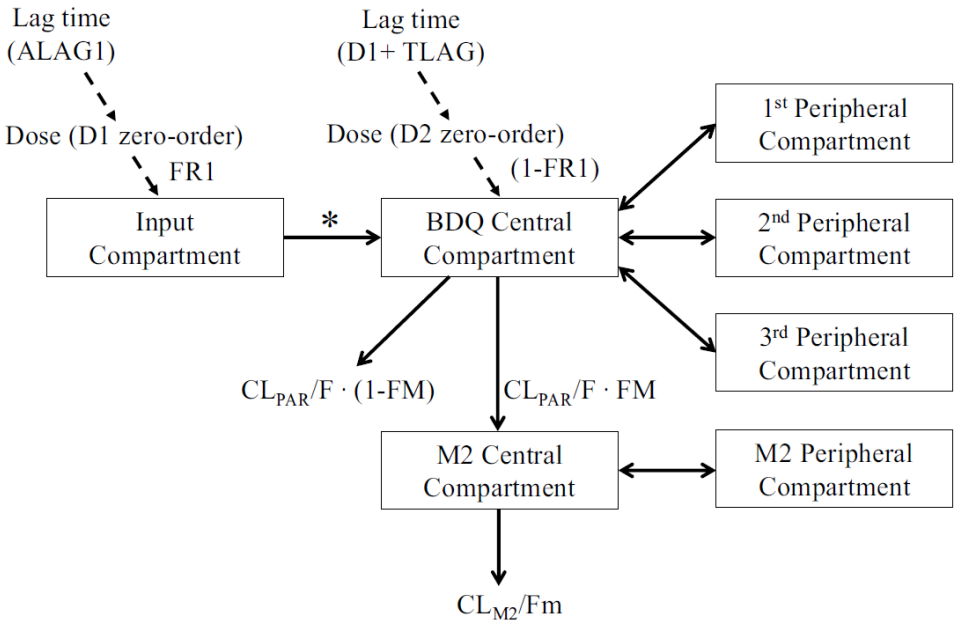


Solid and dashed lines show the median of M2 and bedaquiline with symbols representing the observed data. Y-axis on log scale. Data below the LLOQ were excluded. Note: PK data following bedaquiline 400 mg on Day 14 from studies R207910-CDE-102 and TMC207-TiDP13-C208 were included and truncated at 24h for visualisation. BDQ = bedaquiline, HV = healthy volunteer, MDR-TB = patients with multi-drug resistant Mycobacterium tuberculosis.

The previously developed structural model for bedaquiline (4-compartment disposition with dual zero-order input and linear elimination) was retained. The PK model for bedaquiline was expanded to include M2 metabolite data, which were described by a two-compartment model with linear elimination. To avoid a structural identifiability problem, the apparent central volume of distribution for the metabolite (Vc,MET/Fm) was fixed to that of the parent, with fraction metabolised (FM) estimated for HVs and patient population. The FM was estimated separately for HVs and patient population based on the PK differences observed in the graphical analysis (data not shown). The random effects included in the prior model were retained, with additional between-subject variability (BSV) terms implemented on apparent clearance for the metabolite (CLMET/Fm), apparent clearance between the central and peripheral compartment for the metabolite (CLp1,MET/Fm), and FM. The residual unexplained variability was described by separate additive error models with a correlation implemented between bedaquiline and M2 observations.

Black race covariate included on apparent clearance for the parent (CLPAR/F) was also included on CLMET/Fm with the same magnitude of covariate effect applied on both parameters. Subjects with Black race had 71% higher CLPAR/F and CLMET/Fm compared to non-Black population. Sex included on apparent central volume of distribution for the parent (Vc,PAR/F) in the previously developed PK model was retained. Females had 25% lower Vc,PAR/F compared to males. Sex effect was also included on Vc,MET/Fm as Vc,MET/Fm was fixed to Vc,PAR/F for parameter identifiability reasons. HVs and patients in study TMC207-TiDP13-C202 (i.e. TB patients) had 45% higher CLPAR/F. There were no significant relationships between weight, age, body mass index (BMI), body surface area (BSA), serum creatinine (SCR), estimated glomerular filtration rate (eGFR), or creatinine clearance (CRCL) and any individual model parameters identified in the final model.

A schematic of the final PK model is presented in Figure 3 with parameter estimates presented in Table 8.



CL_{PAR}/F = apparent clearance for the parent, CL_{MET}/Fm = apparent clearance for the metabolite, F = bioavailability, FM = fraction metabolized, Fm = bioavailability corrected with fraction metabolized (i.e., Fm = F · FM), D1 = duration of zero-order input into the first compartment, D2 = duration of zero-order input into the second compartment, ALAG1 = absorption lag time for the first pathway, TLAG = absorption lag time for the second pathway, FR1 = fraction of the dose absorbed via the first pathway, BDQ = bedaquiline. * Rate parameter was fixed to 1000. Note: $V_{c,MET}/Fm$ was fixed to $V_{c,PAR}/F$ to avoid parameter identifiability problem.

Figure 3 Schematic of the final parent-metabolite PK model for bedaquiline

Table 8: Parameter estimates for the final parent-metabolite PK model for bedaquiline and M2

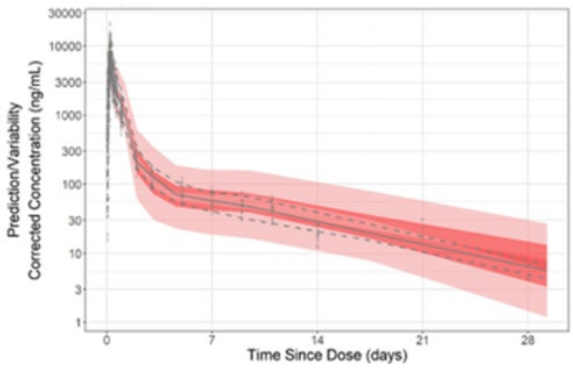
Parameter Name (Unit)	Parameter Description	Prior BDQ PKModel Estimate Value (%RSE†)	Final BDQ-M2 PKModel Estimate Value (%RSE‡‡)	95%CI‡‡
Bedaquiline				
CL_{PAR}/F (L/h)	Apparent clearance	2.78 (5.1)	2.62 (4.4)	2.40 - 2.85
$Effect_{Black,CL_{PAR}/F}$ (%)[a]	-Effect ofblack raceon CL_{PAR}/F	52.0 (21.2)	71.1(13.4)	51.9 - 89.2
$Effect_{HV,202,CL_{PAR}/F}$ (%)[b]	-Effect ofHVs or studyC202 on CL_{PAR}/F	37.5 (35.2)	45.0 (28.6)	23.9 - 72.6
$V_{c,PAR}/F$ (L)	Apparent central volumeofdistribution	164(5.0)	117 (8.0)	98 - 134
$Effect_{Sex,Vc_{PAR}/F}$ (%)[c]	-Effect ofsex on $V_{c,PAR}/F$	-15.7 (42.5)	-25.8 (35.9)	-42.7 - -6.2
CL_{p1}/F (L/h)	Apparent clearancebetween thecentral and first peripheral compartment	11.8 (7.6)	23.3(6.8)	20.1 - 26.6
V_{p1}/F (L)	Apparent volumeofdistribution for thefirst peripheral compartment	178 (8.1)	124(5.0)	113 - 137
CL_{p2}/F (L/h)	Apparent clearancebetween thecentral and second peripheral compartment	8.03(4.9)	8.61(3.8)	8.01 - 9.25
V_{p2}/F (L)	Apparent volumeofdistribution for thesecond peripheral compartment	3010 (9.0)	2770 (5.6)	2466 - 3062
CL_{p3}/F (L/h)	Apparent clearancebetween thecentral and third peripheral compartment	3.58 (9.0)	3.35 (4.3)	3.11 - 3.68
V_{p3}/F (L)	Apparent volumeofdistribution for thethird peripheral compartment	7350 (5.8)	7670 (3.0)	7255 - 8166
FR1*	Fraction ofthedoseabsorbed via thefirst pathway	1.41(11.1)	1.06(11.9)	0.85 - 1.34
D1(h)	Duration ofzero-order input for first absorption pathway	2.22 (1.0)	2.53(4.0)	2.33 - 2.71
$ALAG1_{solution}$ (h)	Absorption lag time(solution)	0.541(5.7)	0.48 (10.6)	0.38 - 0.59
$ALAG1_{tablet}$ (h)	Absorption lag time(tablet)	0.917 (0.6)	0.921(0.5)	0.911 - 0.930
D2 (h)	Duration ofzero-order input for second absorption pathway	1.48 (3.2)	2.31(5.8)	2.07 - 2.60
TLAG (h)**	Lag timefor second absorption pathway	1.48 (3.2)	0.815 (13.7)	0.525 - 0.989
$F_{208,209}$	Relativebioavailabilityfor studies C208 and C209	1Fixed	1Fixed	-
$F_{HV\text{-}MD}$	Relativebioavailabilityfor studies 102 and C104	1.51(7.5)	1.49 (9.7)	1.23 - 1.82
$F_{HV\text{-}SD,DS\text{-}TB}$	Relativebioavailabilityfor studies C109,C110,C111,C202,and TBC1003	2.03(4.7)	1.93(5.3)	1.74 - 2.14
FM_{TB}	Fraction metabolized for patients with MDR-TB	-	0.542 (6.3)	0.471 - 0.603
$Effect_{HV,FM}$ (%)[d]	-Effect ofHV on FM	-	48.1(10.2)	38.1 - 57.4
M2 Metabolite				
CL_{MET}/Fm(L/h)	Apparent clearance	-	4.95 (6.9)	4.21 - 5.65
$Effect_{Black,CL_{MET}/Fm}$ (%)	-Effect ofblack raceon CL_{MET}/Fm	-	Fixed to $Effect_{Black,CL_{PAR}/F}$	-
$V_{c,MET}/Fm$(L)	Apparent central volumeofdistribution	-	Fixed to $V_{c,PAR}/F$	-
$CL_{p1,MET}/Fm$(L/h)	Apparent clearancebetween thecentral and peripheral compartment	-	104(15.7)	77 - 140
$V_{p1,MET}/Fm$(L)	Apparent peripheral volumeofdistribution	-	862 (6.7)	748 - 970

$BSV_{CL_{PAR}/F}$ (%)	Between subject variabilityfor CL_{PAR}/F	50.4(12.3)	44(7.7)	40.8 - 47.4
$BSV_{V_{c,PAR}/F}$ (%)	Between subject variabilityfor $V_{c,PAR}/F$	39.1(15.6)	71.1(13.5)	61.1 - 81.3
BSV_{FR1} (%)	Between subject variabilityfor FR1	113(15.9)	97 (16.1)	81.2 - 112.8
BSV_F (%)	Between subject variabilityfor F	39.6(9.3)	36.9 (7.4)	33.9 - 39.5
$BSV_{CL_{MET}/Fm}$ (%)	Between subject variabilityfor CL_{MET}/Fm	-	45.3(8.5)	41.4- 48.8
BSV_{FM} (%)	Between subject variabilityfor FM	-	27.9 (14.6)	24.1 - 31.8
$BSV_{CL_{p1,MET}/Fm}$ (%)	Between subject variabilityfor $CL_{p1,MET}/Fm$	-	158 (18.4)	124 - 183
	-Correlation Between CL_{PAR}/F –CL_{MET}/Fm	-	0.908 (7.5)	0.852 - 0.957
$RUV_{BDQ,HV}$ (%)	Residual unexplained variaiblityfor BDQ in HVs	20.6(3.3)	23.9 (2.3)	23.5 - 24.5
$RUV_{BDQ,TB}$ (%)	Residual unexplained variaiblityfor BDQ in Patients with MDR-TB (%)	27.7 (3.2)	28.8 (1.9)	28.3 - 29.3
RUV_{M2} (%)	Residual unexplained variaiblityfor M2 (%)	-	24.8 (0.9)	24.5 - 25.0
	-Correlation Between $RUV_{BDQ,HV}$-RUV_{M2}	-	0.652 (2.7)	0.624 - 0.678
	-Correlation Between $RUV_{BDQ,MDR-TB}$-RUV_{M2}	-	0.492 (2.8)	0.470 - 0.518

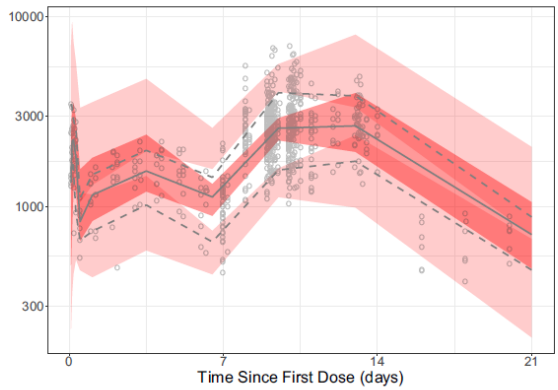
RSE = relativestandard error,CI = confidenceinterval,BDQ = bedaquiline. [a]Effect ofBlack raceon $CL_{/}F$ was parameterized as 1 + 0.711[Race] whereEffect = 1 for Black raceand 0 for non-Black race. [b]Effect ofHV or studyR207910-CDE-102 on $CL_{/}F$ was parameterized as 1+ 0.450[Study] whereEffect = 1 for HV or studyR207910-CDE-102 and 0 for other subjects. [c]Effect ofsex on $V_{c/}F$ was parameterized as 1 + 0.450[Sex] whereEffect = 1for femaleand 0 for male. [d]Fraction metabolized for HVs was parameterized as FM_{MDR-TB} (1-0.481). *Parameterized as FR1/(1+FR1),**Parameterized as ALAG2 = D1+ TLAG. [e] Derived from$COV in NONMEM. [f] Derived from SIR

Prediction and variability corrected visual predictive checks (pvcVPCs) were constructed and are shown in Figure 4 Figure 5 and Figure 6.

A: Single dose



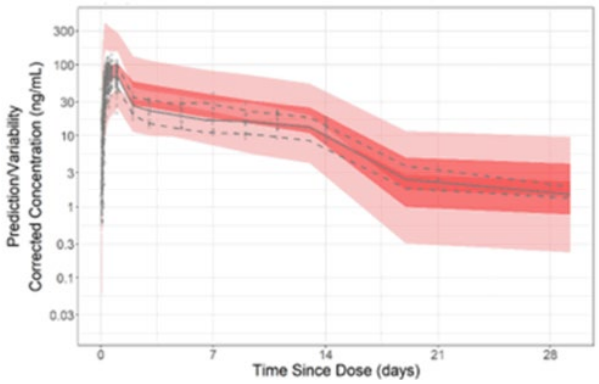
B: 400 mg QD for 14 days



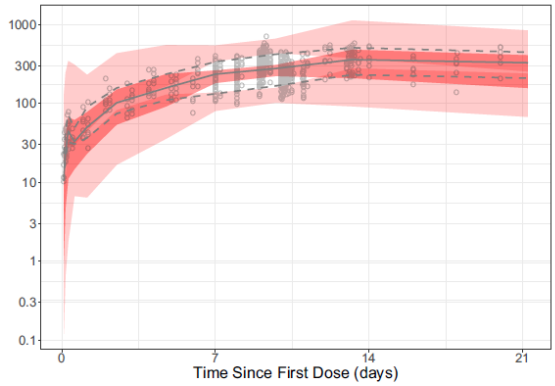
Open circles = individual prediction/variability corrected observed data, dashed lines = observed 10th and 90th percentiles, solid line = obser median, shaded red area = 95% confidence interval for the simulated percentiles. Note: data from studies R207910-CDE-102, TMC207-TiDP C104, TMC207-TiDP13-C109, TMC207-TiDP13-C110, TMC207-TiDP13-C111, and TMC207-TBC1003 were included. QD = once daily.

Figure 4 pvcVPC for the final parent-metabolite PK model - bedaquiline (HVs)

A: Single dose



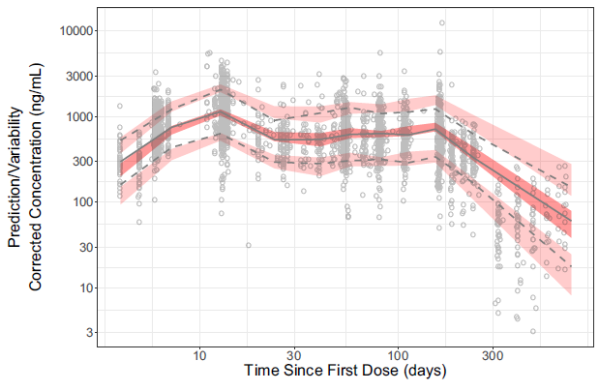
B: 400 mg QD for 14 days



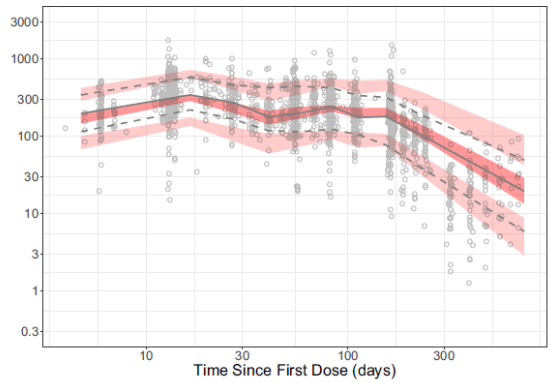
Open circles = individual prediction/variability corrected observed data, dashed lines = observed 10th and 90th percentiles, solid line = observ median, shaded red area = 95% confidence interval for the simulated percentiles. Note: data from studies R207910-CDE-102, TMC207-TiDP1 C104, TMC207-TiDP13-C109, TMC207-TiDP13-C110, TMC207-TiDP13-C111, and TMC207-TBC1003 were included. QD = once daily.

Figure 5 pvcVPC for the final parent-metabolite PK model - M2 (HVs)

A: Bedaquiline



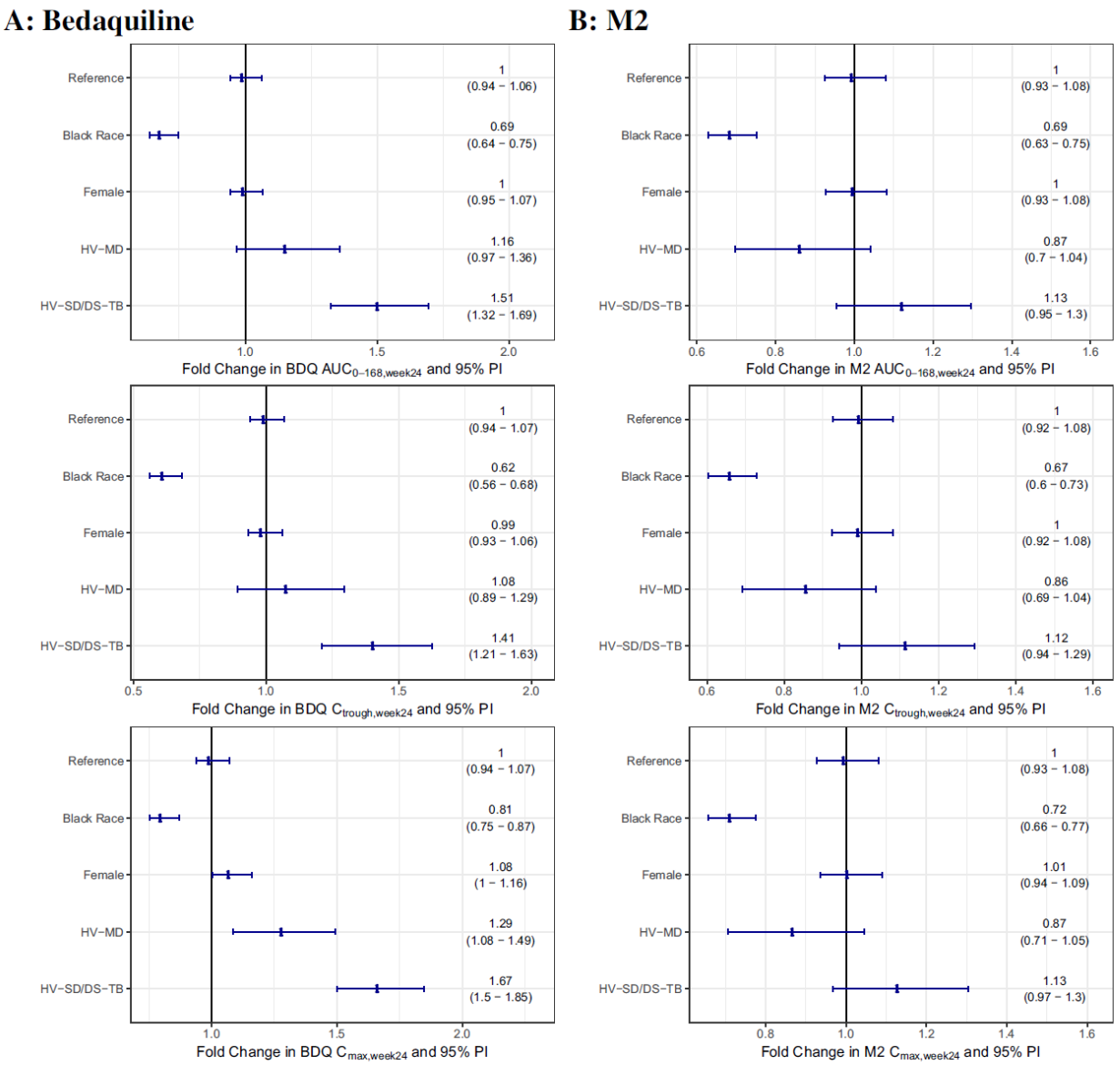
B: M2



Open circles = individual prediction/variability corrected observed data, dashed lines = observed 10th and 90th percentiles, solid line = observed median, shaded red area = 95% confidence interval for the simulated percentiles. Note: log-log scale is used. Data from studies TMC207-TiDP13-C202, TMC207-TiDP13-C208, and TMC207-TiDP13-C209 were included. QD = once daily.

Figure 6 pvcVPC for the final parent-metabolite PK model - bedaquiline (patients with TB)

The impact of covariates including Black race, sex, and disease on bedaquiline and M2 exposure (area under the plasma concentration-time curve from time 0 to 168 hours (AUC0-168), C_{max}, and trough concentration (C_{trough})) at Week 24 are summarised in Figure 7. Subjects with Black race were predicted to have 31% lower bedaquiline and M2 AUC0-168 compared to the reference population (male non-Black patients with MDR-TB). The magnitude of the effect of sex on bedaquiline and M2 exposure were considered minor. HV have slightly higher bedaquiline exposures (<30%) and slightly lower M2 exposures (<20%) compared with patients with TB.



The solid black line represents no impact of the covariate with the reference subject referring to a male non-Black patient with MDR-TB with F of 1. The blue dots and error bars represent the median and 95% (2.5^{th} to 97.5^{th} percentiles of the simulations) prediction intervals (PI) of the covariate effect based on 1000 simulated subjects within each group including uncertainty on the fixed effect. BDQ = bedaquiline, F = bioavailability, HV-MD = healthy volunteer following multiple-dose (studies R207910-CDE-102 and TMC207-TiDP13-C104), HV-SD/DS-TB = healthy volunteer following single dose (studies TMC207-TiDP13-C109, TMC207-TiDP13-C110, TMC207-TiDP13-C111, TMC207-TBC1003) or patients with drug-sensitive tuberculosis (study TMC207-TiDP13-C202).

Figure 7 Model predicted fold change in bedaquiline and M2 exposure metrics at week 24

The CHMP noted that for bedaquiline, the same structure and covariates were included as in the previous PK model where all the bedaquiline parameters were re-estimated. This is considered a reasonable strategy and as the final model was able to describe the observed bedaquiline data overall well according to pvcVPCs, the bedaquiline sub-model is in principle considered acceptable.

The major new addition to the current model was the M2 sub-model which consisted of a two-compartment disposition model. The fraction metabolised was estimated, and in order to avoid identifiability issues, the central volume for M2 was fixed to that of the parent (and the covariates of the parent on Vc were also introduced for M2). Therefore, the parameter estimates of M2, including fraction metabolised should be interpreted with some caution since the assumption that the volume is

identical for BDQ and M2 cannot be verified with the current state of knowledge (metabolite parameters in absence of administration of the metabolite directly). Nevertheless, the M2 sub-model is considered overall acceptable and the model gave acceptable description of the observed M2 data according to pvcVPCs.

The CHMP considered the parameter estimates and RSEs to be overall acceptable. However, the covariates should be interpreted with caution. There may be underlying confounding/correlations between certain covariates, studies and potentially also between study sites. The very influential covariate black race (~70% higher clearance of the parent and metabolite) should be interpreted with caution since the estimate may be biased (black race may be confounded with region/study and potentially also HIV co-infection/co-medication). Given the evidence presented by the MAH, black race is not considered a clinically significant covariate (i.e. no altered dosing recommendations are needed). This conclusion is also supported by subgroup analyses of efficacy data (see the Clinical efficacy section below).

The shrinkage was ~20-30% for M2 CL and the central volume. Since the covariate model development relied on EBEs, this is a limitation of the analysis. However, since the PopPK analysis is considered to have low impact, this issue is not further pursued.

The forest plots confirmed that black race is an influential covariate, along with a patient vs healthy volunteer effect.

Since there may be confounding between covariates the model may not be entirely appropriate for clinical trial simulations. Furthermore, when this model was applied to PK data from STREAM Stage 2, the model tended to overpredict the M2 concentrations which is another sign suggesting that the model may not be applicable outside the setting of the dataset used to develop the PopPK model. Of note, there were no clinical trial simulations that had a relevant impact on the benefit-risk assessment in the current procedure.

In conclusion, the CHMP considered the PopPK analysis to be overall reasonable.

2.3.2.2.2. Evaluation and application of PopPK model in STREAM Stage 2

Objectives

- Evaluate the parent metabolite population pharmacokinetic (PK) model for bedaquiline and M2 on the data from the STREAM Stage 2 study.
- Determine the individual PK model parameter estimates for bedaquiline and M2 for participants recruited in the STREAM Stage 2 study and provide individual estimates for the following exposure metrics at Weeks 2, 12, 24, and 40:
    - At Week 2, the following exposure metrics will be determined after the last 400 mg once daily (QD) loading dose of bedaquiline, i.e. prior to commencement of maintenance dosing:
        - Trough concentration (C_{trough})
        - Maximum plasma concentration (C_{max})
        - Area under the plasma concentration-time curve from time 0 to 24hours (AUC0-24)
        - Average plasma concentration (Cave) (AUC0-24/24)

- At Weeks 12, 24, and 40 (Week 40 only for Regimen C (bedaquiline)), the following exposure metrics will be determined for maintenance dosing:
  - C_{trough}
  - C_{max}
  - Area under the plasma concentration-time curve from time 0 to 168 hours (AUC0-168)
  - Cave (AUC0-168/168)

The CHMP considered the objectives to be acceptable.

Data

PK observations were available from STREAM Stage 2 for patients at sites pre-selected for the PK sub-study at pre-specified time points as outlined in Table 9

Table 9: PK sample collection timings

Visit	Pre-bedaquiline dose PK blood sample	Pre-ART dose blood sample	Post-bedaquiline dose PK blood sample	Additional post-bedaquiline dose 12-lead ECG
Randomisation	√	√		
2	√	√	√	√
4	√			
12	√	√	√	√
24	√		√	√
40	√		√ (Arm C only)	√ (Arm C only)
76	√			
120[1]	√			
132[1]	√			

[1] PK samples will not be taken after the projected Week 96 visit of the last patient randomised i.e. approximately end of November 2021.

In total, 6155 PK observations (3087 bedaquiline concentrations, and 3068 M2 concentrations) were available from 282 participants. The baseline characteristics of these patients are summarised in Table 10.

Table 10: Summary of demographics

	Age (yr)	Weight (kg)	Body mass index (kg/m^2)	Albumin (g/L)	CrCL (mL/min)	Sex	Race	Regimen
N	282	282	282	282	282	Male: 174	White: 53	C: 173
Mean	35.8	53.9	19.7	38	104.1	(61.7%)	(18.8%)	(61.3%)
SD	11.1	12.3	4.2	5	30.4	Female: 108	Black: 91	D: 109
CV %	30.9	22.8	21.6	13.2	29.2	(38.3%)	(32.3%)	(38.7%)
Median	33.7	51.6	19	38	101.8		Asian: 138	
Min	16	28	11.6	24	21.7		(48.9%)	
Max	68.9	123.4	47.6	49	278.9			

N = number of participants, SD = standard deviation, CV = coefficient of variation, Min = minimum, Max = maximum

Graphical evaluations of the PK observations are shown in Figure 8 (versus time since first dose) and Figure 9 (versus time since most recent dose, stratified by visit).

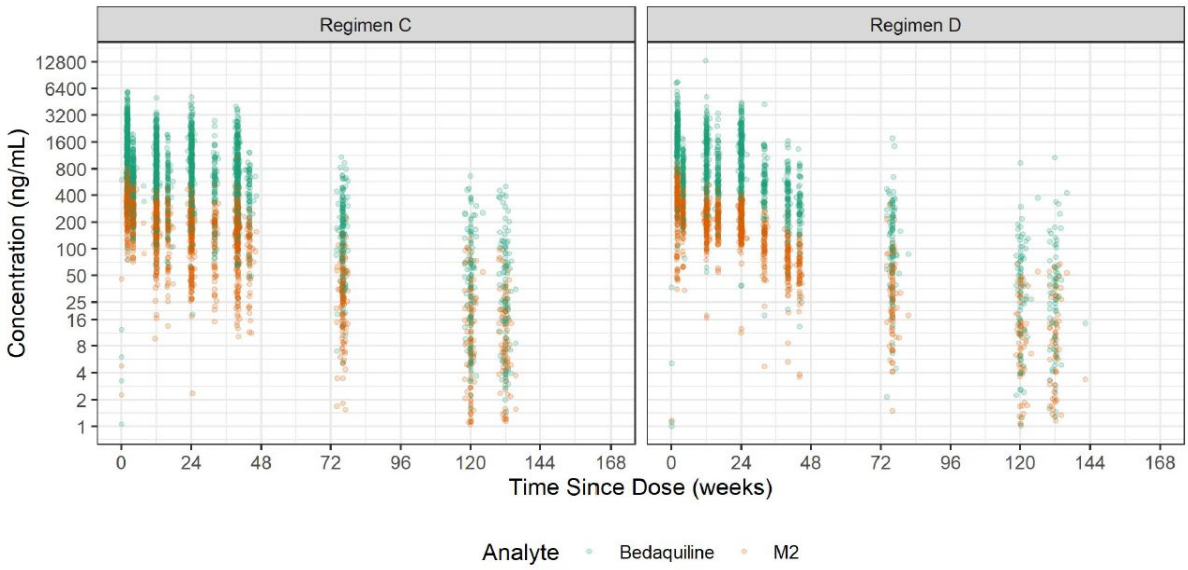
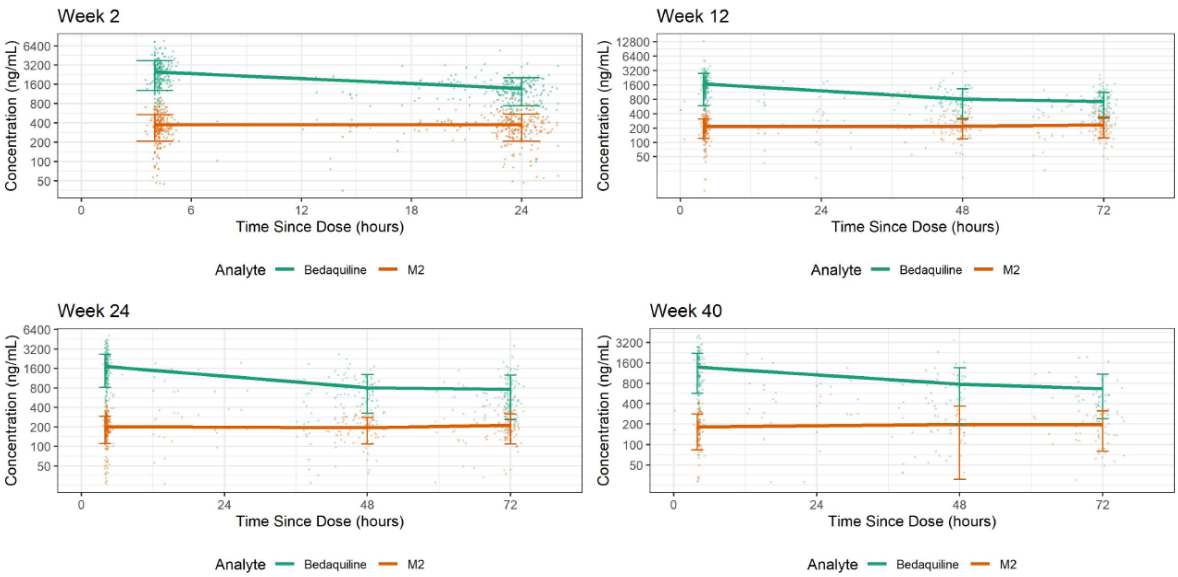


Figure 8 Bedaquiline and M2 PK concentrations



Horizontal lines = mean trend, error bars = mean +/- SD.

Figure 9 Bedaquiline and M2 PK concentrations by week

A summary of the data excluded from the analysis is shown in Table 11. A total of 644 observations (303 bedaquiline and 341 M2 observations, 9.5%) were excluded from the population PK NONMEM dataset. The majority of these observations were excluded as they were collected prior to the first dose (n = 518). Post-dose BLQ observations accounted for 1.2% of all observations.

Table 11: Summary of excluded PK data

	BDQ	M2	Total
Original observations	3390	3409	6799
Day1 Pre-dose	259 (7.6%)	259 (7.6%)	518 (7.6%)
Duplicate time	17 (0.5%)	16 (0.5%)	33 (0.5%)
No Valid Data	5 (0.1%)	5 (0.1%)	10 (0.1%)
No Valid Dose	1 (0%)	1 (0%)	2 (0%)
Post-dose BLQ	21 (0.6%)	60 (1.8%)	81 (1.2%)
Analysis observations	3087	3068	6155

The CHMP noted that the dataset comprised 6155 PK observations (3087 bedaquiline concentrations, and 3068 M2 concentrations) from 282 participants. As sparse sampling was used, a PopPK approach to analyse these data is considered a relevant choice. The covariate distributions are considered acceptable given the objectives.

The CHMP considered the exclusions of data points reasonable. Apart from pre-dose samples, there were generally only few samples excluded.

Methods

The parent metabolite model for bedaquiline and M2 was evaluated on the STREAM Stage 2 dataset with the parameters fixed to the final estimates previously obtained for the MDR-TB participants. Model evaluation techniques to assess the quality of model fit included diagnostic plots, visual predictive checks (VPCs), and individual profiles.

Following model evaluation individual exposure metrics were derived in NONMEM by fixing the parameters to the final model estimates and setting MAXEVAL=0 (i.e. estimation of the individual random effects only). Individual predictions were obtained at dummy time points (every one hour),

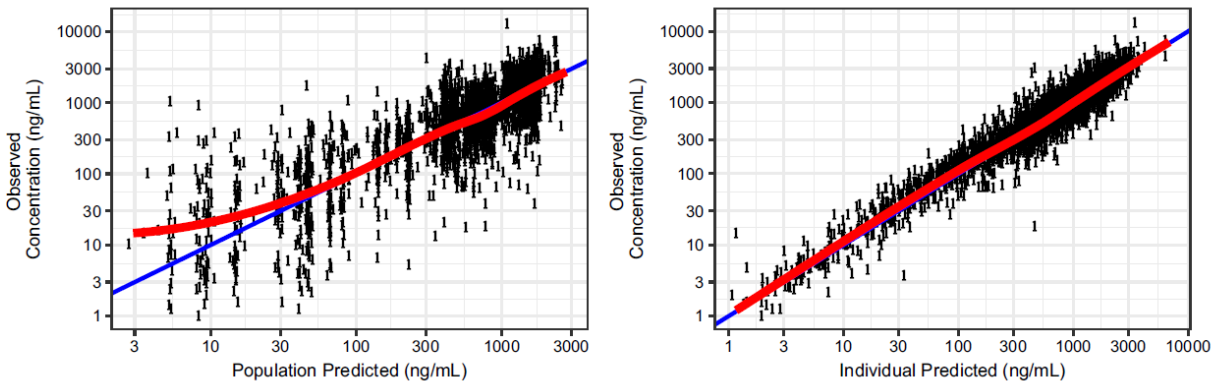
supporting the calculation of bedaquiline and M2 AUC0-24 (Week 2), AUC0-168 (Weeks 12,24,40), C_{max} (Weeks 2, 12, 24, 40) and C_{trough} (Weeks 2, 12, 24, 40).

The CHMP noted that the MAH applied a previously developed PopPK model without re-estimating any parameters (i.e. "MAXEVAL=0"-setting). This could be considered a reasonable strategy as it may not be appropriate to re-estimate the rather complex PopPK model on data from only 282 patients with sparse PK sampling. However, a potentially better alternative would be to pool the STREAM Stage 2 PK data with the previous PopPK dataset and perform a pooled analysis. However, the current approach is most likely sufficient and is considered good enough given the impact of PK in the current procedure.

The CHMP considered that reasonable evaluation techniques were applied to evaluate the model fit for the STREAM Stage 2 data.

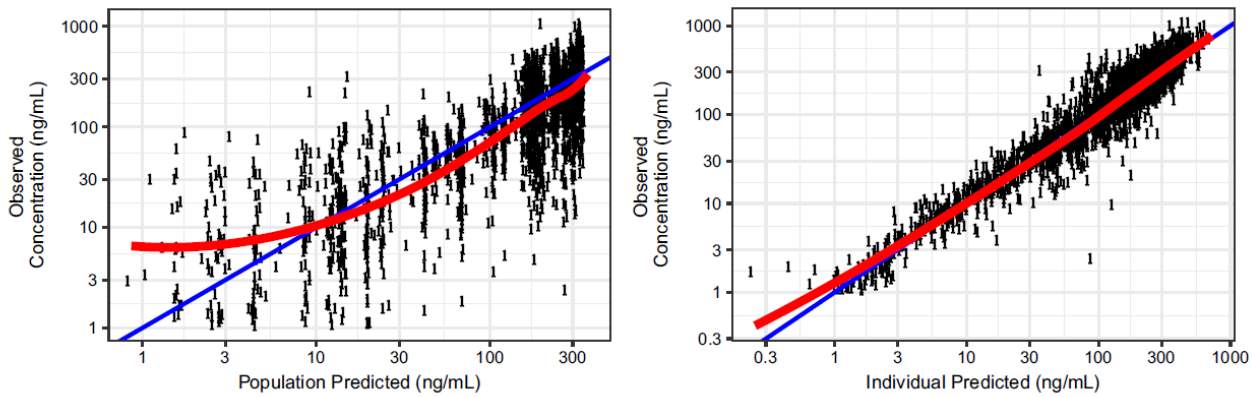
Results

Plots of observed versus population predicted plasma concentrations and observed versus individual predicted plasma concentrations for bedaquiline and M2 are presented in Figure 10 and Figure 11.



The blue lines represent the line of unity, the red lines show the trend in the data (Loess smooth)

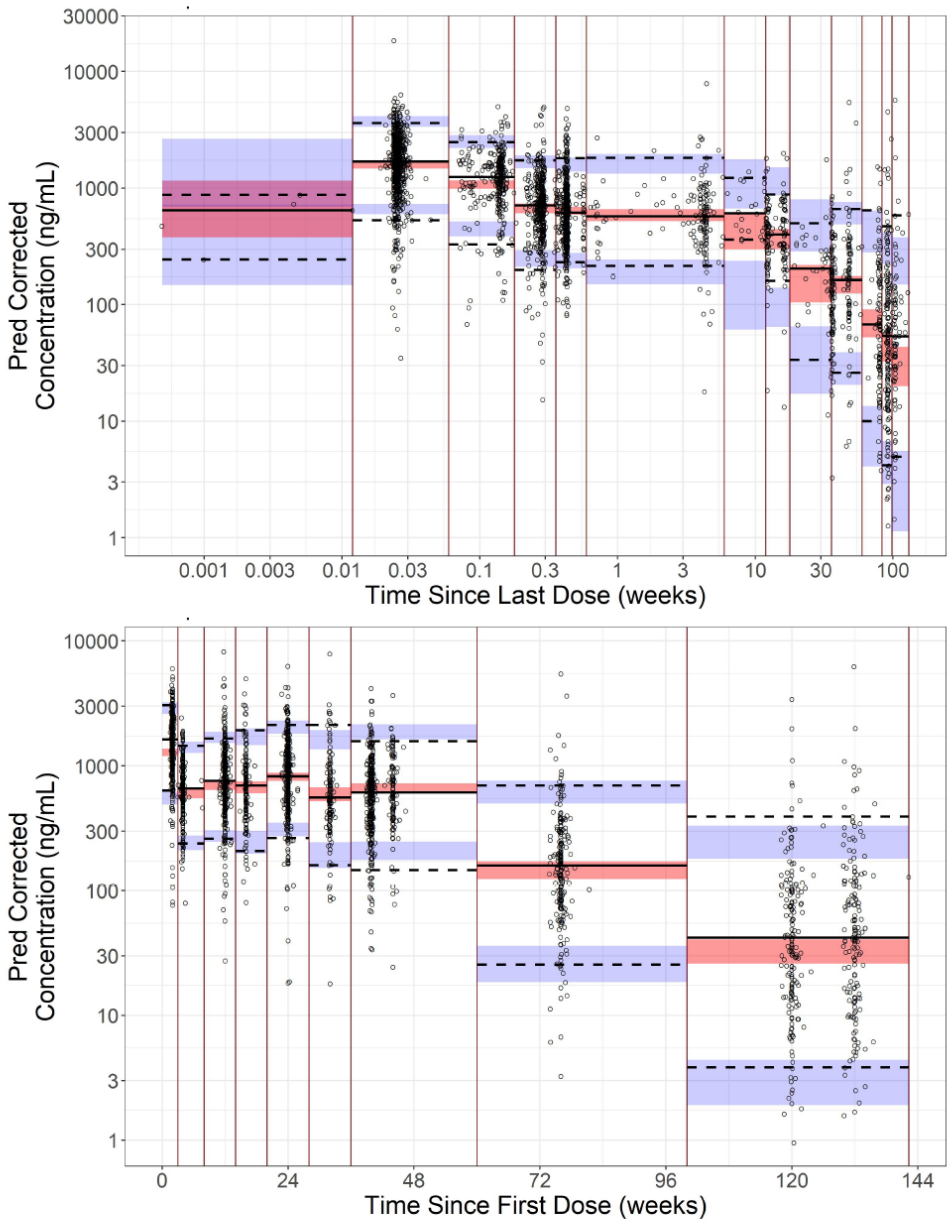
Figure 10 Goodness of fit plots for the prior parent-metabolite PK model - bedaquiline



The blue lines represent the line of unity, the red lines show the trend in the data (Loess smooth)

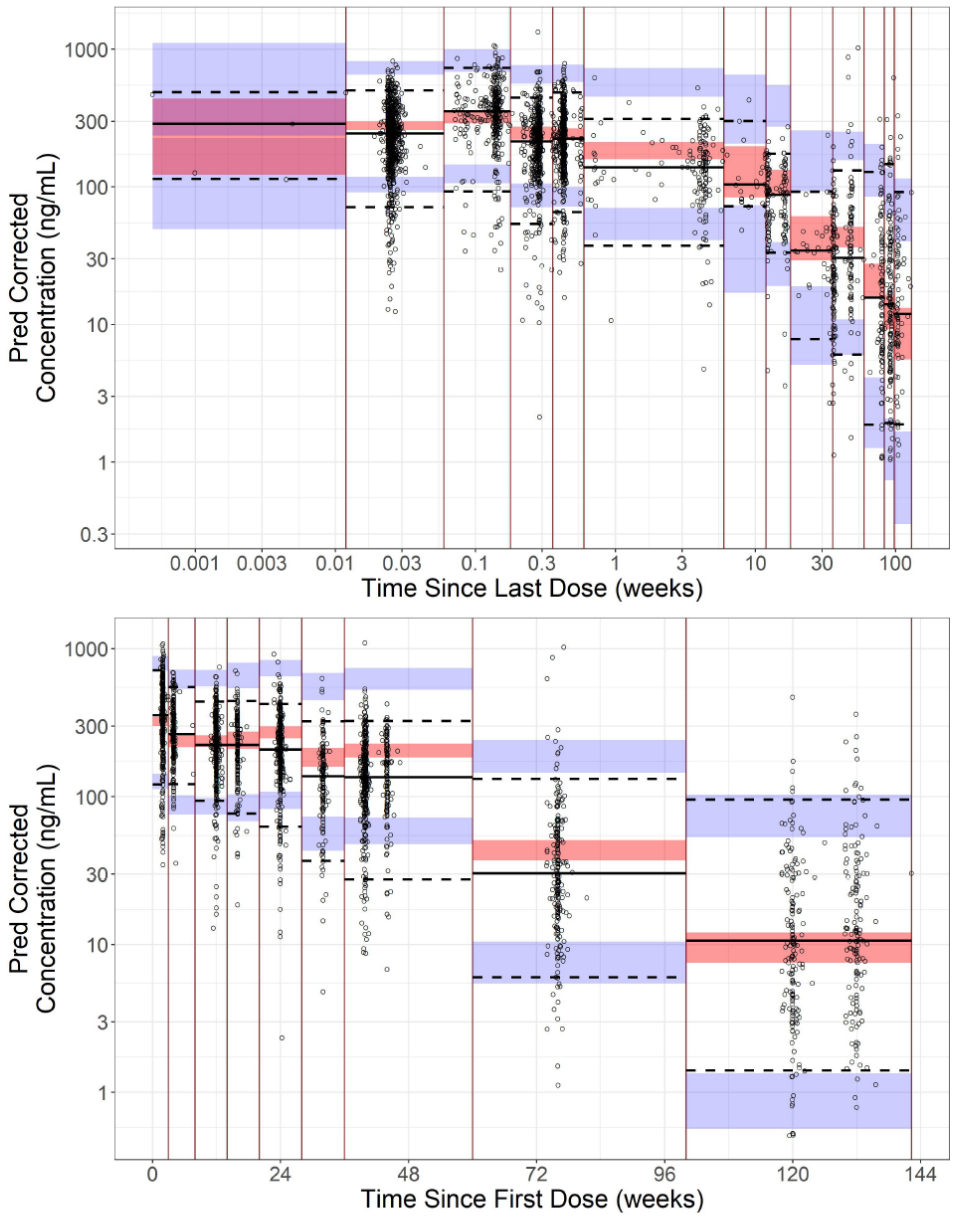
Figure 11 Goodness of fit plots for the prior parent-metabolite PK model - M2

To further validate the model graphically, prediction corrected visual predictive checks (pcVPCs) were constructed and are shown in Figure 12 and Figure 13.



Open circles = individual prediction corrected observed data, dashed blue lines = observed 5th and 95th percentiles, solid blue line = observed median, shaded red and purple areas = 95% confidence interval for the simulated percentiles , red lines = bin limits. Note: log-log scale is used on the top plot, log-y is used on the bottom plot.

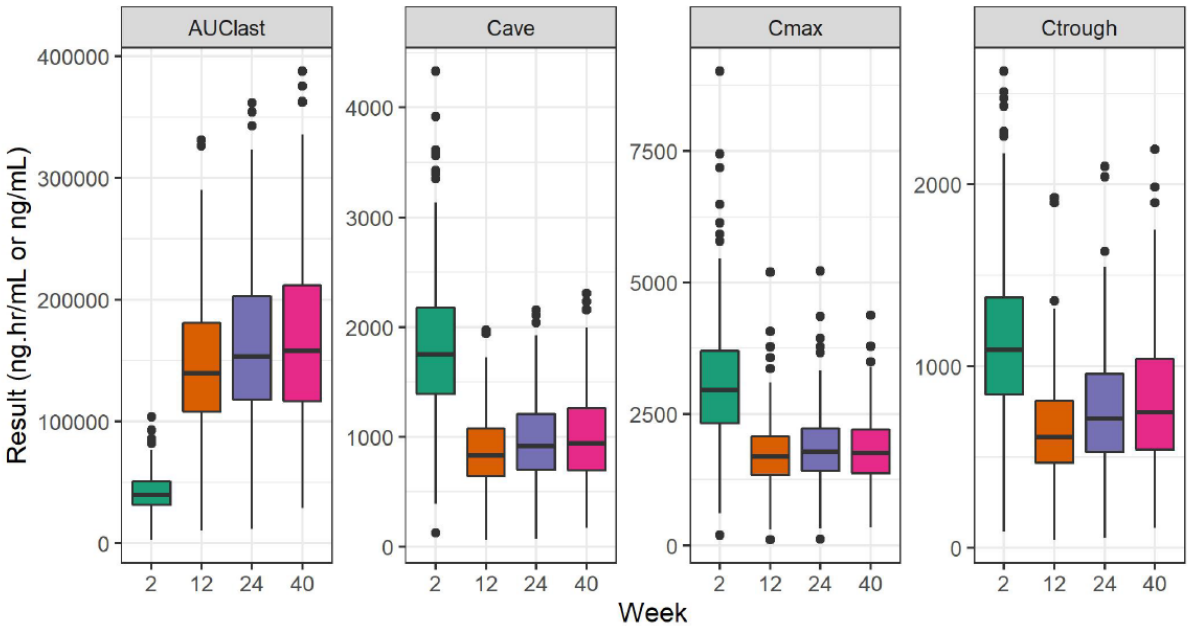
Figure 12 pcVPC for the prior parent-metabolite PK model - Bedaquiline



Open circles = individual prediction corrected observed data, dashed blue lines = observed 5th and 95th percentiles, solid blue line = observed median, shaded red and purple areas = 95% confidence interval for the simulated percentiles , red lines = bin limits. Note: log-log scale is used on the top plot, log-y is used on the bottom plot

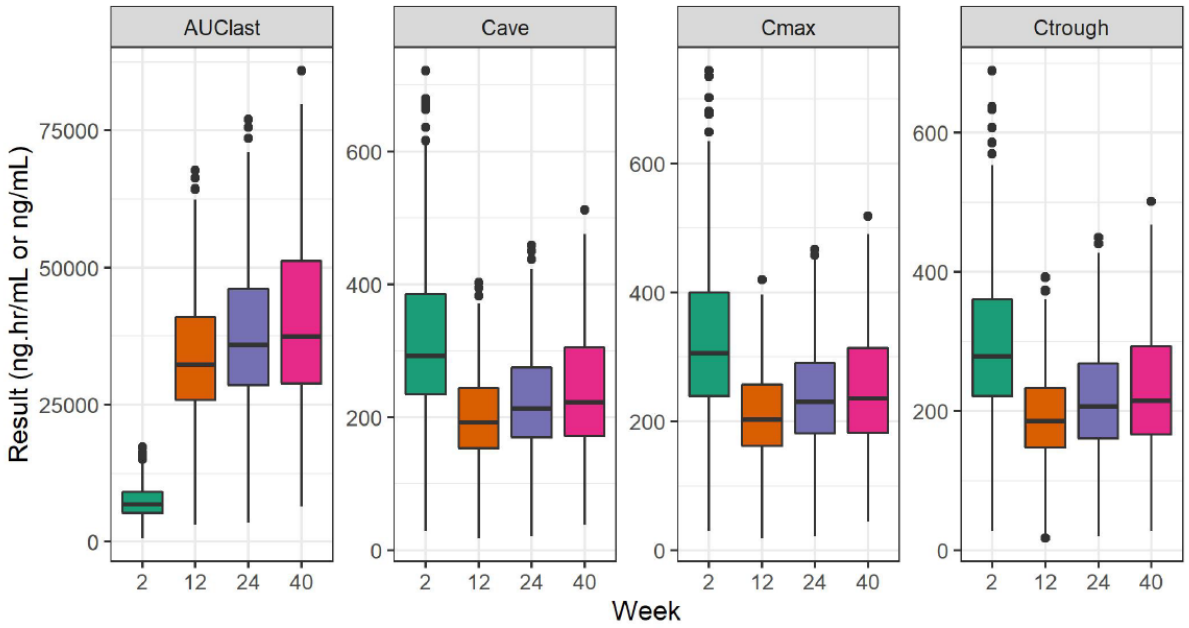
Figure 13 pcVPC for the prior parent-metabolite PK model - M2

Boxplots of exposure metrics for both bedaquiline and M2 are displayed in Figure 14 and Figure 15, respectively. A tabular summary of exposure metrics for bedaquiline and M2 are displayed in Table 12 and Table 13 for Week 2 and in Table 14 and Table 15: 3 for Week 40, respectively.



AUClast = $AUC_{0\text{-}24}$ at Week 2 and $AUC_{0\text{-}168}$ at other weeks

Figure 14 Boxplot of bedaquiline exposure metrics by week



AUClast = $AUC_{0\text{-}24}$ at Week 2 and $AUC_{0\text{-}168}$ at other weeks

Figure 15 Boxplot of M2 exposure metrics by week

Table 12: Exposure metric summary, bedaquiline week 2

	AUC_{0-24} (ng.h/mL)	C_{ave} (ng/mL)	C_{max} (ng/mL)	C_{trough} (ng/mL)
N	281	281	281	281
Mean	41500	1800	3060	1130
95% CI	39700 – 43300	1730 – 1880	2930 – 3190	1080 – 1180
SD	15100	646	1120	437
CV%	36.3	35.8	36.7	38.6
GeoMean	38500	1680	2840	1040
GeoMean CV%	44.2	43.3	43.1	46.8
Min	3000	125	188	90.8
Median	39900	1750	2960	1090
Max	104000	4330	9030	2620

SD = standard deviation, CV = coefficient of variation, CI = confidence interval. Values were reported with 3 significant digits. Median (range) T_{last} 24.0 h (12.2 h – 24.0 h).

Table 13: Exposure metric summary, M2 week 2

	AUC_{0-24} (ng.h/mL)	C_{ave} (ng/mL)	C_{max} (ng/mL)	C_{trough} (ng/mL)
N	281	281	281	281
Mean	7270	315	326	296
95% CI	6910 – 7620	300 – 330	310 – 342	282 – 311
SD	3030	127	135	119
CV%	41.7	40.5	41.3	40.2
GeoMean	6560	286	296	270
GeoMean CV%	52.4	50.2	50.7	49.9
Min	677	29.0	29.3	27.9
Median	6840	292	305	278
Max	17300	722	744	690

SD = standard deviation, CV = coefficient of variation, CI = confidence interval. Values were reported with 3 significant digits. Median (range) T_{last} 24.0 h (12.2 h – 24.0 h).

Table 14: Exposure metric summary, bedaquiline week 40

	AUC_{0-168} (ng.h/mL)	C_{ave} (ng/mL)	C_{max} (ng/mL)	C_{trough} (ng/mL)
N	144	144	144	144
Mean	168000	1000	1790	812
95% CI	156000 – 181000	929 – 1080	1680 – 1900	746 – 879
SD	74500	443	666	404
CV%	44.2	44.2	37.3	49.7
GeoMean	151000	900	1660	708
GeoMean CV%	52.4	52.4	43.2	60.6
Min	29000	173	339	111
Median	158000	940	1750	746
Max	388000	2310	4370	2190

SD = standard deviation, CV = coefficient of variation, CI = confidence interval. Values were reported with 3 significant digits.

Table 15: Exposure metric summary, M2 week 40

	AUC_{0-168} (ng.h/mL)	C_{ave} (ng/mL)	C_{max} (ng/mL)	C_{trough} (ng/mL)
N	144	144	144	144
Mean	39500	235	246	228
95% CI	36700 – 42400	218 – 252	229 – 263	211 – 245
SD	17200	102	103	102
CV%	43.5	43.5	42	44.9
GeoMean	35200	209	220	201
GeoMean CV%	56.4	56.4	53.9	59.6
Min	6380	37.9	44.6	27.3
Median	37400	223	236	215
Max	86000	512	518	501

SD = standard deviation, CV = coefficient of variation, CI = confidence interval. Values were reported with 3 significant digits.

The CHMP noted that for bedaquiline, both the DV vs PRED, DV vs IPRED and the pcPVCs indicate that the model gave acceptable description of the observed data and that the previous PopPK model is reflective of the STREAM Stage 2 bedaquiline PK data.

For M2, both the DV vs PRED and pcVPCs indicated that the model overpredicts M2 concentrations. This is considered a limitation. However, it should be acknowledged that the DV vs IPRED plot seems acceptable which indicates that the individual parameters (EBEs) which have been derived from STREAM Stage 2 patients are fit-for-purpose. This, along with no clear misspecifications in the individual plots (see paragraph below) suggests that the individual parameters derived for M2 may be acceptable despite a model misspecification in the pcVPC for M2. In this case, the individual parameters are used for describing the PK in STREAM Stage 2, performing PK subgroup analyses and for performing exposure-response analyses.

Apart from the diagnostic plots included above a selection of individual profiles (also known as "individual plots", showing individual and population predictions along with the observations) at pivotal visits for participants included in the analysis were provided in the PopPK report. This is considered a relevant diagnostic given this analysis but were not included in the current AR for brevity. This included individual profiles for a limited number of subjects and are not considered conclusive but at the same time did not identify any clear misspecification which should be acknowledged.

The individual predicted exposure metrics were used to conduct several PK subgroup analyses of STREAM Stage 2 including DDIs.

In conclusion, the CHMP considered the application of the previous PopPK model to describe PK in STREAM Stage 2 to be overall acceptable. Limitations of the analysis are present; however, the model is considered acceptable for descriptive purposes.

2.3.2.2.3. PopPK model development of DDI studies

Objectives

The objective of this analysis was to assess the effect of selected key CYP3A4 perpetrators on BDQ exposure, using simulations based on a previously developed BDQ PopPK model built on Phase 1 and Phase 2 data from participants with MDR-TB and healthy participants (hereafter referred to as the "base model"). The selected perpetrators studied were ritonavir (RTV)-boosted lopinavir (LPV) (RTV is a strong CYP3A4 inhibitor) and nevirapine (NVP; a weak CYP3A4 inducer), which are commonly used by patients coinfected with TB and HIV.

This analysis included the following steps:

- Quantify the impact of CYP3A4 perpetrators on BDQ PopPK model parameters based on single-dose Phase 1 studies and integrate into the base model to develop single-dose DDI models.
- Validate the adequacy of the estimated DDI effects of the single-dose DDI PopPK models in patients by comparing multiple-dose DDI PopPK model-based predictions with PK data from participants with rifampicin-resistant (RR) or MDR-TB (hereafter referred to as "RR/MDR-TB") receiving BDQ and CYP3A4 perpetrators in the Phase 3 study STREAM Stage 2 (a subpopulation with RR/MDR-TB).
- Derive the DDI effect size on the multiple-dose exposure metrics (AUC, average plasma concentration [C_{avg}], trough concentration [C_{trough}], and maximum plasma concentration [C_{max}]) in the general adult population with MDR-TB, using multiple-dose DDI PopPK model simulations of the approved BDQ dose regimen or alternative dose regimens.

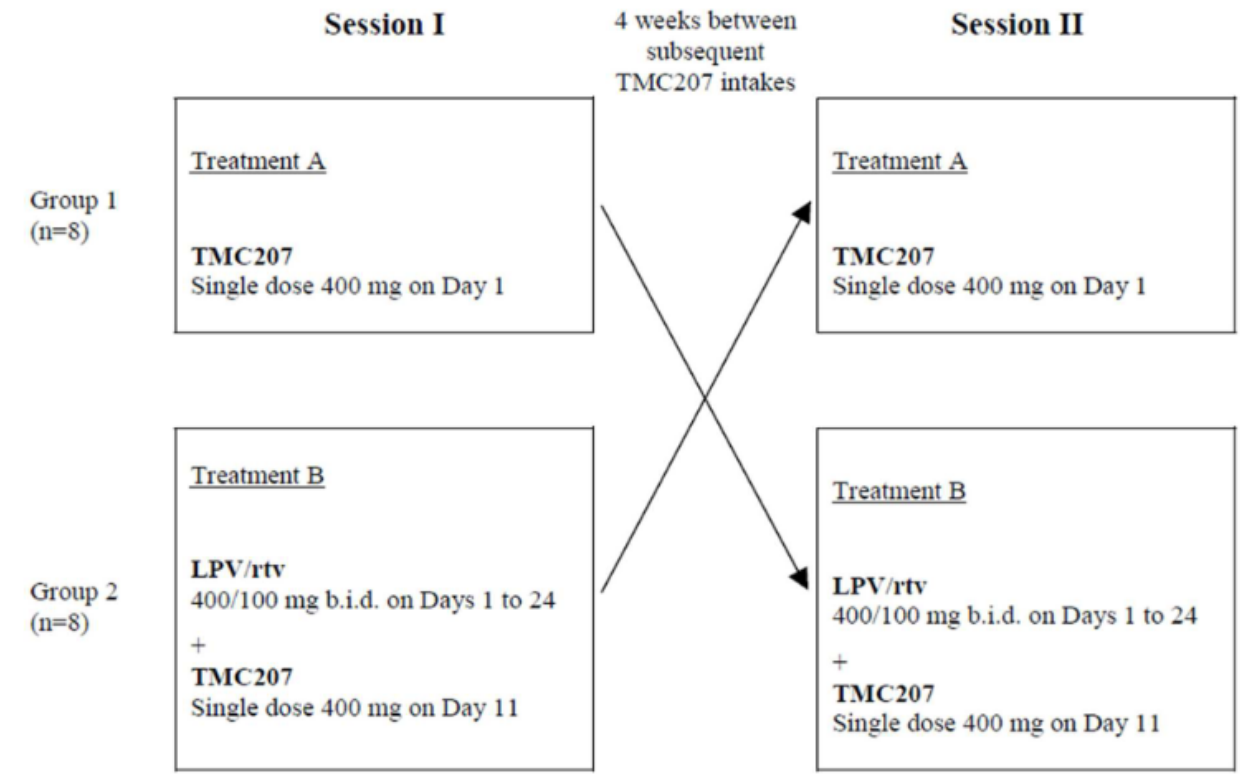
The CHMP considered the objectives to be acceptable. The overall goal of this analysis in this procedure is to support the benefit-risk in special populations (in particular HIV co-infected patients). Two DDI studies have been analysed using PopPK methodology, including nevirapine, a mild CYP3A4 inducer, and lopinavir/ritonavir, categorised as strong CYP3A4 inhibitor(s). The MAH is proposing in section 4.2 of the SmPC to allow co-administration with mild CYP3A4 inducers and strong CYP3A4 inhibitors.

Previous non-compartmental analyses (NCA) were performed on the clinical pharmacology studies included in the current PopPK analysis. Thus, the current PopPK analysis is supportive to the already existing NCA results based on the same data. Furthermore, since the original submission, there are more experience with using bedaquiline in HIV co-infected patients, including efficacy and safety data from STREAM Stage 2. The current PopPK analysis is supportive to the efficacy and safety data (low impact).

Data

Two clinical DDI studies were included in the current analysis and were analysed separately. The included studies were Study C110, a DDI study in healthy volunteers administered LPV/RTV and C117, a DDI study in HIV-positive participants administered NVP.

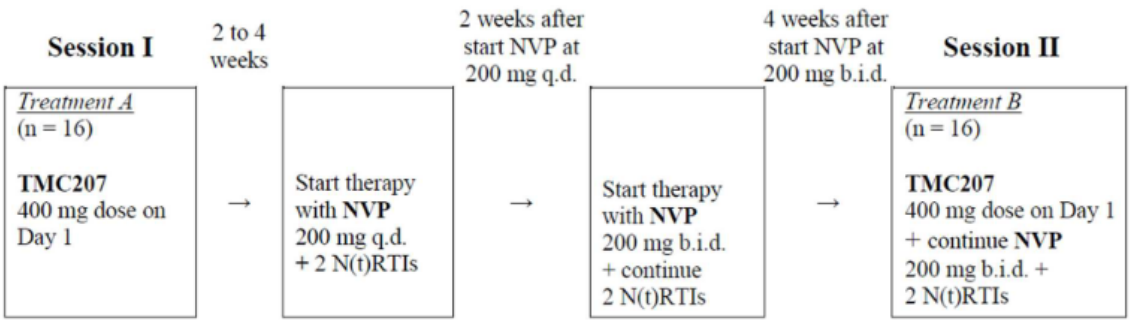
Study C110 was a cross-over study with rich plasma PK sampling of BDQ in each period (Figure 16). The washout between the two periods were 4 weeks. NCA results of Study C110 was submitted in the original submission (111:2012/66501) where more details on the study design can be found. 479 BDQ PK samples were included from 16 patients. Individual BDQ plasma PK profiles until 14 days post-dose were available from 16 healthy participants receiving a single dose of 400 mg BDQ with and without LPV/RTV (400/100 mg twice daily for 24 days) in the randomised, 2-sequence, crossover Study C110. BDQ doses were administered with food 4 weeks apart. Participants were mostly male (93.8%) and non-black (62.5%), with a mean body weight of 77.1 kg.



BDQ=bedaquiline; b.i.d.=twice daily; LPV=lopinavir; n=number of participants; rtv=ritonavir; TMC207=BDQ.

Figure 16 Schematic overview of Study C110

Study C117 explored BDQ PK using a rich PK sampling design and explored BDQ PK before and after administration of NVP (Figure 17). NCA results of Study C110 was submitted in the original submission (111:2012/66501) where more details on the study design can be found. 527 BDQ PK samples were included from 16 patients. Individual BDQ plasma PK profiles until 14 days post-dose were available from 16 HIV-positive participants receiving a single dose of 400 mg BDQ with and without NVP (200 mg once daily for 14 days followed by 200 mg twice daily) in the single-sequence Study C117. BDQ doses were administered with food. Participants were mostly male (62.5%) and half were black (50.0%), with a mean body weight of 56.6 kg.



BDQ=bedaquiline; b.i.d.=twice daily; n=number of participants; N(t)RTI=nucleoside/nucleotide reverse transcriptase inhibitor; NVP=nevirapine; q.d.=once daily; TMC207=BDQ.

Figure 17 Schematic overview of Study C117

Data from STREAM Stage 2 was used for external validation of the respective models. DDI-relevant subgroups of STREAM Stage 2 participants (referred to as the subpopulation with RR/MDR-TB) were used to assess whether the DDI effect sizes estimated based on single-dose data in healthy

participants were predictive of the DDI effect after multiple doses of BDQ in patients with MDR-TB. In STREAM Stage 2, participants with RR/MDR-TB in the BDQ-containing regimens received BDQ 400 mg once daily for 2 weeks, followed by 200 mg 3 times a week for 22 weeks (Regimen D) or 38 weeks (Regimen C (bedaquiline)). PK exposure metrics and estimated GMRs during BDQ treatment were derived by PopPK modelling for the 3 DDI subgroups of STREAM Stage 2 participants that were used in this analysis: the reference (N=18-34), LPV/RTV (N=11-23), and NVP (N=9-22) groups. The LPV/RTV and NVP ART subgroups were defined for each PK visit as all participants receiving the CYP3A4 perpetrator for at least 2 weeks before the visit, and the reference subgroup consisted of all HIV-negative black participants, a PK-influencing covariate for BDQ in the subgroups.

The CHMP considered that the study design of C110 is generally a relevant design for a conventional PK DDI study. In particular, the cross-over design with different sequences is acknowledged. However, BDQ has a very long terminal half-life and the washout period of 4 weeks between BDQ administrations is not sufficient to wash out all residual drug concentrations. A PopPK approach is better suited to account for the insufficient washout compared to a traditional analysis using NCA (Svensson et al 2016 AAPS J 18(1):171-9).

The study design of C117 has a clear limitation in that only a fixed sequence was explored (BDQ in absence of NVP followed by BDQ and NVP in all subjects). It is unclear if the weak interaction can be detected using a PopPK approach.

The external data consisted of a rather limited subset of STREAM Stage 2 which is a clear limitation of the external validation. Not all subjects were sampled for PK and only black subjects were selected for the external validation.

The PopPK datasets for the respective studies (including the external validation data) only includes BDQ and not M2 which is a limitation. M2 may cause QT prolongation and shares (partly) the same elimination pathway as BDQ. If M2 concentrations would have been included, the analysis may have provided additional insight in the expected change in the ratio of BDQ:M2 when BDQ is co-administered with NVP or LPV/RTV.

Methods

The base model for the DDI analysis was developed based on 5222 BDQ PK concentrations from 480 participants in Phase 1 and Phase 2 single- and multiple-dose studies. The pooled data used for model development included a small portion of the data used in the current DDI analysis, i.e., the BDQ-only arm of the LPV/RTV DDI Study C110 (N=8). No data from the NVP DDI Study C117 were used. The PopPK model for BDQ had a 4-compartment disposition with dual zero-order input and linear elimination, with the following covariates: black race and population (healthy, DS-TB, or MDR-TB) on apparent clearance, population on relative bioavailability, and sex on central volume of distribution.

The parameters from the single-dose DDI PopPK model were either fixed to the final estimates of the base model or re-estimated depending on the exploratory data analysis or the base model evaluation, and the DDI parameters were estimated. Residual variability was also re-estimated. IIV was kept fixed to retain a single IIV structure across all populations (Phase 1, DDI subgroups in the subpopulation of STREAM Stage 2 participants with RR/MDR-TB, and the general population with MDR-TB).

The potential perpetrator effect was explored on the different base model parameters. To this end, separate IIVs for the treatment group with perpetrator co-administration were added to the model, allowing separate inter-individual random effects to be estimated for the same individual with and

without the perpetrator. Data were generated using the PopPK model with all population parameters fixed and all IIVs increased 3-fold, the latter to allow greater shifts in model parameters potentially affected by the presence of the DDI. Model parameters that showed systematic changes with and without the perpetrator were selected for the single-dose DDI PopPK model building.

The DDI effect of the perpetrator was assumed to start at full inhibition/induction immediately before BDQ co-administration and to remain present at the full level during the co-administration time (corresponding to the last PK sample).

The single-dose DDI PopPK model building consisted of the following steps:

- Fit the base model on the data corresponding to the administration of BDQ alone, potentially adjusting for covariate effects for the studies not included in the data used to develop the model (ie, Study C117) to avoid biasing the DDI parameter due to any potential small misfits of the data. Parameter updates were done with the full dataset for each study in order to have sufficient data for parameter estimation.
- Test potential DDI models starting from the model in Step 1. The DDI effects were tested primarily on clearances and if required on other parameters according to the IIV exploration, as appropriate and accounting for multiple testing and clinical consideration, until an appropriate single-dose DDI PopPK model was identified. They were parametrised as relative change (Equation 1) unless required otherwise.
    - Equation 1: $\theta_{perpetrator} = \theta_{no\ perpetrator} \times (1 + \theta_{DDI})$

Strong CYP3A4 inhibitor: LPV/RTV

The effect of LPV/RTV on BDQ PK was estimated as a covariate effect on clearance using BDQ concentrations from Study C110. The adequacy of the single-dose DDI PopPK model was evaluated using GOF plots, VPCs, and comparison of the model-based exposure metrics with the original NCA analysis results. The translatability of the estimated DDI effect size from single-dose data in healthy participants to multiple-dose data in patients with MDR-TB was evaluated based on external data from the Phase 3 Study STREAM Stage 2 where BDQ-containing TB regimens were co-administered with the LPV/RTV (see STREAM Stage 2 external validation section below).

Weak CYP3A4 inducer: NVP

The effect of NVP on BDQ PK was estimated as a covariate effect on clearance using BDQ concentrations from Study C117. The adequacy of the single-dose DDI PopPK model was evaluated using GOF plots, VPCs, and comparison of the model-based exposure metrics with the original NCA analysis results. The translatability of the estimated DDI effect size from single-dose data in healthy participants to multiple-dose data in patients with MDR-TB was evaluated based on external data from the Phase 3 Study STREAM Stage 2 where BDQ-containing TB regimens were co-administered with NVP (see STREAM Stage 2 external validation section below).

STREAM Stage 2 external validation

The point estimates of the DDI effect sizes estimated based on Phase 1 studies were used to simulate STREAM Stage 2 PK endpoints (N=1000/DDI subgroup, matching the demographic characteristics from the selected STREAM Stage 2 DDI subgroups). The external validation was considered successful if the simulated values were included in the 95% CI of the observed values in STREAM Stage 2.

Simulation in the general population with MDR-TB

BDQ PK was simulated in the general population with MDR-TB, with and without the perpetrator (N=1000/DDI subgroup, with equal proportions regarding sex [male and female] and race [black and non-black]), assuming full compliance and per protocol dosage of BDQ and the CYP3A4 perpetrator. Key BDQ PK exposure metrics (AUC, C_{avg}, C_{trough}, and C_{max} at Weeks 2, 12, and 24, and related GMRs with and without LPV/RTV) were computed.

The CHMP noted that the base model for development of the respective PopPK models were the BDQ PopPK model from the initial submission (111:2012/66501), which is considered a reasonable strategy.

Based on graphical exploration of the PK data and based on the goodness-of-fit of the base model, an informed decision was made by the MAH regarding which parameters to re-estimate using the DDI data and how to explore effect sizes of the interactions and on which PK parameter. The CHMP considered this to be an overall reasonable strategy.

The goodness-of-fit was evaluated using standard goodness-of-fit plots and using VPCs which is adequate. An external evaluation step was also performed using data from STREAM Stage 2. This step of evaluating the model is acknowledged, however, the external evaluation dataset is rather limited and will not allow any firm conclusions to be drawn.

Results

Strong CYP3A4 inhibitor: LPV/RTV

The perpetrator-free data of Treatment Period 1 from Study C110 (N=8 participants) were included in the development of the base model. GOF plots of this subset of data in the base model were in general acceptable. The DDI effect was implemented as covariate on clearance for the single-dose DDI PopPK model development. In addition, because the individual clearances in absence of LPV/RTV also showed slight trends (most clearances being higher than the population value), the population clearance (without DDI) was also re-estimated to avoid any bias in the DDI estimate.

The final single-dose DDI PopPK model, including an estimated DDI effect on the re-estimated clearance, described Study C110 PK data well.

The estimated change in BDQ clearance with LPV/RTV was mild (−39.3%; 95% CI: −27.9% to −50.7%; RSE: 14.9%) (Table 16). The population clearance without DDI in this study was estimated to be 5.39 L/h, i.e., 41% higher than estimated for other studies with healthy participants.

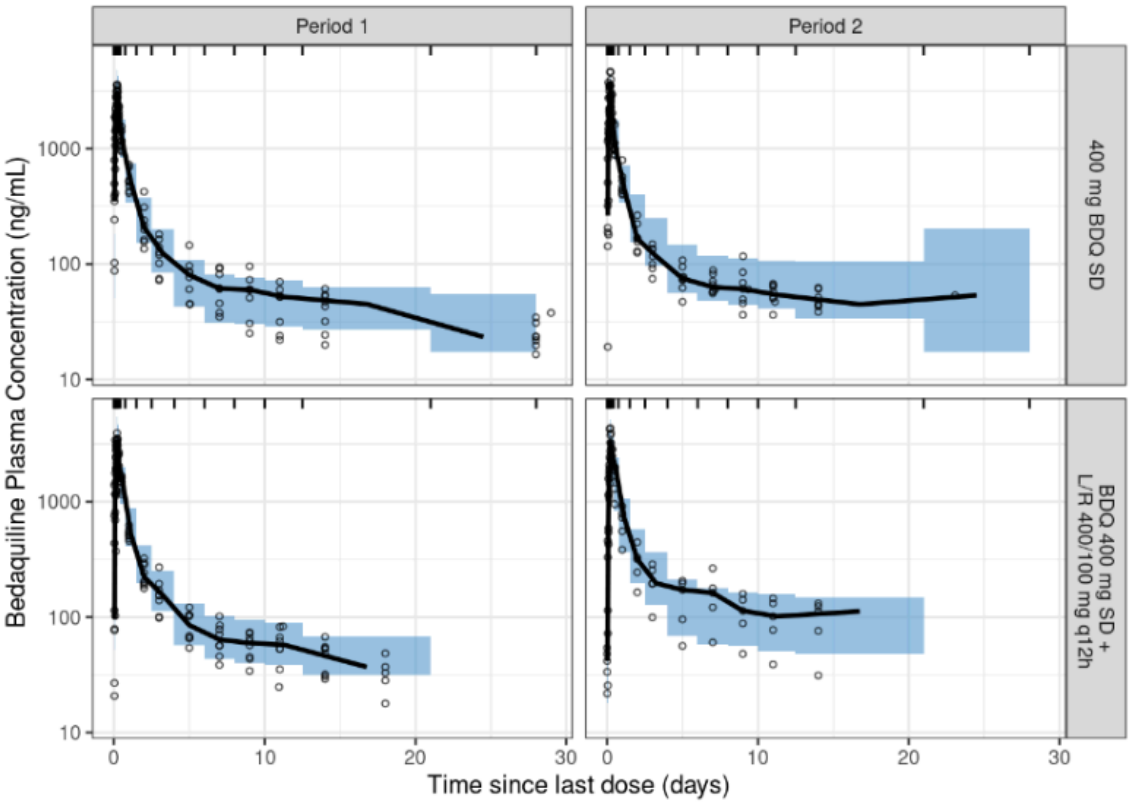
Table 16: Population PK exposure metrics estimates of the single-dose DDI PopPK model for LPV/RTV and BDQ

Parameter	Parameter Description	Single-dose DDI PopPK Model for LPV/RTV and BDQ Parameter Estimate (RSE as 95% CI[a])
CL/F (L/h)	Apparent clearance	5.39 (2.76, 8.02)
$Effect_{LPV/rtv,CL/F}$	– Fraction change in CL/F due to interaction with LPV/RTV	−0.393 (−0.507, −0.279)
RUV (%)	Residual unexplained variability	0.155 (0.143, 0.167)

BDQ=bedaquiline; CI=confidence interval; CL=clearance; DDI=drug-drug interaction; F=bioavailability; LPV=lopinavir; NONMEM=non-linear mixed-effects modeling; PK=pharmacokinetic; popPK=population pharmacokinetic; RSE=residual standard error; RTV=ritonavir.

[a] RSEs were obtained from the NONMEM covariance step.

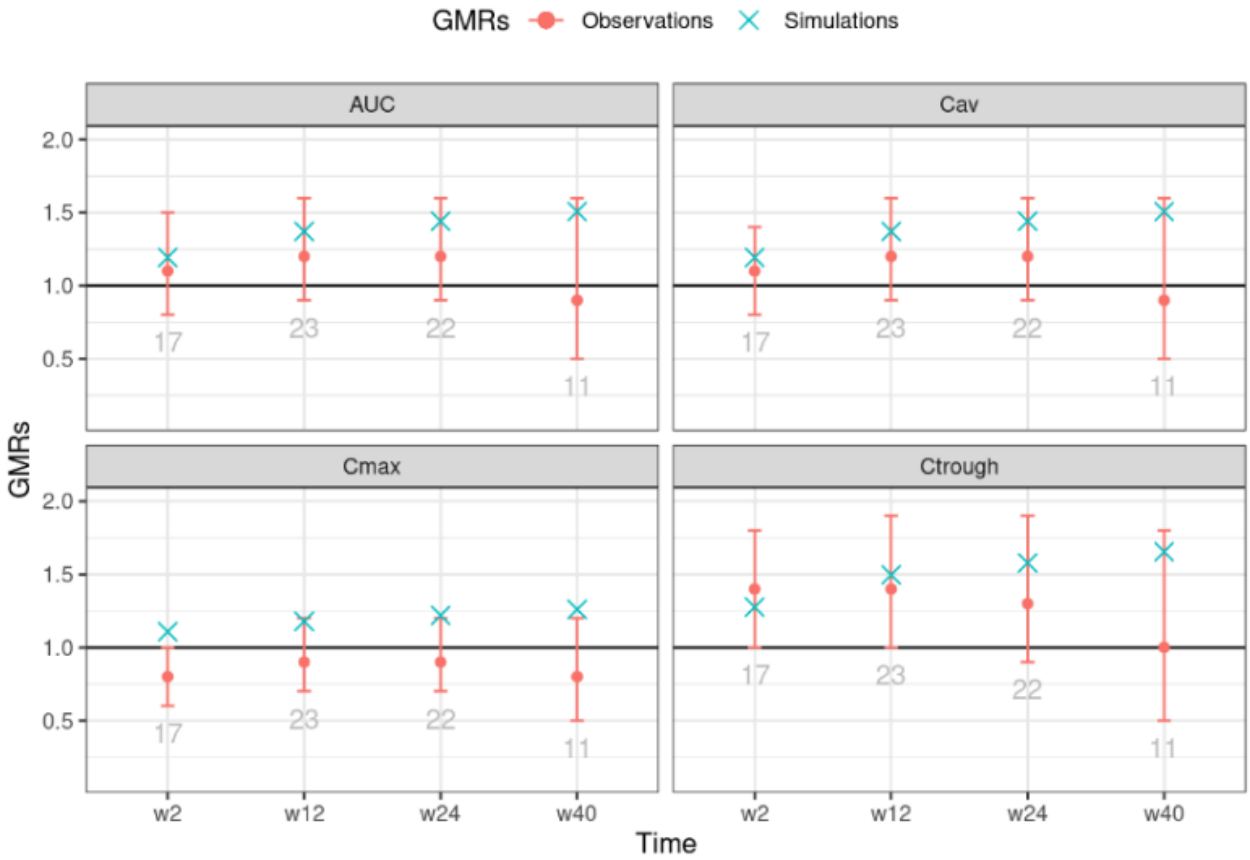
Results of the VPCs are shown graphically by treatment in Figure 18.



BDQ=bedaquiline; DDI=drug-drug interaction; L/R=lopinavir/ritonavir; LPV=lopinavir; popPK=population pharmacokinetic; q12h=every 12 hours; RTV=ritonavir; SD=single dose.
The solid lines represent the median of the observed data and the shaded areas represent the 90% prediction interval around the median (N=500 study replicates). The circles represent the observations and the vertical ticks mark the binning intervals.

Figure 18 Visual predictive check for the single-dose DDI PopPK model for LPV/RTV and BDQ

GMRs from simulated PK exposure metrics were also well aligned with the STREAM Stage 2 PK data (Figure 19). All GMRs from simulated PK exposure metrics were within the 95% CI of the GMRs from observed PK exposure metrics for all parameters and at all timepoints, except for C_{max}, for which the GMR from simulated PK exposure metrics was just above the upper bound of the 95% CI of the GMRs from observed PK exposure metrics at Weeks 2 and 40.



AUC=area under the plasma concentration-time curve (AUC_{24h} for Week 2, AUC_{168h} otherwise); BDQ=bedaquiline; Cav=average plasma concentration; CI=confidence interval; C_{max}=maximum plasma concentration; Ctrough=trough concentration; DDI=drug-drug interaction; GMR=geometric mean ratio; HIV=human immunodeficiency virus; LPV=lopinavir; RR/MDR-TB=rifampicin-resistant/multidrug-resistant tuberculosis; popPK=population pharmacokinetic; RTV=ritonavir; w=week.

Dot and red error bars are the GMR and 95% CI obtained from the STREAM Stage 2 data using the HIV-negative black participants as the reference, with the corresponding number of observations in the LPV/RTV group indicated by the numbers in gray. Blue crosses are the GMRs from simulated PK exposure metrics (for N=1,000 participants/DDI subgroup).

Figure 19 External validation of the multiple-dose DDI PopPK model for LPV/RTV and BDQ on the GMRs of STREAM Stage 2 participants with RR/MDR-TB

Weak CYP3A4 inducer: NVP

The BDQ data observed without co-administration of NVP (Treatment Period 1) proved to be well-described when setting the apparent clearance and relative bioavailability to that estimated for healthy participants. The DDI effect was implemented as covariate on clearance for the single-dose DDI PopPK model development.

The single-dose DDI PopPK model for NVP and BDQ, using fixed parameters of the base model for healthy participants and re-estimated fraction absorbed via the first pathway with the DDI parameter as fractional change in clearance and the residual error, described Study C117 PK data well.

The estimated effect of change in BDQ clearance with NVP was a mild and statistically non-significant change of −7.2% (95% CI: −2.6% to −11.6%; RSE: 133%) (Table 17).

Table 17: Population PK exposure metrics estimates of the single-dose DDI PopPK model for NVP and BDQ

Parameter	Parameter Description	Single-dose DDI PopPK Model for NVP and BDQ Parameter Estimate (RSE as 95% CI[a])
FR1[b]	Logit fraction of the dose absorbed via the first pathway	1.41 Fixed
COVFR1[c]	Change in FR1 for Study C117 (HIV patients)	−0.896 (−0.971, −0.821)
DDI	Relative change in clearance	−0.0724 (−0.261, − 0.116)
RUV (%)	Residual unexplained variability	0.275 (0.258, 0.292)

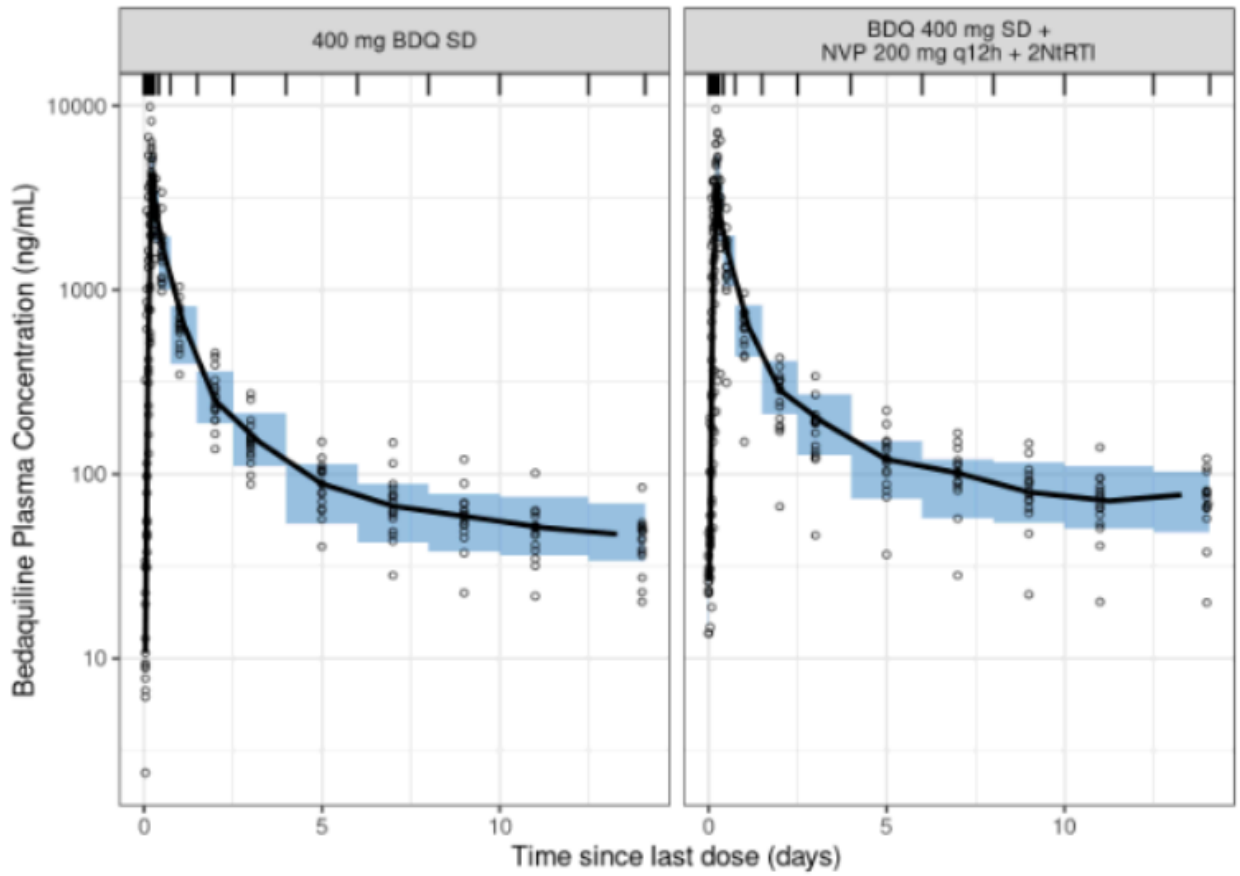
BDQ=bedaquiline; CI=confidence interval; DDI=drug-drug interaction; HIV=human immunodeficiency virus; NONMEM=non-linear mixed-effects modeling; NVP=nevirapine; PK=pharmacokinetic; popPK=population pharmacokinetic; RSE=residual standard error.

[a] RSE were obtained from the NONMEM covariance step.

[b] FR1=F1/(1-F1) or vice versa where F1, the fraction via the first pathway, is 1.41/(1+1.41)=0.585.

[c] COVFR1 is the relative change in FR1, ie. FR1*(1+COVFR1), thus F1 estimated for Study C117 is 1.41*(1−0.896))/(1+1.41*(1−0.896))=0.0942.

Results of the VPCs are shown graphically by treatment in Figure 20.

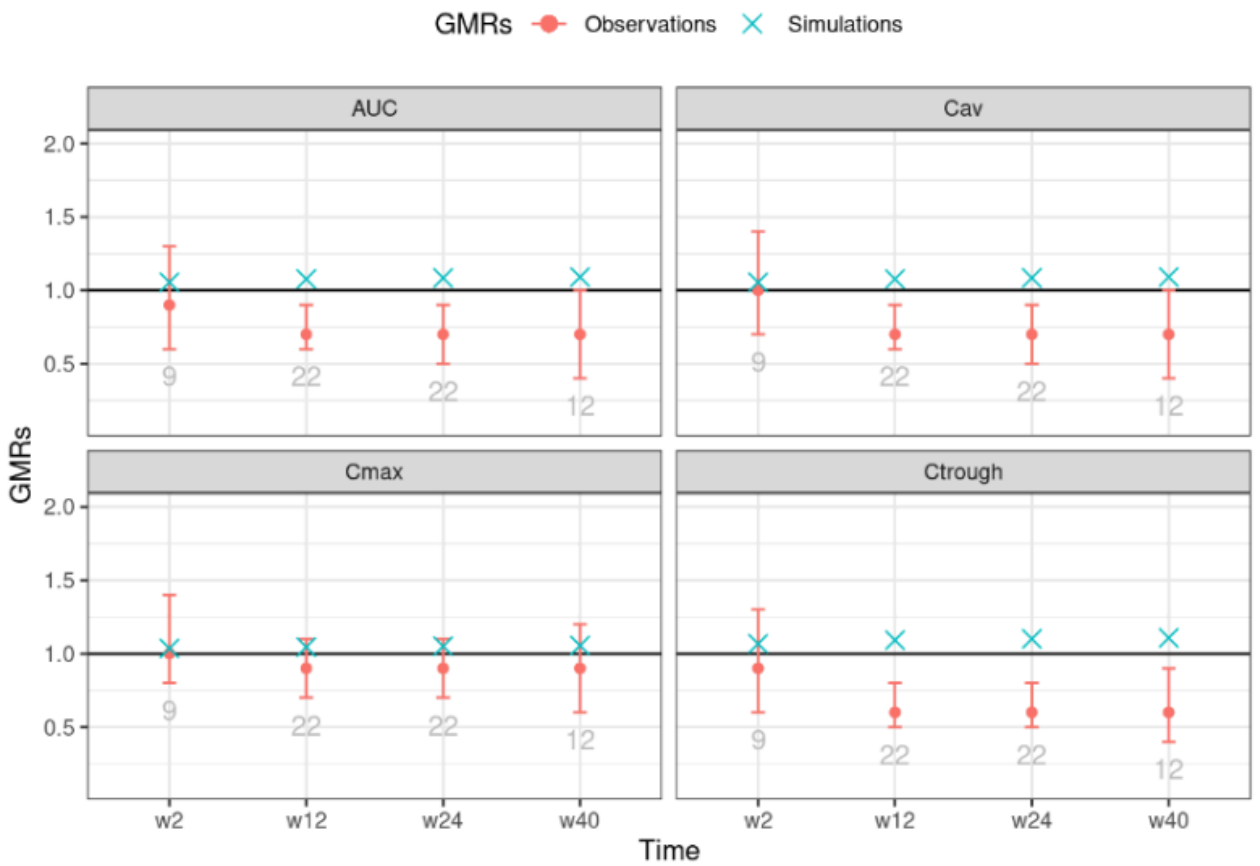


BDQ=bedaquiline; DDI=drug-drug interaction; NtRTI=nucleotide reverse transcriptase inhibitor; NVP=nevirapine; popPK=population pharmacokinetic; q12h=every 12 hours; SD=single dose.

The solid lines represent the median of the observed data and the shaded areas represent the 90% prediction interval around the median (N=500 study replicates). The circles represent the observations and the vertical ticks mark the binning intervals.

Figure 20 Visual predictive check for the single-dose DDI PopPK model for NVP and BDQ

GMRs from simulated PK exposure metrics were not fully aligned with the STREAM Stage 2 PK data (Figure 21).



AUC=area under the plasma concentration-time curve (AUC_{24h} for Week 2, AUC_{168h} otherwise); BDQ=bedaquiline; Cav=average plasma concentration; CI=confidence interval; C_{max}=maximum plasma concentration; Ctrough=trough concentration; DDI=drug-drug interaction; GMR=geometric mean ratio; HIV=human immunodeficiency virus; LPV=lopinavir; NVP=nevirapine; PK=pharmacokinetic; popPK=population pharmacokinetic; RR/MDR-TB=rifampicin-resistant/multidrug-resistant tuberculosis; RTV=ritonavir; w=week.
Dot and red error bars are the GMR and 95% CI obtained from the STREAM Stage 2 data using the HIV-negative black participants as the reference, with the corresponding number of observations in the LPV/RTV group indicated by the numbers in gray. Blue crosses are the GMRs from simulated PK exposure metrics (for N=1,000 participants/DDI subgroup).

Figure 21 External validation of the multiple-dose DDI PopPK model for NVP and BDQ on the GMRs of STREAM Stage 2 participants with RR/MDR-TB

The CHMP considered that for LPV/RTV, the VPC indicated acceptable description of the concentration vs time profiles for both periods with and without concomitant treatment. However, the number of subjects per panel is limited and as a consequence, the confidence intervals in the VPC are rather wide in relation to the magnitude of the DDI which is to be described in this analysis. The external validation showed that the exposure metrics simulated from the model were generally in line with results from subgroups of STREAM Stage 2.

For LPV/RTV, the re-estimated population CL was ~40% higher than estimated for other studies with healthy participants which is considered a limitation. This may be due to systematic difference in the PK behaviour in Study C110 compared to other studies and conclusions drawn based on this analysis alone should be interpreted with caution.

The CHMP noted that the PopPK analysis of the LPV/RTV DDI data points in the same direction as the NCA results submitted in the original submission. The PopPK results indicates that the magnitude of the interaction is slightly larger (~40% reduction in CL) compared to the magnitude of the interaction estimated using NCA (~20% reduction in CL). This indicates that the results derived using NCA under-predicted the interaction. These results are supportive to the previously submitted DDI data for LPT/RTV and the efficacy and safety data from STREAM Stage 2. Whether this is considered a clinically relevant interaction is based on totality of data including efficacy and safety data from STREAM Stage 2.

For NPV, the CHMP considered that the VPC indicated acceptable description of the concentration vs time profiles for both periods. However, the number of subjects per panel is limited and as a consequence, the confidence intervals in the VPC are wide in relation to the magnitude of the DDI which is to be described in this analysis. The estimated interaction on CL predicted a small reduction of CL (~10%) which is paradoxical for a CYP3A4 inducer. The model simulations could not reproduce the data for the external validation which shows that the observed data indicates lower exposure for the interaction (i.e. the opposite of what the simulations suggest).

Taken together, the CHMP could not draw firm conclusions regarding this analysis of NVP data. This may be due to the limited sample size of the study and the study design itself which only included one sequence (first BDQ alone and then BDQ co-administered with NVP). Overall, the CHMP did not consider this analysis sensitive enough to answer the core question (magnitude of DDI for a CYP3A4 inducer).

2.3.2.3. Pharmacokinetic interaction studies

Several analyses of pharmacokinetic interactions were included in the dossier. This includes a population PK analysis of DDI studies included in the initial submission, a subgroup analysis of PK data of the patients in STREAM Stage 2 and a new DDI study with clarithromycin.

2.3.2.3.1. Subgroup analyses of HIV-Coinfected patients in STREAM Stage 2

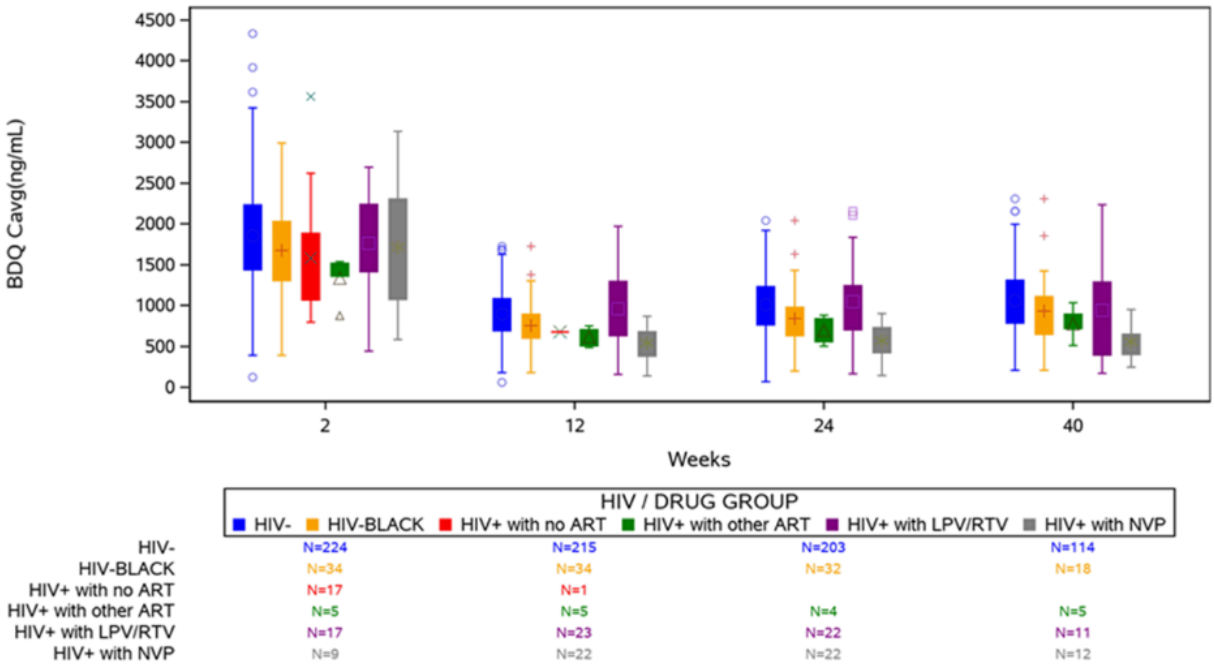
To inform on DDIs between BDQ and ARTs of interest (NVP and LPV/RTV), a comparative analysis of the PK parameters was planned between subgroups of HIV-positive participants on ARTs and HIV-negative participants as primary analysis. However, due to the imbalance in racial distribution (100% black participants in the HIV-positive subgroups vs 15% black participants in the HIV-negative reference subgroup, a known covariate for the PK of BDQ and M2), a subgroup analysis was performed comparing the 4 HIV-positive subgroups with the reference group of black HIV-negative participants only (Figure 22 and Figure 23). The PK exposure was C_{avg} per visit and was calculated from the individual predicted PK parameters from the PopPK application in STREAM Stage 2 patients.

Based on this subgroup analysis:

- Co-administration of LPV/RTV with BDQ did not increase BDQ C_{avg} substantially (C_{avg} increased by 10% and 20% at Weeks 2 and 24, respectively). M2 C_{avg} decreased by 60% and 20% at Weeks 2 and 24, respectively.
- Co-administration of NVP with BDQ did not affect BDQ C_{avg} at Week 2. At Week 24, BDQ C_{avg} was decreased by 30%. This lower exposure for HIV-positive participants on NVP is not associated with lower efficacy as 18 of 20 participants (90.0%) on NVP had a favourable

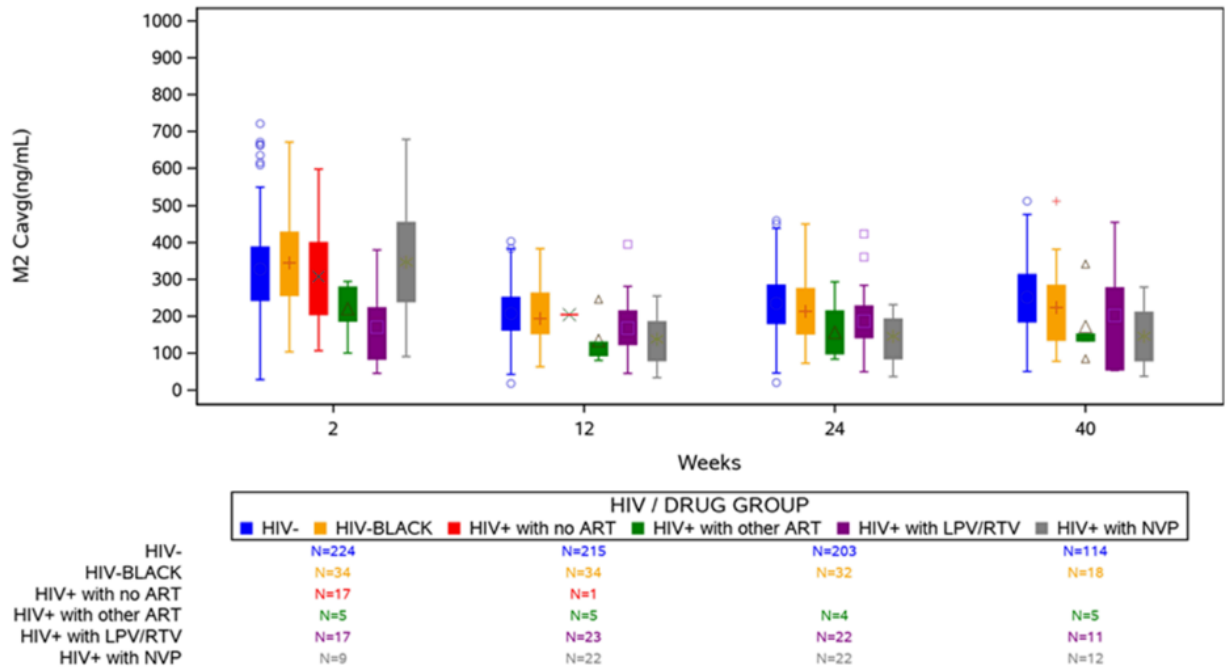
outcome at Week 76, suggesting that NVP had no clinically relevant effect on BDQ exposure. M2 C_{avg} decreased by 10% and 30% at Weeks 2 and 24, respectively.

Mean albumin levels were not substantially different between the black HIV-negative reference group and the black HIV-positive groups for most PK visits, although it was somewhat lower in the NVP subgroup. This may have contributed to some extent to a higher drug clearance and the observed lower exposure in the NVP subgroup.



ART=antiretroviral therapy; BDQ=bedaquiline; C_{av}=average plasma concentration; C_{avg}=average plasma concentration; HIV=human immunodeficiency virus; IQR=interquartile range; LPV/RTV=lopinavir/ritonavir; N=number of participants; NVP=nevirapine; PK=pharmacokinetic(s); Q=quartile.
Box: represents 25th percentile to 75th percentile. Symbols in the boxes represent the median. Whiskers represent the maximum observation below Q3+1.5IQR (upper) and the minimal observation above Q1-1.5*IQR (lower). Values outside of box and whiskers represent outliers.
Source: Mod5.3.5.1/STREAM Stage 2 CSR/GPKPK9919c

Figure 22 Boxplot of BDQ C_{avg} by ART subgroup for Regimens C and D (STREAM Stage 2; PK Analysis Set)



ART=antiretroviral therapy; C_{av}=average plasma concentration; C_{avg}=average plasma concentration; HIV=human immunodeficiency virus; IQR=interquartile range; LPV/RTV=lopinavir/ritonavir; M2=n-monodesmethyl metabolite of BDQ; N=number of participants; NVP=nevirapine; PK=pharmacokinetic(s); Q=quartile.
Box: represents 25th percentile to 75th percentile. Symbols in the boxes represent the median. Whiskers represent the maximum observation below Q3+1.5IQR (upper) and the minimal observation above Q1-1.5*IQR (lower). Values outside of box and whiskers represent outliers.
Source: Mod5.3.5.1/STREAM Stage 2 CSR/GPKPK9920c

Figure 23 Boxplot of M2 C_{avg} by ART subgroup for Regimens C and D (STREAM Stage 2; PK Analysis Set)

The CHMP noted that the MAH performed a subgroup analysis of the PK data in STREAM Stage 2 to explore the exposure differences in patients with HIV co-medications LPV/RTV (strong CYP3A4 inhibitor) or NVP (weak CYP3A4 inducer). This comparison was focused only on HIV+ black participants. The comparison was based only on patients with black race since black race was demonstrated to be such an influential covariate. This is considered overall acceptable considering the complexity of the PK dataset but it should be noted that the resulting number of subjects for making the comparison are rather limited (LPV/RTV: N=11-23 depending on the visit, and NVP: N=9-22 depending on the visit). This should be taken into account when drawing conclusions based on this subgroup analysis.

For LPV/RTV, BDQ C_{avg} did not increase substantially (increased by 10% to 20%) whereas M2 C_{avg} decreased by 60% to 20%. The CHMP agreed that this comparison indicates that the increase in BDQ C_{avg} is rather limited and could support the conclusion that the increase in BDQ exposure is not clinically significant. M2 is known to be formed by metabolism via CYP3A4 and by inhibiting this pathway, it seems logical that the M2 exposure would decrease.

For NVP, BDQ C_{avg} was decreased by (up to) 30% whereas M2 decreased by 10 to 30%. Though from a PK perspective, this is clear evidence of a PK DDI, the CHMP did not consider this to be of clinical relevance. This is supported by subgroup analyses for the efficacy data which showed that the favourable outcome was still sufficiently high in the NVP treated subgroup.

2.3.2.3.2. DDI study of clarithromycin

The MAH provided an additional DDI study with a strong CYP3A4 inhibitor clarithromycin. Study TMC207NTM1001 is a phase I study performed at SGS Clinical Pharmacology unit in Antwerp, Belgium, in 2019, to assess the effect of steady-state clarithromycin at a dose of 500 mg once every 12 hours (q12h) on the pharmacokinetic (PK) parameters of bedaquiline and its main metabolite N-monodesmethylbedaquiline (M2) after a single 100-mg dose of bedaquiline.

This was a Phase 1, single-centre, 2-sequence, open-label, randomised, 2-way crossover study in healthy adult subjects to assess the drug-drug interaction between steady-state clarithromycin and a single dose of bedaquiline.

The study population consisted of 16 healthy adult subjects, who were randomised to 2 treatment sequence groups. Each subject sequentially received 2 treatments (in Periods I and II): A-B in Treatment Sequence Group 1 and B-A in Treatment Sequence Group 2

The treatments were as follows:

Treatment A: a single dose of 100 mg bedaquiline (administered as 1x100-mg oral commercial tablet F001) on Day 1, taken with a standardised breakfast.

Treatment B: 14 days of 500 mg clarithromycin q12h (Days 1-14) (administered as 1x500-mg oral commercial tablet), with a single dose of 100 mg bedaquiline (administered as 1x100-mg oral commercial tablet F001) on Day 5, taken with a standardised breakfast.

The washout period for bedaquiline was at least 28 days.

Full PK plasma profiles of bedaquiline and its main metabolite (M2) were determined over 240 hours (10 days) after administration in each treatment period. Plasma samples were analysed to determine concentrations of bedaquiline and M2, and clarithromycin and 14-OH-clarithromycin, respectively, using validated, specific and sensitive liquid chromatography-mass spectrometry/mass spectrometry methods under the supervision of the sponsor's bioanalytical laboratory.

The primary PK parameters C_{max}, T_{max}, C_{min}, AUC72h, and AUC240h were determined for bedaquiline as well as M2. Metabolite to parent ratio as well as clarithromycin PK were also determined. The least square means (LS means) of the log-transformed primary PK parameters for each treatment were estimated with a linear mixed-effects model, controlling for treatment, sequence and period as fixed effects, and subject as a random effect. A 90% CI was constructed around the difference between the LS means of test and reference. Both the difference between the LS means and the 90% CIs were retransformed to the original scale to provide relative bioavailability estimates with corresponding CIs.

The CHMP noted that performing a drug-drug interaction study with bedaquiline is a difficult task given the very long half-life of both parent compound and metabolite M2. The MAH has chosen a 10 day co-administration of the CYP3A4-inhibitor clarithromycin in treatment B and a 4 weeks washout. This design is better than the previous study with ketoconazole, where only 3 days of co-administration of ketoconazole was used and the wash-out was only 7 days. Carry-over between the periods is however unavoidable, as well as an underestimation of the interaction effect given that 3A4-inhibitition is only evident for 10 days and not during the long terminal elimination phase.

T_{max} and C_{max} of bedaquiline was similar both when given alone and with clarithromycin, whereas mean AUCs were slightly higher after administration of bedaquiline in presence of clarithromycin compared to bedaquiline alone. AUC0-240h of bedaquiline was 14% higher when co-administered with clarithromycin (Table 18).

Table 18:. Summary of PK parameters of bedaquiline after administration alone (A) or in combination with clarithromycin (B)

Table 5: Summary of the Statistical Analysis of the Pharmacokinetic Parameters of Bedaquiline After Administration of Bedaquiline Alone at 100 mg (Treatment A) and in Combination With Clarithromycin at 500 mg q12h for 14 Days (Treatment B); Pharmacokinetics Data Analysis Set (Study TMC207NTM1001)

		Geometric Means		Bedaquiline + Clarithromycin versus Bedaquiline alone			
PK Parameter	n	Bedaquiline 100 mg (Treatment A, reference)	Bedaquiline 100 mg + Clarithromycin at 500 mg q12h for 14 days (Treatment B, test)	Geometric Mean Ratio (%)	Lower Limit 90% CI (%)	Upper Limit 90% CI (%)	Intra-subject CV(%)
C_{max} (ng/mL)	16	1277	1285	100.66	91.22	111.08	15.9
AUC_{72h} (ng.h/mL)	16	13831	15458	111.77	106.52	117.27	7.7
AUC_{240h} (ng.h/mL)	16	18482	21065	113.97	108.88	119.30	7.3

Crossreference: Attachment TABPK16

In line with the long terminal half-life, a period effect was also evident. AUC240h was 8% (Treatment B) to 18% (Treatment A) higher in Period 2 compared to Period 1.

For M2, the plasma levels increased slower when bedaquiline was co-administered with clarithromycin. Given the long half-life of M2, substantial plasma concentrations were evident pre-dose in period 2 (Figure 24). After reaching a peak, M2 mean plasma concentrations tended to slowly decrease with a slight re-increase in treatment period 2. Given the large carry-over between periods, data for M2 is displayed separately for period 1 and 2 in Table 19: PK results of M2 presented separately per period.

Figure 3: Mean Plasma Concentration-time Profile of M2; Pharmacokinetics Data Analysis Set (Study TMC207NTM1001)

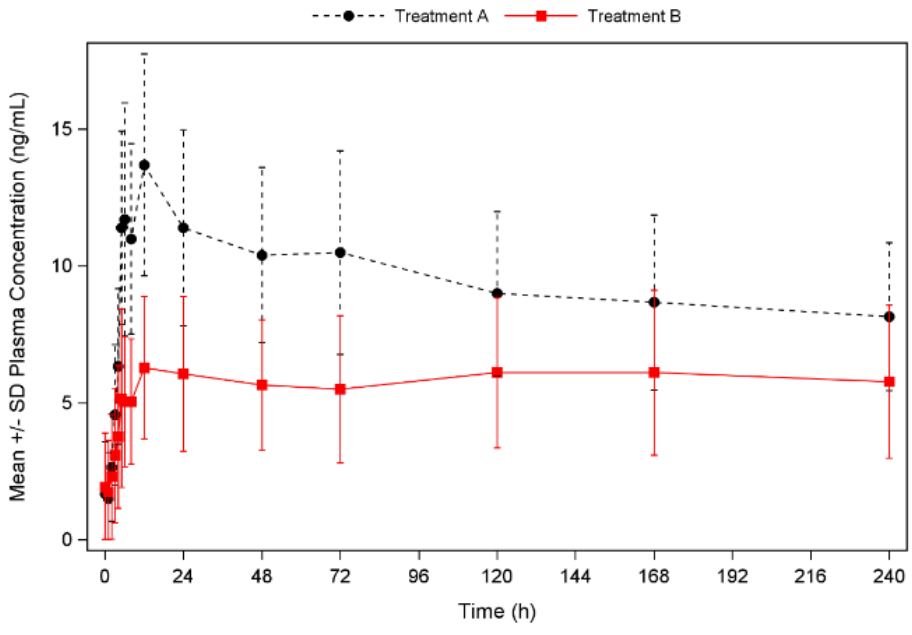


Figure 24 Mean plasma concentration time profile of M2 after administration of bedaquiline alone (A) or in combination with clarithromycin (B).

Table 19: PK results of M2 presented separately per period.

Table 7: Pharmacokinetic Results of M2 After Administration of Bedaquiline Alone at 100 mg (Treatment A) and in Combination With Clarithromycin at 500 mg q12h for 14 Days (Treatment B) per Period; Pharmacokinetics Data Analysis Set (Study TMC207NTM1001)

Pharmacokinetics of M2 mean (SD), t_{max}: median (range)	Bedaquiline 100 mg - Day 1 (Treatment A, reference)		Bedaquiline 100 mg + Clarithromycin at 500 mg q12h for 14 days - Day 5 (Treatment B, test)	
	Period 1	Period 2	Period 1	Period 2
n	8	8	8	8
C_{max} (ng/mL)	12.0 (3.27)	16.3 (3.83)	4.66 (1.54)	9.89 (2.04)
t_{max} (h)	12.00 (5.00 - 239.77)	12.00 (6.00 - 72.28)	35.92 (11.92 - 120.20)	23.90 (11.92 - 220.62)
AUC_{72h} (ng.h/mL)	637 (177)	898 (211)	260 (78.1)	543 (132)
AUC_{240h} (ng.h/mL)	1839 (422)	2691 (715)	886 (268)	1884 (370)
M/P Ratio C_{max} *	0.00936 (0.00318)	0.0142 (0.00514)	0.00390 (0.00153)	0.00798 (0.00294)
M/P Ratio AUC_{72h} *	0.0481 (0.0154)	0.0670 (0.0190)	0.0183 (0.00639)	0.0347 (0.00872)
M/P Ratio AUC_{240h} *	0.110 (0.0299)	0.141 (0.0390)	0.0460 (0.0155)	0.0881 (0.0202)

*: M/P ratios corrected for molecular weight (bedaquiline: 550.50 g/mol; M2: 541.47 g/mol)
Crossreference: Attachment TABPK09 and Attachment TABPK14

The CHMP noted that the results of the current study, with a 14% higher AUC240h of bedaquiline when co-administered with the strong CYP3A4 inhibitor clarithromycin, are in line with the results from the previous DDI study with the other strong CYP3A4 inhibitor ketoconazole, where a 22% increase in AUC was observed. Given the very long half-life of both bedaquiline and its metabolite M2 the exact magnitude of the interaction after longer co-administration and longer sampling is unknown, which should be clarified in the SmPC. The formation of the metabolite M2 is substantially slower when bedaquiline is co-administered with clarithromycin, but given the long half-life of both formation and elimination of the metabolite the data is difficult to interpret and it is agreed with the MAH not to mention them in the SmPC.

The CHMP considered it useful to add the information regarding the clarithromycin study with the information of the ketoconazole study, to highlight the risk for underestimation of the effect for both compounds:

The short term co administration of bedaquiline and ketoconazole (strong CYP3A4 inhibitor) in healthy adults increased the mean bedaquiline exposure (AUC) by 22% [90% CI (12; 32)]. In healthy adults, 10 days of co-administration of another strong CYP3A4 inhibitor, clarithromycin, with single dose bedaquiline increased the mean bedaquiline exposure (AUC) by 14% [90% CI (9; 19)]. A more pronounced effect on bedaquiline may be observed during prolonged co administration of CYP3A4 inhibitors.

2.3.2.3.3. Proposed changes in the SmPC recommendations regarding CYP3A4 inhibitors and inducers

Based mainly on the subgroup analysis from the STREAM Stage 2 study both regarding PK, efficacy and safety, the MAH proposed changes in the SmPC recommendations regarding concomitant use of CYP3A4 inhibitors and inducers.

1) Weak inducers

The MAH proposed to delete the general information in section 4.4 and 4.5 that bedaquiline exposure may be reduced during co-administration with inducers of CYP3A4, and restrict the warning to moderate and strong inducers.

The MAH also proposed to add information from the PK subgroup analysis described above, indicating that the C_{avg} was on average 30% lower at week 24 for patients receiving nevirapine compared with black HIV-negative patients without ART co-treatment.

Table 20 Model-derived PK of BDQ in plasma after administration of BDQ withing regimen C or D in HIV-negative participants or HIV-positive participants with or without coadministration of ARV (STREAMT stage 2;PK Analysis set)

	Mean (SD); %CV						GMR (95% CI) (Test:Reference [HIV-negative, Black])			
	HIV-negative		HIV-positive[a]						Other	
Parameter	All	Black	LPV/RTV	NVP	Other ART	No ART	LPV/RTV	NVP	ART	No ART
Week 24										
n	203	32	22	22	4	0	22[b]	22[b]	4[b]	0[b]
C_{av}, ng/mL	1,009.3 (359.56); 35.6	841.3 (383.02); 45.5	1,048.1 (554.94); 52.9	569.5 (207.00); 36.3	697.5 (171.64); 24.6	-	1.2 (0.9-1.6)	0.7 (0.5-0.9)	0.9 (0.5-1.5)	-
C_{max}, ng/mL	1,896.1 (640.08); 33.8	1,676.3 (624.59); 37.3	1,650.4 (1,000.02); 60.6	1,450.7 (470.04); 32.4	1,166.2 (294.40); 25.2	-	0.9 (0.7-1.2)	0.9 (0.7-1.1)	0.7 (0.5-1.1)	-
C_{trough}, ng/mL	786.3 (303.87); 38.6	627.9 (310.98); 49.5	908.6 (533.34); 58.7	382.0 (154.45); 40.4	559.3 (194.10); 34.7	-	1.3 (0.9-1.9)	0.6 (0.5-0.8)	1.0 (0.5-1.7)	-
AUC_{168h}, ng.h/mL	169,563.8 (60,406.75); 35.6	141,345.9 (64,347.27); 45.5	176,079.3 (93,229.66); 52.9	95,682.4 (34,776.45); 36.3	117,187.2 (28,835.28); 24.6	-	1.2 (0.9-1.6)	0.7 (0.5-0.9)	0.9 (0.5-1.5)	-

18 of the 20 patients with concomitant nevirapine treatment had a favourable clinical outcome, which is in line with the general study population.

The CHMP agreed that nevirapine can be classified as a weak CYP3A4 inducer, and that there is now available data from STREAM Stage 2 suggesting a slightly lower bedaquiline exposure in patients taking nevirapine, but with no sign of a lower efficacy in this subgroup.

The estimation of the effect size of the impact of weak CYP3A4 induction on bedaquiline exposure made from STREAM Stage 2 can be considered uncertain, given the between-group comparison of small numbers of patients and the known risk of confounding with factors like race and albumin. However, even if the exact magnitude of the PK interaction is uncertain, it is agreed that co-administration with weak inducers can now be considered acceptable given that the efficacy in the subgroup receiving nevirapine was in line with the full population, and that the clinical experience with co-administration of bedaquiline with ARDs has increased substantially over the years.

Given the limited data available, the CHMP agreed the following statement to describe the nevirapine interaction:

In the Phase III study, co-administration of the weak CYP3A4 inducer nevirapine and SIRTURO as part of combination therapy for up to 40 weeks in patients co-infected with HIV resulted in a mild decrease in average bedaquiline exposure (AUC) compared to a subgroup without HIV co-infection. This exposure difference was however not associated with a reduction in therapeutic effect. Therefore, no dose adjustment is needed when co-administering SIRTURO with weak CYP3A4 inducers.

2) Moderate and strong CYP3A4 inhibitors

The MAH proposed that restrictions regarding concomitant use with moderate and strong CYP3A4 inhibitors are no longer needed, and that co-administration can be made without dose adjustments. In addition, the MAH wanted to add results from the PK subgroup analysis described above, describing that lopinavir/ritonavir in patients co-infected with HIV resulted in a 20% increase of bedaquiline exposure at Week 24.

The CHMP noted that the MAH considers the combination of lopinavir and ritonavir as a net strong CYP3A4 inhibitor, which is in line with the conclusions made by the Washington drug interaction

database. This appears reasonable even if the interaction can be considered complex with lopinavir being a CYP3A4 inducer. There is now available data from STREAM Stage 2 suggesting a slightly higher bedaquiline exposure in patients taking lopinavir/ritonavir, but with no signs of higher toxicity.

The CHMP considered the estimation of the effect size of the impact of strong CYP3A4 inhibition on bedaquiline exposure made from STREAM Stage 2 to be uncertain, given the between-group comparison of small numbers of patients and the known risk of confounding with factors like race and albumin. However, even if the exact magnitude of the PK interaction is uncertain, the CHMP agreed that co-administration with moderate and strong CYP3A4 inhibitors can now be considered acceptable given that the adverse events in the subgroup receiving lopinavir/ritonavir was in line with that in the full population, and that the clinical experience with co-administration of bedaquiline with ARDs has increased substantially over the years.

Given the limited data available, the CHMP agreed the following statement to describe the lopinavir/ritonavir interaction:

Co-administration of SIRTURO and CYP3A4 inhibitors does not have a clinically relevant effect on bedaquiline exposure. Therefore, the co-administration of SIRTURO and CYP3A4 inhibitors is allowed, and no dose adjustment is needed.

The short-term co-administration of bedaquiline and ketoconazole (strong CYP3A4 inhibitor) in healthy adults increased the mean bedaquiline exposure (AUC) by 22% [90% CI (12; 32)]. In healthy adults, 10 days of co-administration of another strong CYP3A4 inhibitor, clarithromycin, with single-dose bedaquiline increased the mean bedaquiline exposure (AUC) by 14% [90% CI (9; 19)]. A more pronounced effect on bedaquiline may be observed during prolonged co-administration of CYP3A4 inhibitors.

In the Phase III trial, long-term co-administration of SIRTURO as part of a combination therapy and lopinavir/ritonavir in patients co-infected with HIV resulted in a mild increase in mean bedaquiline exposure at Week 24 compared to a subgroup without HIV co-infection. No dose adjustment is required.

2.3.3. Pharmacodynamics

The primary and secondary pharmacodynamics of bedaquiline were well described by non-clinical data previously submitted as part of the original registration dossier, which are not re-discussed in this assessment. New data pertaining to the further characterisation of drug-drug interactions (DDI) and safety pharmacology are discussed within the relevant sections.

2.3.4. PK/PD modelling

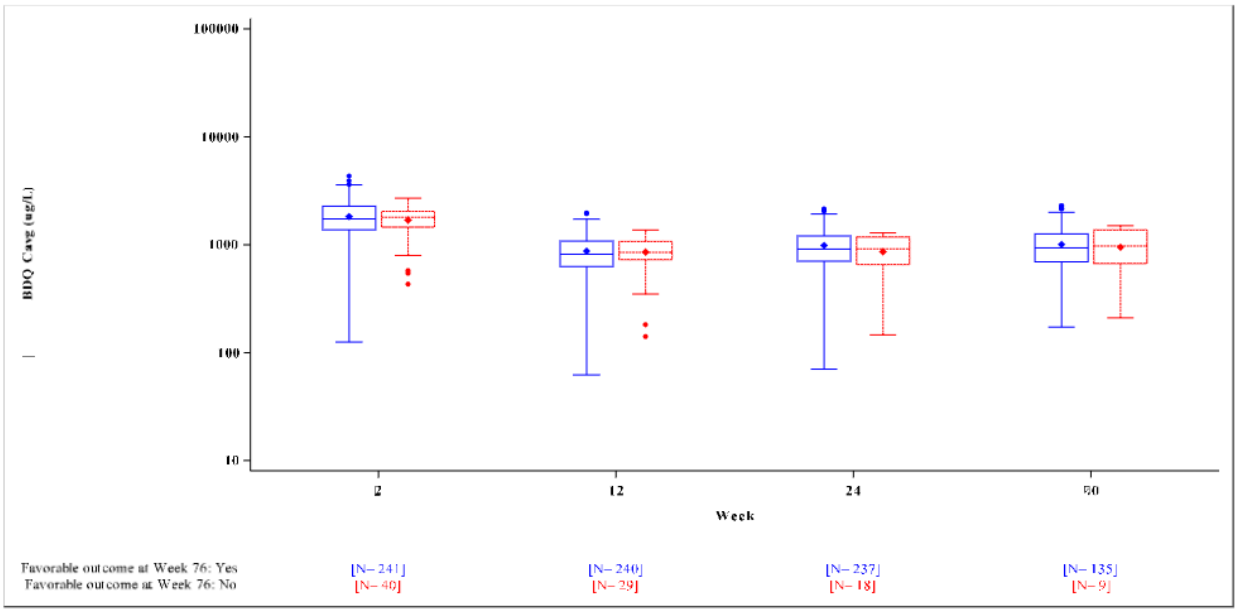
PK/PD relationships of bedaquiline (and M2) were evaluated both for efficacy and safety endpoints. The antimycobacterial activity of BDQ and the relationship between BDQ exposure and antimycobacterial activity was evaluated in the original submission and again evaluated in STREAM Stage 2 for the culture conversion and favourable outcome endpoints. For safety, a concentration-QT analysis was performed based on studies C208 and C209. Since the initial approval of BDQ, extensive research has been performed, providing quantitative estimates on the QT-prolonging effect of BDQ. Some of these published literature sources are cited and used to support the assessment of QT prolongation in the current procedure.

The CHMP noted the PK/PD analyses for both efficacy and safety endpoints performed by the MAH. The efficacy endpoints include culture conversion and favourable outcome and the safety endpoint included QT prolongation.

The exposure-response analyses are considered supportive only and have low impact in the context of the robust clinical data package. The CHMP considered clinical efficacy and safety data to be the most important for drawing the necessary conclusions needed for assessing the benefit-risk.

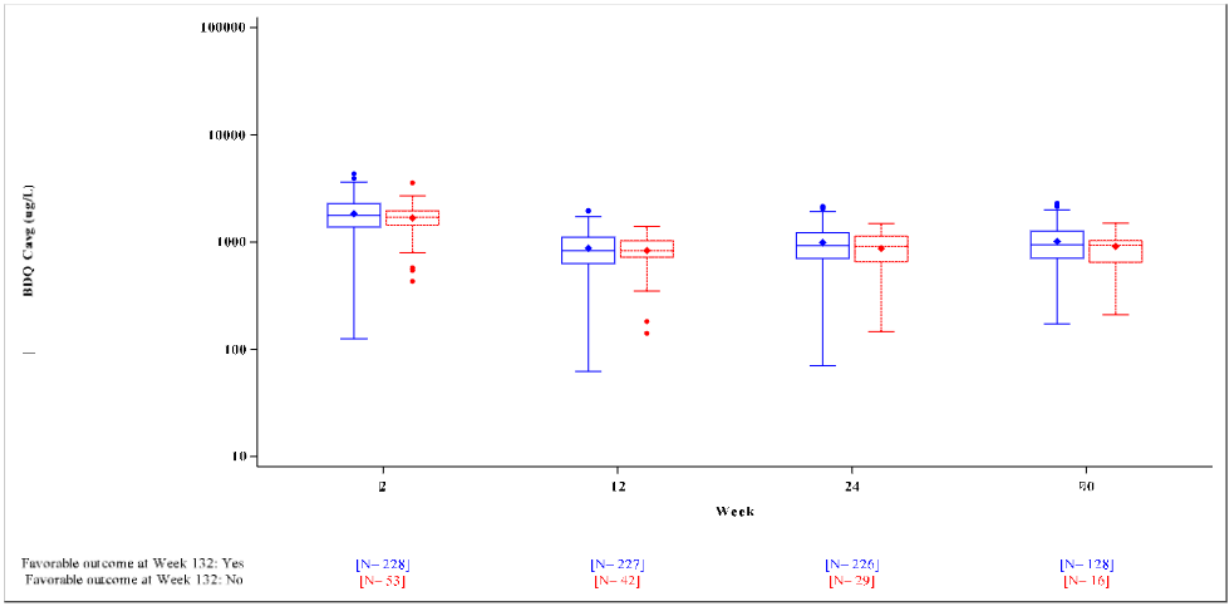
2.3.4.1. Favourable outcome

In STREAM Stage 2, the relationship between BDQ and M2 exposure and the primary endpoint (favourable/non-favourable) was explored through boxplots, presenting the exposure measures by TB outcome (favourable/unfavourable) at Week 76 and Week 132 (shown for BDQ C_{avg} in Figure 25 and Figure 26, respectively). BDQ concentrations for the subgroups defined based on outcome overlapped. Given the limited number of cases with non-favourable outcome, no exposure-response relationship could be observed.



Note: N is the number of subjects with non-missing values.
Note: Visits are nominal visits.
*Note: Box: Represents 25th percentile to 75th percentile. Solid line represents the median. Whiskers represent the maximum observation below Q3 + 1.5IQR (upper) and the minimal observation above Q1-1.5*IQR (lower). Values outside of box and whiskers represent outliers.*

Figure 25 Boxplot of bedaquiline C_{avg} by favourable outcome at week 76 for Regimens C (bedaquiline)+D



Note: N is the number of subjects with non-missing values.
Note: Visits are nominal visits.
Note: Box: Represents 25th percentile to 75th percentile. Solid line represents the median. Whiskers represent the maximum observation below Q3 + 1.5IQR (upper) and the minimal observation above Q1-1.5*IQR (lower). Values outside of box and whiskers represent outliers.
Note: The No in favorable treatment outcome of week 132 include non-assessable.

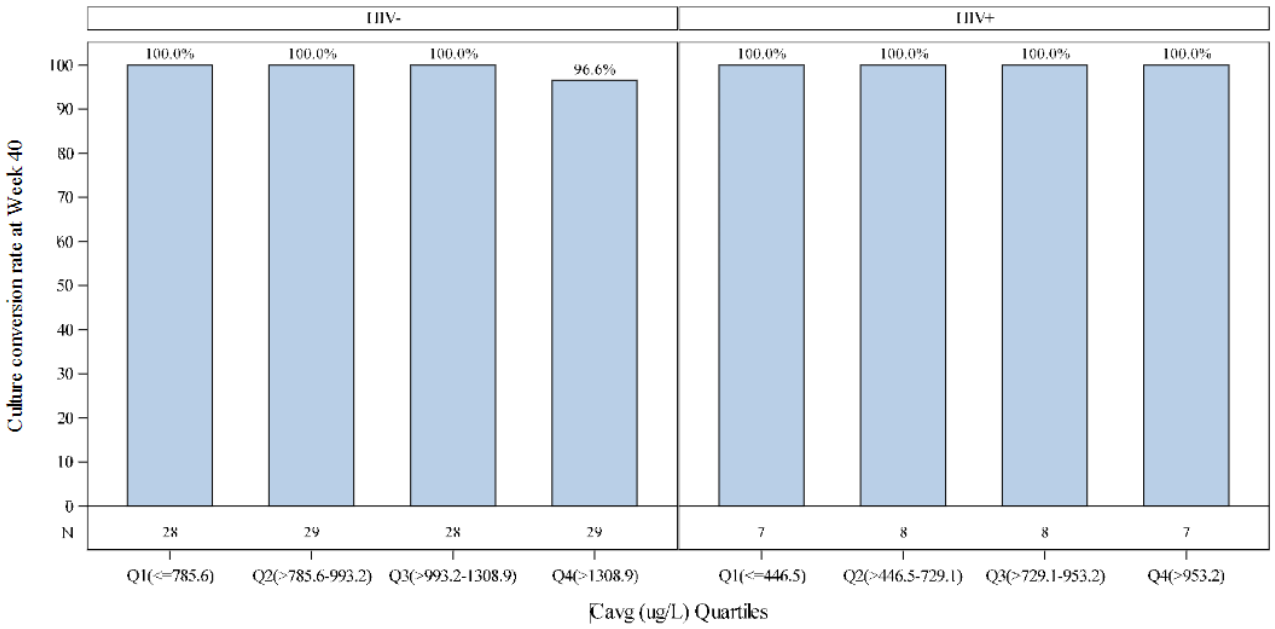
Figure 26 Boxplot of bedaquiline C_{avg} by favourable outcome at week 132 for Regimen C (bedaquiline)+D

The CHMP noted the exposure-response analysis performed between BDQ exposure and favourable outcome in STREAM Stage 2. The data was stratified by outcome (favourable outcome, yes or no) and the distribution of the PK exposure in each stratum was visualised in boxplots per visit. The CHMP agreed with the MAH conclusion that no exposure-response trends are evident. This may indicate that the PK exposure at the proposed dosing regimen is approaching a plateau. However, this exposure-response analysis has limitations (as outlined below) and it is not possible to draw any firm conclusions.

The CHMP noted that exposure-response analysis was based only on a single dose level/regimen which was studied in STREAM Stage 2 (400 mg once daily for two weeks followed by 200 mg three times per week). Having only a single dose level usually leads to a relatively narrow exposure range where it may be difficult to detect any exposure-response trends. Furthermore, the number of patients without favourable outcome was limited which makes it even more difficult to draw firm conclusions.

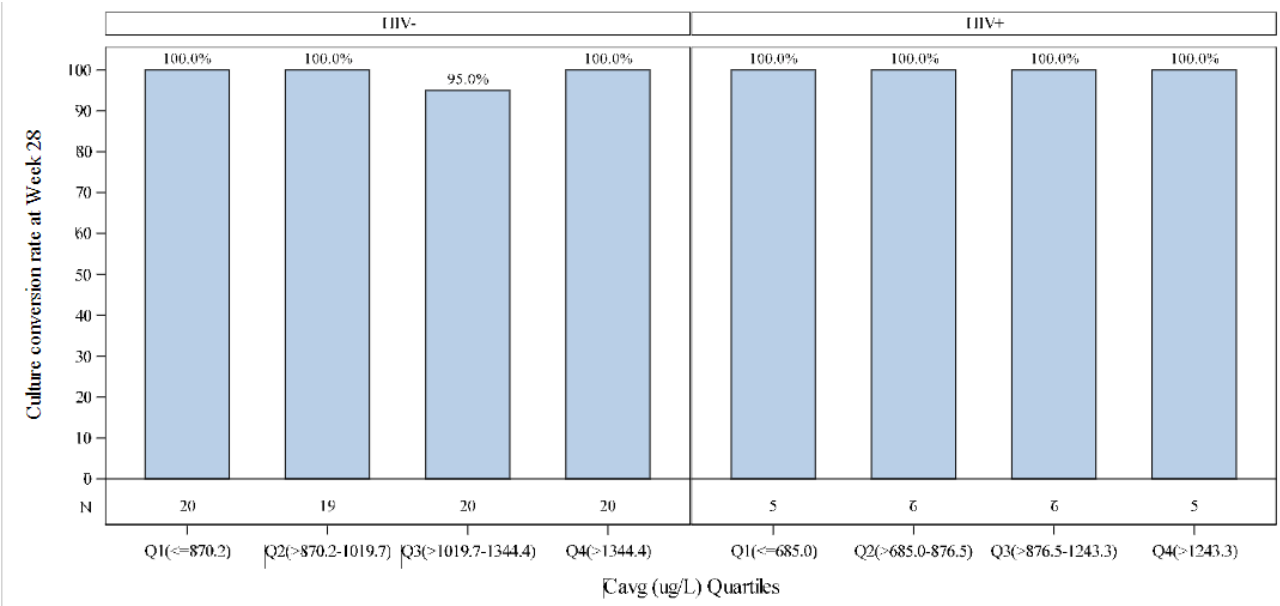
2.3.4.2. Culture conversion

In STREAM Stage 2, the relationship between BDQ exposure and the culture conversion rate for participants completing the full course of BDQ treatment was explored through bar plots, presenting the percentage converted at end of treatment by exposure and exposure/MIC quartile range based on HIV status (positive/negative) and baseline MIC (≤0.25 or >0.25 µg/mL). Figure 27 and Figure 28 show the culture conversion vs C_{avg} quartile for Regimen C (bedaquiline) and D, respectively. No trend for an exposure-dependent conversion rate was observed for any of the regimens or in any of the pre-determined subgroups.



Note: No BDQ resistant strains at baseline.

Figure 27 Culture conversion rates versus bedaquiline C_{avg} quartiles per HIV and BDQ resistance subgroup (Regimen C (bedaquiline), Week 40)



Note: No BDQ-resistant strains at baseline.

Figure 28 Culture conversion rates versus bedaquiline C_{avg} quartiles per HIV and BDQ resistance subgroup (Regimen D, week 24)

The CHMP noted that an exposure-response analysis was performed between BDQ exposure and culture conversion in STREAM Stage 2. The data was stratified by BDQ C_{avg} quartile and bar plots showed the proportion of patients with culture conversion in each exposure quartile. As concluded by the MAH, it can be agreed that no exposure-response trends are evident. This may indicate that the PK exposure at the proposed dosing regimen is approaching a plateau. However, this exposure-response analysis has limitations (as outlined below) and it is not possible to draw any firm conclusions.

The CHMP noted that exposure-response analysis was based only on a single dose level/regimen which was studied in STREAM Stage 2 (400 mg once daily for two weeks followed by 200 mg three times per week). Having only a single dose level usually leads to a relatively narrow exposure range where it may be difficult to detect any exposure-response trends. Furthermore, the number of patients without culture conversion was very limited which makes it even more difficult to draw firm conclusions.

2.3.4.3. QT analysis

Several analyses regarding concentration-QTc have been included in the dossier. Reference is made to several published concentration-QTc analyses. A model-based analysis was performed based on BDQ Phase 2 data. Finally, a subgroup analysis has been performed of STREAM Stage 2 data.

The CHMP noted that analyses described in this section are viewed as supportive evidence. They are supportive to (1) the results from the thorough QT study which was included in the original submission (111:2012/66501) and (2) the safety analysis of the QTc data collected in STREAM Stage 2.

2.3.4.3.1. Literature references

Different authors, applying different analysis methodologies and using data generated in different studies with participants with active TB, have come to the same conclusions:

- Patients with active TB, when enrolled in a study, have elevated HR. HR decreases during the treatment period when patients improve.
- In patients with TB, QTcF corrects sub-optimally for HR, resulting in an upward bias of ΔQTcF while HR decreases.
- PK/PD models require implementing drug-related and non-drug-related effects to enable accurate estimation of the drug exposure-QTc relationship.

Briefly, using the data from Studies C208 and C209, Tanneau (Tanneau et al 2021 CPT:PSP 10(12):1538-1549) developed a BDQ/M2 exposure-QT model accounting for circadian rhythm patterns and a secular trend (not drug-related) with a maximum secular trend on ΔQTcF of 6.5 ms (estimated t1/2, ie, time needed to achieve 50% of the maximum effect: 6.44 weeks). The authors argued that the secular trend was due to the suboptimal HR correction of QTcF. Tanneau (Tanneau et al 2022 Clin Pharmacokinet 61(8):1538-1549) and van Beek (van Beek et al 2022 Open Forum Infect Dis 9(8)) applied the same exposure-QT model using data from the DELIBERATE study and the PROBeX study, respectively, confirming the findings of Tanneau (2021). The estimates for the drug-related parameters (Emax, EC50) for BDQ/M2 and non-drug-related parameters (QT_{max}) were consistent across studies, with the mean ΔQT_{max} estimated to be in the range of 6 to 9 ms.

Alternative approaches to optimally correct for HR when estimating QTc in patients with TB have been proposed:

- Ollario (Ollario et al 2017 AAC 61(7):e01834-16), based on pre-treatment ECGs, estimated an optimal population correction factor of 0.4081.
- Li (Li et al 2019 AAC 63(10):e00445-19), using data from the PMD development program including the BPaL regimen, also observed the tendency for increasing ΔQTcF after treatment, which correlated with decreasing HR. The authors applied a different modelling approach to dissociate the drug-related effect from the secular trend. A linear exposure-QT model was fitted to each study-by-visit-by-time-post-dose grouping of data. The authors observed a time-

independent slope (drug effect) constant throughout treatment but an intercept (ΔQT at zero drug concentration) increasing with time-in-study. The authors evaluated 3 different HR correction methods: QTcF, QTcB, and a population-specific correction factor obtained from the pre-treatment ECG data (QTcN, correction factor=0.42, which is similar to the correction factor of 0.4081 that has been proposed previously by Olliaro [2017]). They concluded that the modelling methodology allowed to capture the time-dependent HR well and to differentiate drug-related and non-drug-related effects: while QTcB, QTcF, and QTcN resulted in a different estimate for the secular trend (confirming HR as driver for this secular trend), the estimated slope (drug-related effect) of the concentration-QTc response model was similar across HR correction factors.

Based on the above findings that QTcF did not optimally correct for HR in a population with TB, the data from Studies C208 and C209 were re-evaluated using PK/HR modelling to enable an improved assessment of the M2-related QT effect. In this analysis, through explorative regression analyses of QTcF vs HR for subsets of data clustered by time since treatment start, it was observed that the slope for QTcF vs HR changed with treatment duration. This observation suggests that, for an accurate estimation of the drug exposure-QTc relationship, a time-dependent HR correction factor is needed rather than a population-specific HR correction factor such as QTcN or the correction factor suggested by Olliaro (2017).

In Table 18, estimates for ΔΔQTc are presented for different exposure-QT models published, at Weeks 2 and 24 based on the mean C_{max} values observed in STREAM Stage 2 at the end of the 2-week loading phase (Week 2; 326.3 ng/mL) and at the end of the 22-week maintenance phase (Week 24; 233.9 ng/mL), respectively. The estimates of the maximum mean effect of M2 on QT (ΔΔQTc) ranged from 4.9 to 8.3 ms at Week 2 and from 4.5 to 7.6 ms at Week 24. At Week 24, ΔQTcF was approximately twice as high as ΔΔQTcF across the different sources, indicating equal contribution of the HR effect and the drug-related effect to the observed ΔQTcF at the end of BDQ treatment. With the time-dependent correction factor, the remaining secular trend was minimal (ΔQTcTBT of 0.4 ms at Week 24) and the estimated M2 QT effect range was similar to that obtained across the other sources, further supporting the conclusion that the mean ΔΔQTc is <10 ms during the entire treatment period.

Collectively, based on the mean C_{max} for M2 observed in STREAM Stage 2, ΔΔQTcF due to BDQ intake is estimated to be in the range of 6 to 8 ms.

Table 21: Exposure-QTc relationship for M2 and effect size of secular trend on QTc based on different exposure-QTc models and datasets

Study; Source Data	QT Correction (Correction Factor)	$E_{max,M2}$, ms (%RSE)	$EC_{50,M2}$, ng/mL (%RSE)	Derived Mean QTc Changes Following BDQ Administration[a,b] ΔΔQTc, ms Week 2[a]	ΔΔQTc, ms Week 24[c]	ΔQTc, ms Week 24[c]	Mean Secular Trend ΔQT_{max}, ms (%RSE)
Tanneau 2021; C208 and C209	QTcF (0.33)	28.6 (13.6)	855 (24.4)	7.9[d]	6.1[d]	12.6[d,e]	6.5 (11.8)
Tanneau 2022; DELIBERATE	QTcF (0.33)	25.9 (14.4)	695 (30.1)	8.3[d]	6.5[d]	13.6[d,e]	7.09 (8.72)
Van Beek 2022; PROBeX	QTcF (0.33)	28.5 (14.8)	844 (29)	7.9[d]	6.2[d]	13.8[d,e]	7.6 (9.3)
		$Slope_{M2}$, ms/(µg/mL) (90% CI)					
Li 2019; Nix-TB (BpaL regimen)	QTcF (0.33)	18.3 (14.1-22.4)		6.0[f]	4.3[f]	13.7[e,f]	9.4 (NA)
	QTcN (0.42)	19.3 (15.2-23.3)		6.3[f]	4.5[f]	8.5[e,f]	4.0 (NA)
	QTcB (0.5)	19.6 (15.2-24)		6.4[f]	4.6[f]	5.9[e,f]	1.3 (NA)
Study C208 PK/HR analysis	QTcF (0.33)	-	-	5.1[b]	7.6[b]	16.1[b]	9.0[b]
	QTcTBT (time-dependent, 0.4081 toward 0.33)	-	-	4.9[b]	7.5[b]	7.9[b]	0.4[b]

ΔQTc=corrected QT change from baseline; ΔΔQTc=drug-related corrected QT interval effect (corrected for placebo); BDQ=bedaquiline; C_{max}=maximum plasma concentration; EC_{50}=half maximum effect concentration; E_{max}=maximum effect; HR=heart rate; NA=not available; PK=pharmacokinetic(s); QTc=corrected QT; QTcF=Fridericia-corrected QT; QTcN=population-specific QT; QT_{max}=maximum QT effect; RSE=relative standard error.

[a] Based on M2 C_{max} at Week 2 in STREAM Stage 2: 326.3 ng/mL, except for Study C208 values.

[b] Based on observed mean pre- and postdose QT values per visit. Unlike the other methods and sources, this does not correspond to an exposure-QT analysis but to a statistical summary of observed ΔΔQTc by visit. As such, the results depend on the QT variability in both placebo and BDQ treatment groups for each visit and are not integrated over the full BDQ treatment duration.

[c] M2 C_{max} at Week 24 in STREAM Stage 2: 233.9 ng/mL, except for Study C208 values.

[d] Value derived as $E_{max,M2} \times M2\ C_{max}/(EC_{50,M2}+M2\ C_{max})$.

[e] Including the maximum secular trend.

[f] Value derived as slope×M2 C_{max}/1,000.

Source: Publications cited; Table 3; data on file for Study C208 PK/HR analysis

The CHMP considered that the literature references identified by the MAH supports the usefulness of a time-dependent correction factor in order to interpret the QT prolongation data. The MAH derived the mean expected QTc changes following BDQ administration given the observed M2 C_{max} in STREAM Stage 2, which indicates a QT prolongation in the range of 6-8 ms.

2.3.4.3.2. Model-based analysis of Phase 2 data

Objectives

The objectives of this analysis were:

- To develop an accurate QT correction method for patients with MDR-TB, which accounts for HR changes due to disease improvement as a result of anti-TB treatment, based on nonlinear mixed effect modelling of the change in HR vs time in patients treated for active TB.

- To evaluate QTc changes in patients with MDR-TB receiving BDQ in addition to standardised background regimens, using the developed correction factor, which decorrelates HR and QT intervals during the entire treatment period.

The CHMP considered the objectives to be relevant. Increased HR in TB patients is known to bias the QT prolongation. Similar issues exist for other infectious diseases (such as malaria). Developing an empirical, data-driven time-varying correction factor to account for the bias caused by the elevated HR in these patients is considered a fit-for-purpose approach to give better insight into the underlying QT prolongation for BDQ.

Data

Data from the Phase 2 studies C208 and C209 were included in this analysis (Table 22). These studies were thoroughly described in the initial submission where additional details can be found.

Table 22: Summary of studies included in the HR analysis

	Study C208	Study C209
Objective	To evaluate the efficacy of BDQ in combination with a background regimen.	To evaluate the safety and tolerability as well as efficacy of BDQ in combination with a background regimen for the treatment of a broader cohort of participants with drug-resistant-TB, including pre-XDR and XDR-TB.
Type of study	Randomized, double-blinded, placebo-controlled study in 2 stages (Stage 1 and Stage 2)	Single-arm, open-label study
Medication	BDQ or placebo	BDQ
Route of administration	Oral	Oral
Formulation	Tablet	Tablet
Dose regimen	400 mg once daily for 14 days and then 200 mg 3 times per week	400 mg once daily for 14 days and then 200 mg 3 times per week
Number of participants	207	233
Treatment duration	Stage 1: 8 weeks Stage 2: 24 weeks	24 weeks
Standardized background regimen duration	18 to 24 months	18 to 24 months
Sampling times	Triplicate ECGs were collected around 8 AM (before treatment) or predose (during treatment) and 1 PM (before treatment) or 5 h postdose (during treatment) at Screening, Day −1, Day 1, and Weeks 2, 8, 12, and 24. Single ECGs were collected up to 1 h predose at Weeks 1, 2, 3, 4, 5, 6, 7, 10, 12, 14, 16, 18, 20, and 22.	Triplicate ECGs were collected around 8 AM (before treatment) or predose (during treatment) and 1 PM (before treatment) or 5 h postdose (during treatment) at Screening, Day −1, Day 1, and Weeks 2, 8, 12, and 24. Single ECGs were collected up to 1 h predose at Weeks 4, 16, and 20.

BDQ=bedaquiline; ECG=electrocardiogram; HR=heart rate; pre-XDR=pre-extensively drug-resistant; TB=tuberculosis; XDR-TB=extensively drug-resistant tuberculosis.

Data from 440 patients were included in the analysis (18657 HR measurements and 18495 QT measurements). Data prior to baseline and during follow-up were excluded.

Individual BDQ and M2 concentrations were predicted at each ECG timepoint using a previously developed population PK model (Svensson et al 2016 CPT:PSP 5(12):682-691, Tanneau et al 2021 CPT:PSP 10(12):1538-1549).

The CHMP noted that the dataset that was used to develop the model included several HR and QT measurements (18657 and 18495 measurements, respectively) from 440 patients which is considered a reasonable dataset to perform a concentration-QT analysis. Bearing this in mind, the dataset has certain limitations. The gold standard is to perform this type of analysis on QT measurements are performed in a similar way in all subjects, even from the same site. In this case, the QT measurements have been derived from different study sites and may lack standardisation which could bias the results and lead to high variability.

Methods

The analyses were carried out in NONMEM 7.4.

HR model

First, a longitudinal PK/HR model was developed to describe the change in HR, consisting of the sum of 3 distinct effects: 1) time on treatment, 2) circadian rhythm, and 3) drug effect, mediated by M2. The developed HR model was subsequently utilised to construct the time-dependent correction factor and to evaluate the QTc prolongation effect of BDQ in Studies C208 and C209.

The HR analysis consisted of the following steps:

1. Develop the HR model using only baseline HR without any changes. Subsequently, the model was expanded to include the linear or asymptotic function to determine which function best described the change in HR over time.

2. Assess the diurnal variation of HR using cosine functions with different numbers of oscillations (i.e., 1, 2, and 3) corresponding to 24- and12-hour cycles.

3. Evaluate the effect of BDQ andM2 on HR.

4. Develop the statistical model to describe the IIV and RUV.

5. Assess all relevant covariates by stepwise addition until no statistically significant covariate remained ($p<0.05$). Subsequently, remove non-significant covariates using a stricter significance level of $p<0.01$.

6. Assess model performance using GOF plots and VPCs.

Time-dependent correction factor

Linear regression analyses using the QT interval and HR measurements from Day −1 to the end of treatment with BDQ (Week 24) were conducted to assess how well different correction factors could decorrelate QT and HR. The QT-HR data were segmented into separate time intervals (bins) based on the quantity of data and the rate of change in correlation in each interval: i) pre-treatment, ii) Week 0 to 1, iii) Week 1 to 2, iv) Week 2 to 4, v) Week 4 to 8, vi) Week 8 to 12, vii) Week 12 to 20, and viii) Week 20 until the end of treatment with BDQ (Week 24). The correlation between QTc and HR was quantified by the slope and r2 value from the regressions performed in each bin. It is expected that the slope and r2 would have values close to 0 for the successful correction. The 95% CI of the slope should cover 0, which means there is no significant difference from 0. To compare the difference in performance between Fridericia and Olliaro correction factors and the time-dependent correction factor, slope estimates and their uncertainty (standard error) from the QTc vs HR linear regression

analysis were analysed using NONMEM. A linear model was used to describe the change in slope over time, and the standard error of the slope was used as weighting factor in the analysis. For successful correction, both the intercept (the QTc-HR correlation at time 0) and the gradient (the change in slope over time) are expected to be close to 0 and the 95% CI should include 0.

QTc prolongation assessment

Visual and numerical summaries of different cardiovascular safety assessments over time in the different arms of the Phase 2 studies were compared using the Fridericia and the time-dependent correction factors. Three cardiovascular safety assessments were investigated: absolute QTc and ΔQTc using pooled data from Studies C208 and C209, and ΔΔQTc using only data from Study C208 as placebo data were not available from Study C209. Pre-treatment (baseline) QTc was defined as Day −1, at around 1 PM for the 5-hour post-dose assessments, and Day −1, pre-dose for all other assessments. The mean of triplicate QT intervals was calculated for each occasion, after which all QT-related assessments were summarised over the same time intervals as used for the correction factor evaluation: i) pre-treatment, ii) Week 0 to 1, iii) Week 1 to 2, iv) Week 2 to 4, v) Week 4 to 8, vi) Week 8 to 12, vii) Week 12 to 20, and viii) Week 20 until the end of treatment with BDQ (Week 24).

The CHMP considered that overall, reasonable methodology has been used for performing this QT analysis. It should be noted that it deviates from how a QT analysis should be performed according to the relevant guidelines (ICH E15). However, the CHMP considered it reasonable to deviate from the standards in this case, due to the known effect of HR in TB patients which can bias the estimate of the underlying QT prolongation.

Results

HR model

The observed HR vs time plots stratified by study and treatment arm (data not shown) showed overall HR decreases over time during the treatment period in all treatment groups of Studies C208 and C209, including the arms with placebo/background treatment.

The correlation matrices of QTc intervals vs HR for different published correction factors were reviewed (data not shown) and none was found to adequately correct the QTc at all relevant time-points. This supports that the correlation between QT interval and HR varies over time and that a single correction factor, regardless of its value, will not be able to adequately correct over the full-time course of treatment.

The final HR model included a component describing the asymptotic change in HR with time, 4- and 12-hour circadian rhythms, and an effect of M2 on HR, described the mean and the variability of the HR data well. The model featured IIV on $HR_{baseline}$, $HR_{recovered}$, and amplitudes. IIV was exponential except for amplitudes where the Box-Cox transformation was applied to aid in the non-normally distributed EBEs. Additionally, exponential IIV was also added to RUV and RUV_{repl} components allowing different magnitudes of residual between individuals. Correlation components (Ω block) were included for $HR_{baseline}$–$HR_{recovered}$, $HR_{baseline}$–Amplitudes, $HR_{recovered}$–Amplitudes, and RUV–RUV_{repl}. The residual error was best described by a proportional error model for RUV and an additive error model for RUV_{repl}. Study, body weight, serum albumin, baseline MGIT and age were included as covariates in the model. The model parameters are shown in Table 23.

The time on anti-TB treatment was estimated to result in a 5.1 bpm asymptotic decrease in HR over time to 73.1 bpm (1.4% RSE) at steady-state, achieving half the HR decrease in 7.74 weeks (95% CI T_{prog}: 5.17 to 10.27 weeks). This suggests that the HR had approached but not fully reached steady-

state by the end of the 24-week treatment period, with an estimated HR of 73.7 bpm at the end of treatment with BDQ (around 85% of steady-state).

Table 23: Parameter estimates of the base and final HR model

Model Feature	Description	Parameter Estimate (95% CI[a]) [%RSE] {%shrinkage}[b]	
		Base Model[c]	Final Model[d]
Time on treatment	Baseline HR (bpm)	80 (78.3, 81.7) [1.1]	78.2 (76.3, 80.1) [1.2]
	Recovered HR (bpm)	74.6 (72.8, 76.4) [1.2]	73.1 (71.1, 75.2) [1.4]
	T_{prog} (weeks)	8.15 (5.47, 10.88) [16.9]	7.74 (5.17, 10.27) [16.8]
Circadian rhythm	Amplitude 24 h (bpm)	6.5 (4.6, 8.4) [14.9]	6.2 (4.5, 7.9) [13.6]
	Peak time 24 h (clock time)	15.7 (15.3, 16.1) [1.4]	15.7 (15.3, 16.2) [1.3]
	Amplitude 12 h (bpm)	1.7 (1, 2.4) [21.2]	1.65 (1, 2.3) [19.7]
	Peak time 12 h (clock time)	10.1 (9, 11.1) [5.2]	10.1 (9.2, 11.1) [4.8]
	Box-cox shape for amplitudes	−0.71 (−0.97, −0.45) [18.6]	−0.77 (−1.1, −0.46) [20.9]
M2 effect on HR	E_{max} (fraction)	0.158 (0.12, 0.196) [12.2]	0.179 (0.14, 0.21) [11.1]
	EC_{50} (ng/mL)	2170 (1286, 3061) [20.9]	2600 (1936, 3260) [13]
Covariate effects	Effect of study on HR (Study C209 vs C208) (fraction)	,	0.047 (0.018, 0.076) [31.3]
	Effect of changes in body weight on HR (power)	,	−0.2 (−0.26, −0.14) [15.2]
	Effect of baseline serum albumin on HR (power)	,	−0.22 (−0.3, −0.14) [17.6]
	Effect of baseline MGIT[e] on baseline HR (power)	,	−0.05 (−0.07, −0.03) [22.9]
	Effect of age on recovered HR (power)	,	0.08 (0.03, 0.13) [30.1]
IIV (%CV[f])	IIV baseline HR	17.6 (16.2, 18.8) [4] {1.7}	15 (13.8, 16.1) [4] {2.5}
	IIV recovered HR	15.8 (14, 17.5) [5] {7.3}	15.1 (13.2, 16.8) [6] {7.3}
	IIV amplitude	97.2 (72.3, 121.8) [9] {24.8}	95.3 (70, 9, 119.2) [9] {25.5}
	IIV EC_{50} M2	1002.5 (602.2, 1663) [6] {45.6}	883.4 (719.9, 1078.6) [2] {45.1}
	IIV proportional RUV	23.6 (19.6, 27.1) [8] {13.9}	23.6 (19.2, 27.3) [8] {13.7}
	IIV Additive triplicate-specific RUV	38.5 (35.1, 41.6) [4] {6.8}	38.5 (35.1, 41.6) [4] {6.8}
Correlation between IIV	Baseline HR: recovered HR	0.42 (0.27, 0.51) [9.3]	0.41 (0.28, 0.54) [9]
	Baseline HR: amplitude	−0.15 (−0.08, −0.01) [24.1]	−0.26 (−0.39, −0.14) [13.8]
	Recovered HR: amplitude	−0.41 (−0.53, −0.28) [10.2]	−0.42 (−0.55, −0.28) [10.2]

	Proportional RUV: additive triplicate-specific RUV	0.37 (0.2, 0.54) [12.4]	0.38 (0.21, 0.55) [12]
Residual error model	Proportional RUV (%CV)	8.4 (8.1, 8.7) [1.7]	8.4 (8.1, 8.7) [2]
	Additive triplicate-specific RUV (SD, bpm)	2.7 (2.6, 2.8) [1.9]	2.7 (2.6, 2.8) [1.9]

%CV=percent of coefficient of variation; EC_{50}=half maximum drug effect concentration; E_{max}=maximum drug effect; HR=heart rate; IIV=inter-individual variability; MGIT=mycobacteria growth indicator tube; NONMEM=nonlinear mixed effects modeling; OFV=objective function value; RSE=residual standard error; RUV=residual unexplained variability; SD=standard deviation; $t_{1/2}$=half-life; T_{prog}=time at which the heart rate had reached 50% of its decrease.

[a] 95% CI calculated as $parameter\ estimates \pm 1.96 \cdot SE$

[b] Median (%RSE) [%Shrinkage] estimates by NONMEM from Studies C208 and C209 dataset.

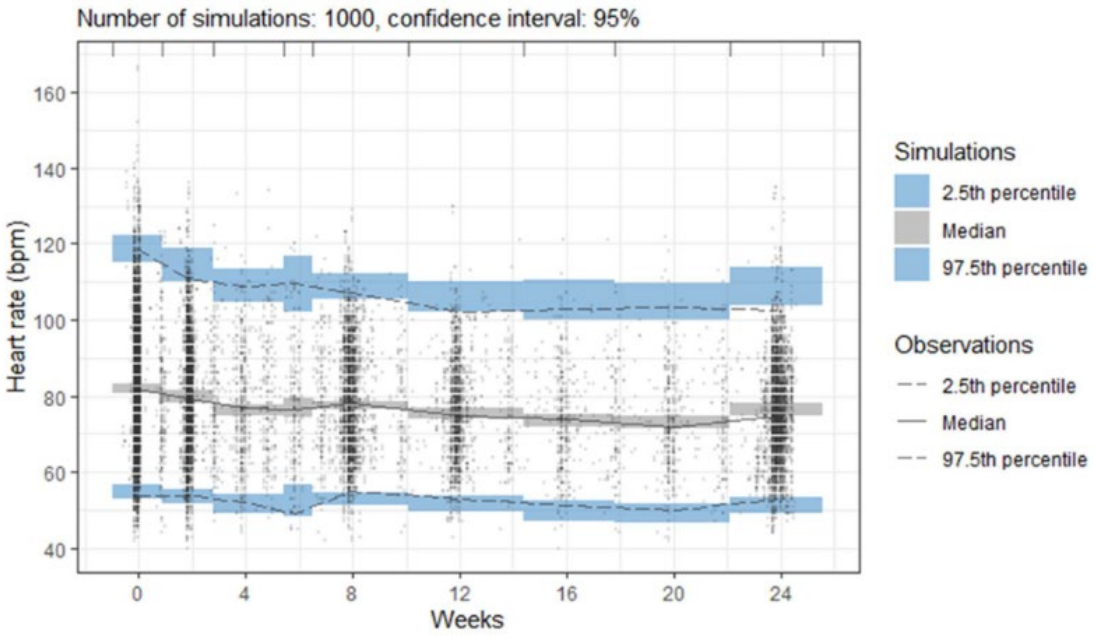
[c] Run number=165; OFV=82,054.011.

[d] Run number=206; OFV=81,882.599.

[e] Time to positivity in MGIT.

[f] %CV and %RSE calculated as $\sqrt{e^{\omega^2} - 1}$

The performance of the final model was evaluated using VPC without stratifications (Figure 29). The VPC results indicated that the final model described the HR data and its variability well.



HR=heart rate; VPC=visual predictive check.
Black dots are observed HR and shaded areas indicate the 95% prediction intervals of the predicted median (gray) and outer 2.5th and 97.5th percentiles (blue) of N=1,000 simulated datasets.

Figure 29 VPC of HR over time for the final HR model

Time-dependent correction factor

Based on the exploration of data from Studies C208 and C209, it was observed that the QT-HR correlation changed with time on treatment, associated with the decrease in HR. The Olliaro correction factor (0.4018), estimated based on pre-treatment data, was found to perform well at the pre-treatment stage while the Fridericia correction factor (0.33) was found to perform well at the end of BDQ treatment stage.

Based on the expectation that the rate of change in HR represents the rate of change in the correlation between QT interval and HR, the rate constant T_{prog} estimated in the HR model was utilised to construct the time-dependent correction factor. As the HR was described by an asymptotic function with a T_{prog} of 7.74 weeks, a longitudinal correction factor was formulated. The correction factor

decreases asymptotically from 0.4081 (Olliaro 2017) toward 0.33 (Fridericia 2003) over the time on treatment.

$$CF(t) = 0.4081 - (0.0781) \times (1 - e^{-K_{prog} \times t}) where\ K_{prog} = \frac{Ln(2)}{T_{prog}}$$

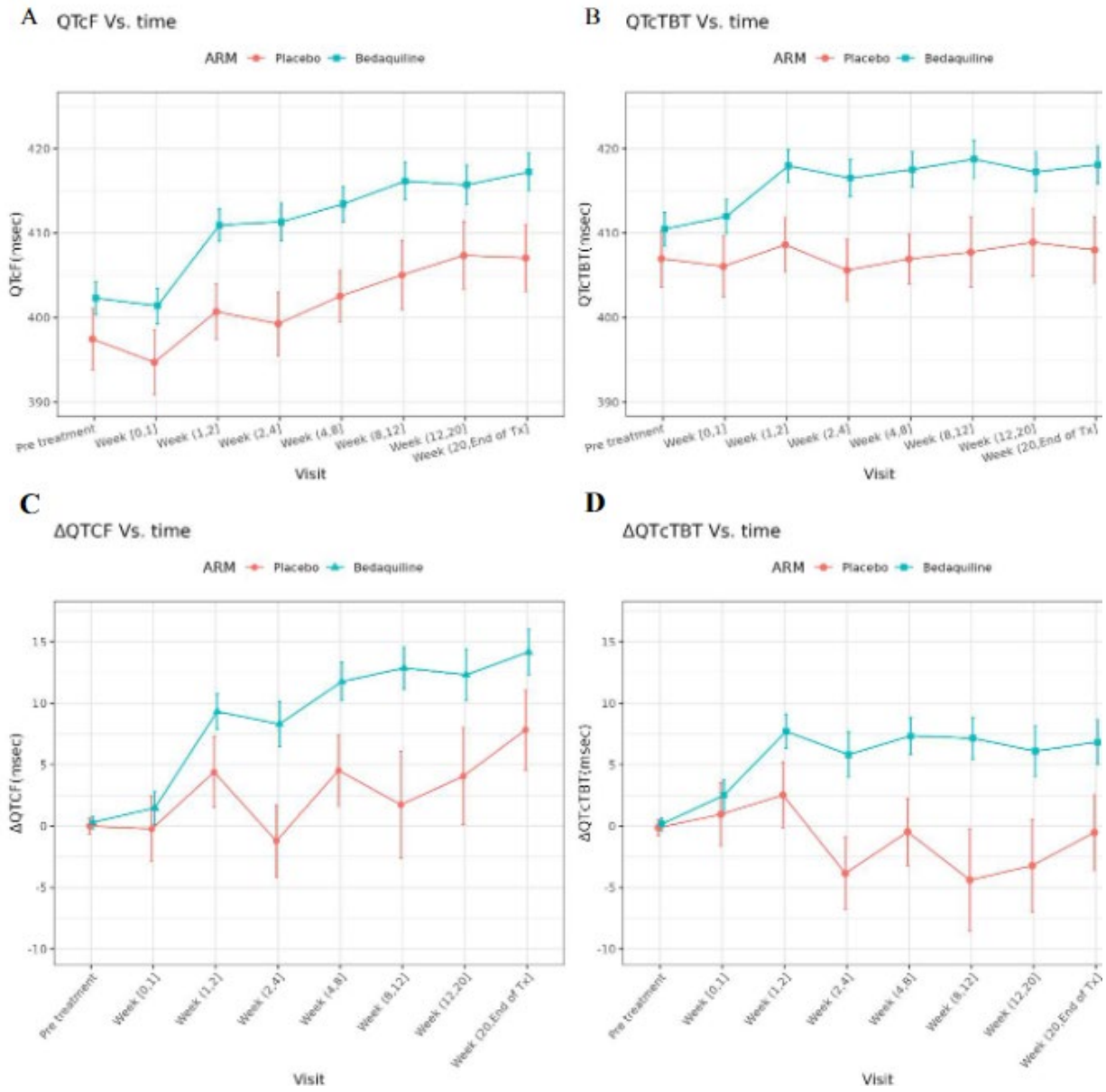
QTc prolongation assessment

Mean absolute QTcF and QTcTBT, ΔQTcF and ΔQTcTBT, and ΔΔQTcF and ΔΔQTcTBT, along with their respective 95% CIs, were calculated for each time point and are presented in Figure 30.

Mean ΔΔQTcF and ΔΔQTcTBT were found to be similar with mean ΔΔQTc mostly plateauing below 10 ms from Week 2 onwards. The observed peak at Week 8 to 12 for both correction factors (ΔΔQTcTBT of 13.4 ms; 95% CI: 9.4 to 17.3 ms, similar for ΔΔQTcF) is likely due to variability as the ΔQTc of the placebo group is particularly low for this timepoint. The fact that ΔΔQTcTBT and ΔΔQTcF fully overlap demonstrates that the time-dependent correction is appropriate and that ΔΔQTcF is able to capture the drug effect on QT accurately, despite the HR bias. This confirms that QT prolongation under BDQ treatment was adequately estimated based on the ΔΔQTcF derived from Study C208, ie, when accounting for the placebo response.

However, in studies where no adequate reference arm is available to dissociate the time-on-treatment effect on HR from drug effect(s) on HR and QT, such as Study C209, which was a single-arm study, or studies with arms containing different combinations of QT-prolonging drugs, ΔΔQTc is often unavailable and the secular trend cannot easily be accounted for. The QT effect of many anti-TB drugs is thus often evaluated based on absolute QTc or ΔQTc, and the conclusions drawn from these values were shown to differ depending on the methodology used and the time of evaluation. Across study arms, mean QTcF values were up to 10.4 ms lower than QTcTBT values until Week 12 of the anti-TB treatment, while mean ΔQTcF values were up to 8.2 ms higher than ΔQTcTBT values from Week 2 onwards. Mean QTcTBT and ΔQTcTBT values of the placebo group were closer to their baseline than mean QTcF and ΔQTcF values, showing a better correction of the secular trend using the time-dependent correction factor compared with the Fridericia correction factor.

In this analysis, QTcF and ΔQTcF were shown to lead to likely biased estimates of the drug-induced QT effect if interpreted in the absence of an adequate description of non-drug-related HR changes, while QTcTBT and ΔQTcTBT were inherently corrected for HR changes due to disease improvement as a result of anti-TB treatment.


A
QTcF Vs. time
ARM Placebo Bedaquiline
QTcF (msec)
420
410
400
390
Pre treatment
Week (0,1]
Week (1,2]
Week (2,4]
Week (4,8]
Week (8,12]
Week (12,20]
Week (20,End of Tx]
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B
QTcTBT Vs. time
ARM Placebo Bedaquiline
QTcTBT (msec)
420
410
400
390
Pre treatment
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Week (4,8]
Week (8,12]
Week (12,20]
Week (20,End of Tx]
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ARM Placebo Bedaquiline
ΔQTCF (msec)
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-5
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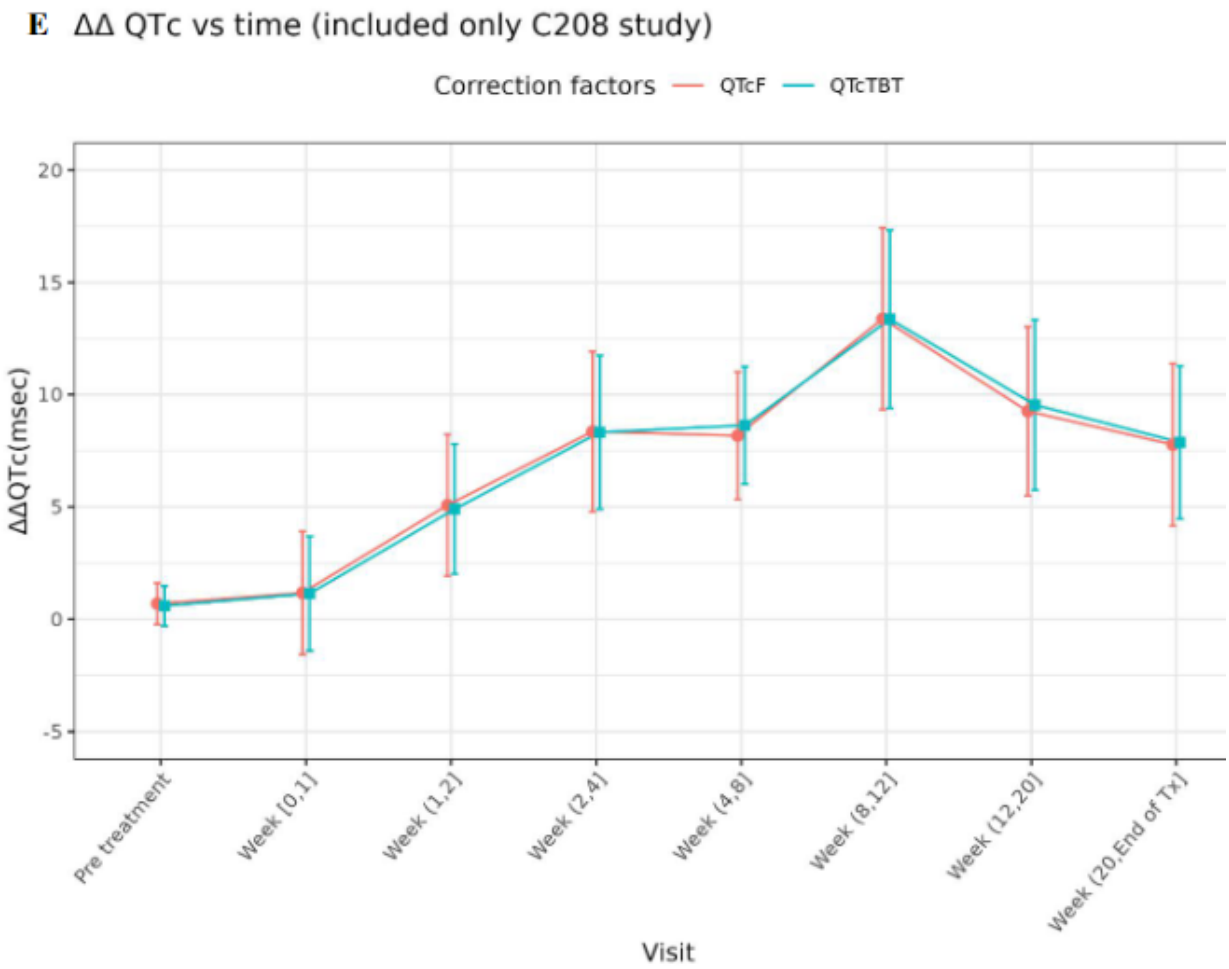
Week (2,4]
Week (4,8]
Week (8,12]
Week (12,20]
Week (20,End of Tx]
Visit



BDQ=bedaquiline; QTc=corrected QT; QTcF=Fredericia-corrected QT; QTcTBT=time-dependent QT; Tx=treatment with BDQ.
Pre-treatment=Day −1 and predose on Day 1; End of Tx with BDQ=Week 24 or on the last day of receiving BD provided that the last day of receiving BDQ>Week 20.
Points (placebo arm) and squares (BDQ arm) represent mean values. Error bars represent the 95% confidence intervals of the mean values based on the total number of subjects in each time bin.
For the time intervals, parentheses mean the week was not included and square brackets mean the week was included.

Figure 30 Absolute, change from baseline and placebo-corrected change from baseline in QTc over time for the Fridericia correction factor (A, C, and E) and time-dependent correction factor (B, D, and E)

The CHMP considered the HR model to be acceptable. The parameter estimates and RSEs were overall reasonable and the final model described the data overall well according to the VPC.

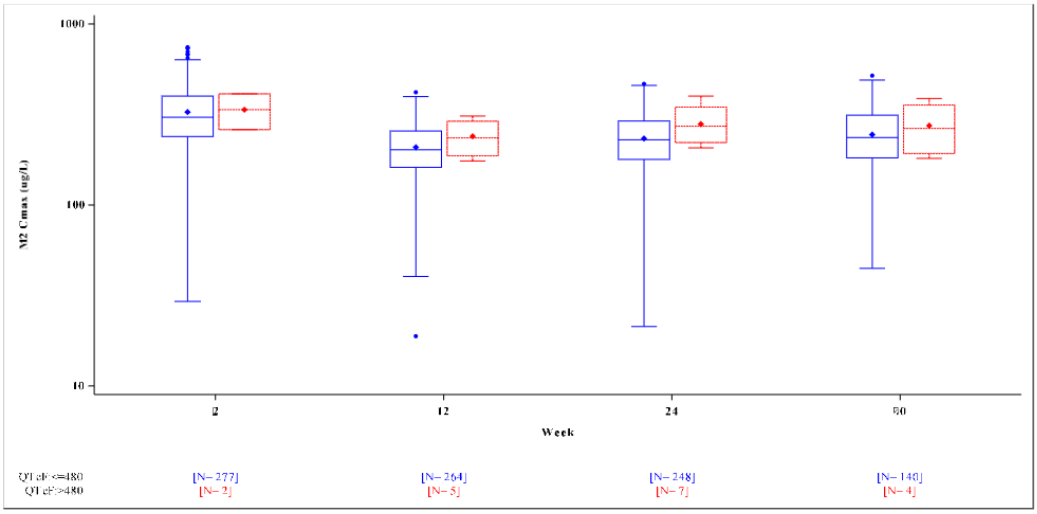
The CHMP noted that time-dependent correction factor combined two known correction factors (Fridericia and Olliaro) using a time-dependent factor derived from the HR model. This is considered an acceptable approximation to give better insight into the actual QT prolongation in patients caused by BDQ.

After correcting for the bias caused by the elevated HR in TB patients, the QT data indicates that BDQ has a QT prolongation of approximately ~7.5 ms. At different time-points throughout the study, the mean QT prolongation (and the confidence intervals) exceeded 10 ms.

The CHMP considered the approximate QT prolongation of 7.5 ms to be in line with the expected QT prolongation based on literature sources, given the observed M2 C_{max} in STREAM Stage 2.

2.3.4.3.3. Subgroup analysis of STREAM Stage 2

The relationship between BDQ and M2 exposure and QT interval prolongation was explored through boxplots, presenting the selected exposure measures by QTcF cut-off, for instance 480 ms as shown in Figure 31. Given the limited number of cases in the QTcF subgroups of interest (>480 or >500 ms), associated BDQ and M2 concentration ranges overlap entirely with the corresponding concentration ranges in the reference groups. Therefore, no relationship between BDQ or M2 exposure and response in terms of QTcF could be detected.



Note: N is the number of subjects with non-missing values.
Note: Visits are nominal visits.
*Note: Box: Represents 25th percentile to 75th percentile. Solid line represents the median. Whiskers represent the maximum observation below Q3 + 1.5IQR (upper) and the minimal observation above Q1-1.5*IQR (lower). Values outside of box and whiskers represent outliers.*
[gsfpk04c.rtf] [\\wilbtia\wilbtia02\JnJ JJTBC3007\Week 132 TFL w ADaM updates\TLF\gsfpk04c.sas] 05APR2023, 3:56:17 PM

Figure 31 Boxplot of M2 C_{max} by absolute QTc value with cutoff 480 at visit level for Regimen C (bedaquiline)+D

The CHMP noted that the MAH performed a very simplified exposure-response analysis for QT prolongation based on the STREAM Stage 2 data. Since there were too few cases meeting the criteria (for instance 480 ms), the plots are not informative. Treating QT as a continuous variable instead may have been more useful, although it is known to be difficult to detect exposure-response relationships with only a single dose level. Therefore, this issue is not pursued further.

2.3.5. Discussion on clinical pharmacology

The CHMP noted that the MAH has performed PK analyses with different purposes in the dossier. The PK analyses are considered supportive to the efficacy and safety data, with overall low impact for the benefit-risk assessment. The main relevance of the PK analyses is to describe PK in the target population and to support dosing recommendations for DDI scenarios.

Two new clinical studies with PK information which were not included in the original submission are presented (STREAM Stage 2 and TMC207NTM1001) in the current procedure.

The PK data from STREAM Stage 2 was used to describe PK in the target population. Sparse PK sampling was used and hence, a PopPK approach was used to describe the PK data which is acceptable. An updated PopPK model was developed to describe the PK behaviour of bedaquiline and its active metabolite M2 by expanding a previously submitted PopPK model to include description of M2 data. The new clinical study STREAM Stage 2 was not included when developing the updated PopPK model. The updated PopPK model is considered overall acceptable. Furthermore, the covariate analysis was based on visual inspection of eta vs covariate plots which is a limitation, since the shrinkage was quite high (20-30%) for important parameters. However, this issue is not pursued given the limited impact of the PopPK model.

The updated PopPK model was used to extract individual PK parameters (EBEs) from the patients in STREAM Stage 2 which were used to calculate various exposure metrics for (1) descriptive purposes, (2) PK subgroup analyses and (3) to perform PK/PD analyses. It would have been preferable to include STREAM Stage 2 when developing the PopPK model but the presented approach is considered acceptable given the rather low impact of the PopPK model. The updated PopPK model described the observed data sufficiently well based on the model diagnostic plots "observations vs individual predictions" and "individual plots". Of note, the VPC for M2 had model misspecifications which means that the simulation properties of the model are not optimal which should be considered if the model is used to perform clinical trial simulations in future Type II variations.

The CHMP was of the view that the drug-drug interaction study with clarithromycin submitted (study TMC207NTM1001) had several shortcomings given the difficulties with designing an interaction study with a substrate with extremely long half-life of both parent compound and metabolite. The results of this study is however in line with what was already known from other dedicated DDI studies as well as PopPK analysis of clinical data, and it is considered acceptable to add the results from the clarithromycin study to the SmPC.

The MAH proposed to change dosing recommendations for DDI scenarios of CYP3A4 strong inhibitors and weak inducers, for which the MAH proposed no dose adjustment. PopPK analyses were performed for two previously submitted DDI studies (TMC207-C110 and TMC207-C117 which were previously only analysed using non-compartmental analysis) for LPV/RTV and NVP. For LPV/RTV (strong CYP3A4 inhibitor), the model-based analysis is considered acceptable and indicated a more pronounced inhibition of bedaquiline CL (~40%) than what was concluded for the non-compartmental analysis of the same study (~20%). For NVP (weak CYP3A4 inducer), the model-based analysis was inconclusive as it did not identify any induction effect at all on bedaquiline PK which may be described by the suboptimal study design of the NVP study. In addition, a PK subgroup analysis in STREAM Stage 2 was also performed which showed that LPV/RTV led to increased bedaquiline exposure (~10-20%) and NPV led to decreased bedaquiline exposure (up to ~30%). This PK subgroup analysis is uncertain mainly due to the sparse PK design and limited number of subjects. In the first round of assessment, it was concluded that quantitative results from this analysis should not be included in the SmPC, and the SmPC was updated to describe the result in a qualitative way. Collectively, the performed analyses regarding DDIs show that LPV/RTV and NVP cause PK interactions with bedaquiline. Given the totality of evidence (see subgroup analyses of efficacy and safety data) the CHMP did not consider these clinically significant DDIs.

Data from STREAM Stage 2 was used to perform exposure-response analyses based on efficacy- and safety-related endpoints. The exposure-response analyses were based only on a single dose level/regimen (400 mg once daily for two weeks followed by 200 mg three times per week). Having

only a single dose level leads to a relatively narrow exposure range and no clinically significant exposure-response trend was noted for any endpoint. The exposure-response analyses are considered supportive only and have low impact. This can be partly explained by the overall robust safety and efficacy data package. The CHMP considered clinical efficacy and safety data to be the most important for drawing the necessary conclusions needed for assessing the benefit-risk.

PK/PD model-based analyses were performed for the QT data including analysis of existing data from the sponsor (Studies C208 and C209). An empirical, data-driven time-varying correction factor was developed to account for the bias caused by the elevated HR in these patients. The CHMP considered this a fit-for-purpose approach to give better insight into the underlying QT prolongation for BDQ. After correcting for the bias caused by the elevated HR in TB patients, the QT data indicates that BDQ has a QT prolongation of approximately ~7.5 ms. At different time-points throughout the study, the mean QT prolongation (and the confidence intervals) exceeded 10 ms.

In addition to the above, an analysis was also performed based on previously published concentration-QTc analyses of bedaquiline. The literature references identified by the MAH supports the usefulness of a time-dependent correction factor in order to interpret the QT prolongation data. The MAH derived the mean expected QTc changes following BDQ administration given the observed M2 C_{max} in STREAM Stage 2 which indicates a QT prolongation in the range of 6-8 ms.

2.3.6. Conclusions on clinical pharmacology

Several clinical pharmacokinetic analyses were performed, which the CHMP considered supportive to the efficacy and safety data (low regulatory impact). The main relevance of the PK analyses is to describe PK in the target population and to support dosing recommendations for DDI scenarios.

The new PK-data on co-administration of CYP3A34 modulators were in line with what was previously known, but given the new clinical efficacy and safety data in patients co-administered with CYP3A4 modulators provided, and the larger clinical experience with bedaquiline, co-administration with CYP3A4 inhibitors as well as weak inducers is now considered acceptable.

Exposure-response analyses were performed but did not indicate any significant exposure-response trends.

Several analyses of QT data were performed using clinical data from the Sponsor and by considering several concentration-QT analyses published in the literature. The CHMP considered that collectively, these analyses supports a modest QT prolongation at the proposed bedaquiline posology in the range of 6-8 ms.

2.4. Clinical efficacy

2.4.1. Main study

2.4.1.1. Title of Study

Study TMC207-STREAM: The Evaluation of a Standard Treatment Regimen of Anti-tuberculosis Drugs for Patients With MDR-TB

2.4.1.2. Methods

STREAM Stage 2 was an international, multicentre, randomised, parallel-group, active-controlled, open-label Phase 3 confirmatory study of efficacy and safety of a BDQ-containing, all-oral 40-week regimen (Regimen C) compared to an injectable-containing 40-week control regimen (Regimen B) in participants ≥15 years of age with rifampicin (RMP)-resistant and isoniazid (INH)-susceptible tuberculosis (TB) (RR-TB) or multidrug-resistant (MDR)-TB.

Study participants

Male and female patients aged ≥15 years (≥18 years before protocol version 7.0) with:

- Diagnosis of pulmonary TB confirmed by a positive AFB sputum smear or GeneXpert result (with a cycle threshold of ≤25) within 4 weeks prior to screening and by a chest X-ray suggestive of active TB disease within 4 weeks of randomisation.
- Evidence of resistance to at least RMP, either by Hain Genotype MTBDRplus LPA, GeneXpert, or phenotypic DST, and evidence of susceptibility to fluoroquinolones and second-line injectables by Hain Genotype MTBDRsl LPA.

Main exclusion criteria:

- Received MDR-TB treatment in 12 weeks prior to screening beyond a maximum 4 weeks of second-line treatment (provided sputum AFB stain still positive).
- Previously treated with BDQ.
- Treated with rifampicin in the 7 days prior to randomisation.
- Tuberculous meningitis or bone and joint tuberculosis.
- Abnormal potassium, magnesium and corrected calcium at screening.
- Critically ill, and pregnant or breastfeeding participants.
- AST or ALT >3x ULN, bilirubin >1.5x ULN, cirrhosis (Child's Pugh B or C).
- Pancreatic amylase >2x ULN.
- Creatinine clearance <30 mL7min (Cockroft-Gault).
- HIV-positive with CD4 count <50 cells/mm3.
- One or more risk factors for QT prolongation:
    - A confirmed prolongation of the QT or QTcF more than or equal to 450 ms in the screening ECG (retesting to reassess eligibility will be allowed once using an unscheduled visit during the screening phase)
    - Pathological Q-waves (defined as Q-wave more than 40 ms or depth more than 0.4-0.5 mV)
    - Evidence of ventricular pre-excitation (e.g., Wolff Parkinson White syndrome)
    - Electrocardiographic evidence of complete or clinically significant incomplete left bundle branch block or right bundle branch block
    - Evidence of second- or third-degree heart block

- Intraventricular conduction delay with QRS duration more than 120 ms
- Bradycardia as defined by sinus rate less than 50 bpm
- Personal or family history of Long QT Syndrome
- Personal history of cardiac disease, symptomatic or asymptomatic arrhythmias, with the exception of sinus arrhythmia
- Syncope (i.e. cardiac syncope not including syncope due to vasovagal or epileptic causes)
- Risk factors for Torsades de Pointes (e.g., heart failure, hypokalaemia, or hypomagnesemia)

All HIV co-infected patients who were taking ART during screening were required to switch to one of the following permissible ART regimens during screening and at least one week prior to randomisation:

- Lopinavir/ritonavir based regimen consisting of lopinavir/ritonavir in combination with any two nucleoside reverse transcriptase inhibitors (NRTI)s
- Nevirapine (NVP) based regimen consisting of NVP in combination with any two NRTIs
- Integrase inhibitor based regimen consisting of an integrase inhibitor (either dolutegravir or raltegravir) in combination with any two NRTIs
- Triple NRTI based regimen, e.g. a regimen made up of zidovudine, lamivudine, and abacavir, or in accordance with local standard of care

Patients randomised to Regimen C (bedaquiline) who started ART while on randomised treatment were required to take one of the permissible ART regimens listed above; they could start alternative ART on completion of their study regimen. Regimens A and B patients could start alternative ART at any time after randomisation at the discretion of the treating clinician.

Systemic use of other moderate and strong CYP3A4 inhibitors and inducers, as well as QT-prolonging drugs, was prohibited with bedaquiline containing regimens.

Treatments

In its initial design, STREAM Stage 2 involved four different regimens. Due to major shifts in the MDR-TB treatment landscape (including implementation of the 2016 WHO treatment guidelines), the original STREAM Stage 2 study design was revised through multiple protocol amendments to cease randomisation to Regimens A or D (both as of protocol 8.0).

The focus of this application and assessment are thus comparisons between Regimen B (comparator) (including an **injectable aminoglycoside**) and Regimen C (all-oral, including **bedaquiline**). The background regimen was essentially the same in both cases:

- 6 other agents (isoniazid, prothionamide, moxifloxacin/levofloxacin*, clofazimine, ethambutol, and pyrazinamide) during the 16-week intensive phase, followed by
- 3 other agents (levofloxacin, ethambutol, and pyrazinamide) during continuation phase, i.e. the continuation phase through to 40 weeks.

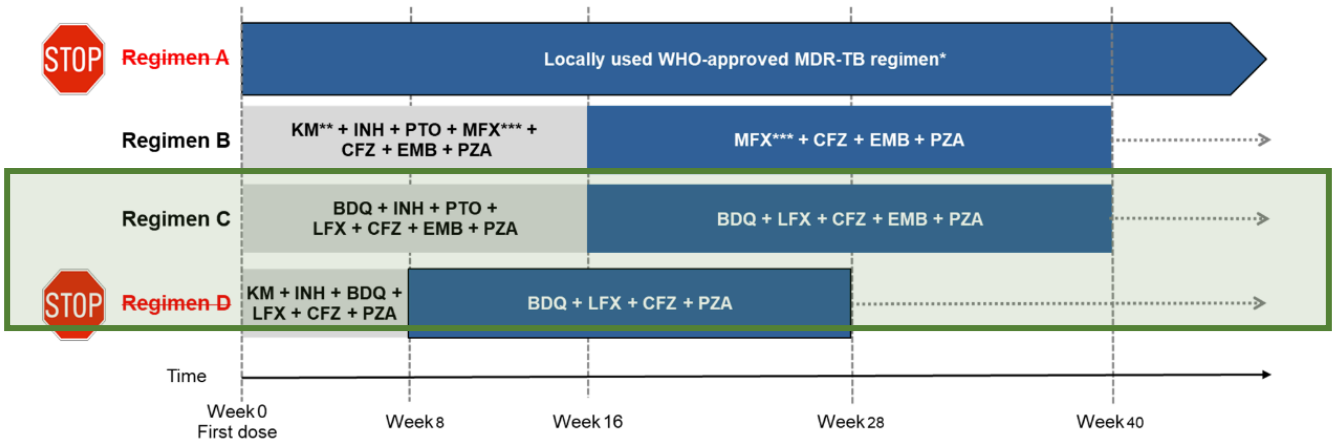
*From protocol 8.0 onwards, moxifloxacin was replaced by levofloxacin in Regimen B (comparator), due to its better safety profile with respect to QT-prolongation.

A pre-defined algorithm based on sputum smear results at pre-determined timepoints was used to determine when a participant could proceed from the intensive to the continuation phase. The algorithm was the same for participants in Regimens B and C (bedaquiline). The intensive phase was extended to 20 or 24 weeks for patients whose smear had not converted by 16 or 20 weeks, respectively. If the intensive phase was extended then so was the overall treatment duration, except for BDQ, which was not to be given for longer than 40 weeks.

Initially, kanamycin was administered as the injectable aminoglycoside in Regimen B (comparator). From protocol version 10.0 onwards, amikacin (preferred according to revised WHO guidance) or kanamycin could be used, depending on availability.

The background regimen was generally aligned with the WHO recommendations the applied at the time of study start, and acceptable even with respect WHO 2021 recommendations.

Figure 32 Regiments used in the STREAM study



AM = amikacin, BDQ = bedaquiline, CFZ = clofazimine, EMB = ethambutol, INH = isoniazid, KM = kanamycin, LFX =levofloxacin, MDR-TB = multidrug-resistant tuberculosis, MFX = moxifloxacin, PTO = prothionamide, PZA = pyrazinamide, WHO = World Health Organization
Grey color: intensive phase; Blue color: continuation phase (see below for details)
*Locally-used (country-based) MDR-TB regimen in accordance with 2011 WHO MDR-TB treatment guidelines.
**From protocol version 10.0 onwards, injectables AM or KM could be used, depending on availability.
***From protocol version 8.0 onwards, MFX was replaced with LFX.

Dosing

Product (doses in mg)	**Weight group**		
	<33 kg	**33 to 50 kg**	**>50 kg**
Bedaquiline	400 mg QD for the first 2 weeks and at 200 mg TIW thereafter		
Moxifloxacin/levofloxacin*	400/750	600/750	800/1000
Clofazimine	50	100	100
Ethambutol	800	800	1200
Pyrazinamide	1000	1500	2000
Isoniazid	300	400	600

Prothionamide	250	500	750
Kanamycin/amikacin**	15mg/kg (max 1g)		

*From protocol 8.0 onwards, moxifloxacin was replaced by levofloxacin.

**From protocol version 10.0 onwards, amikacin or kanamycin could be used, depending on availability.

The CHMP noted that the doses used in the STREAM Stage 2 study generally align with the upper ranges of those recommended in the WHO 2013 guidelines in place at the time of study start. Doses of clofazimine, isoniazid and prothionamide for patients <33 kg are thus a little lower than those recommended according to the WHO 2022 update for a similar weight bracket. This applies equally to Regimen B (comparator) and Regimen C (bedaquiline) and is not considered to be clinically meaningful nor to significantly impact comparison of the clinical usefulness of the injectable-based versus all-oral regimen.

Late identification of drug-resistance or drug-sensitivity

Any participant whose initial TB infection was found to be susceptible to RMP (DS-TB) after they had been randomised, as confirmed by gene sequencing, should have had their treatment amended appropriately and followed up according to the study schedule.

In case participants were identified post-baseline as having DS-TB or pre-XDR-TB, the participant was not to be discontinued from the study.

However, if participants were found to have XDR-TB (defined as MDR-TB with resistance to fluoroquinolones and second-line injectables from phenotypic DST), these participants were withdrawn from study treatment and treated according to national guidelines.

2.4.1.2.1. Objectives

Primary: Efficacy

To assess whether the proportion of participants with a favourable efficacy outcome at Week 76 in Regimen C (bedaquiline) (40- week BDQ-containing all-oral regimen) was noninferior to that in Regimen B (comparator) (40-week non-BDQ containing regimen, including an injectable), using a 10% margin of noninferiority.

Secondary (non-exhaustive): Safety

To compare the safety, including the effect on mortality and tolerability, of 40 weeks of BDQ in combination with the other drugs of Regimen C (bedaquiline) with Regimen B (comparator) during treatment and follow-up.

2.4.1.2.2. Outcomes/endpoints

Primary efficacy outcome

- Proportion of participants with favourable outcome (last 2 consecutive culture results collected at 2 separate visits at least 1 day apart were negative) at Week 76 (window defined as Week 70 to 82).

The Week-76 window was extended to Week 90 if the visit was scheduled to occur during the COVID-19 pandemic and did not occur due to restrictions on movement, unacceptable risk of exposure to COVID-19 in connection with the scheduled visit, or any other reason related to the pandemic.

Patients that didn't have a culture result within the Week 76 window (or the extended window for reasons related to Covid-19) because they were unable to produce sputum or because their sample was contaminated were classified as favourable if their last two cultures before the Week 76 window were negative and they had not previously been classified as unfavourable.

An unfavourable outcome was documented if:

1. They were discontinued from their allocated study intervention and subsequently restarted on a different MDR-TB regimen.

2. Treatment was extended beyond the scheduled EOT for any reason other than making up for days when no treatment was given (missed treatment) for a maximum of 8 weeks. (Up to 14 days were permitted, for any reason, before this was classed as treatment extension).

[Note: Extension of the intensive treatment phase was not classified as unfavourable if it followed the pre-specified algorithm, nor was discontinuation of a single agent that was not replaced.]

3. They were restarted on any MDR-TB treatment after the scheduled EOT, but before 76 weeks after randomisation.

4. They changed their allocated study intervention for any reason other than (1) the replacement of a single drug (excluding changes from KM to AM) or (2) for participants allocated to Regimen A, when the change was a result of changes in local guidelines and not related to any change in the participants' circumstances or condition.

5. BDQ was started in Regimen B (comparator).

6. A second-line injectable agent was started in Regimen C (bedaquiline).

7. A drug from the class of nitroimidazoles (DLM, PMD) or LZD [favoured salvage regimen following BDQ use following WHO 2018 guidance] was started in any regimen.

8. They died at any point during treatment or follow-up (up to Week 76).

9. At least 1 of their last 2 culture results, from sputum samples taken on 2 separate visits at least 1 day apart, was positive. Missing or contaminated cultures were excluded from this evaluation.

10. They did not have a culture result within the visit window, except when the participant could not produce the sputum sample or sample was contaminated.

The CHMP noted that replacing a single TB drug was not considered for study purposes to be a substantial change to the regimen and therefore did not result in an unfavourable outcome, with the exception of adding bedaquiline in Regimen B (comparator), a second-line injectable in Regimen C (bedaquiline) or a drug from the class of nitroimidazoles or linezolid (in any regimen). The open-label design is likely to have influenced treatment decisions to change regimens. On the other hand, the individualisation of background regimen might be considered a strength of the study in the sense that it better reflects how BDQ with multi-agent regimens is used in clinical practice. Importantly, introduction of bedaquiline or other key second line agents against MDR-TB in participants not allocated to these treatments by randomisation <u>was</u> considered an unfavourable outcome for the purposes of primary efficacy analysis.

Secondary efficacy outcomes (non-exhaustive)

- Proportion of participants with favourable outcome at Week 132.
- Microbiological status (culture conversion, AFB smear conversion, development of resistance) at EOT, Week 76, Week 132.
- Time to smear conversion.
- Time to culture conversion.

Outcomes were classified as unfavourable at Week 132 it had been unfavourable at Week 76, or if they had had a positive culture result, started MDR-TB treatment, or died since a previously favourable outcome at Week 76.

Culture conversion (last 2 consecutive negative cultures (collected at 2 separate visits assigned to separate analysis visits)) was the sum of:

Culture negative: Achieved if the last two consecutive negative culture results assigned to separate analysis visits (including the last assessment in the visit window), were negative (confirmed).

Culture negative with no sputum sample available within analysis visit window: No culture results available within analysis visit window because no sputum could be produced and culture negative status (two consecutive negative cultures [confirmed]) was previously satisfied.

Culture negative not confirmed within analysis visit window: No culture results available within analysis visit window due to premature study discontinuation, death, loss to follow-up, etc or sample culture was contaminated (missing in analysis) or visit missed but culture negative status (two consecutive negative cultures [confirmed]) was previously satisfied at the last assessment available (last time participant was assessed).

Sputum AFB smear conversion was similarly defined as 2 consecutive negative smears (collected at 2 separate visits assigned to separate analysis visits).

Time to sputum culture conversion (conversion status maintained) was defined as the time from randomisation to the first of two consecutive negative culture results.

Time to sputum AFB smear conversion was defined as the time from randomisation to the first of two consecutive negative smear results.

Any culture result that was missing because the participant was no longer able to produce sputum was treated as a negative result, provided the last 2 available culture results (from sputum samples taken on 2 separate visits at least 1 day apart) were negative.

Similarity or not of post-baseline *M. tuberculosis* strain to that identified at baseline determined categorisation of post-baseline infection following an initial favourable outcome as relapse or reinfection.

Resistance to BDQ was documented when the MIC was >0.25 µg/mL (ie, the critical concentration) or in the presence of mutations in the *atpE*, *Rv0678* and *pepQ* genes.

Safety outcomes

- All-cause mortality during treatment or follow-up.
- Proportion of participants experiencing a Grade 3 or greater AE, as defined in the DAIDS criteria, during treatment and follow-up.
- Change of regimen for AEs

- Number of AEs occurring on treatment and during the follow-up period

2.4.1.2.3. Sample size

Initially, the planned sample size was 165 patients in Regimen A and 330 patients in each of Regimens B, C, and D. As of protocol amendment 8.0, at a point when 70% (n=228/413) of patients in Regimens B and C (bedaquiline) had been recruited, Regimens A and D were dropped and the primary objective of the study was changed from a superiority to a non-inferiority comparison of Regimens B and C (bedaquiline). A new sample size calculation was also made, which resulted in a reduction of the planned sample size from 330 to 200 patients in each of Regimens B (comparator) and C (bedaquiline).

The new sample size was determined based on the assumption that the proportion of participants with a favourable outcome at Week 76 (primary endpoint) was 80% for Regimen B (comparator) (estimated based on preliminary STREAM Stage 1 results) and 82% for Regimen C (bedaquiline) (based on an anticipated minimum benefit in efficacy of using 40 weeks treatment with BDQ compared with 16 weeks treatment with KM).

Using a noninferiority margin (or rather "equivalence" margin for the regimens, since an M1 based on aminoglycoside contribution to regimen efficacy cannot be identified) of 10% and a one-sided significance level of 2.5%, 172 evaluable participants were required in each of the 2 regimens to demonstrate noninferiority of Regimen C (bedaquiline) to Regimen B (comparator) with 80% power. To account for at least 14% of participants likely to be excluded from the Per-protocol analysis set, a total of 400 participants was required to be enrolled in Regimens B and C (bedaquiline). Also, with a minimum sample size of 200 participants per regimen and an assumed mortality rate of 8% in the control group (Regimen B (comparator)), an increased mortality of 8% could be ruled out with 80% power.

Protocol amendment 8.0 also included a plan for an interim analysis with a blinded and independent sample size re-estimation. This interim analysis was to be performed when at least 40% of the 400 participants had completed 24 weeks of treatment and 10% had completed 76 weeks of follow-up.

A report of the interim analysis was finalised in March 2019, nearly 2 years after the plan to conduct a sample size re-estimation had been adopted in protocol version 8.0 (April 2017). Based on this blinded assessment of the primary endpoint determined by Kaplan-Meier analysis of time to unfavourable outcome, and assuming a 2% treatment difference in favour of Regimen C (bedaquiline), the estimated pooled Week 76 favourable outcome rate was ≥75%. This resulted in the decision that no further sample size increase was required.

Randomisation

Patients were randomised using a web-based randomisation system. Separate randomisation lists for each combination of strata was prepared using varying block sizes. If web access was not available at the time of randomisation, a manual alternative using sealed envelopes was provided.

Randomisation was stratified by site and by HIV status and CD4 count status (three categories: HIV-negative, HIV-positive with low CD4 count of less than 350 cells/mm3, or HIV-positive with high CD4 count of more than or equal to 350 cells/mm3).

The randomisation ratio was changed when Regimens A and D were discontinued, as shown in the table below.

Protocol version	Allocation ratio	Regimens
6.2	1:2:2:2	A:B:C:D
6.3 or 7.0	1:1:1	B:C:D in countries where the local NTP adopted or has imminent plans to adopt the WHO 2016 short regimen; as for v6.0 elsewhere
8.0 onwards	1:1	B:C

Blinding (masking)

STREAM Stage 2 was an open-label trial, so no blinding procedures were applicable to study site staff or patients. However, laboratory assessments were performed blinded, and the sponsor and Janssen staff involved in the analysis or in decision making were not provided with datasets/analyses including dummy treatment codes.

An IDMC evaluated unblinded safety and efficacy data from the study at pre-specified intervals. The primary purpose of the IDMC was to ensure the safety of participants in the study. Based on the IDMC reviews, no direct changes (only recommendations) were made to the protocol.

The IDMC reports were prepared by the trial statisticians, and they were the only persons outside the IDMC who had access to these (unblinded) reports. If any modifications to the trial design were required, the unblinded statisticians were excluded from the discussion.

2.4.1.2.4. Statistical methods

Analysis sets

The Intent-to-treat (ITT) Analysis Set included all randomised participants.

The Modified Intent-to-treat (mITT) Analysis Set included all randomised participants who had a positive culture for *M. tuberculosis* at screening or randomisation, except for participants with isolates taken before randomisation that were subsequently found to be susceptible to RMP, and participants with isolates taken before randomisation that were subsequently found to be resistant to both fluoroquinolones and second-line injectables (i.e., XDR-TB) on phenotypic DST. Participants randomised in error, ie, late screening failures, were excluded from the mITT Analysis Set.

The Per-protocol (PP) Analysis Set included all participants from the mITT Analysis Set, with the exclusion of participants who did not complete a protocol-adherent course of treatment (taken 80% of doses within 120% of the minimum duration in both the intensive phase and in the whole treatment period), other than for treatment failure (defined as failure to attain and maintain culture negativity until the end of allocated treatment), change of treatment for an AE, or death.

The modified PP (mPP) Analysis Set included all participants from the mITT Analysis Set with the exclusion of participants who did not complete a protocol-adherent course of treatment (as defined in the SAP), other than for treatment failure or death.

Favourable outcome at Week 76 (primary efficacy analysis)

The difference in proportion of participants with a favourable outcome between Regimen B (comparator) and Regimen C (bedaquiline) with corresponding two-sided 95% CI and p-value was estimated using a stratified analysis of the risk difference from each stratum using Cochran-Mantel-Haenszel weights, with 2 stratification factors: the protocol version under which participants were enrolled (version 6.2; versions 6.3 or 7.0; versions 8.0 or 10.0) and HIV and baseline CD4 cell count status (HIV-negative; HIV-positive with CD4 count less than 350 cells/mm3; and HIV-positive with CD4 count more than or equal to 350 cells/mm3). A sensitivity analysis was also conducted in which a third stratification factor, site, was included.

Noninferiority was declared if the upper bound of the 95% CI was less than the 10% margin of noninferiority. This had to be shown in both the mITT and PP Analysis Sets. A sensitivity analysis was performed on the mPP Analysis Set.

The 10% margin of non-inferiority was considered by the sponsor an acceptable reduction in efficacy given the reduced pill burden and duration and the expected increase in adherence in reducing a treatment regimen from a standard of 104 (as with Regimen A) weeks to 40 weeks (as with Regimens B and C)). This is not a margin based on retention of a proportion of comparator (aminoglycoside) contribution to regimen efficacy (i.e., no M1 has been formulated)

If noninferiority was demonstrated, superiority could be declared if the upper bound of the 95% CI was less than zero. For the superiority analysis, the mITT Analysis Set was primary, the PP Analysis Set was secondary, and the mPP Analysis Set was used for sensitivity analyses.

There were several sensitivity analyses of the primary outcome:

- Ignoring substitutions of levofloxacin for moxifloxacin and vice versa as treatment changes.
- Not counting starting linezolid alone as unfavourable.
- Excluding patients with no sputum sample available at Week 76 due to Covid-19 who are not otherwise classified as unfavourable.
- Reclassifying any participants with missing Week 76 culture results because of COVID-19 as favourable if they meet the definition of favourable, with the latest of the 2 negative culture results being within the Week 68 window, unfavourable otherwise.
- With a patient's outcome only classified as favourable if the patient's last culture result within the Week 76 window was negative and there was a previous negative culture result from sputa taken at least 25 days earlier.
- Reclassifying any participants who died as a result of trauma (as adjudicated by independent review) as "non-assessable" rather than unfavourable.
- Reclassifying any participants with reinfection (based on genotype) as "non-assessable" rather than unfavourable.
- In the ITT analysis population
- In the safety analysis population

All primary efficacy analyses were repeated:

1. Unadjusted for any covariates except randomisation protocol.

2. Adjusted for randomisation stratification factors HIV status and centre. Small strata with fewer than 10 patients will be combined within geographical regions within country.
3. Adjusted for randomisation stratification factors and any additional important covariates such as cavitation at baseline, or baseline bacillary load (baseline log10(CFU count)).

Time points of efficacy analyses beyond Week 76

For the efficacy analyses beyond Week 76, data collection was curtailed at the point when the last recruited participant was projected to reach Week 96 (i.e., 30 November 2021). A participant's last scheduled efficacy visit was considered as his/her latest scheduled study visit on or before 30 November 2021. The long-term efficacy data therefore include data up to at least Week 96 for all participants, and up to Week 132 for 145/187 (77.5%) participants in Regimen B (comparator) and 146/196 (74.5%) participants in Regimen C (bedaquiline). The timepoints for the secondary efficacy analyses are still referred to as 'Week 132'. For analyses including data beyond 30 November 2021, the wording 'Week 132 (all data)' has been used.

Favourable outcome at Week 132 (secondary efficacy analysis)

The proportion of participants with a favourable outcome at Week 132 was estimated by analysis of time to unfavourable outcome, thereby using information on all participants. Data from participants whose scheduled last efficacy visit was before Week 132 were censored at the time of their last visit, unless they had already become unfavourable. Non-assessable participants were included in the time to event analysis and censored at the time of their last visit.

The survival curve for each combination of strata and randomised group was calculated using a Cox proportional hazard regression model adjusting for stratification factors and randomised group. The average survival curve for each randomised group was estimated as a weighted average of the corresponding stratum-specific survival curves, with weights proportional to the number of individuals in each stratum in the randomised group at baseline. The mean of these differences at week 132 was the point estimate for the difference in overall survival function between Regimen C (bedaquiline) and Regimen B (comparator). A two-sided bias-corrected 95% CI for the difference in proportion (Regimen C – Regimen B) was calculated with bootstrap standard errors. Bootstrap standard errors for the risk difference was used so that the CI of the risk difference (estimated by the risk difference ±1.96se assuming the bootstrap distribution is approximately Normal) is bounded between -1 and 1. The bootstrapping sampled 1000 times and was stratified by stratification factors.

Non-inferiority and superiority were declared using the same principles as in the primary analysis.

A sensitivity analysis estimated the proportion unfavourable at Week 132 on the subset of participants randomised at least 132 weeks on or before the end of November 2021. For this analysis, non-assessable participants were excluded. This analysis was done on the mITT, PP and mPP populations.

The above analyses were repeated for the following comparisons, restricting the population in each case to include only concurrent controls within sites: Regimen B_{lev} (comparator including levofloxacin) and Regimen C (bedaquiline), Regimen B_{mox} (comparator including moxifloxacin) and Regimen C (bedaquiline), Regimen D and Regimen B, Regimen B and Regimen A, Regimen C and Regimen A, Regimen D and Regimen A. The analysis will also be repeated (in both mITT and PP analysis populations) in subgroups according to HIV status.

Microbiological status (secondary efficacy analysis)

Microbiological status was tabulated by Regimen at end of treatment, at Week 76, and using all data (including culture results after Week 76) in the mITT set. The time window of the analysis at Week 76

was extended if culture result was missing due to Covid-19 related reason, as was done in the primary analysis.

The difference in proportion of responders between Regimen B (comparator) and Regimen C (bedaquiline) with corresponding two-sided 95% CI and p-value was estimated using a stratified analysis of the risk difference from each stratum using Cochran-Mantel-Haenszel weights, stratified by the protocol version under which participants were enrolled (version 6.2; versions 6.3 or 7.0; versions 8.0 or 10.0). Whilst HIV status and CD4 count category was also a randomisation stratification factor, it was not used as a stratification factor in the analysis model because there were few HIV-positive participants, although it was part of the subgroup analyses.

In the analysis of microbiological status, a "no overruling" approach was used. This means that participants who prematurely discontinued study participation and who had limited culture results available were categorised as responder/non-responder based on the data available up to the time point of last available assessment. In addition, change in treatment regimen was not taken into consideration and data were utilised regardless of salvage TB treatment, re-treatment etc (intention-to-treat principle).

Time to microbial response (secondary efficacy analysis)

Time to sputum culture conversion (conversion status maintained) was defined as the time from randomisation to the first of two consecutive negative culture results, assigned to separate analysis visits (culture conversion status maintained [implied no further intervening positive culture result assigned to an analysis visit until the last collection of sputum that yielded the last culture result]). Participants that did not achieve culture conversion were censored at the date of sputum collection that yielded their last culture result. Similarly, participants with a positive baseline culture result and for whom culture conversion could not be determined due to lack of post-baseline "evaluable" culture results/insufficient post-baseline culture results were censored at Day 1.

Median time to sputum culture conversion (conversion status maintained) was analysed utilising Kaplan-Meier estimates. The equality of survivor functions for time to sputum culture conversion (conversion status maintained) was compared (for the primary and secondary comparisons noted above) using a log rank test, stratified by randomisation protocol (version 6.2, versions 6.3 or 7.0, versions 8.0 or 10.0).

Drug resistance (exploratory efficacy analysis)

Drug resistance at screening or baseline was tabulated by treatment arm, with separate tables for genotypic and phenotypic DSTs. In addition, acquired resistance to any drugs was also described and tabulated by treatment arm using any available post-randomisation DST result (i.e. classifying as resistant if any result is resistant), for each drug.

Baseline MIC values for bedaquiline were tabulated by microbiological outcome. To explore possible cross-resistance between bedaquiline and other Anti-TB drugs, baseline resistance to anti-TB drugs were tabulated by baseline bedaquiline MIC. If subjects had any post-baseline bedaquiline MIC >= 4*baseline bedaquiline MIC, those subjects were defined as having 4-fold increase in bedaquiline MIC. 4-fold increase (Yes/No) in bedaquiline MIC (based on any available MIC) were tabulated by acquired resistance to anti-TB drugs (based on any available DST) and also by baseline DST, for each drug.

Critical concentration of bedaquiline was classified as: 1) at least one post-baseline bedaquiline MIC > 0.25 ug/ml; 2) all post-baseline bedaquiline MIC =< 0.25 ug/ml. Critical concentration of bedaquiline classification were tabulated by baseline DST and by acquired resistance to each anti-TB drugs (based on any available DST data).

Multiplicity

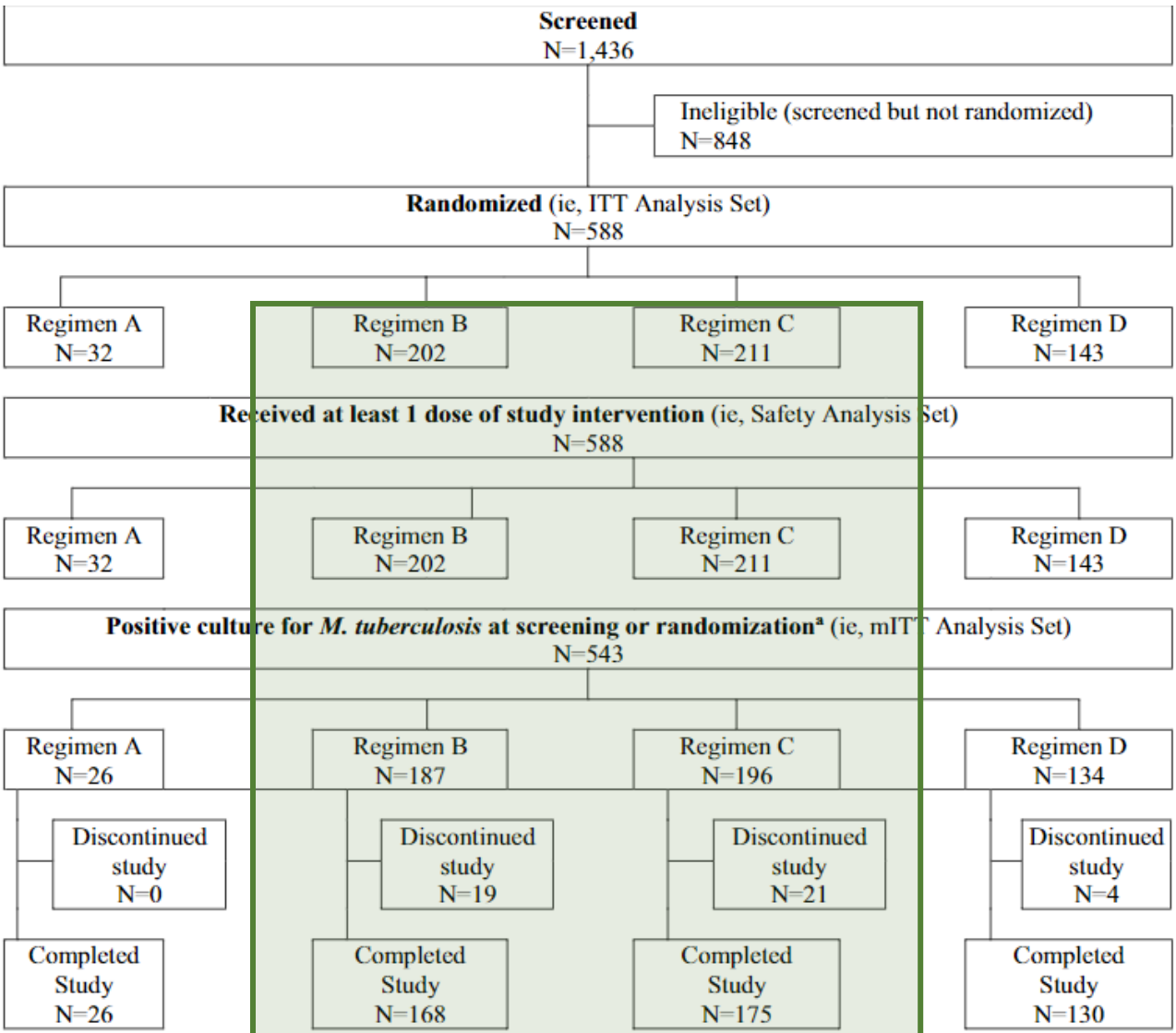
No adjustment for multiplicity was made.

2.4.1.3. Results

2.4.1.3.1. Participant flow

Of 1,436 participants screened for the study, 588 (40.9%) were enrolled, randomised and treated with at least 1 dose of study intervention. The primary reasons for ineligibility were microbiology-related, e.g., negative sputum samples, resistance to fluoroquinolones/injectables.

In the mITT Analysis Set, 44/543 (8.1%) participants prematurely terminated study participation before the Week 132 visit due to death (19 [3.5%] participants), withdrawal of consent (12 [2.2%]), lost to follow-up (11 [2.0%]), or another, not further specified reason (2 [0.4%]). Reasons for termination were comparable between the regimens.



[a] See Section 3.7.3 for definition of the mITT Analysis Set

N: number of participants

Sources: Attachment TSIDS01 and Attachment TSIDS03b.

Figure 33: Participant Disposition (Study TMC207TBC3007)

2.4.1.3.2. Conduct of the study

The study was conducted at 13 sites that enrolled participants in Ethiopia (2 sites), Georgia (1 site), India (3 sites), Moldova (1 site), Mongolia (1 site), South Africa (4 sites), and Uganda (1 site).

Study start: 27 March 2016

Efficacy follow-up curtailed as of: 30 Nov 2021

Last patient last visit: 02 August 2022

Final protocol version: 11.0. (Note that the first version that applied to STREAM Stage 2 was 6.0, as earlier version concerned STREAM Stage 1 only). The first participant was enrolled under version 6.2.

STREAM Stage 2 was initially designed as a superiority study comparing Regimen C (bedaquiline) with Regimen B (comparator) (primary regulatory objective). Comparisons to assess NI of Regimen C (bedaquiline) versus Regimen B (comparator) and of Regimen D versus Regimen B were planned as secondary analyses. Due to major shifts in the MDR-TB treatment landscape, namely favouring shorter, all-oral treatment regimens, the original STREAM Stage 2 study design was revised through multiple protocol amendment to stop randomisation to Regimen A and Regimen D as of protocol 8.0 and make NI of Regimen C (bedaquiline) versus Regimen B (comparator) the primary objective.

Major changes to protocol (non-exhaustive)

Version 6.2 (16 February 2015) included the following changes:

- Follow-up was limited to Week 132 instead of Week 144.

Version 6.3 (16 April 2018; local version in India) included the following changes:

- Randomisation to Regimen A stopped in India, as the country had adopted the shortened regimen, therefore making recruitment to Regimen A (20-24 month long regimen) unethical.

Version 7.0 (23 December 2016) included the following changes:

- Regimen A adjusted to the 2011 WHO MDR-TB treatment guidelines (not further detailed here).
- Sample size (and power) sections were adjusted accordingly, clarifying randomisation in countries where recruitment to Regimen A had been dropped (aiming to recruit at least 330 participants to Regimen B (comparator), Regimen C (bedaquiline), and Regimen D, in a ratio of 1:1:1).
- 'Time to unfavourable efficacy outcome'; 'The proportion of participants in each category meeting the WHO classification of outcome as applicable at the time of analysis'; and 'Time to cessation of clinical symptoms based on PI assessment' changed from secondary to exploratory outcomes.

Version 8.0 (13 April 2017) included the following changes:

- MFX was replaced with LFX in Regimen B (comparator) on the basis of improved safety profile.

- Randomisation to Regimen A was stopped (most participating countries had adopted or had imminent plans to adopt the WHO 2016 MDR-TB regimen). Randomisation to Regimen D was stopped, to accommodate with the elimination of injectables from the treatment of MDR-TB.
- Efficacy follow-up was adjusted to be terminated when the last participant randomised reached Week 76 (instead of the planned Week 132).
- Superiority of Regimen C (bedaquiline) compared to Regimen B (comparator) was removed as a primary objective in favour of non-inferiority, leading to revision of the statistical considerations, including rationale and power calculations, and sample size. A sample size re-estimation interim analysis, to be performed by an independent Statistical Support Group, was added to determine the final sample size needed to achieve adequate power. Secondary objectives were modified to align with the change in primary objective from superiority to noninferiority of Regimen C (bedaquiline) to Regimen B (comparator), to reflect assessments to be performed at Weeks 76 and 132, and to reflect estimate differences between the regimens in the proportion of participants with a favourable outcome. Mortality evaluation was extended to all participants.

Version 9.0 was prepared, but never implemented or submitted to the sites.

Version 10.0 (17 April 2019) included the following changes:

- Regimen B (comparator) allowed the use of KM or AM in the intensive phase, depending on availability.

Version 11.0 (15 December 2020) included the following changes:

- Safety follow-up continued for all participants up to Week 132, but the long-term efficacy follow-up was curtailed at the pre-defined cut-off date of 30 November 2021, ie, the point when the last recruited participant was projected to reach Week 96.
- Clarification of the secondary objectives and of secondary and exploratory outcomes was added, including definitions to prevent participants who were successfully treated and were not able to produce sputum being classified as having an unfavourable outcome in error. Two sensitivity analyses were added to assess the impact of changes to the protocol on the criteria for an unfavourable outcome.

Pre-specified and alternative analysis approaches

Local and central laboratory results were processed hierarchically according to a pre-specified data handling protocol, to determine microbiological results, including drug sensitivity data. An alternative methodology for this was defined in the Microbiology Report. This differed in several respects from the pre-specified analysis methodology detailed in the SAP. Both approaches were documented and signed off prior to database lock. The main differences are summarised below:

Table 24: Main differences between data handling in the prespecified and post hoc alternative statistical analysis (study TMC207TB3007)

Prespecified Analyses	Alternative Analyses
Culture results collected from sputum sampling at least 1 day apart contributed to the average CFU count and subsequent culture status for that visit ("separate visits" = sampling at least 1 day apart)	All culture results assigned to windowed analysis visits contributed to the average CFU count and subsequent culture status for that analysis visit ("separate visits" = windowed analysis visits)
Only Ogawa/LJ assays were utilized for culture conversion and microbiological status at key timepoints	Ogawa/LJ assays or MGIT (if required conditions met) were utilized for culture conversion and microbiological status at key timepoints
Time to culture conversion defined as the time from randomization to the first of 2 consecutive negative culture results obtained from separate visits at least 1 day apart and regardless of status being maintained	Time to culture conversion (conversion status maintained) defined as the time from randomization to the first of 2 consecutive negative culture results, assigned to separate windowed analysis visits (culture conversion status maintained implied no further intervening positive culture result assigned to a windowed analysis visit until the last collection of sputum that yielded the last culture result)

Table 25: Differences between the pre-specified and alternative statistical analyses for drug susceptibility testing results: Resistant/Susceptible assignment

Pre-specified Analyses	Alternative Analyses
Joint microbiologist/clinician review of RMP resistance (see Section 3.3.2 below)	Local DST result (GeneXpert/MTBDR*plus*/ MTBDR*sl*) compared to central phenotypic DST result and if discrepant, decision is made based on available genotypic DST in collaboration with expert-level interpretation of the mutations (see Section 3.3.1.4 above for details)
Use of only central microbiology laboratory DST results	Use of local DST results as last resort and in the absence of central phenotypic/genotypic DST
Any evidence of resistance in screening/baseline period as based on central microbiology laboratory data assigned as R = Resistant	Hierarchy of DST categorization followed (see Section 3.3.1.4 above for details)
For RMP, INH, fluoroquinolones and injectables (at a minimum), if impact of mutation was considered uncertain/unknown, the genotypic DST was not taken into account and considered missing	For all anti-TB drugs, in case impact of mutations was uncertain/unknown, "worst-case" was assumed with assignment of R = Resistant
For INH and OFX, no differentiation between concentrations was made and resistance was derived if any resistance observed across all tested concentrations	Concentration of INH and OFX taken into consideration in overall assignment of Resistant/Susceptible
CS/TRD not accounted for in determining number of active anti-TB drugs in Regimen A	CS/TRD accounted for in determining number of active anti-TB drugs in Regimen A

The CHMP noted the MAH assertion that the alternative approach is most conservative and closest to the methods applied in BDQ Phase 2 studies, in this regard. In the Summary of clinical efficacy, while the pre-specified approach has been applied to primary and secondary clinical efficacy outcomes (favourable outcome, time to favourable outcome), the alternative approach has been applied to secondary analyses concerning microbiological status and drug susceptibility.

Protocol deviations

In the mITT Analysis Set, critical protocol deviations were reported in 4.3% in Regimen B (comparator) and 4.1% in Regimen C (bedaquiline), while major protocol deviations (excluding COVID-19-related deviations) were reported in 35.3% in Regimen B (comparator) and 26.5% in Regimen C (bedaquiline). Protocol deviations in each regimen are broken down by category in the table below.

Protocol deviations related to COVID-19 were recorded separately. Reporting of COVID-19 related protocol deviations was comparable between Regimens B and C (bedaquiline).

Table 26 Critical, major and COVID-19-related protocols deviations; mITT analysis set (Study TMC207TBC3007)

	A	B	C	D	Overall
mITT Analysis Set	26	187	196	134	543
Participants with critical protocol deviations	4(15.4%)	8(4.3%)	8(4.1%)	9(6.7%)	29(5.3%)
Informed consent	2(7.7%)	2(1.1%)	2(1.0%)	4(3.0%)	10(1.8%)
Concomitant medication criteria	2(7.7%)	4(2.1%)	0	0	6(1.1%)
IP compliance	0	0	3(1.5%)	3(2.2%)	6(1.1%)
Study procedures criteria	0	2(1.1%)	2(1.0%)	1(0.7%)	5(0.9%)
Eligibility and entry criteria	0	1(0.5%)	1(0.5%)	1(0.7%)	3(0.6%)
Participants with major protocol deviations (excluding COVID-19-related deviations)	8(30.8%)	66(35.3%)	52(26.5%)	52(38.8%)	178(32.8%)
Serious adverse event criteria	4(15.4%)	33(17.6%)	23(11.7%)	23(17.2%)	83(15.3%)
Informed consent	2(7.7%)	9(4.8%)	8(4.1%)	11(8.2%)	30(5.5%)
Study procedures criteria	1(3.8%)	17(9.1%)	8(4.1%)	4(3.0%)	30(5.5%)
Laboratory assessment criteria	0	1(0.5%)	9(4.6%)	11(8.2%)	21(3.9%)
IP compliance	1(3.8%)	7(3.7%)	3(1.5%)	7(5.2%)	18(3.3%)
Visit schedule criteria	0	7(3.7%)	5(2.6%)	1(0.7%)	13(2.4%)
Eligibility and entry criteria	1(3.8%)	2(1.1%)	3(1.5%)	2(1.5%)	8(1.5%)
Administrative criteria	0	2(1.1%)	2(1.0%)	1(0.7%)	5(0.9%)
Efficacy criteria	0	0	2(1.0%)	0	2(0.4%)
Other criteria	0	1(0.5%)	0	1(0.7%)	2(0.4%)
Participants with COVID-19-related protocol deviations	4(15.4%)	87(46.5%)	90(45.9%)	63(47.0%)	244(44.9%)
Participants with at least one minor COVID-19-related protocol deviation	4(15.4%)	87(46.5%)	90(45.9%)	63(47.0%)	244(44.9%)
Participants with at least one major COVID-19-related protocol deviation	1(3.8%)	36(19.3%)	34(17.3%)	21(15.7%)	92(16.9%)

Note: Participants may appear in more than one category.
Note: Critical deviation: Any deviation from protocol-related procedures that significantly affects the integrity of data, adversely affects participants and/or could invalidate acceptability of the study or part of it.
Note: Major deviation: Any deviation considered to impact on the efficacy outcome or treatment of the participant.

2.4.1.3.3. Numbers analysed

Table 27 Number of participants per analysis set (study TMC207TBC3007)

	A	B	C	D	Overall
ITT Analysis Set (Randomized Participants)	32 (100%)	202 (100%)	211 (100%)	143 (100%)	588 (100%)
Safety Analysis Set	32 (100%)	202 (100%)	211 (100%)	143 (100%)	588 (100%)
mITT Analysis Set	26 (81.3%)	187 (92.6%)	196 (92.9%)	134 (93.7%)	543 (92.3%)
Protocol version					
v6.2	26 (81.3%)	63 (31.2%)*	66 (31.3%)	71 (49.7%)	226 (38.4%)
v6.3, v7.0	0	64 (31.7%)*	65 (30.8%)	63 (44.1%)	192 (32.7%)
v8.0, v10.0	0	60 (29.7%)**	65 (30.8%)	0	125 (21.3%)
PP Analysis Set	26 (81.3%)	166 (82.2%)	177 (83.9%)	122 (85.3%)	491 (83.5%)
mPP Analysis Set	18 (56.3%)	136 (67.3%)	166 (78.7%)	117 (81.8%)	437 (74.3%)
PK Analysis Set	-	-	173 (82.0%)	109 (76.2%)	282 (79.7%)

Note: Analysis sets are defined in Section 1.4.2.
Note: Percentage derived relative to total participants randomized, except for PK Analysis Set where percentage is derived relative to total participants randomized to Regimens C and D only.
*Regimen B_{mox}
**Regimen B_{lev}

Modified based on Mod5.3.5.1/STREAM Stage 2 CSR/Tab9

Table 28 Study disposition; mITT analysis set (study TMC207TBC3007)

	A	B	C	D	Overall
Analysis set: mITT	26	187	196	134	543
Subjects completed study	26(100%)	168(89.8%)	175(89.3%)	130(97.0%)	499(91.9%)
Subjects prematurely terminated study participation	0	19(10.2%)	21(10.7%)	4(3.0%)	44(8.1%)
Death	0	7(3.7%)	10(5.1%)	2(1.5%)	19(3.5%)
Withdrawal of Consent	0	6(3.2%)	6(3.1%)	0	12(2.2%)
Lost to Follow-up	0	5(2.7%)	4(2.0%)	2(1.5%)	11(2.0%)
Other	0	1(0.5%)	1(0.5%)	0	2(0.4%)

Note: Presented by randomized regimen.

Mod5.3.5.1/STREAM Stage 2 CSR/AttTSIDS03b

2.4.1.3.4. Baseline data

Baseline demographics

In the mITT Analysis Set (N=543), the majority of participants were male (61.3%), Asian (48.4%) or Black (34.6%), with median age 32.7 [range: 16, 69] years and median BMI 19.2 [range: 12, 40] kg/m^2. Demographics and baseline characteristics were comparable between the regimens and across analysis sets but varied between country and site.

Demographics and baseline characteristics (mITT Analysis Set)

	A	B	C	D	Overall
N	26	187	196	134	543
Sex					
Female	13(50.0%)	72(38.5%)	72(36.7%)	53(39.6%)	210(38.7%)
Male	13(50.0%)	115(61.5%)	124(63.3%)	81(60.4%)	333(61.3%)
Age: median(range), years	37.1(20; 53)	32.8(18; 64)	32.6(16; 65)	30.9(18; 69)	32.7(16; 69)
Race					
Asian	13(50.0%)	87(46.5%)	92(46.9%)	71(53.0%)	263(48.4%)
Black or African American*	9(34.6%)	63(33.7%)	68(34.7%)	48(35.8%)	188(34.6%)
White	4(15.4%)	37(19.8%)	36(18.4%)	15(11.2%)	92(16.9%)
Weight: median(range), kg	55.5(40; 66)	55.0(32; 109)	51.9(31; 91)	51.9(28; 96)	53.0(28; 109)
Height: median(range), cm	163.0(151; 183)	166.0(148; 202)	165.0(132; 187)	165.0(145; 187)	165.0(132; 202)
Body mass index: median(range), kg/m^2	19.1(14; 26)	19.3(13; 35)	19.0(12; 37)	19.2(12; 40)	19.2(12; 40)
Country					
Ethiopia	4(15.4%)	20(10.7%)	19(9.7%)	18(13.4%)	61(11.2%)
Georgia	0	13(7.0%)	12(6.1%)	7(5.2%)	32(5.9%)
India	3(11.5%)	42(22.5%)	46(23.5%)	47(35.1%)	138(25.4%)
Moldova (The Republic Of)	4(15.4%)	24(12.8%)	24(12.2%)	8(6.0%)	60(11.0%)
Mongolia	10(38.5%)	45(24.1%)	46(23.5%)	24(17.9%)	125(23.0%)
South Africa	5(19.2%)	22(11.8%)	25(12.8%)	21(15.7%)	73(13.4%)
Uganda	0	21(11.2%)	24(12.2%)	9(6.7%)	54(9.9%)
Smoking history					
Current	5(19.2%)	40(21.4%)	51(26.0%)	22(16.4%)	118(21.7%)
Ex	4(15.4%)	28(15.0%)	31(15.8%)	16(11.9%)	79(14.5%)
Never	17(65.4%)	119(63.6%)	114(58.2%)	96(71.6%)	346(63.7%)

Note: N for each parameter reflects nonmissing values.
Note: Age (years): Per inclusion criterion, participants 15 years of age or older were eligible for study participation in Stage 2 if otherwise valid. As such, 3 participants < 18 years of age enrolled, 2 participants from Mongolia and 1 participant from Uganda.
*All participants were black

Baseline disease characteristics

Cavitation was observed in most participants (74.9%), predominantly as multiple cavities (56.2%). A higher proportion of participants in Regimen C (bedaquiline) (62.5%) had multiple cavities compared to Regimen B (comparator) (46.6%).

Overall, most participants (97.6%) had previously used anti-TB drugs, including 65.5% using first-line anti-TB drugs only, 20.4% second-line only, and 11.7% both first- and second-line. These proportions were similar cross regimens.

Significant comorbidities

Ongoing medical history at screening was reported for 42.0% of participants overall. Most participants (85.5%) were HIV-negative. As enrolment was prematurely stopped in South Africa, the overall proportion of HIV-positive participants (n=52) in the study was lower than originally expected.

Overall, 30.0% and 4.8% of participants tested positive for hepatitis B and C, respectively. These proportions were similar across all regimens.

Prior anti-TB drugs

In the mITT Analysis Set, 75/187 participants (40.1%) in Regimen B (comparator) and 94/196 participants (48.0%) in Regimen C (bedaquiline) received prior anti-TB drugs. The most frequently used anti-TB drugs prior to randomisation (by ≥5.0% of participants overall) included: RMP (45.5%), INH (45.3%), EMB (45.1%), PZA (44.8%), and streptomycin (SM) (6.6%).

Number of Active Drugs in BR at Baseline

Almost all participants received 3 or more active anti-mycobacterial drugs at baseline from their baseline study regimen. Only a few participants (4/187 and 2/196 in Regimens B and C, respectively) were estimated to be receiving just 1 or 2 active drugs at baseline from their allocated regimen.

Concomitant anti-TB drugs

The most frequently (≥3%) added anti-TB drugs (drugs received at or after the date of randomisation) included:

- Regimen B (comparator) (n=187): LZD (31 [16.6%]), BDQ (29 [15.5%]), CS (10 [5.3%]), and ETO (6 [3.2%])
- Regimen C (bedaquiline) (n=196): KM (8 [4.1%]) and LZD (7 [3.6%])

Concomitant drugs other than anti-mycobacterials

In the mITT Analysis Set, in the subset of HIV-positive participants, all participants received concomitant ART during the study (drugs received at or after the date of randomisation). Of note, some ARTs (such as EFV) were disallowed during the Treatment Phase for participants on BDQ regimens, but restart was allowed after completion of the regimen, at the discretion of the treating clinician. Overall, the most frequently used concomitant ARTs (≥3% in the BDQ-containing Regimens C and/or D) were the direct-acting antivirals:

- efavirenz: 5.3% and 2.6% of participants in Regimens B and C, respectively
- nevirapine: 3.2% and 6.6%, respectively
- tenofovir: 8.0% and 9.2%, respectively
- efavirenz/emtricitabine/tenofovir disoproxil fumarate: 2.1% and 5.1%, respectively
- emtricitabine: 4.3% and 4.1%, respectively
- lamivudine: 9.1% and 8.7%, respectively
- abacavir: 4.8% and 3.1%, respectively
- lopinavir/ritonavir: 7.5% and 5.1%, respectively
- dolutegravir: 2.1% and 4.6%, respectively

Other concomitant drugs were used by 100% of participants and there were no meaningful differences between regimens.

Baseline microbiological data

At baseline and consistent with the inclusion criteria, all 543 participants were culture positive at the local laboratory. At baseline, AFB smear results were positive for 97.4% of participants and negative for 2.6% of participants. Based on AFB score, the participants in the different treatment regimens had a similar distribution of bacterial load.

The following tables shows the extent of baseline resistance in each treatment arm as per central drug susceptibility testing, with good correlation with local testing (not shown here), generally comparable rates of both individual drug resistance and MDR- or pre-XDR-TB resistance profiles between treatment arms B and C (bedaquiline).

Baseline susceptibility data when determined according to the alternative analysis methodology (not shown here) was concordant with that determined according to pre-specified analysis methodology (see the Conduct of the study section above).

Based on the baseline BDQ DST results from the central microbiology laboratory, 3 (0.6%) participants in the mITT Analysis Set had baseline resistance to BDQ: 2 of 186 (1.1%) participants in Regimen B (comparator) and 1 of 195 (0.5%) participants in Regimen C (bedaquiline).

There were no obvious correlations between baseline BDQ MIC and baseline resistance to other anti-TB drugs for the mITT analysis set (data not shown here).

Table 29: Baseline susceptibility to bedaquiline and other anti-TB drugs for participants with central microbiology laboratory data primary analysis; mITT analysis set (study STREAM stage 2)

	A	B	C	D	Overall
Analysis set: mITT	26	187	196	134	543
Drug susceptibility patterns					
First-line drugs					
Rifampicin[a]	26	187	196	134	543
Susceptible	0	0	0	0	0
Resistant	26 (100.0%)	187 (100.0%)	196 (100.0%)	134 (100.0%)	543 (100.0%)
Isoniazid[a]	26	187	196	134	543
Susceptible	2 (7.7%)	28 (15.0%)	27 (13.8%)	11 (8.2%)	68 (12.5%)
Resistant	24 (92.3%)	159 (85.0%)	169 (86.2%)	123 (91.8%)	475 (87.5%)
Pyrazinamide[b]	26	187	196	132	541
Susceptible	10 (38.5%)	102 (54.5%)	106 (54.1%)	62 (47.0%)	280 (51.8%)
Resistant	16 (61.5%)	85 (45.5%)	90 (45.9%)	70 (53.0%)	261 (48.2%)
Ethambutol[a]	26	186	196	134	542
Susceptible	12 (46.2%)	108 (58.1%)	117 (59.7%)	72 (53.7%)	309 (57.0%)
Resistant	14 (53.8%)	78 (41.9%)	79 (40.3%)	62 (46.3%)	233 (43.0%)
Second-line drugs					
Fluoroquinolones					
Ofloxacin[a]	26	183	190	130	529
Susceptible	25 (96.2%)	176 (96.2%)	182 (95.8%)	118 (90.8%)	501 (94.7%)
Resistant	1 (3.8%)	7 (3.8%)	8 (4.2%)	12 (9.2%)	28 (5.3%)
Injectables					
Kanamycin[a]	26	187	196	134	543
Susceptible	23 (88.5%)	174 (93.0%)	183 (93.4%)	130 (97.0%)	510 (93.9%)
Resistant	3 (11.5%)	13 (7.0%)	13 (6.6%)	4 (3.0%)	33 (6.1%)
Capreomycin[a]	26	186	196	134	542
Susceptible	26 (100.0%)	185 (99.5%)	195 (99.5%)	133 (99.3%)	539 (99.4%)
Resistant	0	1 (0.5%)	1 (0.5%)	1 (0.7%)	3 (0.6%)
Ethionamide[a]	26	183	190	130	529
Susceptible	15 (57.7%)	130 (71.0%)	148 (77.9%)	98 (75.4%)	391 (73.9%)
Resistant	11 (42.3%)	53 (29.0%)	42 (22.1%)	32 (24.6%)	138 (26.1%)
Clofazimine[c]	25	180	189	128	522
Susceptible	25 (100.0%)	179 (99.4%)	189 (100.0%)	128 (100.0%)	521 (99.8%)
Resistant	0	1 (0.6%)	0	0	1 (0.2%)
Bedaquiline[d]	26	186	195	134	541
Susceptible	26 (100.0%)	184 (98.9%)	194 (99.5%)	134 (100.0%)	538 (99.4%)
Resistant	0	2 (1.1%)	1 (0.5%)	0	3 (0.6%)

Table 30 Baseline susceptibility to bedaquiline and other anti-TB drugs for participants with central microbiology laboratory data primary analysis; mITT analysis set (study STREAM stage 2)

	A	B	C	D	Overall
Baseline extent of MTB resistance **(primary analysis)**					
DS-TB	0	0	0	0	0
RR-TB	2 (7.7%)	28 (15.0%)	27 (13.8%)	11 (8.2%)	68 (12.5%)
MDR-TB	20 (76.9%)	140 (74.9%)	149 (76.0%)	106 (79.1%)	415 (76.4%)
Pre-XDR-TB	4 (15.4%)	19 (10.2%)	20 (10.2%)	17 (12.7%)	60 (11.0%)
Fluoroquinolone-resistant	1 (3.8%)	7 (3.7%)	7 (3.6%)	14 (10.4%)	29 (5.3%)
Injectable-resistant	3 (11.5%)	12 (6.4%)	13 (6.6%)	3 (2.2%)	31 (5.7%)
XDR-TB	0	0	0	0	0

Key: MIC = minimum inhibitory concentration, DST = drug susceptibility testing.
[a] Löwenstein-Jensen proportion method used for rifampicin, isoniazid and ethambutol. 7H11 agar method used for ethionamide, kanamycin, capreomycin and ofloxacin.
[b] Pyrazinamide susceptibility/resistance measured using *pncA* gene sequencing.
[c] For clofazimine, MIC performed on 7H11 agar medium with critical concentration of 1 ug/mL used (>critical concentration = resistance). Highest MIC value is retained at a given timepoint if more than one value is assigned to that timepoint.
[d] For bedaquiline, MIC performed on 7H11 agar medium with critical concentration of 0.25 ug/mL used (>critical concentration = resistance). Highest MIC value is retained at a given timepoint if more than one value is assigned to that timepoint.
Note: N = total number of subjects with data (non-missing/non-contaminated values) per anti-TB drug.
Note: Baseline is defined as the last available DST assessment, based on the relevant positive culture result, prior to randomization. Central DST results are used only where there is a local positive culture result.
Note: Baseline extent of MTB resistance: DS-TB: If susceptible to rifampicin. RR-TB: If resistant to rifampicin and susceptible to isoniazid. MDR-TB: If resistant to rifampicin and to isoniazid. Pre-XDR-TB: If resistant to rifampicin, to isoniazid and additionally fluoroquinolone-resistant or injectable-resistant. XDR-TB: If resistant to rifampicin, isoniazid and additionally resistant to kanamycin/amikacin/capreomycin and at least one fluoroquinolone.

[tefmb03cp1.rtf] [tmc207/stream/dbr_week132/re_week132/tefmb03cp1.sas] 23MAR2023, 16:55

Late identification of drug-resistance or drug-sensitivity

Based on central microbiology laboratory data, none of the isolates of the participants in the mITT Analysis Set (N=543) showed susceptibility to RMP following the pre-specified analyses methodology for the baseline DST results. However, using the alternative analyses methodology, 3 participants (1 in Regimen B (comparator) and 2 in Regimen C (bedaquiline)) had MTB isolates susceptible to RMP. The discrepancy is not considered likely to have a meaningful effect on the results of study analyses.

Based on the central microbiology laboratory DST (following the pre-specified approach), 5.3% of the isolates of participants in the mITT Analysis Set displayed resistance to the fluoroquinolone ofloxacin, 6.1% displayed resistance to the injectable kanamycin, and 0.6% displayed resistance to the injectable capreomycin. These rates were comparable between regimens.

2.4.1.3.5. Patient exposure and compliance

The median exposure was 280 days for both 40-week Regimens B and C (bedaquiline) (range: 1 to 441 and 1 to 424 respectively), while the mean (SD) exposures were 250.5 (85.33) and 261.8 (75.53), respectively.

Overall, treatment compliance was very high. In the mITT Analysis Set, the rate of >90% compliance with allocated treatment regimen was slightly higher in Regimen C (bedaquiline) (96.4%) compared to Regimen B (comparator) (92.0%).

2.4.1.3.6. Outcomes and estimation

Primary efficacy analysis

Table 31: Favourable outcome at Week 76 (pre-specified approach)

Summary of Efficacy Results	A	B	C	D
Primary efficacy endpoint				
Favorable outcome at Week 76 (mITT Analysis Set)				
Unadjusted analysis[a]	17/26(65.4%)	133/187(71.1%)	162/196(82.7%)	122/134(91.0%)
Adjusted analysis		71.4%	82.4%	
Difference[b,c] Regimen B vs Regimen C (95% CI)		-11.0% (-19.0%,-2.9%)		
Noninferiority p-value (δ=10%)		<0.001		
Superiority p-value (δ=0)		0.004		
Favorable outcome at Week 76 (PP Analysis Set)				
Unadjusted analysis[a]	17/26(65.4%)	126/166(75.9%)	155/177(87.6%)	114/122(93.4%)
Adjusted analysis		76.4%	87.1%	
Difference[b,c] Regimen B vs Regimen C (95% CI)		-10.7% (-18.5%,-2.9%)		
Noninferiority p-value (δ=10%)		<.001		
Superiority p-value (δ=0)		0.004		

Both statistical noninferiority (p<0.001) and superiority (p<0.004) of Regimen C (bedaquiline) to Regimen B (comparator) in terms of favourable outcome at Week 76 were declared in the mITT analysis set (and similarly in the PP analysis set) according to pre-specified adjusted analysis (stratified by randomisation protocol, and HIV and CD4 cell count status). Unadjusted analysis produced a similar result. Results (not shown here) of sensitivity analyses in the mPP and ITT analysis sets, as well as sensitivity analyses using adjustment with different combinations of stratification factor and applying different approaches for handling of missing data (see the section Statistical methods above), were all supportive of the conclusions.

For the participants with an unfavourable outcome at Week 76 (109/543), the reasons were as follows:

Table 32: Microbiological outcome at time of unfavourable outcome event through week 76; mITT analysis set (Study TMC207TBC3007)

	A	B	C	D
Analysis set: mITT	26	187	196	134
Subjects with unfavorable outcome	9(34.6%)	54(28.9%)	34(17.3%)	12 (9.0%)
Culture status at time of unfavorable outcome				
Culture negative	6(23.1%)	25(13.4%)	17 (8.7%)	9 (6.7%)
Never culture converted (bacteriological failure)	3(11.5%)	16 (8.6%)	12 (6.1%)	1 (0.7%)
Culture positive: relapse	0	7 (3.7%)	1 (0.5%)	2 (1.5%)
Culture positive: reinfection	0	0	0	0
Culture positive: genotype missing	0	6 (3.2%)	4 (2.0%)	0
Reasons for unfavorable outcome				
Discontinued allocated regimen and restarted a new regimen	0	8 (4.3%)	2 (1.0%)	1 (0.7%)
Treatment extended beyond scheduled end of treatment	0	6 (3.2%)	5 (2.6%)	1 (0.7%)
TB treatment restarted after scheduled end of treatment and before Week 76	0	7 (3.7%)	3 (1.5%)	2 (1.5%)
Started bedaquiline in Regimen A or B	3(11.5%)	8 (4.3%)	0	0
At least one of last 2 cultures positive	0	2 (1.1%)	1 (0.5%)	0
Don't have culture results within Week 76 window	0	7 (3.7%)	12 (6.1%)	2 (1.5%)
Started second line injectable agent in Regimen C	0	0	6 (3.1%)	0
Started nitroimidazoles or linezolid drug	3(11.5%)	13 (7.0%)	0	1 (0.7%)
Started >=2 new drugs	3(11.5%)	1 (0.5%)	0	3 (2.2%)
Death	0	2 (1.1%)	5 (2.6%)	2 (1.5%)

Note: Please refer to Section 1.4.4.1 for detailed Unfavorable outcome. Microbiological outcome is defined using culture result up to and including the time that this outcome occurred.
Note: Microbiological outcome is evaluated at the time of the event leading to the unfavorable outcome.
Note: Culture negative: Culture negative status (two consecutive negative cultures from sputa collected on different days without an intervening positive) was satisfied at the time of the unfavorable outcome event.
Note: Never culture converted (bacteriological failure): The subject never achieved culture negative status at any time during the study prior to the unfavorable outcome event.
Note: Culture positive: Culture negative status was achieved at some point during the study but was not satisfied at the time of the unfavorable outcome event (at least one of the last two non-missing cultures was positive).
Note: Culture positive further classified as Culture positive: Reinfection if it has been shown that the M. tuberculosis strain of the positive culture is different to baseline; and Culture positive: Relapse otherwise.
Note: Participants are classified by the first event that made the participant unfavorable.

Modified based on Mod5.3.5.1/STREAM Stage 2 CSR/Tab17

The majority of unfavourable outcomes at Week 76 were thus driven by changes in treatment regimen prior to Week 76. In fact, unfavourable outcome attributed due to positive culture at Week 76 was uncommon: 2/187 (1.1%) in Regimen B (comparator) and 1/196 (0.5%) in Regimen C (bedaquiline). Unfavourable outcomes due to death were also uncommon: 2/187 (1.1%) in Regimen B (comparator) and 5/196 (2.6%) in Regimen C (bedaquiline).

Subgroup analysis: primary outcome

Subgroup analysis of favourable outcome at Week 76 in the mITT Analysis Set confirmed Regimen C (bedaquiline) being numerically better than Regimen B (comparator) independent of age, sex, weight, anti-TB drug history, baseline anti-TB drug resistance, and baseline disease characteristics. However notable differences were observed in terms of HIV status.

In the subgroup of HIV-positive participants, the observed proportions of participants with a favourable outcome were 9/25 (36.0%) at both Weeks 76 and 132 in Regimen B (comparator) and 26/27 (96.3%) and 25/27 (92.6%) at Weeks 76 and 132, respectively, in Regimen C (bedaquiline). The reasons for unfavourable outcome at Week 76 amongst HIV-positive participants in Regimen B (comparator) were generally dominated by treatment regimen changes adding a second-line oral anti-TB drug (linezolid or bedaquiline):

Table 33: Reason for Unfavourable Outcome at Week 76 - HIV+; mITT Analysis Set (study TMC207TBC3007)

TEFFO9903HIVPOS: Reason for Unfavorable Outcome at Week 76 in HIV+; mITT Analysis Set (Study TMC207TBC3007)

	A	B	C
Analysis set: mITT	6	25	27
Unfavorable Outcome	3 (50.0%)	16 (64.0%)	1 (3.7%)
Reason for Unfavorable			
Started LZD	0	5 (20.0%)	0
Started BDQ	3 (50.0%)	4 (16.0%)	0
Restarted MDR-TB treatment after scheduled end of treatment	0	2 (8.0%)	0
Died during trt or follow-up	0	1 (4.0%)	0
Discontinue allocated trt, start new regimen	0	1 (4.0%)	0
Extended treatment beyond that allowed	0	1 (4.0%)	1 (3.7%)
No culture at 76 weeks	0	1 (4.0%)	0
Started >=2 drugs	0	1 (4.0%)	0

[teffo9903hivpos.rtf] [tmc207/stream/dbr_week132/re_week132/teffo9903hiv]

The CHMP noted that Regimen B (comparator) appears to have performed particularly poorly amongst HIV-positive participants, and Regimen C (bedaquiline) somewhat better, as compared to the overall study population. Unfavourable outcomes at Week 76 amongst HIV-positive participants in Regimen B (comparator) were due to regimen changes in over half of cases, namely addition of oral linezolid or bedaquiline. The total number of HIV-positive participants was small and thus this subgroup analysis should be interpreted with caution. This may reflect a perception in clinical practice of better efficacy and/or safety of oral alternatives over injectables particular to the HIV-positive population.

The CHMP was of the view that the discrepancy in the HIV-positive subgroup, the majority of whom were Black, drives the apparent difference in outcomes amongst Black participants.

For participants with baseline RR-TB, the observed proportions of participants with a favourable outcome at Week 76 were 15/28 (53.6%) in Regimen B (comparator) vs 21/27 (77.8%) in Regimen C (bedaquiline). Whereas for participants with baseline MDR-TB, the observed proportions of participants with a favourable outcome at Week 76 were 104/140 (74.3%) in Regimen B (comparator) vs 124/149 (83.2%) in Regimen C (bedaquiline).

The reasons for unfavourable outcome at Week 76 amongst RR-TB participants in Regimen B (comparator) were generally dominated (10 of 13 cases) by regimen changes, specifically discontinuation of allocated regimen and start of a new one (2), addition of BDQ (3), addition of nitroimidazole drug in (5). In Regimen C (bedaquiline), just 1 of 6 cases of unfavourable outcome was related to addition of a second line injectable drug, and 1 other related to treatment restart after scheduled EOT.

The CHMP considered that the RR-TB subgroup analysis should be interpreted with caution given that regimen changes, including in response to baseline resistance data as results emerged, were permitted at the discretion of the local investigator. In the face of individual results indicating RR-TB, it seems

likely that an injectable-based regimen would be replaced more readily than an all-oral regimen for ease of administration, and possibly also for safety and tolerability reasons.

Secondary efficacy analyses

Table 34: Favourable outcome at Week 132 (pre-specified approach)

Summary of Efficacy Results	A	B	C	D
Key secondary efficacy endpoints				
Favorable outcome at Week 132[c,f]				
(mITT Analysis Set)				
Unadjusted analysis[a]	17/26(65.4%)	129/187(69.0%)	154/196(78.6%)	116/134(86.6%)
Adjusted analysis		69.2%	78.2%	
Difference[b,g] (95% CI) Regimen B vs Regimen C		-9.0% (-17.5%,-0.6%)		

In the mITT Analysis Set, the adjusted difference in proportions of participants with a favourable outcome at Week 132 between Regimen B (comparator) (69.2%) and Regimen C (bedaquiline) (78.2%) was -9.0% (95% CI: -17.5%, -0.6%). In this analysis, actual last efficacy visit (rather than scheduled) was used to define the efficacy visit window and non-assessable outcomes due to missing sputum culture results were categorised as unfavourable. Results in the PP Analysis Set were similar.

Results (not shown here) of sensitivity analyses in the mPP and ITT analysis sets, as well as sensitivity analyses using adjustment with different combinations of stratification factor and applying different approaches for handling of missing data (see the section Statistical methods above), were all supportive of the above conclusion.

Microbiological status (alternative approach)

The rate of culture conversion at End of Treatment (EOT), Week 76 (primary analysis) and Week 132 were high in all treatment arms. Comparison of microbiological status was numerically similar or favourable for Regimen C (bedaquiline) as compared with Regimen B (comparator) at all time points. Results of sensitivity analyses were consistent with this, as were the results for AFB smear conversion at all time points (not shown here).

There was no decrease in culture or AFB smear conversion rates in Regimen B (comparator) and C (bedaquiline) over time (after end of treatment), suggesting a sustained effect of the treatment.

Table 35: Summary of microbiological status primary comparison: culture conversion rate over time (no overruling analysis); mITT analysis set (Study STREAM stage 2)

	Pairwise Comparison			
		B vs C		
	A	B	C	D
Analysis set: mITT	26	187	196	134
Baseline culture results				
N	26	187	196	134
Negative	0	0	0	0
Positive	26 (100.0%)	187 (100.0%)	196 (100.0%)	134 (100.0%)
EOT, N	26	174	178	124
Non-responder	1 (3.8%)	16 (9.2%)	8 (4.5%)	5 (4.0%)
Never culture converted	1 (3.8%)	6 (3.4%)	3 (1.7%)	1 (0.8%)
Culture positive	0	10 (5.7%)	5 (2.8%)	4 (3.2%)
Responder	25 (96.2%)	158 (90.8%)	170 (95.5%)	119 (96.0%)
95% Wilson score confidence interval[a]	(81.1; 99.3)	(85.6; 94.3)	(91.4; 97.7)	(90.9; 98.3)
Difference in proportion of responders vs Regimen C controlling for protocol version[b]				
Difference (point estimate)			-4.6	
95% confidence interval			(-9.8; 0.7)	
p-value			0.091	
Week 76, N	26	176	179	124
Non-responder	0	12 (6.8%)	2 (1.1%)	1 (0.8%)
Never culture converted	0	4 (2.3%)	0	1 (0.8%)
Culture positive with missing genotyping	0	4 (2.3%)	1 (0.6%)	0
Culture positive: Relapse	0	4 (2.3%)	1 (0.6%)	0
Culture positive: Re-infection	0	0	0	0
Responder	26 (100.0%)	164 (93.2%)	177 (98.9%)	123 (99.2%)
95% Wilson score confidence interval[a]	(87.1; 100.0)	(88.5; 96.1)	(96.0; 99.7)	(95.6; 99.9)
Difference in proportion of responders vs Regimen C controlling for protocol version[b]				
Difference (point estimate)			-5.7	
95% confidence interval			(-9.8; -1.7)	
p-value			0.006	
Week 132 (all data), N	26	176	179	124
Non-responder	0	9 (5.1%)	2 (1.1%)	3 (2.4%)
Never culture converted	0	3 (1.7%)	0	1 (0.8%)
Culture positive with missing genotyping	0	3 (1.7%)	1 (0.6%)	0
Culture positive: Relapse	0	3 (1.7%)	1 (0.6%)	2 (1.6%)
Culture positive: Re-infection	0	0	0	0
Responder	26 (100.0%)	167 (94.9%)	177 (98.9%)	121 (97.6%)
95% Wilson score confidence interval[a]	(87.1; 100.0)	(90.6; 97.3)	(96.0; 99.7)	(93.1; 99.2)
Difference in proportion of responders vs Regimen C controlling for protocol version[b]				
Difference (point estimate)			-4.0	
95% confidence interval			(-7.6; -0.4)	
p-value			0.032	

Key: COVID-19 = 2019 novel coronavirus, NE = not estimable.

a 95% confidence interval for the binomial proportion of responders.
b Stratified difference in proportion of responders versus Regimen C (bedaquiline): Frequency procedure controlling for the randomisation stratification factor, randomisation protocol (version 6.2, versions 6.3 or 7.0, versions 8.0 or 10.0), 2-sided 95% confidence limits with Mantel-Haenszel weights for the common risk difference are presented. Significant regimen difference in proportion of responders if p-value <0.05.
Note: N = total number of subjects with data (non-missing/non-contaminated values) and excludes subjects with non-evaluable culture results post-baseline such that microbiological status cannot be determined.

Time to microbiological response (alternative approach)

Based on the mITT Analysis Set (no overruling), median time to culture conversion (conversion status maintained) was 8.0 weeks (4.29 – 8.14) in Regimen B (comparator) and 4.1 weeks (4.14 – 4.43) in Regimen C (bedaquiline), regardless of country, baseline HIV status and CD4 count category, and baseline extent of MTB resistance, in the mITT Analysis Set and sensitivity mITT Analysis Set, except for:

- For participants with pre-XDR-TB at baseline, median time to culture conversion (conversion status maintained) was similar, at 8.1 weeks in Regimen B (comparator) (N=19) and 8.1 weeks in Regimen C (bedaquiline) (N=20).

Based on the mITT Analysis Set (no overruling), median time to AFB smear conversion (conversion status maintained) was similar in Regimen C (bedaquiline) and Regimen B (comparator) (ie, 8.1 weeks for both regimens) regardless of country, baseline HIV status and CD4 count category, and baseline extent of MTB resistance, in the mITT Analysis Set and sensitivity mITT Analysis Set, except for:

- For participants with pre-XDR-TB at baseline, median time to AFB smear conversion (conversion status maintained) was shorter at 4.3 weeks in Regimen B (comparator) (N=19) compared to 10.1 weeks Regimen C (bedaquiline) (N=20).

The CHMP noted that there appears to be a numerical trend to shorter median time to culture and AFB smear conversion amongst pre-XDR-TB participants on Regimen B (comparator) as compared to Regimen C (bedaquiline). Some of the subgroups were small and the above comparisons must be interpreted with caution.

Development of bedaquiline resistance (alternative approach)

One of 31 (3.2%) participants with paired data in Regimen C (bedaquiline) based demonstrated a post-baseline BDQ MIC of 0.5 µg/mL when the baseline strain was susceptible according to genotyping, but was culture negative at Week 132.

Two participants in Regimen D acquired resistance to BDQ based on an increased BDQ MIC. For 1 participant this was confirmed with a mutation in the *Rv0678* gene. Microbiological outcomes at Week 132 were relapse and never culture converted for these 2 participants in Regimen D.

In addition, five of 30 (16.7%) participants in Regimen C (bedaquiline) and 4 of 25 (16.0%) participants in Regimen D had a ≥4-fold increase in BDQ MIC post-baseline. For all participants except 2, the increase did not reach a MIC >0.25 µg/mL (7H11 agar method) indicating a decreased BDQ susceptibility but not acquired resistance. Microbiological outcomes at Week 132 were:

- Culture negative (confirmed) for 4 participants.
- Culture negative not confirmed for 1 Participant.
- Never culture converted for 1 Participant.
- Culture positive after having being culture negative (confirmed) for 1 Participant.
- Relapse for 2 Participants.

The CHMP noted that on-treatment evolution of higher bedaquiline MIC was uncommon. Although it was measured during the study, the clinical implications (if any) of a ≥4-fold increase in BDQ MIC remains unclear.

Development of other anti-mycobacterial resistance (alternative approach)

Overall, based on paired data (i.e., participants with baseline and post-baseline non-missing values), acquired resistance to at least one other anti-TB drug was limited and similar in Regimen B (comparator) and Regimen C (bedaquiline). Rates of on-treatment development of resistance by individual first- and second-line drug are tabled below.

Table 36: proportion of participants with acquired resistance to other anti-TB drugs versus baseline susceptibility; mITT analysis set (study STREAM stage 2)

	A	B	C	D
	n/N (%)	n/N (%)	n/N (%)	n/N (%)
Analysis set: mITT	26	187	196	134
Any acquired resistance	2/5 (40.0%)	21/59 (35.6%)	13/31 (41.9%)	9/25 (36.0%)
95% Wilson score confidence interval[a]	(11.8; 76.9)	(24.6; 48.3)	(26.4; 59.2)	(20.2; 55.5)
Isoniazid (0.2 ug/mL)[b]	0	2/12 (16.7%)	1/6 (16.7%)	1/2 (50.0%)
Isoniazid (1.0 ug/mL**)[b]	0	1/14 (7.1%)	1/6 (16.7%)	0/4
Isoniazid (5.0 ug/mL**)[b]	0/3	2/41 (4.9%)	1/17 (5.9%)	0/17
Pyrazinamide[c]	0	1/24 (4.2%)	2/9 (22.2%)	0/2
Ethambutol[b]	0/1	8/43 (18.6%)	2/21 (9.5%)	1/11 (9.1%)
Fluoroquinolones				
Ofloxacin (2.0 ug/mL)[b]	0/5	7/58 (12.1%)	4/31 (12.9%)	4/23 (17.4%)
Ofloxacin (8.0 ug/mL**)[b]	0/5	7/59 (11.9%)	4/31 (12.9%)	3/24 (12.5%)
Levofloxacin[f]	0	3/13 (23.1%)	1/3 (33.3%)	2/3 (66.7%)
Moxifloxacin[f]	0	3/12 (25.0%)	1/3 (33.3%)	2/2 (100.0%)
Injectables				
Kanamycin[b]	0/4	5/52 (9.6%)	2/26 (7.7%)	1/22 (4.5%)
Capreomycin[b]	0/5	3/59 (5.1%)	0/31	0/25
Amikacin[e]	0/1	1/21 (4.8%)	0/10	0/6
Ethionamide[b]	2/2 (100.0%)	5/42 (11.9%)	4/26 (15.4%)	2/20 (10.0%)
Clofazimine[d]	0/3	3/38 (7.9%)	3/16 (18.8%)	1/10 (10.0%)
Linezolid[e]	0	1/8 (12.5%)	0	0/3

Key: DST = drug susceptibility testing, MIC = minimum inhibitory concentration.
Note that N is defined as the total number of paired baseline/post-baseline isolates available for testing. If '0' is displayed in the table, there were no paired isolates to assess acquired resistance.
a 95% confidence interval for the binomial proportion of subjects with acquired resistance to any other anti-TB drugs at any time during the study.
Note: Baseline is defined as the last available DST assessment, based on the relevant positive culture result, prior to randomisation and utilising the hierarchical approach: Phenotypic DST else if missing genotypic DST else local DST (as last resort and if available). Central DST results are used only where there is a local positive culture result.

The CHMP noted that only participants with paired data available, that is, patients failing microbiologically (59/187 in Regimen B (comparator) and 31/196 in Regimen C (bedaquiline)) contributed to results for on-treatment acquired anti-TB drug resistance; thus the rates above do not reflect the true tendency to on-treatment resistance in each regimen for the overall/ mITT population.

Some of the subgroups were small and comparisons between regimen must be interpreted with caution.

The CHMP considered that data from the Phase 2 studies of bedaquiline revealed a possible trend for increased MICs to clofazimine amongst isolates with higher MICs to bedaquiline. At the time that CMA was granted, there were not enough clinical data to confirm that finding, which was considered relevant for further investigation within the confirmatory study. The frequency of baseline or post-baseline isolates with higher bedaquiline MICs in STREAM Stage 2 was very low and thus no meaningful analysis of the new data for this trend is possible.

Ancillary analyses

Comparisons across clinical studies

Results from STREAM Stage 2 are generally consistent with the results observed in the Phase 2 studies.

Direct comparison of outcomes between the studies should be made with caution, as they enrolled slightly different populations, treatment regimens, microbiological methods and treatment duration.

Unlike the Phase 2 studies that supported the original CMA, HIV-injected subjects receiving antiretroviral therapy (ART) or those who might need to start ART during the course of the study were not excluded from STREAM Stage 2. Additionally, while in C208-Stage 2 participants with MDR-TB previously treated with anything other than first-line TB drugs were excluded, in C209 and STREAM Stage 2 participants with MDR-TB treated with previous second-line treatment (of limited duration) were eligible, which better reflects the population to be treated in the real-world clinical context.

Exclusion criteria applied in the Phase 2 studies permitted enrolment of participants with pre-XDR-TB and even XDR-TB as long as the isolate was susceptible to at least 3 of the 5 classes of TB drugs used to treat MDR-TB, whereas in STREAM Stage 2 evidence of susceptibility to fluoroquinolones and second-line injectables was required at screening. More than two thirds of participants in both Phases 2 and 3 had cavitations, but the proportion with multiple cavitations was higher in STREAM Stage 2 than in Phase 2 studies, which therefore provides additional efficacy data in these more difficult-to-treat patients.

Across the completed clinical studies, the background regimens were allowed to be changed. However, permitted changes in the Phase 2 studies were pre-determined and had to be reported as an AE, while changes in the STREAM Stage 2 were at the discretion of the investigator. However, the approach in both Phase 2 and 3 used the mITT analysis population for the primary analysis, i.e. applying an intention-to-treat principle disregarding individual regimen changes for the purposes of comparison of outcomes. In this sense, STREAM Stage 2 better reflects how bedaquiline will be used as part of multi-drug regimens in clinical practice.

Major features and results of the three clinical studies are summarised below:

Trial	STREAM Stage 2	TMC207-C208 Stage 2	TMC207-C209
Population	RR-TB, MDR-TB	MDR-TB, pre-XDR-TB	MDR-TB, pre-XDR-TB, XDR-TB
mITT sample size (randomisation ratio)	543 (1:1)	132 (1:1)	205 (N/A)
BDQ dosing	400mg QD for 2 weeks, then 200 MG TIW		
BDQ treatment duration	Regimen C (bedaquiline): 40 weeks	24 weeks	24 weeks
Follow-up period	96 (132) weeks*	96 weeks	96 weeks
Comparator	Regimen B (comparator): injectable-containing control regimen	Placebo	N/A
Background regimen		KAN, OFL, ETH, PZA, cycloserine/terizidone	Individualised
Primary efficacy endpoint	Proportion with favourable outcome at Week 76	Time to sputum culture conversion at Week 24	Time to sputum culture conversion at Week 24
Post-baseline culture method		MGIT	MGIT
Key efficacy outcomes	Adjusted favourable outcome (no overruling) at Week 76 82.4% on BDQ versus 71.4% on comparator (superiority p=0.004). Culture conversion rate at EOT (no overruling)	Culture conversion rate at Week 24 (no overruling) 80.3% on BDQ versus 65.2% on placebo (p=0.049). Time to culture conversion (no overruling) 72 days on BDQ versus 127 days on placebo.	Culture conversion rate at Week 24 (no overruling) 80.5%. Time to culture conversion (no overruling) 57 days. 4.9% with at least a 4-fold increase from baseline in BDQ MIC.

	95.5% on BDQ versus 90.8% on comparator. Time to culture conversion (no overruling) 4.1 weeks on BDQ versus 4.3 weeks on comparator. 16.7% in BDQ regimen with at least a 4-fold increase from baseline in BDQ MIC. Evolution to a higher extent of MTB resistance in 6 (3.2%) BDQ and 7 (3.6%) comparator participants.	3.0% in both arms with at least a 4-fold increase from baseline in BDQ MIC. Evolution to a higher extent of MTB resistance in 0 BDQ and 7 (10.6%) placebo participants.	Evolution to a higher extent of MTB resistance in 1.5%.

*In STREAM Stage 2, although safety assessments were continued through Week 132, efficacy data collection was curtailed at the point where all participants were projected to reach Week 96.

2.4.1.3.7. Summary of main study

The following tables summarise the efficacy results from the main study 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 37 Summary of Efficacy for Study TMC207-STREAM (STREAM Stage 2)

<table>
<tr><th colspan="5">Title: The Evaluation of a Standard Treatment Regimen of Anti-tuberculosis Drugs for Patients With MDR-TB</th></tr>
<tr><td>Study identifier</td><td colspan="4">TMC207-STREAM</td></tr>
<tr><td rowspan="2">Design</td><td colspan="4">International, multicentre, randomized, parallel-group, active-controlled, open-label Phase 3 confirmatory study of efficacy and safety of a BDQ-containing, all-oral 40-week regimen (Regimen C (bedaquiline)) compared to an injectable-containing 40-week control regimen (Regimen B (comparator)) in participants ≥15 years of age with rifampicin (RMP)-resistant and isoniazid (INH)-susceptible tuberculosis (TB) (RR-TB) or multidrug-resistant (MDR)-TB.</td></tr>
<tr><td colspan="4">Duration intensive Tx phase: 16 weeks
Duration continuation Tx phase: Through 40 weeks
Duration efficacy follow-ups: Through 76 weeks</td></tr>
<tr><td>Hypothesis</td><td colspan="4">Non-inferiority followed by Superiority</td></tr>
<tr><td rowspan="2">Treatments groups</td><td colspan="2">Regimen B (comparator)</td><td>Background regimen:

INH, PTO, MFX/LFX, CFZ, EMB, PZA (intensive phase)

followed by

MFX/LFX, CFZ, EMB, PZA (continuation phase)</td><td>Plus kanamycin/amikacin (intensive phase only)

15mg/kg (max 1g) daily</td></tr>
<tr><td colspan="2">Regimen C (bedaquiline)</td><td>Plus bedaquiline (intensive and continuation phases)

400mg QD first 2 weeks, 200mg TIW thereafter</td></tr>
<tr><td rowspan="2">Endpoints and definitions</td><td>Primary endpoint</td><td>Proportion with favourable outcome</td><td colspan="2">Favourable outcome required last 2 consecutive culture results (collected at 2 separate visits at least 1 day apart) to be negative.

Patients who died, started a new second-line MDR-TB regimen, restarted MDR-TB treatment after having previously discontinued, or whose treatment was extended beyond the scheduled end of treatment were assigned unfavourable outcome.</td></tr>
<tr><td>Secondary endpoints</td><td>Proportion with culture conversion</td><td colspan="2">Culture conversion (last 2 consecutive negative cultures (collected at 2 separate visits assigned to separate analysis visits)) was the sum of Culture negative (confirmed), Culture negative with no sputum sample available within analysis visit window and Culture negative not confirmed within analysis visit window.</td></tr>
</table>

		Time to **culture conversion** Proportion with **AFB smear conversion** Time to **AFB smear conversion** Rate of acquired on-treatment **resistance**	**Sputum AFB smear conversion** was similarly defined as 2 consecutive negative smears (collected at 2 separate visits assigned to separate analysis visits). **Resistance to BDQ** was documented when the MIC was >0.25 µg/mL (ie, the critical concentration) or in the presence of mutations in the *atpE*, *Rv0678* and *pepQ* genes. *Alternative approach* (see 2.4.1.3.2. Conduct of the study section).
Database lock			
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Modified Intention to Treat Week 76		
Descriptive statistics and estimate variability	Treatment group	Regimen B (comparator)	Regimen C (bedaquiline)
	Number of subjects	187	196
	Proportion with **favourable** outcome (adjusted)	71.4%	82.4%
Effect estimate per comparison	Primary endpoint	Comparison groups	Regimen B (comparator) minus C
		Difference	-11.0%
		95% CI	-19.0% to -2.9%
		P-value Non-inferiority	<0.001
		P-value Superiority	0.004
Notes	The majority of unfavourable outcomes at Week 76 were driven by **changes in treatment regimen** prior to Week 76. Unfavourable outcome attributed due to positive culture or death at Week 76 was uncommon.		
Analysis description	**Key secondary analyses**		
Analysis population	Modified Intention to Treat		

Descriptive statistics and estimate variability (95% CI)	Treatment group	Regimen B (comparator)	Regimen C (bedaquiline)
	Number of subjects	187	196
	Proportion with **favourable** outcome (adjusted) Week 132	69.2%	78.2% (-9.0%, 95%CI -17.5% to -0.6%)
	Proportion with **culture conversion** EOT	90.8% (85.6% - 94.3%)	95.5% (91.4% - 97.7%)
	Proportion with **culture conversion** Week 76	93.2% (88.5% - 96.1%)	98.8% (96.0% - 99.7%)
	Proportion with **culture conversion** Week 132	94.9% (90.6% - 97.3%)	98.9% (96.0% -99.7%)
	Median time to **culture conversion**	8.0 weeks (4.29 – 8.14 weeks	4.1 weeks (4.14 – 4.43 weeks)

2.4.2. Discussion on clinical efficacy

Design and conduct of clinical studies

STREAM Stage 2 was an international, multicentre, randomised, parallel-group, active-controlled, open-label Phase 3 confirmatory study of the efficacy and safety of a BDQ-containing, all-oral 40-week regimen (Regimen C (bedaquiline)) compared to an injectable-containing 40-week control regimen (Regimen B (comparator)) in participants ≥15 years of age with rifampicin (RMP)-resistant and isoniazid (INH)-susceptible pulmonary tuberculosis (TB) (RR-TB) or multidrug-resistant (MDR)-TB. The primary endpoint was the proportion of patients with favourable outcome at Week 76 (a composite of clinical and microbiological status).

Protocol and major amendments

The study protocol went through several major amendments while the study, which is open-label, was enrolling. The amendments, which are summarised below, were made mostly in response to the changing clinical landscape, revisions to international treatment guidelines, and to difficulties in recruiting enough participants.

In its initial design, STREAM Stage 2 involved four different Regimens, A to D, but enrolment into Regimens A and D were later discontinued.

The initial protocol also stated the primary analysis would test whether Regimen C (bedaquiline) was superior to Regimen B (comparator), and a secondary analysis would test whether Regimen C (bedaquiline) was noninferior, with regard to the primary endpoint. A protocol amendment later switched these analyses, so that the noninferiority test was primary and the superiority test was secondary. The target sample size was decreased from 336 to 200 patients in Regimens B and C (bedaquiline). At the same time, an interim analysis with sample-size re-estimation was added, although the sample size was not revised again after this analysis. The MAH states that the sample size re-estimation was conducted by a blinded statistician, but information leakage cannot be ruled out since the study was open-label.

The MAH states that the sponsor staff and MAH staff involved in analysis or decision making were not provided with datasets/analyses. Despite this setup, changes to the study design and analysis could not have been made in a blinded fashion.

Switching from superiority to noninferiority in the primary analysis is usually strongly discouraged because it inflates the type 1 error (see EMA guideline on adaptive designs in confirmatory trials, CHMP/EWP/2459/02). CHMP also generally discourages from recalculating the sample size during an ongoing phase III trial.

However, since the antimicrobial efficacy of bedaquiline was already established and not in doubt, the aim of the study was essentially to demonstrate the clinical usefulness of a regimen where oral bedaquiline replaces the aminoglycoside. The impact of these protocol changes is thus less critical here than in the setting of a pivotal efficacy trial and the data are considered interpretable in their regulatory and clinical context.

Local and central laboratory results were processed hierarchically according to a pre-specified data handling protocol, to determine microbiological results, including drug sensitivity data. An alternative methodology for this that differed in several respects from the pre-specified analysis methodology detailed in the SAP was presented in the Microbiology Report. Both approaches were documented and

signed off prior to database lock. The MAH asserts that the alternative approach is most conservative and closest to the methods applied in BDQ Phase 2 studies. Only the alternative approach is presented in this report for secondary analyses of microbiological outcomes, for brevity. In practice, microbiological outcomes determined according to the pre-specified or alternative approaches were generally concordant, with very few discrepancies. Conclusions from secondary analyses applying these two approaches are also in agreement.

Noninferiority margin

The noninferiority analysis was based on a noninferiority margin of 10% margin, which was specified in before the start of patient enrolment. MAH has not presented a rationale for this margin. It is not considered possible to provide one based on the available evidence, as a robust effect size estimate for the comparator (kanamycin/amikacin) is not available. Nor can the clinical effect of bedaquiline versus a comparator be isolated in an open-label trial where individualisation of the background regimen is permitted. The NI margin should be interpreted as representing an equivalence margin with respect to the usefulness of a regimen where oral bedaquiline replaces the aminoglycoside, rather than retention of a certain fraction of the efficacy of the aminoglycoside.

Primary endpoint and estimand

The primary endpoint was defined so that patients who were unable to produce sputum or whose samples had been contaminated could still be classified as having a favourable outcome at Week 76 if their last two cultures before the Week 76 window were negative and they had not previously been classified as unfavourable. This is essentially a last-observation-carried-forward approach for handling missing data. Although such an approach is often discouraged because it can advantage the new treatment (not be conservative), it seems reasonable here because of the strict condition for previously favourable results. Furthermore, the main results are supported by a sensitivity analysis in which a patient's outcome was only classified as favourable if the last culture within the Week 76 window was negative, as well as the culture before that.

The MAH used the estimand framework in the statistical analysis plan but not in the study protocol. In any case, the definition of the primary endpoint implies that a treatment policy strategy was used to handle treatment discontinuations (these were ignored). It also implies that a composite strategy was used to handle patients who died, started a new MDR-TB regimen, restarted MDR-TB treatment after having previously discontinued, or whose treatment was extended beyond the scheduled end of treatment (these events were considered unfavourable outcomes).

Secondary endpoints

In the regulatory and clinical context, microbiological outcomes from STREAM Stage 2 are of particular interest even if formally classified as secondary outcomes. These included proportion with culture conversion and AFB smear conversion, median time to culture conversion and AFB smear conversion, and evolution of on-treatment resistance.

Randomisation

Randomisation was stratified by site and HIV status. The randomisation ratio was updated twice during the trial but the ratio of patients allocated to the main comparison (Regimens B and C) stayed constant at 1:1.

Treatment discontinuation and replacement

The study protocol allowed discontinuation of the allocated treatment regimen and replacement of individual drugs in the initial regimen with alternate therapy to some extent. This was the decision of the investigator, without pre-specified criteria for changing treatment regimen. The open-label design

is likely to have influenced treatment decisions to change regimens. On the other hand, the individualisation of background regimen might be considered a strength in the sense that it better reflects how BDQ with multi-agent regimens is used in clinical practice. Importantly, introduction of BDQ or other important second line agents against MDR-TB in participants not allocated to these treatments by randomisation was considered an unfavourable outcome for the purposes of primary efficacy analysis.

Population

The study permitted enrolment of participants with RR-TB and MDR-TB, but evidence of susceptibility to fluoroquinolones and second-line injectables was required at screening to exclude pre-XDR-TB and XDR-TB. The focus on MDR-TB is appropriate, considering the results of the completed Phase 2 studies and the current CMA indication. Participants with MDR-TB treated with previous second-line treatment (of limited duration) were eligible, which reflects the population to be treated in the real-world clinical context, where resistant TB remains largely a problem driven by prior anti-mycobacterial treatment with suboptimal compliance or treatment duration.

HIV-injected participants with a CD4 count >50 cells/mm3 receiving antiretroviral therapy (ART) or those who might need to start ART during the course of the study were not excluded. However, participants with pre-existing liver disease or end stage renal failure were excluded.

Timepoints of analyses

For efficacy outcomes (favourable outcome, time to favourable outcome) beyond Week 76, data collection was curtailed at the point when the last recruited participant was projected to reach Week 96, in agreement with regulatory authorities. From protocol version 11.0 (dated 15 December 2020) onwards, sputum microbiology was only undertaken after Week 96 if clinically indicated. The long-term efficacy data thus include data up to at least Week 96 for all participants, and up to Week 132 for 145/187 (77.5%) participants in Regimen B (comparator) and 146/196 (74.5%) participants in Regimen C (bedaquiline).

Therefore, although in the submission the timepoint for the secondary efficacy analyses are still referred to as 'Week 132', a participant's last efficacy visit could have taken place at any time from Week 96. Similarly, for microbiology-related analyses including data beyond 30 November 2021, the wording 'Week 132 (all data)' has been used, but participants may have no further microbiological data available after Week 96. The MAH asserts that the reduction the total person-years of follow-up for the efficacy analysis was small, i.e., only 3% in Regimens B and C (bedaquiline).

Efficacy data and additional analyses

Numbers analysed

Following 1,436 participants screened for the study, the final mITT Analysis Set included 543 participants. Reasons for ineligibility were microbiology-related, e.g., negative sputum samples, resistance to fluoroquinolones/injectables. In the mITT Analysis Set, 44/543 (8.1%) participants prematurely terminated study participation before the Week 132 visit, with reasons for termination comparable between the regimens.

Baseline characteristics and concomitant ART

The majority of participants were male (61.3%), Asian (48.4%) or Black (34.6%), with median age 32.7 [range: 16, 69] years and median BMI 19.2 [range: 12, 40] kg/m2. Essentially all participants had previous exposure to anti-TB drugs, with around two thirds exposed to first-line drugs only and one third exposed additionally to second-line drugs. At baseline, the rates of resistance to individual

anti-mycobacterial agents as well as the rates of RR-TB (12.5%), MDR-TB (76.4%), and pre-XDR-TB (11.0%) were similar between regimens. There were no participants with baseline XDR-TB.

Thus, the enrolled population adequately reflects the population covered by the indication, namely MDR-TB, as well as the real-world clinical context for these patients (i.e., prior exposure to anti-TB drugs). A higher proportion of participants in Regimen C (bedaquiline) had multiple cavities (62.5%) compared to Regimen B (comparator) (46.6%), which is considered conservative from the perspective of efficacy analyses. Almost all participants were receiving at least 3 or more active anti-TB drugs in the background regimen at baseline.

In the enrolled subset of HIV-positive participants (n=52, 13.6%), all participants received concomitant ART during the study.

Extent of exposure

The median exposure was 280 days for both 40-week Regimens B and C (bedaquiline) (range: 1 to 441 and 1 to 424 respectively), while the mean (SD) exposures were 250.5 (85.33) and 261.8 (75.53), respectively. The rate of >90% compliance with allocated treatment regimen was slightly higher in Regimen C (bedaquiline) (96.4%) compared to Regimen B (comparator) (92.0%).

Primary analysis

For the primary efficacy analysis, the proportion of participants with favourable outcome at Week 76 was higher in Regimen C (bedaquiline) (82.7%)) versus Regimen B (comparator) (71.4%, difference -11.0% [95%CI -19.0%, -2.9%]) and both statistical "noninferiority" ($p<0.001$) and superiority ($p<0.004$) were declared in the mITT analysis set. However, the observed difference was driven almost entirely by fewer changes in (or extension or restart of) treatment regimen amongst participants on Regimen C (bedaquiline), with very few unfavourable outcomes attributable to other reasons such as positive culture result or death.

The interpretation of this difference in terms of clinical benefit is hampered by the study's lack of blinding and the freedom to adjust treatment regimen at the discretion of the local investigator rather than according to pre-defined criteria. Thus, the observed difference reflects rational preferences with respect to adverse effects and convenience, as well as, possibly, lower antimicrobial efficacy of the control regimen.

Subgroup analysis indicates a numerically higher rate of favourable outcome at Week 76 for Regimen C (bedaquiline) independent of age, sex, weight, anti-TB drug history, baseline anti-TB drug resistance, and baseline disease characteristics. The difference between regimens appears to be markedly amplified in favour of Regimen C (bedaquiline) in particular for the HIV-positive and baseline RR-TB subgroups. These subgroups are small and should be interpreted with caution. Given the open-label setting, these differences possibly reflect a lower threshold in clinical practice to move participants in these subgroups away from an injectable regimen.

Secondary analyses

In the mITT Analysis Set at Week 132, the proportions of participants with a favourable outcome were generally sustained for both Regimen B (comparator) (69.2%) and Regimen C (bedaquiline) (78.2%).

The proportion of patients with culture conversion at week 76 was above 90% in the mITT population in both arms, with numerically higher estimates in the bedaquiline arm. All other indicators of microbiological status including culture and AFB smear conversion rates, time to smear and culture conversion, and relapse or re-infection, were numerically similar or more favourable in Regimen C (bedaquiline) compared to Regimen B (comparator) at EOT and Week 76. In the small subgroup of

pre-XDR TB, microbiological responses favoured the control arm. However, there is no biological rationale for this finding, which is not statistically convincing.

Rates of acquired resistance to other anti-TB drugs were based on paired data only (i.e., only the subset of participants that were failing microbiologically) and were similar between Regimens B and C (bedaquiline). Acquired resistance to BDQ was very limited in participants in Regimens C (40 weeks) and D (28 weeks): 3 of 330 (0.9%) total participants receiving BDQ as part of their allocated treatment regimen.

Overall, 21 participants died during the study with 8/202 (4.0%) in Regimen B (comparator), 11/211 (5.2%) in Regimen C (bedaquiline), and 2/143 (1.4%) in Regimen D. No participants did in regimen A. The difference in the fatal rate between Regimen B (comparator) and C (bedaquiline) was statistically not significant (p-value=0.551), with an adjusted difference in proportions of -1.2% (95% CI: -5.2%,2.8%). Deaths are further discussed below, under the heading of Clinical Safety.

In summary, while STREAM Stage 2 was an open label study that underwent key protocol amendments, it is considered to have delivered additional evidence of the efficacy of a bedaquiline-based regimen for MDR-TB.

Definitions

The WHO definitions of extent of MTB resistance have changed during the course of the BDQ clinical programme and since initial CMA was granted for Sirturo:

Comparison of WHO 2013 and WHO 2020 definitions of extent of MTB resistance

	WHO 2013 definition	**WHO 2020 definition**
MDR-TB	Resistance to at least both isoniazid and rifampicin	
Pre-XDR-TB	(*Informal definition*) MDR/RR-TB and also resistance to any fluoroquinolone[a] or second-line injectable (but not both)	(*Formalised definition*) MDR/RR-TB and also resistance to any fluoroquinolone[a]
XDR-TB	MDR/RR-TB and also resistance to any fluoroquinolone and at least one of three second-line injectable drugs (capreomycin, kanamycin and amikacin)	MDR/RR-TB and also resistance to any fluoroquinolone and at least one additional Group A drug[b]

a. Including levofloxacin and moxifloxacin.

b. Including levofloxacin, moxifloxacin, bedaquiline and linezolid.

These definitions of TB resistance have changed with time and will continue to do so. On this basis, the MAH argues that defining the resistance profile of the target population explicitly within the authorised indication (*"resistance to at least both isoniazid and rifampicin"* rather than *"MDR-TB"*) ensures that the indicated population is unambiguous and remains so even with further variation and fluctuation in common terminology. This can be agreed.

2.4.3. Conclusions on the clinical efficacy

The CHMP was of the view that the phase III trial, STREAM Stage 2, had major limitations in terms of a lack of blinding, substantial amendments while the trial was ongoing, and a primary endpoint that is difficult to interpret. However, the antimicrobial efficacy of bedaquiline was already established in the

phase II trials of bedaquiline, and the aim of STREAM Stage 2 was to demonstrate the safety and clinical usefulness of a regimen where oral bedaquiline replaces the aminoglycoside. This clinical utility has been confirmed by STREAM Stage 2.

The results showed that the rate of favourable outcome at Week 76 was higher in Regimen C (bedaquiline) than in Regimen B (comparator) and sustained through Week 132. This difference was driven almost entirely by participants in Regimen B (comparator) initiating new treatments, extending current treatments, or restarting previous treatments, which were considered unfavourable outcomes.

Very few unfavourable outcomes were attributable to other reasons such as positive culture result or death. Moreover, the proportion of patients with culture conversion at Week 76 was above 90% in the mITT population in both arms, with numerically higher estimates in the bedaquiline arm. The CHMP therefore considered that the utility of bedaquiline has been confirmed by the STREAM 2 study.

2.5. Clinical safety

Introduction

Safety was evaluated based on AEs, clinical laboratory tests, vital signs, ECG findings, visual acuity and colour tests, hearing tests, and alcohol use.

All AEs and laboratory findings were graded according to severity using DAIDS criteria; AEs of confirmed hearing loss based on audiometry findings were graded using Brock's Criteria.

All toxicities leading to the study intervention being temporarily or permanently discontinued and all toxicity effects of at least Grade 3 required thorough investigation with relevant clinical laboratory tests, as clinically indicated. These were to be repeated as needed until final resolution or stabilisation of the toxicity; if this was after the end of the study, follow-up was the responsibility of the treating clinician.

There was a focus on all-cause mortality during treatment or follow-up. Safety data obtained during the study were reviewed on a routine basis by an unblinded IDMC, as described above.

Patient exposure

The Safety Analysis Set included all randomised participants who had received at least 1 dose of treatment (N=588).

Safety data were collected up to the end of the study (i.e., Week 132 or discontinued earlier) for all participants. The safety analyses were therefore based on all data up to Week 132 (long-term safety data).

Regimen C (bedaquiline) below contained bedaquiline 200 mg TIW for a planned 40 weeks. Regimen D had the same bedaquiline dose for a planned 28 weeks.

Table 38: STREAM Stage 2 - Number of participants per analysis set

Number of Participants per Analysis Set					
	A	**B**	**C**	**D**	**Overall**
ITT Analysis Set (Randomized Participants)	32 (100%)	202 (100%)	211 (100%)	143 (100%)	588 (100%)
Safety Analysis Set	32 (100%)	202 (100%)	211 (100%)	143 (100%)	588 (100%)
mITT Analysis Set	26 (81.3%)	187 (92.6%)	196 (92.9%)	134 (93.7%)	543 (92.3%)
Protocol version					
v6.2	26 (81.3%)	63 (31.2%)*	66 (31.3%)	71 (49.7%)	226 (38.4%)
v6.3, v7.0	0	64 (31.7%)*	65 (30.8%)	63 (44.1%)	192 (32.7%)
v8.0, v10.0	0	60 (29.7%)**	65 (30.8%)	0	125 (21.3%)
PP Analysis Set	26 (81.3%)	166 (82.2%)	177 (83.9%)	122 (85.3%)	491 (83.5%)
mPP Analysis Set	18 (56.3%)	136 (67.3%)	166 (78.7%)	117 (81.8%)	437 (74.3%)
PK Analysis Set	-	-	173 (82.0%)	109 (76.2%)	282 (79.7%)

Note: Analysis sets are defined in the Statistical Methods section below.
Note: Percentage derived relative to total participants randomized, except for PK Analysis Set where percentage is derived relative to total participants randomized to Regimens C and D only.
*Regimen B_{mox}
**Regimen B_{lev}

Table 39: STREAM Stage 2 - Disposition of participants

Disposition of participants					
	A	**B**	**C**	**D**	**Overall**
Screened					1,436
ITT Analysis Set (Randomized Participants)	32 (100%)	202 (100%)	211 (100%)	143 (100%)	588 (100%)
Safety Analysis Set	32 (100%)	202 (100%)	211 (100%)	143 (100%)	588 (100%)
mITT Analysis Set	26 (81.3%)	187 (92.6%)	196 (92.9%)	134 (93.7%)	543 (92.3%)
Completed study	26 (100%)	168 (89.8%)	175 (89.3%)	130 (97.0%)	499 (91.9%)

The CHMP noted that of 1,436 participants initially screened, 588 were enrolled. The majority of screening failures had microbiological reasons. The Safety Analysis Set included all randomised participants who had received at least 1 dose of treatment (588). Safety data were collected up to the end of the study (i.e., Week 132 or discontinued earlier) for all participants.

Adverse events

Adverse Events

During the Treatment Phase, at least 1 AE was reported for almost all participants, ie, 32 (100%), 197/202 (97.5%), 206/211 (97.6%), and 142/143 (99.3%) participants in Regimens A, B, C and D, respectively. During the Follow-up Phase, proportions of participants with at least 1 reported AE were 37.5%, 68.8%, 71.1%, and 84.6%, respectively.

Table 40: Summary of adverse event, by analysis treatment and/or follow-up phase; safety analysis set (study TMC207TBC3007)

	A	B	C	D
Safety Analysis Set	32	202	211	143
Overall (Analysis Treatment + Follow-up Phase)				
Any AEs	32(100%)	198(98.0%)	206(97.6%)	143(100%)
SAEs	7(21.9%)	42(20.8%)	44(20.9%)	32(22.4%)
Treatment-related SAEs[a]	6(18.8%)	12(5.9%)	5(2.4%)	6(4.2%)
AEs leading to death[b]	0	8(4.0%)	11(5.2%)	2(1.4%)
AEs of at least Grade 3	21(65.6%)	115(56.9%)	119(56.4%)	82(57.3%)
AEs of Grade 4	7(21.9%)	35(17.3%)	32(15.2%)	27(18.9%)
SAEs leading to permanent discontinuation of BDQ	0	0	1(0.5%)*	0
SAEs leading to permanent discontinuation of other anti-TB drugs	2(6.3%)	7(3.5%)	2(0.9%)	3(2.1%)
Analysis Treatment Phase				
Any AEs	32(100%)	197(97.5%)	206(97.6%)	142(99.3%)
SAEs	7(21.9%)	31(15.3%)	30(14.2%)	19(13.3%)
Treatment-related SAEs[a]	6(18.8%)	11(5.4%)	5(2.4%)	6(4.2%)
AEs leading to death[b]	0	4(2.0%)	6(2.8%)	2(1.4%)
AEs of at least Grade 3	20(62.5%)	103(51.0%)	112(53.1%)	71(49.7%)
AEs of Grade 4	6(18.8%)	26(12.9%)	23(10.9%)	16(11.2%)
SAEs leading to permanent discontinuation of BDQ	0	0	1(0.5%)	0
SAEs leading to permanent discontinuation of other anti-TB drugs	2(6.3%)	6(3.0%)	2(0.9%)	3(2.1%)
Analysis Follow-up Phase				
Any AEs	12(37.5%)	139(68.8%)	150(71.1%)	121(84.6%)
SAEs	0	15(7.4%)	19(9.0%)	16(11.2%)
Treatment-related SAEs[a]	0	1(0.5%)	0	0
AEs leading to death[b]	0	4(2.0%)	5(2.4%)	0
AEs of at least Grade 3	2(6.3%)	27(13.4%)	34(16.1%)	28(19.6%)
AEs of Grade 4	1(3.1%)	13(6.4%)	13(6.2%)	14(9.8%)

[a] SAE is categorized as related if assessed by the investigator as possibly, probably, or definitely related to study drug.
[b] AEs leading to death are based on AE outcome of fatal.
Note: Number of participants in each regimen is used as denominator.
Note: AE grades are based on DAIDS criteria.
Note: Analysis Treatment Phase: From date of randomization to date of last dose of any anti-TB drugs (including treatment extension and/or retreatment for relapse) +7 days.
Note: Analysis Follow-up Phase: From end of Analysis Treatment Phase to last participant contact (scheduled or unscheduled, or other contact eg, phone call).
Note: AEs are coded using MedDRA v21.0.
* A participant in Regimen C with an SAE of Vomiting had an erroneously reported action taken with BDQ of permanent discontinuation, as reported by the investigator on CRF Form 9b (Serious Adverse Event [SAE] Report). However, it was subsequently established that this participant completed the BDQ course (see Section 3.7.8.9 for details). In addition, AEs leading to BDQ discontinuation were identified through programmatic and medical review. The identified 20 participants (see Section 5.2.2.7) do not include the aforementioned participant with an SAE of Vomiting.

The CHMP noted that almost all participants reported an AE during the treatment in all treatment arms. During the follow up, proportions of participants with at least 1 reported AE were 37.5%, 68.8%, 71.1%, and 84.6% in the four study arms, respectively. AE frequencies were, thus, comparable between study arm B and C (bedaquiline).

For 21.9%, 15.3%, 14.2%, and 13.3% of participants in Regimens A, B, C, and D, reported AEs were serious, and, thus, roughly comparable for Regimen B (comparator) and C (bedaquiline) and lower than for Regimen A.

AEs by SOC and PT

AEs Reported During the Treatment Phase

Table 41 Participants with adverse events in the analysis treatment phase (≥5% occurrence in any treatment group), by body system and preferred term, safety analysis set (study TMC207TB3007)

MedDRA System Organ Class Dictionary-derived Term	A	B	C	D
Safety Analysis Set	32	202	211	143
Any adverse event, n(%)	32(100%)	197(97.5%)	206(97.6%)	142(99.3%)
Investigations	22(68.8%)	156(77.2%)	172(81.5%)	110(76.9%)
Electrocardiogram QT prolonged	7(21.9%)	113(55.9%)	128(60.7%)	80(55.9%)
Blood uric acid increased	9(28.1%)	43(21.3%)	52(24.6%)	34(23.8%)
Alanine aminotransferase increased	1(3.1%)	40(19.8%)	37(17.5%)	20(14.0%)
Aspartate aminotransferase increased	4(12.5%)	36(17.8%)	40(19.0%)	16(11.2%)
Weight decreased	5(15.6%)	13(6.4%)	22(10.4%)	17(11.9%)
Blood bicarbonate decreased	3(9.4%)	17(8.4%)	20(9.5%)	10(7.0%)
Hepatic enzyme increased	1(3.1%)	9(4.5%)	18(8.5%)	5(3.5%)
Amylase increased	4(12.5%)	14(6.9%)	9(4.3%)	5(3.5%)
Blood creatine phosphokinase increased	6(18.8%)	9(4.5%)	9(4.3%)	5(3.5%)
Blood creatinine increased	3(9.4%)	14(6.9%)	5(2.4%)	7(4.9%)
Lipase increased	0	14(6.9%)	6(2.8%)	6(4.2%)
Blood magnesium decreased	3(9.4%)	7(3.5%)	5(2.4%)	3(2.1%)
Blood potassium decreased	2(6.3%)	8(4.0%)	4(1.9%)	1(0.7%)
Blood glucose increased	4(12.5%)	3(1.5%)	4(1.9%)	1(0.7%)
Blood sodium decreased	2(6.3%)	5(2.5%)	2(0.9%)	3(2.1%)
Blood cholesterol increased	2(6.3%)	4(2.0%)	3(1.4%)	1(0.7%)
Gastrointestinal disorders	26(81.3%)	168(83.2%)	169(80.1%)	95(66.4%)
Nausea	16(50.0%)	127(62.9%)	114(54.0%)	61(42.7%)
Vomiting	18(56.3%)	125(61.9%)	113(53.6%)	41(28.7%)
Abdominal pain upper	9(28.1%)	37(18.3%)	39(18.5%)	17(11.9%)
Dyspepsia	8(25.0%)	29(14.4%)	29(13.7%)	12(8.4%)
Abdominal pain	3(9.4%)	14(6.9%)	22(10.4%)	8(5.6%)
Diarrhoea	3(9.4%)	17(8.4%)	12(5.7%)	10(7.0%)
Hyperchlorhydria	0	11(5.4%)	11(5.2%)	11(7.7%)
Abdominal distension	0	9(4.5%)	15(7.1%)	8(5.6%)
Constipation	3(9.4%)	9(4.5%)	12(5.7%)	4(2.8%)
Rectal haemorrhage	2(6.3%)	0	0	0
Musculoskeletal and connective tissue disorders	26(81.3%)	96(47.5%)	119(56.4%)	95(66.4%)
Arthralgia	20(62.5%)	67(33.2%)	94(44.5%)	78(54.5%)
Pain in extremity	3(9.4%)	18(8.9%)	26(12.3%)	11(7.7%)
Myalgia	1(3.1%)	6(3.0%)	19(9.0%)	12(8.4%)
Back pain	2(6.3%)	7(3.5%)	8(3.8%)	13(9.1%)
Musculoskeletal pain	2(6.3%)	3(1.5%)	9(4.3%)	14(9.8%)
Muscle spasms	5(15.6%)	5(2.5%)	2(0.9%)	4(2.8%)
Arthritis	2(6.3%)	1(0.5%)	2(0.9%)	2(1.4%)
Arthropathy	2(6.3%)	0	0	0
Metabolism and nutrition disorders	20(62.5%)	96(47.5%)	109(51.7%)	61(42.7%)
Decreased appetite	8(25.0%)	40(19.8%)	51(24.2%)	27(18.9%)
Hyperuricaemia	5(15.6%)	39(19.3%)	40(19.0%)	33(23.1%)
Hypocalcaemia	3(9.4%)	11(5.4%)	16(7.6%)	7(4.9%)
Hyperglycaemia	6(18.8%)	6(3.0%)	18(8.5%)	6(4.2%)
Hypoglycaemia	3(9.4%)	7(3.5%)	11(5.2%)	7(4.9%)
Hypokalaemia	7(21.9%)	11(5.4%)	8(3.8%)	1(0.7%)
Hypomagnesaemia	3(9.4%)	11(5.4%)	8(3.8%)	5(3.5%)
Hyponatraemia	5(15.6%)	7(3.5%)	10(4.7%)	5(3.5%)
Hyperkalaemia	1(3.1%)	2(1.0%)	11(5.2%)	5(3.5%)
Hyperlipasaemia	2(6.3%)	2(1.0%)	2(0.9%)	2(1.4%)
Hyperamylasaemia	2(6.3%)	1(0.5%)	0	2(1.4%)

Table 42 Participants with adverse events in the analysis treatment phase (≥5% occurrence in any treatment group), by body system and preferred term, safety analysis set (study TMC207TB3007)

MedDRA System Organ Class Dictionary-derived Term	A	B	C	D
Skin and subcutaneous tissue disorders	22(68.8%)	78(38.6%)	101(47.9%)	74(51.7%)
Pruritus	11(34.4%)	40(19.8%)	56(26.5%)	35(24.5%)
Rash	7(21.9%)	15(7.4%)	28(13.3%)	16(11.2%)
Dry skin	1(3.1%)	16(7.9%)	25(11.8%)	17(11.9%)
Skin discolouration	1(3.1%)	6(3.0%)	19(9.0%)	23(16.1%)
Skin hyperpigmentation	1(3.1%)	11(5.4%)	16(7.6%)	12(8.4%)
Night sweats	2(6.3%)	3(1.5%)	4(1.9%)	6(4.2%)
Rash papular	2(6.3%)	2(1.0%)	2(0.9%)	0
Dermatitis	2(6.3%)	2(1.0%)	0	1(0.7%)
General disorders and administration site conditions	17(53.1%)	82(40.6%)	76(36.0%)	72(50.3%)
Pyrexia	7(21.9%)	22(10.9%)	43(20.4%)	24(16.8%)
Chest pain	6(18.8%)	24(11.9%)	33(15.6%)	24(16.8%)
Asthenia	3(9.4%)	19(9.4%)	15(7.1%)	12(8.4%)
Malaise	3(9.4%)	20(9.9%)	11(5.2%)	8(5.6%)
Injection site pain	7(21.9%)	17(8.4%)	0	17(11.9%)
Fatigue	3(9.4%)	8(4.0%)	13(6.2%)	8(5.6%)
Pain	1(3.1%)	7(3.5%)	5(2.4%)	8(5.6%)
Oedema peripheral	2(6.3%)	1(0.5%)	1(0.5%)	1(0.7%)
Chest discomfort	2(6.3%)	2(1.0%)	0	0
Nervous system disorders	19(59.4%)	91(45.0%)	76(36.0%)	57(39.9%)
Dizziness	8(25.0%)	42(20.8%)	37(17.5%)	30(21.0%)
Headache	11(34.4%)	36(17.8%)	36(17.1%)	23(16.1%)
Poor quality sleep	2(6.3%)	17(8.4%)	10(4.7%)	7(4.9%)
Paraesthesia	2(6.3%)	8(4.0%)	16(7.6%)	4(2.8%)
Hypoaesthesia	3(9.4%)	1(0.5%)	0	2(1.4%)
Respiratory, thoracic and mediastinal disorders	12(37.5%)	72(35.6%)	73(34.6%)	67(46.9%)
Cough	7(21.9%)	34(16.8%)	39(18.5%)	33(23.1%)
Dyspnoea	4(12.5%)	37(18.3%)	30(14.2%)	28(19.6%)
Productive cough	0	19(9.4%)	22(10.4%)	26(18.2%)
Haemoptysis	1(3.1%)	10(5.0%)	13(6.2%)	16(11.2%)
Infections and infestations	16(50.0%)	69(34.2%)	81(38.4%)	50(35.0%)
Nasopharyngitis	1(3.1%)	12(5.9%)	6(2.8%)	9(6.3%)
Hepatitis B	2(6.3%)	11(5.4%)	10(4.7%)	2(1.4%)
Candida infection	5(15.6%)	1(0.5%)	6(2.8%)	4(2.8%)
Vulvovaginal candidiasis	2(6.3%)	2(1.0%)	7(3.3%)	5(3.5%)
Respiratory tract infection	3(9.4%)	3(1.5%)	1(0.5%)	4(2.8%)
Oral candidiasis	3(9.4%)	1(0.5%)	4(1.9%)	2(1.4%)
Fungal infection	2(6.3%)	0	0	4(2.8%)
Ear and labyrinth disorders	18(56.3%)	83(41.1%)	48(22.7%)	53(37.1%)
Deafness	8(25.0%)	39(19.3%)	22(10.4%)	27(18.9%)
Tinnitus	4(12.5%)	33(16.3%)	9(4.3%)	15(10.5%)
Deafness unilateral	3(9.4%)	20(9.9%)	11(5.2%)	10(7.0%)
Ear pain	2(6.3%)	1(0.5%)	1(0.5%)	1(0.7%)
Deafness neurosensory	2(6.3%)	0	0	2(1.4%)
Cardiac disorders	5(15.6%)	43(21.3%)	46(21.8%)	25(17.5%)
Palpitations	3(9.4%)	13(6.4%)	21(10.0%)	7(4.9%)
Sinus tachycardia	2(6.3%)	6(3.0%)	7(3.3%)	3(2.1%)
Renal and urinary disorders	12(37.5%)	37(18.3%)	36(17.1%)	28(19.6%)
Proteinuria	7(21.9%)	21(10.4%)	25(11.8%)	16(11.2%)
Haematuria	4(12.5%)	15(7.4%)	13(6.2%)	9(6.3%)
Renal impairment	3(9.4%)	4(2.0%)	0	1(0.7%)

Table 43 Participants with adverse events in the analysis treatment phase (≥5% occurrence in any treatment group), by body system and preferred term, safety analysis set (study TMC207TB3007)

MedDRA System Organ Class Dictionary-derived Term	A	B	C	D
Blood and lymphatic system disorders	6(18.8%)	25(12.4%)	32(15.2%)	36(25.2%)
Anaemia	1(3.1%)	19(9.4%)	23(10.9%)	26(18.2%)
Leukocytosis	2(6.3%)	2(1.0%)	3(1.4%)	4(2.8%)
Psychiatric disorders	9(28.1%)	35(17.3%)	37(17.5%)	16(11.2%)
Insomnia	5(15.6%)	19(9.4%)	30(14.2%)	11(7.7%)
Depression	3(9.4%)	3(1.5%)	3(1.4%)	2(1.4%)
Hepatobiliary disorders	7(21.9%)	29(14.4%)	18(8.5%)	12(8.4%)
Hepatitis toxic	1(3.1%)	19(9.4%)	10(4.7%)	6(4.2%)
Hepatotoxicity	4(12.5%)	4(2.0%)	5(2.4%)	5(3.5%)
Reproductive system and breast disorders	4(12.5%)	12(5.9%)	7(3.3%)	10(7.0%)
Amenorrhoea	2(6.3%)	2(1.0%)	3(1.4%)	0
Endocrine disorders	4(12.5%)	1(0.5%)	2(0.9%)	4(2.8%)
Hypothyroidism	3(9.4%)	0	0	1(0.7%)

Note: Participants are counted only once for any given event, regardless of the number of times they actually experienced the event.
Note: Number of participants in each regimen is used as denominator.
Note: Analysis Treatment Phase: From date of randomization to date of last dose of any anti-TB drugs (including treatment extension and/or retreatment for relapse) +7 days.
Note: AEs are coded using MedDRA v21.0.
Modified based on Attachment TSFAE02a_TP

The CHMP noted that the most frequent SOCs were Investigations, Gastrointestinal Disorders, Musculoskeletal and Connective Tissue Disorders, Metabolism and Nutrition Disorders and Skin and Subcutaneous Tissue Disorders. Here, Regimen A generally had the highest frequencies. Regimens B (comparator) and C (bedaquiline) differed with up to 10% in frequencies.

The most frequent PTs were QT prolongation, nausea, vomiting, arthralgia, pruritus and blood uric acid increases. Regimen A showed the highest frequencies. Regimen B (comparator) and C (bedaquiline) where roughly comparable regarding frequencies in most of the PTs.

The CHMP noted that frequencies for hepatic enzymes increased (4,5% vs 8,5%), abdominal pain (6,9% vs 10,4%) /abdominal distension (4,5% vs 7,1%), arthralgia (33,2% vs. 44,5%), myalgia (3,0% vs. 9,0%), hyperkalaemia (1,0% vs 5,2%), rash (7,4% vs. 13.3%), skin discoloration (3,0% vs 9,0%), pyrexia (10,9% vs 20,4%), and different forms of candida infections (2,0% vs. 7,3%) are higher in Regimen C (bedaquiline) than Regimen B (comparator). Arthralgia and myalgia are already mentioned in section 4.8 of the SmPC.

Similarly, skin discoloration, and allergic reactions including rash and pruritus are more often observed in Regimen C (bedaquiline) compared to Regimen B (comparator). The MAH was requested to evaluate the possibility of a causal relationship between BDQ and adverse events of skin discoloration, rash and pruritus. The comparison is confounded by the administration of aminoglycosides in Regimen B, and multiple other classes of anti-TB drug in the background regimen in both arms. In fact, the totality of clinical data (including earlier completed studies against placebo) does not appear to indicate disproportionate occurrence of these events in association with BDQ. Reports of skin discoloration are limited (and indeed attributable) to instances of concomitant administration of clofazimine (CFZ), for which this is a known adverse effect). Meanwhile rash and pruritis are commonly reported in MDR-TB and arise secondary to underlying condition and multiple classes of anti-TB drug. There are no mechanistic reasons to suspect such off-target effects for BDQ, nor pre-clinical safety signals. There is

no evidence to indicate a causal association between skin discoloration, rash or pruritis and BDQ treatment.

AEs Reported During the Follow-up Phase

The CHMP noted that during the Follow-up Phase, at least 1 AE was reported for 37.5% of participants in Regimen A, 68.8% in Regimen B (comparator), 71.1% in Regimen C (bedaquiline), and 84.6% in Regimen D. Thus, AEs in the follow up phase were comparably in Regimens B (comparator) and C (bedaquiline).

Notable Events

The following notable events were to be identified and reported to the Main Clinical Study Conduct Partner:

- Pregnancy in a participant or partner of a participant during study intervention or follow-up
- QT or QTcF prolongation ≥500 ms while on treatment
- ALT/AST increase to ≥10xULN, or ALT/AST increase ≥3xULN in the presence of total bilirubin increase ≥2xULN
- Creatinine kinase ≥10xULN
- Pancreatic amylase ≥2xULN
- Any AE of at least Grade 3 (including medical conditions at randomisation worsening to an AE of at least Grade 3)
- Any toxicity that led to withholding or stopping of allocated study intervention for more than 24 hours
- A clinically significant dysrhythmia, such as an episode of ventricular tachycardia, with ≥3 irregular beats in a row
- An overdose of any study intervention

Investigators were to notify the Main Clinical Study Conduct Partner of all SAEs and notable events as defined above, within one working day of them becoming aware of the event. The Main Clinical Study Conduct Partner was undertaking the duties of study management and was responsible for ensuring that sites provided the sponsor's research ethics committee and the regulatory authorities that have approved the study with the safety reports that they required.

All Notable Events During the Treatment Phase

During the Treatment Phase, at least 1 notable event was reported for 20/32 (62.5%) participants in Regimen A, 93/202 (46.0%) in Regimen B (comparator), 102/211 (48.3%) in Regimen C (bedaquiline), and 61/143 (42.7%) in Regimen D.

Most of the notable events were of at least Grade 3 and were reported for 59.4%, 42.6%, 47.4%, and 40.6% of participants in Regimens A, B, C, and D, respectively. The only event of at least Grade 3 reported in more than 10% of participants in Regimens B, C, and D was Electrocardiogram QT prolonged.

- By PT, the most frequently reported notable events (≥5.0% of participants in the BDQ containing Regimens C and/or D, in decreasing order for Regimen C (bedaquiline)) included:
- Electrocardiogram QT prolonged: 6.3%, 22.3%, 26.5%, and 23.8% of participants in Regimens A, B, C, and D, respectively, of which none were reported as serious.
- Aspartate aminotransferase increased: 0%, 8.4%, 7.1%, and 0%, respectively.
- Hyperuricemia: 3.1%, 5.0%, 6.2%, and 6.3%, respectively

Table 44:Subjects with notable events by DAIDS grade in the analysis treatment phase, by body system and preferred term; safety analysis set (study TMC207 TBC3007)

MedDRA System Organ Class Dictionary-derived Term Analysis set: Safety	A 32	B 202	C 211	D 143
Any notable event, n(%)	20(62.5%)	93(46.0%)	102(48.3%)	61(42.7%)
Grade <3	1(3.1%)	7(3.5%)	2(0.9%)	3(2.1%)
Grade >=3	19(59.4%)	86(42.6%)	100(47.4%)	58(40.6%)
Investigations	11(34.4%)	69(34.2%)	82(38.9%)	44(30.8%)
Grade <3	0	0	0	0
Grade >=3	11(34.4%)	69(34.2%)	82(38.9%)	44(30.8%)
Electrocardiogram QT prolonged	2(6.3%)	45(22.3%)	56(26.5%)	34(23.8%)
Aspartate aminotransferase increased	0	17(8.4%)	15(7.1%)	0
Blood uric acid increased	5(15.6%)	6(3.0%)	8(3.8%)	3(2.1%)
Alanine aminotransferase increased	0	9(4.5%)	7(3.3%)	1(0.7%)
Weight decreased	4(12.5%)	2(1.0%)	4(1.9%)	3(2.1%)
Hepatic enzyme increased	1(3.1%)	1(0.5%)	6(2.8%)	2(1.4%)
Blood creatine phosphokinase increased	1(3.1%)	5(2.5%)	2(0.9%)	0
Amylase increased	2(6.3%)	3(1.5%)	1(0.5%)	1(0.7%)
Lipase increased	0	2(1.0%)	1(0.5%)	1(0.7%)
Blood bicarbonate decreased	1(3.1%)	0	1(0.5%)	1(0.7%)
Blood creatinine increased	0	2(1.0%)	0	1(0.7%)
Transaminases increased	0	2(1.0%)	0	1(0.7%)
Blood cholesterol increased	0	1(0.5%)	1(0.5%)	0
Blood magnesium decreased	0	2(1.0%)	0	0
Blood bilirubin increased	0	0	1(0.5%)	0
Blood glucose increased	0	0	1(0.5%)	0
Blood sodium increased	0	0	1(0.5%)	0
Blood triglycerides increased	0	0	1(0.5%)	0
Creatinine renal clearance decreased	0	0	0	1(0.7%)
Platelet count decreased	0	0	1(0.5%)	0
Metabolism and nutrition disorders	6(18.8%)	15(7.4%)	20(9.5%)	10(7.0%)
Grade <3	0	0	0	0
Grade >=3	6(18.8%)	15(7.4%)	20(9.5%)	10(7.0%)
Hyperuricaemia	1(3.1%)	10(5.0%)	13(6.2%)	9(6.3%)
Abnormal loss of weight	0	2(1.0%)	2(0.9%)	0
Hyponatraemia	1(3.1%)	1(0.5%)	2(0.9%)	0
Hypernatraemia	0	1(0.5%)	2(0.9%)	0
Hyperamylasaemia	1(3.1%)	0	0	1(0.7%)
Hypokalaemia	2(6.3%)	0	0	0
Decreased appetite	0	1(0.5%)	0	0
Hyperglycaemia	1(3.1%)	0	0	0
Hyperkalaemia	0	0	1(0.5%)	0
Hyperlipasaemia	0	1(0.5%)	0	0
Hypocalcaemia	0	0	1(0.5%)	0
Hypoglycaemia	0	0	1(0.5%)	0
Hypomagnesaemia	0	0	1(0.5%)	0
Ear and labyrinth disorders	4(12.5%)	17(8.4%)	3(1.4%)	4(2.8%)
Grade <3	2(6.3%)	10(5.0%)	0	1(0.7%)
Deafness	1(3.1%)	5(2.5%)	0	1(0.7%)
Deafness unilateral	0	2(1.0%)	0	0
Ototoxicity	1(3.1%)	1(0.5%)	0	0
Deafness bilateral	0	1(0.5%)	0	0
Vertigo	0	1(0.5%)	0	0
Grade >=3	2(6.3%)	7(3.5%)	3(1.4%)	3(2.1%)
Deafness unilateral	0	4(2.0%)	2(0.9%)	1(0.7%)
Deafness	0	3(1.5%)	0	2(1.4%)

Table 45: Subjects with notable events by DAIDS grade in the analysis treatment phase, by body system and preferred term; safety analysis set (study TMC 207TBC3007)

MedDRA System Organ Class Dictionary-derived Term	A	B	C	D
Deafness neurosensory	2(6.3%)	0	0	0
Deafness bilateral	0	0	1(0.5%)	0
Hepatobiliary disorders	2(6.3%)	6(3.0%)	3(1.4%)	1(0.7%)
Grade <3	0	0	1(0.5%)	0
Hepatotoxicity	0	0	1(0.5%)	0
Grade >=3	2(6.3%)	6(3.0%)	2(0.9%)	1(0.7%)
Hepatitis toxic	0	6(3.0%)	1(0.5%)	0
Hepatotoxicity	2(6.3%)	0	1(0.5%)	1(0.7%)
Injury, poisoning and procedural complications	0	1(0.5%)	2(0.9%)	4(2.8%)
Grade <3	0	1(0.5%)	2(0.9%)	2(1.4%)
Overdose	0	1(0.5%)	2(0.9%)	2(1.4%)
Grade >=3	0	0	0	2(1.4%)
Overdose	0	0	0	2(1.4%)
Gastrointestinal disorders	2(6.3%)	3(1.5%)	1(0.5%)	0
Grade <3	0	2(1.0%)	0	0
Vomiting	0	2(1.0%)	0	0
Grade >=3	2(6.3%)	1(0.5%)	1(0.5%)	0
Vomiting	1(3.1%)	1(0.5%)	1(0.5%)	0
Nausea	1(3.1%)	0	0	0
Blood and lymphatic system disorders	0	1(0.5%)	1(0.5%)	2(1.4%)
Grade <3	0	0	0	0
Grade >=3	0	1(0.5%)	1(0.5%)	2(1.4%)
Anaemia	0	1(0.5%)	1(0.5%)	2(1.4%)
General disorders and administration site conditions	0	2(1.0%)	1(0.5%)	1(0.7%)
Grade <3	0	0	0	0
Grade >=3	0	2(1.0%)	1(0.5%)	1(0.7%)
Pyrexia	0	1(0.5%)	1(0.5%)	1(0.7%)
Injection site reaction	0	1(0.5%)	0	0
Musculoskeletal and connective tissue disorders	1(3.1%)	1(0.5%)	1(0.5%)	1(0.7%)
Grade <3	0	0	1(0.5%)	1(0.7%)
Arthralgia	0	0	1(0.5%)	1(0.7%)
Grade >=3	1(3.1%)	1(0.5%)	0	0
Arthralgia	1(3.1%)	0	0	0
Myositis	0	1(0.5%)	0	0
Renal and urinary disorders	1(3.1%)	1(0.5%)	1(0.5%)	1(0.7%)
Grade <3	1(3.1%)	0	0	1(0.7%)
Acute kidney injury	0	0	0	1(0.7%)
Renal impairment	1(3.1%)	0	0	0
Grade >=3	0	1(0.5%)	1(0.5%)	0
Ketonuria	0	1(0.5%)	0	0
Nephropathy toxic	0	0	1(0.5%)	0
Vascular disorders	1(3.1%)	2(1.0%)	0	0
Grade <3	0	0	0	0
Grade >=3	1(3.1%)	2(1.0%)	0	0
Deep vein thrombosis	0	1(0.5%)	0	0
Embolism venous	1(3.1%)	0	0	0
Hypertension	0	1(0.5%)	0	0

Table 46: Subjects with notable events by DAIDS grade in the analysis treatment phase, by body system and preferred term; safety analysis set (study TMC 207TBC3007)

MedDRA System Organ Class Dictionary-derived Term	A	B	C	D
Cardiac disorders	0	0	1(0.5%)	1(0.7%)
Grade <3	0	0	0	0
Grade >=3	0	0	1(0.5%)	1(0.7%)
Arrhythmia	0	0	0	1(0.7%)
Cardiac failure congestive	0	0	1(0.5%)	0
Eye disorders	0	0	1(0.5%)	0
Grade <3	0	0	0	0
Grade >=3	0	0	1(0.5%)	0
Visual impairment	0	0	1(0.5%)	0
Infections and infestations	0	0	0	1(0.7%)
Grade <3	0	0	0	0
Grade >=3	0	0	0	1(0.7%)
Pneumonia	0	0	0	1(0.7%)
Respiratory, thoracic and mediastinal disorders	0	0	1(0.5%)	0
Grade <3	0	0	0	0
Grade >=3	0	0	1(0.5%)	0
Pneumothorax	0	0	1(0.5%)	0
Skin and subcutaneous tissue disorders	0	0	1(0.5%)	0
Grade <3	0	0	0	0
Grade >=3	0	0	1(0.5%)	0
Dermatitis allergic	0	0	1(0.5%)	0
Surgical and medical procedures	0	0	1(0.5%)	0
Grade <3	0	0	0	0
Grade >=3	0	0	1(0.5%)	0
Abortion induced	0	0	1(0.5%)	0

Key: DAIDS=Division of Acquired Immunodeficiency Syndrome, MedDRA=Medical Dictionary for Regulatory Activities.
Note: Number of subjects in each regimen is used as denominator.
Note: Notable events presented based on the investigators assessment as collected on the Notable Event (NE) Report CRF.
Note: AE grades are based on DAIDS criteria.
Note: Analysis treatment phase: From date of randomization to date of last dose of any anti-TB drugs (including treatment extension and/or retreatment for relapse) +7 days.
Note: Adverse events are coded using MedDRA v21.0.

[TSFAE16_TP.RTF] [\\WILBTIA\WILBTIA02\JNJ JJTBC3007\WEEK 132 TFL W ADAM UPDATES\TLF\TSFAE16_TP.SAS]
08MAR2023, 02:51

The CHMP noted that the only notable event of at least Grade 3 reported in more than 10% of participants in Regimens B, C, and D was 'Electrocardiogram QT prolonged', which was slightly higher in Regimen C (bedaquiline) compared with Regimen B (comparator) (22,3% vs 26,5%). The CHMP noted that 'Electrocardiogram QT prolonged' is already well reflected in sections 4.4 and 4.8 of the SmPC.

Notable Events Considered Related to BDQ or Other Anti-TB Drugs in the Regimen (Excluding BDQ) by the Investigator

At Least Grade 3 Adverse Events

During the Treatment Phase, AEs of at least Grade 3 were reported for 62.5% of participants in Regimen A, 51.0% in Regimen B (comparator), 53.1% in Regimen C (bedaquiline), and 49.7% in Regimen D. By grade, the following distribution was observed:

- Grade 3: 17 (53.1%), 92 (45.5%), 100 (47.4%), and 62 (43.4%) participants in Regimens A, B, C, and D, respectively
- Grade 4: 6 (18.8%), 26 (12.9%), 23 (10.9%), and 16 (11.2%) participants, respectively

- Grade 5 (fatal): 0, 4 (2.0%), 6 (2.8%), and 2 (1.4%) participants, respectively

Grade 4 AEs occurred in 2 (6.3%), 7 (3.5%), 11 (5.2%), and 6 (4.2%) participants, respectively, and were mainly due to:

- Aspartate aminotransferase increased in 1 (3.1%), 3 (1.5%), 3 (1.4%), and 0 participants, respectively
- Blood uric acid increased in 1 (3.1%), 1 (0.5%), 2 (0.9%), and 2 (1.4%) participants, respectively
- Hepatic enzyme increased in 1 (3.1%), 0, 3 (1.4%), and 2 (1.4%) participants, respectively
- No Grade 5 AEs were observed in this SOC

Adverse Events of Special Interest (AESIs) and Other Significant AEs

AESIs During the Treatment Phase

Table 47 Participants with AESIs in the analysis treatment phase, safety analysis set (study TMC207TB3007)

SMQ Term, Sub-SMQ Terms and Dictionary-derived Term	A	B	C	D
Safety Analysis Set	32	202	211	143
Any AESIs, n(%)	15(46.9%)	149(73.8%)	159(75.4%)	99(69.2%)
Torsade de pointes/QT prolongation (SMQ)	7(21.9%)	114(56.4%)	128(60.7%)	81(56.6%)
Electrocardiogram QT prolonged	7(21.9%)	113(55.9%)	128(60.7%)	80(55.9%)
Syncope	0	0	1(0.5%)	1(0.7%)
Loss of consciousness	0	0	0	1(0.7%)
Sudden death	0	1(0.5%)	0	0
Acute pancreatitis (SMQ)	8(25.0%)	33(16.3%)	18(8.5%)	15(10.5%)
Amylase increased	4(12.5%)	14(6.9%)	9(4.3%)	5(3.5%)
Lipase increased	0	14(6.9%)	6(2.8%)	6(4.2%)
Blood bilirubin increased	0	9(4.5%)	4(1.9%)	2(1.4%)
Hyperlipasaemia	2(6.3%)	2(1.0%)	2(0.9%)	2(1.4%)
Hyperbilirubinaemia	1(3.1%)	4(2.0%)	1(0.5%)	0
Hyperamylasaemia	2(6.3%)	1(0.5%)	0	2(1.4%)
Pancreatic pseudocyst	1(3.1%)	0	0	1(0.7%)
Pancreatitis	1(3.1%)	1(0.5%)	0	0
Severe cutaneous adverse reactions (SMQ)	0	9(4.5%)	10(4.7%)	14(9.8%)
Skin exfoliation	0	2(1.0%)	4(1.9%)	6(4.2%)
Conjunctivitis	0	2(1.0%)	5(2.4%)	4(2.8%)
Mouth ulceration	0	4(2.0%)	1(0.5%)	1(0.7%)
Genital ulceration	0	0	0	2(1.4%)
Pemphigus	0	0	0	1(0.7%)
Skin erosion	0	1(0.5%)	0	0
Stevens-Johnson syndrome	0	1(0.5%)	0	0
Stomatitis	0	0	0	1(0.7%)
Cardiac failure (SMQ)	0	0	1(0.5%)	0
Cardiac failure congestive	0	0	1(0.5%)	0
HEPATIC DISORDERS	8(25.0%)	81(40.1%)	78(37.0%)	39(27.3%)
Liver-related investigations, signs and symptoms (SMQ)	5(15.6%)	62(30.7%)	66(31.3%)	32(22.4%)
Alanine aminotransferase increased	1(3.1%)	40(19.8%)	37(17.5%)	20(14.0%)
Aspartate aminotransferase increased	4(12.5%)	36(17.8%)	40(19.0%)	16(11.2%)
Hepatic enzyme increased	1(3.1%)	9(4.5%)	18(8.5%)	5(3.5%)
Blood bilirubin increased	0	9(4.5%)	4(1.9%)	2(1.4%)
Gammaglutamyltransferase increased	1(3.1%)	4(2.0%)	3(1.4%)	3(2.1%)
Transaminases increased	0	2(1.0%)	3(1.4%)	4(2.8%)
Hyperbilirubinaemia	1(3.1%)	4(2.0%)	1(0.5%)	0
Bilirubin urine present	0	3(1.5%)	0	0
Urine bilirubin increased	0	2(1.0%)	1(0.5%)	0
Ascites	0	0	1(0.5%)	0
Bilirubin conjugated increased	0	0	1(0.5%)	0
Hypertransaminasaemia	0	0	0	1(0.7%)

SMQ Term, Sub-SMQ Terms and Dictionary-derived Term	A	B	C	D
Hepatitis, noninfectious (SMQ)	1(3.1%)	21(10.4%)	11(5.2%)	6(4.2%)
Hepatitis toxic	1(3.1%)	19(9.4%)	10(4.7%)	6(4.2%)
Hepatitis acute	0	1(0.5%)	1(0.5%)	0
Hepatitis	0	1(0.5%)	0	0
Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions (SMQ)	4(12.5%)	5(2.5%)	6(2.8%)	5(3.5%)
Hepatotoxicity	4(12.5%)	4(2.0%)	5(2.4%)	5(3.5%)
Druginduced liver injury	0	1(0.5%)	1(0.5%)	0
Ascites	0	0	1(0.5%)	0
Cholestasis and jaundice of hepatic origin (SMQ)	1(3.1%)	5(2.5%)	2(0.9%)	0
Hyperbilirubinaemia	1(3.1%)	4(2.0%)	1(0.5%)	0
Druginduced liver injury	0	1(0.5%)	1(0.5%)	0
Jaundice	0	0	1(0.5%)	0
Liver-related coagulation and bleeding disturbances (SMQ)	0	0	1(0.5%)	0
Prothrombin time ratio abnormal	0	0	1(0.5%)	0

Note: AESIs are identified using SMQs.
Note: Analysis Treatment Phase: From date of randomization to date of last dose of any anti-TB drugs (including treatment extension and/or retreatment for relapse) +7 days.
Note: Number of participants in each regimen is used as denominator.
Note: AEs are coded using MedDRA v21.0.

Modified based on Attachment TSFAE12_TP

Torsade de Pointes/QT Prolongation

During the Treatment Phase, the proportion of participants with at least 1 AE coding to Torsade de pointes/QT prolongation (SMQ) was 21.9% in Regimen A, 56.4% in Regimen B (comparator), 60.7% in Regimen C (bedaquiline), and 56.6% in Regimen D.

Many of these AEs were reported due to increases from baseline in QTcF. By PT, the only AE coding to this SMQ reported in more than 1 participant in the BDQ-containing Regimens C (>0.5%) or D (>0.7%) was Electrocardiogram QT prolonged, i.e., 21.9%, 55.9%, 60.7%, and 55.9% in Regimens A, B, C, and D, respectively (Table 47).

SAEs coding to Torsade de pointes/QT prolongation (SMQ) were reported for 1/202 (0.5%) participant in Regimen B (comparator) and 1/143 (0.7%) participant in Regimen D (Syncope, no QTcF abnormalities reported), which resolved, and the participant completed treatment.

During the Follow-up Phase, at least 1 AE coding to Torsade de pointes/QT prolongation (SMQ) was reported for 12.4% of participants in Regimen B (comparator), 14.2% in Regimen C (bedaquiline), and 15.4% in Regimen D.

No AEs coding to the PT of Torsade de Pointes or SAEs coding to the PT of Electrocardiogram QT prolonged were reported.

Hepatic Disorders/Hepatic Toxicity

During the Treatment Phase, the proportion of participants with at least 1 AE coding to Hepatic disorders/hepatic toxicity (based on selected sub-SMQ's) was 25.0% and 40.1% in non-BDQ containing Regimens A and B, respectively, and 37.0% and 27.3% in BDQ-containing Regimens C and D, respectively (Table 47).

More details regarding participants' liver function in this study (meeting laboratory criteria for Hy's law or Temple's corollary) can be found in the section laboratory values.

By PT, the most frequently reported AEs coding to this SMQ (≥2 participants in the BDQ-containing Regimens C [≥0.9%] or D [≥1.4%]) were (see also Table 47above):

- Alanine aminotransferase increased: 3.1%, 19.8%, 17.5%, and 14.0% of participants in Regimens A, B, C, and D, respectively
- Aspartate aminotransferase increased: 12.5%, 17.8%, 19.0%, and 11.2%, respectively
- Hepatic enzyme increased: 3.1%, 4.5%, 8.5%, and 3.5%, respectively
- Blood bilirubin increased: 0%, 4.5%, 1.9%, and 1.4%, respectively
- Gammaglutamyltransferase increased: 3.1%, 2.0%, 1.4%, and 2.1%, respectively
- Transaminases increased: 0%, 1.0%, 1.4%, and 2.8%, respectively
- Hepatitis, non-infectious (SMQ): reported for 3.1%, 10.4%, 5.2%, and 4.2% participants in Regimens A, B, C, and D, respectively. By PT, the only AE reported coding to this SMQ for ≥2 participants in the BDQ-containing Regimens C (≥0.9%) or D (≥1.4%) was Hepatitis toxic, reported for 3.1%, 9.4%, 4.7%, and 4.2% of participants, respectively.
- Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions (SMQ): reported for 12.5%, 2.5%, 2.8%, and 3.5% of participants in Regimens A, B, C, and D, respectively. By PT, the only AE reported coding to this SMQ for ≥2 participants in the BDQ-containing Regimens C (≥0.9%) or D (≥1.4%) was Hepatotoxicity, reported for 12.5%, 2.0%, 2.4%, and 3.5% of participants, respectively.
- Cholestasis and jaundice of hepatic origin (SMQ): reported for 3.1%, 2.5%, 0.9%, and 0% of participants in Regimens A, B, C, and D, respectively. By PT, all AEs were reported for at most 1 participant in the BDQ-containing Regimens C (0.5%) or D (0%).
- Liver-related coagulation and bleeding disturbances (SMQ): reported for 0.5% of participants in Regimen C (bedaquiline) (Prothrombin time ratio abnormal) SAEs coding to Hepatic disorders/hepatic toxicity were reported for 1.4% of participants in BDQ-containing Regimen C (bedaquiline), no participants in BDQ-containing Regimen D, and for 3.1% and 2.0% in non-BDQ-containing Regimens A and B, respectively.

For 1 participant in Regimen B (comparator), a fatal AE related to liver toxicity was reported (i.e., AST increased, ALT increased, and GGT increased).

During the Follow-up Phase, at least 1 AE coding to Hepatic disorders/hepatic toxicity (based on selected sub-SMQs) was reported for 6.3% of participants in Regimen A, 12.9% in Regimen B (comparator), 17.5% in Regimen C (bedaquiline), and 21.0% in Regimen D.

No AEs (PTs) including the term "hepatic failure" were reported. Events related to hepatic toxicity led to discontinuation of BDQ in a small proportion of participants.

Acute Pancreatitis

During the Treatment Phase, AEs coding to Acute pancreatitis (SMQ) (Category A, B, and C (bedaquiline) terms) were reported for fewer participants in the BDQ-containing Regimens C and D

(8.5% and 10.5% of participants, respectively) compared with the Regimens A and B (25.0% and 16.3%, respectively). Amylase increased: 12.5%, 6.9%, 4.3%, and 3.5% of participants in Regimens A, B, C, and D, respectively

- Lipase increased: 0%, 6.9%, 2.8%, and 4.2%, respectively
- Blood bilirubin increased: 0%, 4.5%, 1.9%, and 1.4%, respectively
- Hyperlipasemia: 6.3%, 1.0%, 0.9%, and 1.4%, respectively
- Hyperamylasaemia: 6.3%, 0.5%, 0%, and 1.4%, respectively
- SAEs coding to Acute pancreatitis (SMQ) were reported for 1/32 (3.1%) participant in Regimen A (Pancreatic pseudocyst) and 1/143 (0.7%) participant in Regimen D (Amylase increased).

The CHMP noted that during the Treatment Phase, AEs coding to Acute pancreatitis (SMQ) (Category A, B, and C (bedaquiline) terms) were reported for fewer participants in the BDQ-containing Regimens C and D (8.5% and 10.5% of participants, respectively) compared with the Regimens A and B (25.0% and 16.3%, respectively).

Rhabdomyolysis/Myopathy
During the Treatment Phase and during the Follow-up Phase, no AEs coding to Rhabdomyolysis/Myopathy (SMQ) were reported in any regimen (Table 47).

Severe Cutaneous Adverse Reactions
During the Treatment Phase, AEs coding to Severe cutaneous adverse reactions (SMQ) were reported for 4.5%, 4.7%, and 9.8% participants in Regimens B, C, and D, respectively, and no such events were reported in Regimen A. By PT, the most frequently reported AEs coding to this SMQ (≥2 participants in the BDQ-containing Regimens C [≥0.9%] or D [≥1.4%]) were (Table 47)

- Skin exfoliation: 1.0%, 1.9%, and 4.2% of participants in Regimens B, C and D, respectively
- Conjunctivitis: 1.0%, 2.4%, and 2.8% of participants in Regimens B, C and D, respectively
- Genital ulceration: 1.4% of participants in Regimen D

One/202 (0.5%) participant in Regimen B (comparator) was reported with an SAE of Stevens-Johnson syndrome.

The CHMP noted that no specific concerns regarding bedaquiline were raised.

Cardiac Failure and Cardiomyopathy
During the Treatment Phase, the only AE coding to Cardiac failure (SMQ) was reported for 1 (0.5%) participant in Regimen C (bedaquiline) (Cardiac failure congestive, nonserious). No events were reported coding to Cardiomyopathy (SMQ) in any regimen (Table 47). During the Follow-up Phase, there were no AEs coding to Cardiac failure (SMQ) or Cardiomyopathy (SMQ).

The CHMP noted that one participant with congestive heart failure was observed in Regimen C (bedaquiline).

Hearing Impairment Adverse Events
During the Treatment and/or Follow-up Phase, AEs related to hearing impairment, identified by the Hearing impairment sub-SMQ, were reported less frequently for participants in Regimen C (bedaquiline) (49/211 [23.2%]) compared with the injectable-containing control Regimen B (comparator) (87/202 [43.1%]) and the injectable- and BDQ-containing Regimen D (56/143 [39.2%]).

By PT, the most frequently reported AEs (≥5.0% of participants in the BDQ-containing Regimens C and/or D) were

- Deafness: 25.0%, 20.8%, 11.4%, and 21.0% in Regimens A, B, C, and D, respectively
- Tinnitus: 12.5%, 16.3%, 4.7%, and 13.3%, respectively
- Deafness unilateral: 12.5%, 10.9%, 5.7%, and 7.7%, respectively

The CHMP noted that AEs related to hearing impairment, identified by the Hearing impairment sub-SMQ, were reported less frequently for participants in Regimen C (bedaquiline) (23.2%) compared with Regimen B (comparator) (43.1%) and Regimen D (39.2%). This is a known side effect of aminoglycosides.

Lung Surgery

No participants underwent lung surgery during the study as confirmed by the Main Clinical Study Conduct Partner.

Pregnancy

During the study, a total of 37/588 (6.3%) participants reported an event of pregnancy, of which 26/37 pregnancy in participants (including 1 ectopic pregnancy) and 11/37 pregnancy in partners of participants. Pregnancies were reported as follows:

- Regimen A: 4/32 (12.5%): all 4 in participants and none in partners
- Regimen B (comparator): 11/202 (5.4%): 7 in participants and 4 in partners
- Regimen C (bedaquiline): 14/211 (6.6%): 9 in participants and 5 in partners
- Regimen D: 8/143 (5.6%): 6 in participants and 2 in partners

AE/SAE summary tables do not include actual pregnancies in participants or partners of participants, but AEs related to pregnancies, listed under the SOCs of Pregnancy, puerperium and perinatal conditions, Social circumstances, and Surgical and medical procedures.

Serious adverse event/deaths/other significant events

All SAEs During the Treatment Phase

During the Treatment Phase, at least 1 SAE (fatal or nonfatal) was reported for 7/32 (21.9%), 31/202 (15.3%), 30/211 (14.2%), and 19/143 (13.3%) participants in Regimens A, B, C, and D, respectively.

Table 48: Participants with serious adverse events in the analysis treatment phase, by body system and preferred term, safety analysis set (study TMC207TBC3007)

MedDRA System Organ Class Dictionary-derived Term	A	B	C	D
Safety Analysis Set	32	202	211	143
Any serious adverse event, n(%)	7(21.9%)	31(15.3%)	30(14.2%)	19(13.3%)
Ear and labyrinth disorders	0	5(2.5%)	3(1.4%)	6(4.2%)
Deafness	0	3(1.5%)	2(0.9%)	3(2.1%)
Deafness unilateral	0	1(0.5%)	1(0.5%)	1(0.7%)
Deafness bilateral	0	1(0.5%)	0	1(0.7%)
Hypoacusis	0	0	0	1(0.7%)
Infections and infestations	0	7(3.5%)	5(2.4%)	2(1.4%)
Pulmonary tuberculosis	0	3(1.5%)	2(0.9%)	1(0.7%)
Empyema	0	0	2(0.9%)	0
Pneumonia	0	1(0.5%)	0	1(0.7%)
Urinary tract infection	0	0	1(0.5%)	1(0.7%)
Anal abscess	0	1(0.5%)	0	0
Herpes zoster	0	1(0.5%)	0	0
Staphylococcal infection	0	1(0.5%)	0	0
Respiratory, thoracic and mediastinal disorders	0	6(3.0%)	5(2.4%)	2(1.4%)
Dyspnoea	0	3(1.5%)	1(0.5%)	0
Respiratory failure	0	1(0.5%)	2(0.9%)	0
Pneumothorax	0	0	1(0.5%)	1(0.7%)
Atelectasis	0	0	0	1(0.7%)
Chronic obstructive pulmonary disease	0	1(0.5%)	0	0
Pleural effusion	0	0	1(0.5%)	0
Respiratory distress	0	1(0.5%)	0	0
General disorders and administration site conditions	1(3.1%)	6(3.0%)	1(0.5%)	2(1.4%)
Treatment failure	0	4(2.0%)	0	1(0.7%)
Asthenia	0	1(0.5%)	0	0
Chest pain	0	0	1(0.5%)	0
Hypothermia	0	0	0	1(0.7%)
Pyrexia	1(3.1%)	0	0	0
Sudden death	0	1(0.5%)	0	0
Investigations	2(6.3%)	2(1.0%)	3(1.4%)	3(2.1%)
Blood uric acid increased	1(3.1%)	1(0.5%)	1(0.5%)	1(0.7%)
Amylase increased	0	0	0	1(0.7%)
Aspartate aminotransferase increased	1(3.1%)	0	0	0
Blood creatinine increased	0	0	0	1(0.7%)
Blood glucose increased	0	0	1(0.5%)	0
Hepatic enzyme increased	1(3.1%)	0	0	0
SARSCoV2 test positive	0	1(0.5%)	0	0
Transaminases increased	0	0	1(0.5%)	0

Table 49 Participants with serious adverse events in the analysis treatment phase, by body system and preferred term, safety analysis set (study TMC207TBC3007)

MedDRA System Organ Class Dictionary-derived Term	A	B	C	D
Gastrointestinal disorders	2(6.3%)	0	5(2.4%)	0
Vomiting	0	0	5(2.4%)	0
Pancreatic pseudocyst	1(3.1%)	0	0	0
Pancreatitis chronic	1(3.1%)	0	0	0
Hepatobiliary disorders	0	4(2.0%)	2(0.9%)	0
Hepatitis toxic	0	4(2.0%)	1(0.5%)	0
Druginduced liver injury	0	0	1(0.5%)	0
Nervous system disorders	0	1(0.5%)	1(0.5%)	3(2.1%)
Neuroglycopenia	0	0	1(0.5%)	0
Polyneuropathy	0	1(0.5%)	0	0
Seizure	0	0	0	1(0.7%)
Syncope	0	0	0	1(0.7%)
Tonic convulsion	0	0	0	1(0.7%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	2(1.0%)	2(0.9%)	0
Breast cancer	0	0	1(0.5%)	0
Hepatic neoplasm	0	1(0.5%)	0	0
Kaposis sarcoma	0	0	1(0.5%)	0
Prostate cancer	0	1(0.5%)	0	0
Surgical and medical procedures	0	0	4(1.9%)	0
Hospitalisation	0	0	2(0.9%)	0
Abortion induced	0	0	1(0.5%)	0
Genitourinary operation	0	0	1(0.5%)	0
Metabolism and nutrition disorders	0	0	1(0.5%)	2(1.4%)
Dehydration	0	0	1(0.5%)	0
Diabetic ketoacidosis	0	0	0	1(0.7%)
Hypoglycaemia	0	0	0	1(0.7%)
Social circumstances	1(3.1%)	0	1(0.5%)	1(0.7%)
Social stay hospitalisation	1(3.1%)	0	1(0.5%)	1(0.7%)
Psychiatric disorders	2(6.3%)	0	0	0
Acute psychosis	1(3.1%)	0	0	0
Depression	1(3.1%)	0	0	0
Vascular disorders	1(3.1%)	0	0	1(0.7%)
Deep vein thrombosis	1(3.1%)	0	0	0
Embolism venous	1(3.1%)	0	0	0
Hypotension	0	0	0	1(0.7%)
Cardiac disorders	0	0	1(0.5%)	0
Acute coronary syndrome	0	0	1(0.5%)	0
Musculoskeletal and connective tissue disorders	1(3.1%)	0	0	0
Muscle spasms	1(3.1%)	0	0	0
Pregnancy, puerperium and perinatal conditions	0	1(0.5%)	0	0
Abortion	0	1(0.5%)	0	0
Renal and urinary disorders	0	1(0.5%)	0	0
Urinary retention	0	1(0.5%)	0	0
Reproductive system and breast disorders	0	0	1(0.5%)	0
Bartholinitis	0	0	1(0.5%)	0

Table 50 Participants with serious adverse events in the analysis treatment phase, by body system and preferred term, safety analysis set (study TMC207TBC3007)

MedDRA System Organ Class Dictionary-derived Term	A	B	C	D
Skin and subcutaneous tissue disorders	0	1(0.5%)	0	0
Stevens-Johnson syndrome	0	1(0.5%)	0	0

Note: Participants are counted only once for any given event, regardless of the number of times they actually experienced the event.
Note: Number of participants in each regimen is used as denominator.
Note: Analysis Treatment Phase: From date of randomization to date of last dose of any anti-TB drugs (including treatment extension and/or retreatment for relapse) +7 days.
Note: AEs are coded using MedDRA v21.0.
Note: COVID-19-related AEs are coded using MedDRA v23.0.
Modified based on Attachment TSFAE04_TP

The CHMP noted that at least 1 SAE (fatal or nonfatal) was reported for 21.9%, 15.3%, 14.2%, and 13.3% of participants in Regimens A, B, C, and D, respectively. Thus, this rate was comparable between Regimens B (comparator) and C (bedaquiline).

At least 1 SAE considered related to BDQ was reported for 3/211 (1.4%) participants in Regimen C (bedaquiline) (Vomiting in 2 participants and Drug-induced liver injury in 1 participant), and 1/143 (0.7%) participant in Regimen D (Amylase increased). All were non-fatal. Vomiting and Transaminases increased are listed in section 4.8 of the SmPC, which is endorsed.

At least 1 SAE was reported for 7.4%, 9.0%, and 11.2% of participants in Regimens B, C, and D, respectively during the Follow-up Phase. No SAEs were reported in Regimen A during the Follow-up Phase. The CHMP noted that none of the SAEs were considered related to BDQ by the investigator.

Deaths

Participants who Died During the Treatment and/or Follow-up Phase

Overall, 21 participants died during the study (Treatment Phase and/or Follow-up Phase): 8/202 (4.0%) participants in Regimen B (comparator), 11/211 (5.2%) participants in Regimen C (bedaquiline), and 2/143 (1.4%) participants in Regimen D. There were no fatal AEs reported in Regimen A during the study (Table 51 and Table 52).

There were 2 cases of sudden death during the study:

- 1 case of Sudden death reported during the Treatment Phase for 1 participant in Regimen B (comparator)
- 1 case of Sudden cardiac death reported during the Follow-up Phase for 1 participant in Regimen C (bedaquiline)

In both participants, all recorded QTcF values remained <500 ms.

Table 51 Participants with fatal adverse events in the analysis treatment phase and/or follow-up phase, by body system and preferred term, safety analysis set (study TMC207TBC3007)

MedDRA System Organ Class Dictionary-derived Term	A	B	C	D
Safety Analysis Set	32	202	211	143
Any fatal adverse event, n(%)	0	8(4.0%)	11(5.2%)	2(1.4%)
Infections and infestations	0	2(1.0%)	3(1.4%)	1(0.7%)
Pulmonary tuberculosis	0	1(0.5%)	3(1.4%)	1(0.7%)
Pneumonia	0	1(0.5%)	0	0
General disorders and administration site conditions	0	2(1.0%)	1(0.5%)	1(0.7%)
Death	0	1(0.5%)	0	0
Hypothermia	0	0	0	1(0.7%)
Sudden cardiac death	0	0	1(0.5%)	0
Sudden death	0	1(0.5%)	0	0
Respiratory, thoracic and mediastinal disorders	0	2(1.0%)	2(0.9%)	0
Respiratory failure	0	1(0.5%)	2(0.9%)	0
Respiratory distress	0	1(0.5%)	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	1(0.5%)	1(0.5%)	0
Hepatic cancer	0	1(0.5%)	0	0
Lung cancer metastatic	0	0	1(0.5%)	0
Cardiac disorders	0	0	1(0.5%)	0
Acute coronary syndrome	0	0	1(0.5%)	0
Injury, poisoning and procedural complications	0	0	1(0.5%)	0
Alcohol poisoning	0	0	1(0.5%)	0
Nervous system disorders	0	0	1(0.5%)	0
Neuroglycopenia	0	0	1(0.5%)	0
Renal and urinary disorders	0	0	1(0.5%)	0
Acute kidney injury	0	0	1(0.5%)	0

Table 52 Participants with fatal adverse events in the analysis treatment phase and/or follow-up phase, by body system and preferred term, safety analysis set (study TMC207TBC3007

MedDRA System Organ Class Dictionary-derived Term	A	B	C	D
Social circumstances	0	1(0.5%)	0	0
Physical assault	0	1(0.5%)	0	0

Note: Participants are counted only once for any given event, regardless of the number of times they actually experienced the event.
Note: Number of participants in each regimen is used as denominator.
Note: Analysis Treatment Phase: From date of randomization to date of last dose of any anti-TB drugs (including treatment extension and/or retreatment for relapse) +7 days.
Note: Analysis Follow-up Phase: From end of Analysis Treatment Phase to last participant contact (scheduled or unscheduled, or other contact eg, phone call).
Note: AEs are coded using MedDRA v21.0.

Modified based on Attachment TSFAE06_TFP

Table 53 Participants with fatal adverse events in the analysis treatment phase by body system and preferred term, safety analysis set (study TMC207TBC3007

MedDRA System Organ Class Dictionary-derived Term	A	B	C	D
Safety Analysis Set	32	202	211	143
Any fatal adverse event, n(%)	0	4(2.0%)	6(2.8%)	2(1.4%)
Infections and infestations	0	1(0.5%)	2(0.9%)	1(0.7%)
Pulmonary tuberculosis	0	0	2(0.9%)	1(0.7%)
Pneumonia	0	1(0.5%)	0	0
Respiratory, thoracic and mediastinal disorders	0	2(1.0%)	2(0.9%)	0
Respiratory failure	0	1(0.5%)	2(0.9%)	0
Respiratory distress	0	1(0.5%)	0	0
General disorders and administration site conditions	0	1(0.5%)	0	1(0.7%)
Hypothermia	0	0	0	1(0.7%)
Sudden death	0	1(0.5%)	0	0
Cardiac disorders	0	0	1(0.5%)	0
Acute coronary syndrome	0	0	1(0.5%)	0
Nervous system disorders	0	0	1(0.5%)	0
Neuroglycopenia	0	0	1(0.5%)	0

Note: Participants are counted only once for any given event, regardless of the number of times they actually experienced the event.
Note: Number of participants in each regimen is used as denominator.
Note: Analysis Treatment Phase: From date of randomization to date of last dose of any anti-TB drugs (including treatment extension and/or retreatment for relapse) +7 days.
Note: AEs are coded using MedDRA v21.0.

Table 54 Participants with fatal adverse events in the analysis follow-up phase, by body system and preferred term, safety analysis set (study TMC207TBC3007

MedDRA System Organ Class Dictionary-derived Term	A	B	C	D
Safety Analysis Set	32	202	211	143
Any fatal adverse event, n(%)	0	4(2.0%)	5(2.4%)	0
General disorders and administration site conditions	0	1(0.5%)	1(0.5%)	0
Death	0	1(0.5%)	0	0

Table 55 Participants with fatal adverse events in the analysis follow-up phase, by body system and preferred term, safety analysis set (study TMC207TBC3007

MedDRA System Organ Class Dictionary-derived Term	A	B	C	D
Sudden cardiac death	0	0	1(0.5%)	0
Infections and infestations	0	1(0.5%)	1(0.5%)	0
Pulmonary tuberculosis	0	1(0.5%)	1(0.5%)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	1(0.5%)	1(0.5%)	0
Hepatic cancer	0	1(0.5%)	0	0
Lung cancer metastatic	0	0	1(0.5%)	0
Injury, poisoning and procedural complications	0	0	1(0.5%)	0
Alcohol poisoning	0	0	1(0.5%)	0
Renal and urinary disorders	0	0	1(0.5%)	0
Acute kidney injury	0	0	1(0.5%)	0
Social circumstances	0	1(0.5%)	0	0
Physical assault	0	1(0.5%)	0	0

Note: Participants are counted only once for any given event, regardless of the number of times they actually experienced the event.
Note: Number of participants in each regimen is used as denominator.
Note: Analysis Follow-up Phase: From end of Analysis Treatment Phase to last participant contact (scheduled or unscheduled, or other contact eg, phone call).
Note: AEs are coded using MedDRA v21.0.
Modified based on Attachment TSFAE06_FP

The CHMP noted that overall, 21 participants died during the study (Treatment Phase and/or Follow-up Phase) with 8/202 (4.0%) in Regimen B (comparator), 11/211 (5.2%) in Regimen C (bedaquiline), and 2/143 (1.4%) in Regimen D. No participants in Regimen A died. The rate of deaths was marginally higher in Regimen C (bedaquiline) compared to Regimen B (comparator), which was not statistically significant (p-value=0.551) with an adjusted difference in proportions of -1.2% (95% CI: -5.2%,2.8%).

The MAH is proposing to remove the warnings on mortality that were instituted in the SmPC due to uncertainties about mortality at the time of approval, given the small size of the safety database. The present expanded safety database is not indicative of any specific concern about excess deaths when bedaquiline is part of the TB treatment regimen. Therefore, the CHMP agreed with the proposal.

Laboratory findings

Summary of Individual Participant Changes

Laboratory abnormalities were graded according to severity using DAIDS criteria and in accordance with the normal ranges of the central safety laboratory for nongraded parameters. Haemoglobin toxicity grades were added programmatically.

Note that the lower number of observations in the laboratory abnormality tables can be partly explained by a high percentage of COVID-related protocol deviations defined as "scheduled lab blood safety tests samples not taken".

The majority of treatment-emergent graded laboratory abnormalities were Grade 1 (Table 56).

Table 56: Treatment-emergent graded laboratory abnormalities (Worst grade) in the analysis treatment phase; safety analysis set (Study TMC207TBC3007)

	A	B	C	D
Safety Analysis Set	32	202	211	143
Chemistry				
Alanine Aminotransferase (Enzyme U/L)				
N	32	199	207	143
Grade 1	7(21.9%)	49(24.6%)	57(27.5%)	25(17.5%)
Grade 2	0	26(13.1%)	18(8.7%)	15(10.5%)
Grade 3	1(3.1%)	12(6.0%)	12(5.8%)	7(4.9%)
Grade 4	1(3.1%)	5(2.5%)	7(3.4%)	1(0.7%)
Albumin (g/L)				
N	32	199	207	143
Grade 1	1(3.1%)	18(9.0%)	24(11.6%)	12(8.4%)
Grade 2	1(3.1%)	7(3.5%)	7(3.4%)	3(2.1%)
Grade 3	0	1(0.5%)	0	0
Grade 4	0	0	0	0
Alkaline Phosphatase (Enzyme U/L)				
N	32	199	207	143
Grade 1	1(3.1%)	13(6.5%)	12(5.8%)	8(5.6%)
Grade 2	1(3.1%)	3(1.5%)	2(1.0%)	2(1.4%)
Grade 3	0	0	0	0
Grade 4	0	0	0	0
Amylase, Pancreatic (Enzyme U/L)				
N	32	199	207	143
Grade 1	3(9.4%)	9(4.5%)	11(5.3%)	7(4.9%)
Grade 2	0	6(3.0%)	7(3.4%)	3(2.1%)
Grade 3	3(9.4%)	1(0.5%)	0	1(0.7%)
Grade 4	0	1(0.5%)	0	1(0.7%)
Aspartate Aminotransferase (Enzyme U/L)				
N	32	199	207	143
Grade 1	11(34.4%)	49(24.6%)	50(24.2%)	24(16.8%)
Grade 2	1(3.1%)	17(8.5%)	24(11.6%)	18(12.6%)
Grade 3	2(6.3%)	15(7.5%)	17(8.2%)	3(2.1%)
Grade 4	1(3.1%)	8(4.0%)	7(3.4%)	4(2.8%)

	A	B	C	D
Bicarbonate (mmol/L)				
N	32	199	207	143
Grade 1	8(25.0%)	72(36.2%)	82(39.6%)	66(46.2%)
Grade 2	2(6.3%)	36(18.1%)	26(12.6%)	20(14.0%)
Grade 3	2(6.3%)	0	1(0.5%)	1(0.7%)
Grade 4	0	0	0	0
Bilirubin (umol/L)				
N	32	199	207	143
Grade 1	0	12(6.0%)	4(1.9%)	2(1.4%)
Grade 2	2(6.3%)	9(4.5%)	2(1.0%)	1(0.7%)
Grade 3	0	0	2(1.0%)	0
Grade 4	0	0	2(1.0%)	0
Cholesterol (mmol/L)				
N	32	199	207	143
Grade 1	0	0	0	0
Grade 2	0	0	1(0.5%)	0
Grade 3	0	0	0	0
Grade 4	0	0	0	0
Creatine Kinase (Enzyme U/L)				
N	32	199	207	143
Grade 1	4(12.5%)	7(3.5%)	6(2.9%)	3(2.1%)
Grade 2	0	0	0	0
Grade 3	1(3.1%)	3(1.5%)	1(0.5%)	0
Grade 4	0	3(1.5%)	0	0
Creatinine (umol/L)				
N	32	199	207	143
Grade 1	7(21.9%)	29(14.6%)	13(6.3%)	13(9.1%)
Grade 2	2(6.3%)	15(7.5%)	2(1.0%)	2(1.4%)
Grade 3	0	3(1.5%)	1(0.5%)	2(1.4%)
Grade 4	0	1(0.5%)	0	1(0.7%)
Lipase (Enzyme U/L)				
N	32	199	207	143
Grade 1	1(3.1%)	12(6.0%)	9(4.3%)	7(4.9%)
Grade 2	3(9.4%)	8(4.0%)	7(3.4%)	3(2.1%)
Grade 3	0	2(1.0%)	0	0
Grade 4	1(3.1%)	1(0.5%)	1(0.5%)	1(0.7%)
Magnesium (mmol/L)				
N	32	199	207	143
Grade 1	9(28.1%)	78(39.2%)	78(37.7%)	50(35.0%)
Grade 2	4(12.5%)	19(9.5%)	9(4.3%)	9(6.3%)
Grade 3	1(3.1%)	3(1.5%)	1(0.5%)	0
Grade 4	0	0	0	0
Triglycerides (mmol/L)				
N	32	199	207	143
Grade 1	0	0	1(0.5%)	0
Grade 2	0	0	0	0
Grade 3	0	0	0	0
Grade 4	0	0	0	0
Urate (umol/L)				
N	32	199	207	143
Grade 1	6(18.8%)	59(29.6%)	54(26.1%)	51(35.7%)
Grade 2	6(18.8%)	44(22.1%)	44(21.3%)	32(22.4%)
Grade 3	10(31.3%)	14(7.0%)	22(10.6%)	18(12.6%)
Grade 4	3(9.4%)	4(2.0%)	5(2.4%)	1(0.7%)

	A	B	C	D
Hematology				
Hemoglobin (g/L)				
N	32	199	207	143
Grade 1	3(9.4%)	19(9.5%)	16(7.7%)	24(16.8%)
Grade 2	1(3.1%)	9(4.5%)	7(3.4%)	6(4.2%)
Grade 3	0	10(5.0%)	5(2.4%)	2(1.4%)
Grade 4	0	1(0.5%)	1(0.5%)	0
Leukocytes (10^9/L)				
N	32	198	207	143
Grade 1	1(3.1%)	5(2.5%)	3(1.4%)	3(2.1%)
Grade 2	1(3.1%)	0	2(1.0%)	0
Grade 3	0	0	0	0
Grade 4	0	0	0	0
Platelets (10^9/L)				
N	32	197	206	143
Grade 1	1(3.1%)	6(3.0%)	10(4.9%)	7(4.9%)
Grade 2	1(3.1%)	3(1.5%)	4(1.9%)	2(1.4%)
Grade 3	0	0	0	0
Grade 4	0	0	0	0

Note: Presentation based on central laboratory results only.
Note: Scheduled and unscheduled laboratory assessments are considered in this summary.
Note: N is the number of participants with at least one postbaseline value for the laboratory parameter.
Note: An abnormality is considered emergent if worse than baseline.
Note: If baseline is missing, the abnormality is always considered as emergent.
Note: Baseline is defined as the last available assessment prior to randomization.
Note: Analysis Treatment Phase: From date of randomization to date of last dose of any anti-TB drugs (including treatment extension and/or retreatment for relapse) +7 days.
Note: The toxicity grades are based on DAIDS criteria.

Modified based on Attachment TSFLAB03_TP

Table 57 Treatment-emergent graded laboratory abnormalities (high and low direction) (worst grage) in the analysis treatment phase and/or follow up phase; safety analysis set (Study TMC207TBC3007)

	A	B	C	D
Safety Analysis Set	32	202	211	143
CHEMISTRY				
Calcium (mmol/L)				
High				
N	32	199	207	143
Grade 1	1 (3.1%)	1 (0.5%)	4 (1.9%)	3 (2.1%)
Low				
N	32	199	207	143
Grade 1	6 (18.8%)	52 (26.1%)	45 (21.7%)	34 (23.8%)
Grade 2	2 (6.3%)	11 (5.5%)	9 (4.3%)	7 (4.9%)
Grade 3	1 (3.1%)	1 (0.5%)	1 (0.5%)	0

	A	B	C	D
Glucose (mmol/L)				
High				
N	32	199	207	143
Grade 1	8 (25.0%)	67 (33.7%)	70 (33.8%)	33 (23.1%)
Grade 2	2 (6.3%)	9 (4.5%)	18 (8.7%)	7 (4.9%)
Grade 3	2 (6.3%)	7 (3.5%)	9 (4.3%)	5 (3.5%)
Grade 4	0	2 (1.0%)	1 (0.5%)	0
Low				
N	32	199	207	143
Grade 1	4 (12.5%)	18 (9.0%)	28 (13.5%)	20 (14.0%)
Grade 2	1 (3.1%)	9 (4.5%)	23 (11.1%)	11 (7.7%)
Potassium (mmol/L)				
High				
N	32	199	207	143
Grade 1	1 (3.1%)	15 (7.5%)	21 (10.1%)	15 (10.5%)
Grade 2	0	2 (1.0%)	10 (4.8%)	1 (0.7%)
Grade 3	0	0	1 (0.5%)	0
Grade 4	0	0	1 (0.5%)	0
Low				
N	32	199	207	143
Grade 1	15 (46.9%)	33 (16.6%)	28 (13.5%)	21 (14.7%)
Grade 2	4 (12.5%)	3 (1.5%)	3 (1.4%)	1 (0.7%)
Grade 3	1 (3.1%)	1 (0.5%)	0	0
Sodium (mmol/L)				
High				
N	32	199	207	143
Grade 1	3 (9.4%)	23 (11.6%)	23 (11.1%)	12 (8.4%)
Grade 2	1 (3.1%)	1 (0.5%)	5 (2.4%)	2 (1.4%)
Grade 3	0	2 (1.0%)	2 (1.0%)	0
Grade 4	0	0	1 (0.5%)	0
Low				
N	32	199	207	143
Grade 1	10 (31.3%)	38 (19.1%)	38 (18.4%)	30 (21.0%)
Grade 2	2 (6.3%)	4 (2.0%)	7 (3.4%)	4 (2.8%)
Grade 3	0	3 (1.5%)	3 (1.4%)	3 (2.1%)
Grade 4	0	1 (0.5%)	0	0

Note: Presentation based on central laboratory results only.
Note: Scheduled and unscheduled laboratory assessments are considered in this summary.
Note: N is the number of participants with at least one postbaseline value for the laboratory parameter.
Note: An abnormality is considered emergent if worse than baseline.
Note: If baseline is missing, the abnormality is always considered as emergent.
Note: Baseline is defined as the last available assessment prior to randomization.
Note: Analysis Treatment Phase: From date of randomization to date of last dose of any anti-TB drugs (including treatment extension and/or retreatment for relapse) +7 days.
Note: Analysis Follow-up Phase: From end of Analysis Treatment Phase to last participant contact (scheduled or unscheduled, or other contact eg phone call).
Note: The toxicity grades are based on DAIDS criteria.

Modified based on Attachment TSFLAB9903

Table 58 Treatment-emergent nongraded laboratory abnormalities (worst grade) without grading in the DAIDs grading scale in the analysis treatment phase; safety analysis set (Study TMC207TBC3007)

	A	B	C	D
Safety Analysis Set	32	202	211	143
Chemistry				
Calcium Corrected (mmol/L)				
N	32	199	207	143
Abnormally low	6(18.8%)	45(22.6%)	31(15.0%)	24(16.8%)
Abnormally high	3(9.4%)	3(1.5%)	4(1.9%)	4(2.8%)
Chloride (mmol/L)				
N	32	199	207	143
Abnormally low	14(43.8%)	29(14.6%)	23(11.1%)	10(7.0%)
Abnormally high	1(3.1%)	19(9.5%)	17(8.2%)	6(4.2%)
Creatine Kinase MB (ug/L)				
N	32	199	207	143
Abnormally low	2(6.3%)	0	4(1.9%)	1(0.7%)
Abnormally high	4(12.5%)	17(8.5%)	6(2.9%)	6(4.2%)
Gamma-glutamyl Transferase (Enzyme U/L)				
N	32	199	207	143
Abnormally low	0	3(1.5%)	0	3(2.1%)
Abnormally high	10(31.3%)	54(27.1%)	49(23.7%)	28(19.6%)
Lactate Dehydrogenase (Enzyme U/L)				
N	32	199	207	143
Abnormally low	0	0	1(0.5%)	1(0.7%)
Abnormally high	8(25.0%)	44(22.1%)	24(11.6%)	15(10.5%)
Protein (g/L)				
N	32	199	207	143
Abnormally low	2(6.3%)	8(4.0%)	8(3.9%)	4(2.8%)
Abnormally high	11(34.4%)	38(19.1%)	23(11.1%)	13(9.1%)
Urea Nitrogen (mmol/L)				
N	32	199	207	143
Abnormally low	10(31.3%)	42(21.1%)	50(24.2%)	15(10.5%)
Abnormally high	6(18.8%)	35(17.6%)	13(6.3%)	17(11.9%)
Hematology				
Ery. Mean Corpuscular Hemoglobin (pg)				
N	32	199	207	143
Abnormally low	1(3.1%)	7(3.5%)	10(4.8%)	10(7.0%)
Abnormally high	4(12.5%)	14(7.0%)	14(6.8%)	6(4.2%)
Ery. Mean Corpuscular Volume (fL)				
N	32	199	207	143
Abnormally low	1(3.1%)	12(6.0%)	13(6.3%)	13(9.1%)
Abnormally high	8(25.0%)	33(16.6%)	39(18.8%)	17(11.9%)
Erythrocytes (10^12/L)				
N	32	199	207	143
Abnormally low	6(18.8%)	43(21.6%)	35(16.9%)	26(18.2%)
Abnormally high	5(15.6%)	7(3.5%)	16(7.7%)	18(12.6%)
Hematocrit (fraction of 1)				
N	32	199	207	143
Abnormally low	5(15.6%)	50(25.1%)	38(18.4%)	37(25.9%)
Abnormally high	3(9.4%)	11(5.5%)	11(5.3%)	6(4.2%)

	A	B	C	D

Note: Presentation based on central laboratory results only.
Note: Scheduled and unscheduled laboratory assessments are considered in this summary.
Note: N is the number of participants with at least one postbaseline value for the laboratory parameter.
Note: An abnormality is considered emergent if worse than baseline.
Note: If baseline is missing, the abnormality is always considered as emergent.
Note: Baseline is defined as the last available assessment prior to randomization.
Note: Analysis treatment phase: From date of randomization to date of last dose of any anti-TB drugs (including treatment extension and/or retreatment for relapse) +7 days.

Modified based on Attachment TSFLAB03A_TP

The CHMP noted that laboratory values were studied regarding trends over time. No meaningful differences between the regimens were observed with regard to blood count and most of the electrolytes. Two Grade 3 / 4 cases of hyperkalaemia are noted in Regimen C (bedaquiline). Furthermore, a higher rate of hyperkalaemia is noted in Regimen C (bedaquiline) compared to Regimen B (comparator) (see above in the AE section).

Disturbances in blood glucose-levels (≥ grade 2) were more prevalent in Regimen C (high: 13.5%; low: 11.1%) than Regimen B (high: 9.0%; low: 4.5%). In addition, higher rates of hyperglycaemia (8.5% vs. 3.0%) and hypoglycaemia (5.2% vs. 3.5%) and one SAE of "blood glucose increased" were reported in Regimen C during the treatment phase. Dysglycaemia, i.e. hypo- and hyperglycaemia is a known adverse drug reaction of moxifloxacin, which was part of the background regimen in Regimens B and C. Information on drug-induced blood disturbances is included in the SmPC for moxifloxacin (Avelox) including recommendations for close follow up of blood glucose levels in diabetic patients.

The MAH was requested to evaluate the possibility of a causal relationship between BDQ and adverse events of hyperkalaemia or dysglycaemia, and discuss whether bedaquiline may exacerbate moxifloxacin-induced blood glucose disturbances. This was because reports relating to these events were seen to be numerically slightly higher in Regimen C in STREAM Stage 2 versus Regimen B. However, the comparison is confounded by the administration of aminoglycosides in Regimen B, and multiple other classes of anti-TB drug in the background regimen in both arms. In fact, the totality of clinical data (including earlier completed studies against placebo) does not appear to indicate disproportionate occurrence of these events in association with BDQ. Meanwhile electrolyte disturbances and dysglycaemia are commonly reported in MDR-TB and arise secondary to underlying condition, comorbidities such as diabetes and some classes of anti-TB drug, including fluoroquinolones. The CHMP considered that there are no mechanistic reasons to suspect such off-target effects for BDQ, nor pre-clinical safety signals, and that there is no evidence to indicate a causal association between hyperkalaemia or dysglycaemia and BDQ treatment.

Otherwise, the majority of AEs linked to laboratory values were Grade 1 and the CHMP was of the view that no further clinically relevant differences between the regimens were observed in treatment-emergent graded or nongraded laboratory abnormalities or SAEs related to laboratory abnormalities.

Laboratory Parameters of Interest -Liver Function

Increases in AST or ALT

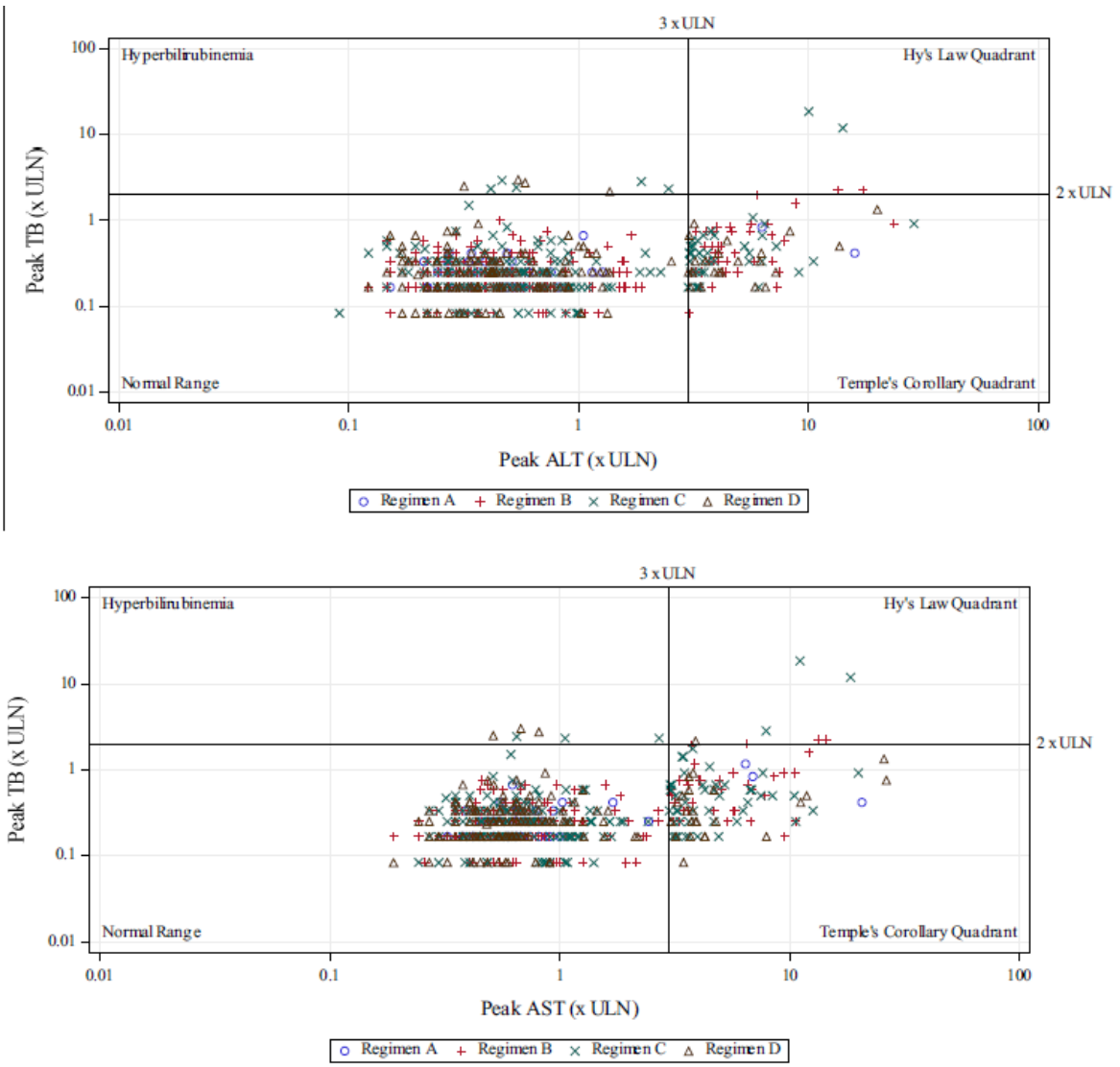
To identify participants with potential serious hepatotoxicity, eDish (electronic tool for drug-induced serious hepatotoxicity) was used, plotting peak serum ALT/AST and total bilirubin levels for each participant throughout the study in quadrants for normal range, hyperbilirubinemia, Temple's Corollary, and Hy's law.

Results of this analysis are provided in Figure 15 for AST (bottom) and ALT (top). Seven participants (3 from Regimen B (comparator), 3 from Regimen C (bedaquiline), and 1 from Regimen D)

experienced a peak AST of at least 3xULN and a peak total bilirubin of at least 2xULN (Hy's law quadrant). Four of these participants (2 from Regimen B (comparator) and 2 from Regimen C (bedaquiline)) were also plotted in the Hy's law quadrant for ALT (Figure 15).

Overall, 7 participants met the laboratory criteria for Hy's law (defined as an ALT or AST value of ≥3xULN and a corresponding total bilirubin of ≥2xULN) during the Treatment and Follow-up Phase. During the Treatment Phase, 3 (1.5%) participants in Regimen B (comparator) and 3 (1.4%) participants in Regimen C (bedaquiline) met the laboratory criteria for Hy's law.

- The event resolved in 6 participants; the event in the remaining participant (treatment related event in Regimen B (comparator)lev) was reported as ongoing/not resolved by the investigator, but the participant had a favourable outcome at Weeks 76 and 132.
- HBV infection and/or alcohol use were possible explanations in 2 participants (1 in Regimen B (comparator) and 1 in Regimen C (bedaquiline)).
- Meeting laboratory criteria for Hy's law was considered possibly treatment related following Janssen medical review (no other clinical explanation including hepatitis B or alcohol use) for 2 participants on BDQ (both in Regimen C (bedaquiline)) and 1 participant each in Regimens B_{lev} (comparator including levofloxacin) and B_{mox} (comparator including moxifloxacin). Refer to the narratives for more details on the participants on BDQ.



Key: BILI = total bilirubin, ALT = alanine aminotransferase, AST = aspartate aminotransferase
Note: Presentation based on central safety laboratory test results only.
Note: Hy's law is defined as an ALT or AST value of >=3xULN and a corresponding total bilirubin of >=2xULN.
Note: Temple's corollary is defined as al ALT or AST value of >=3xULN and no corresponding total bilirubin of >=2xULN.
Note: ALT, AST, and BILI (as relevant) from the same analysis visit window, if not matched on same date/time.
[gsflab01.rtf] [\\wilbtia\wilbtia02\JnJ JJTBC3007\Week 132 TFL w ADaM updates\TLF\GSFLAB01.sas] 28MAR2023, 8:38:16 PM

Figure 34: eDISH Plot, safety analysis set (Study TMC207TBC3007)

The CHMP noted that laboratory criteria for Temple's corollary (ALT or AST value of ≥3xULN and no corresponding total bilirubin of ≥2xULN) were met by 3 (9.4%) participants in Regimen A, 45 (22.3%) in Regimen B (comparator), 45 (21.3%) in Regimen C (bedaquiline), and 23 (16.1%) in Regimen D. Events were thus lowest in Regimen A and roughly comparable in Regimens B (comparator) and C (bedaquiline). During the Follow-up Phase, criteria were met by 0, 12 (5.9%), 23 (10.9%), and 8 (5.6%) participants, respectively.

Seven participants met the laboratory criteria for Hy's law (defined as an ALT or AST value of ≥3xULN and a corresponding total bilirubin of ≥2xULN), of which 3 were in Regimen B (comparator) and 3 in Regimen C (bedaquiline) during the Treatment Phase, and 1 in Regimen D during the Follow-up Phase (from Day 490). Thus, Regimens B (comparator) and C (bedaquiline) were comparable regarding the rate of this event.

AEs of increased transaminases are reflected in sections 4.4. and 4.8 of the SmPC, which includes information on the necessity to regularly control liver values to monitor for potential liver toxic signs in association with BDQ, which the CHMP considered to be sufficient.

Vital Signs

Individual Abnormalities in Vital Signs

Table 59: Vital Signs abnormalities (worst abnormalities) emerging in the analysis treatment phase, safety analysis set (Study TMC207TBC3007)

	A	B	C	D
Safety Analysis Set	32	202	211	143
Analysis treatment phase				
Body temperature (°C)				
N	32	198	206	143
Grade 1 or mild	3(9.4%)	2(1.0%)	2(1.0%)	3(2.1%)
Grade 2 or moderate	0	0	5(2.4%)	1(0.7%)
Grade 3 or severe	0	1(0.5%)	1(0.5%)	0
Grade 4 or potentially life-threatening	0	0	0	0
DBP (mm Hg)				
N	32	198	206	143
Abnormally Low	1(3.1%)	12(6.1%)	10(4.9%)	7(4.9%)
Grade 1 or mild	1(3.1%)	18(9.1%)	17(8.3%)	8(5.6%)
Grade 2 or moderate	1(3.1%)	4(2.0%)	6(2.9%)	3(2.1%)
Grade 3 or severe	1(3.1%)	0	1(0.5%)	0
Pulse (beats/min)				
N	32	198	206	143
Abnormally Low	2(6.3%)	5(2.5%)	6(2.9%)	2(1.4%)
Abnormally high	8(25.0%)	21(10.6%)	21(10.2%)	8(5.6%)
SBP (mm Hg)				
N	32	198	206	143
Abnormally Low	15(46.9%)	62(31.3%)	51(24.8%)	37(25.9%)
Grade 1 or mild	2(6.3%)	9(4.5%)	7(3.4%)	2(1.4%)
Grade 2 or moderate	0	4(2.0%)	4(1.9%)	0
Grade 3 or severe	1(3.1%)	0	1(0.5%)	0

Note: Scheduled and unscheduled vital signs assessments are considered in this summary.
Note: N is the number of participants with at least one postbaseline value for the vital signs parameter.
Note: An abnormality is considered emergent if worse than baseline.
Note: If baseline is missing, the abnormality is always considered as emergent.
Note: Baseline defined as the last available assessment prior to randomization.
Note: Analysis Treatment Phase: From date of randomization to date of last dose of any anti-TB drugs (including treatment extension and/or retreatment for relapse) +7 days.
Modified based on Attachment TSFVIT03

The CHMP noted that shifts in SBP, DBP and pulse rate were roughly comparable between treatment regimens. Frequencies of AEs linked to tachycardia/sinus tachycardia where only modestly different between Regimen B (comparator) and C (bedaquiline) (4.5% vs 7.1%) in the treatment phase. Pyrexia was less often observed in Regimen B (comparator) compared to the other regimens (21.9%, 10.9%, 20.4%, and 16.8% in Regimens A, B, C, and D) in the treatment phase.

Electrocardiograms

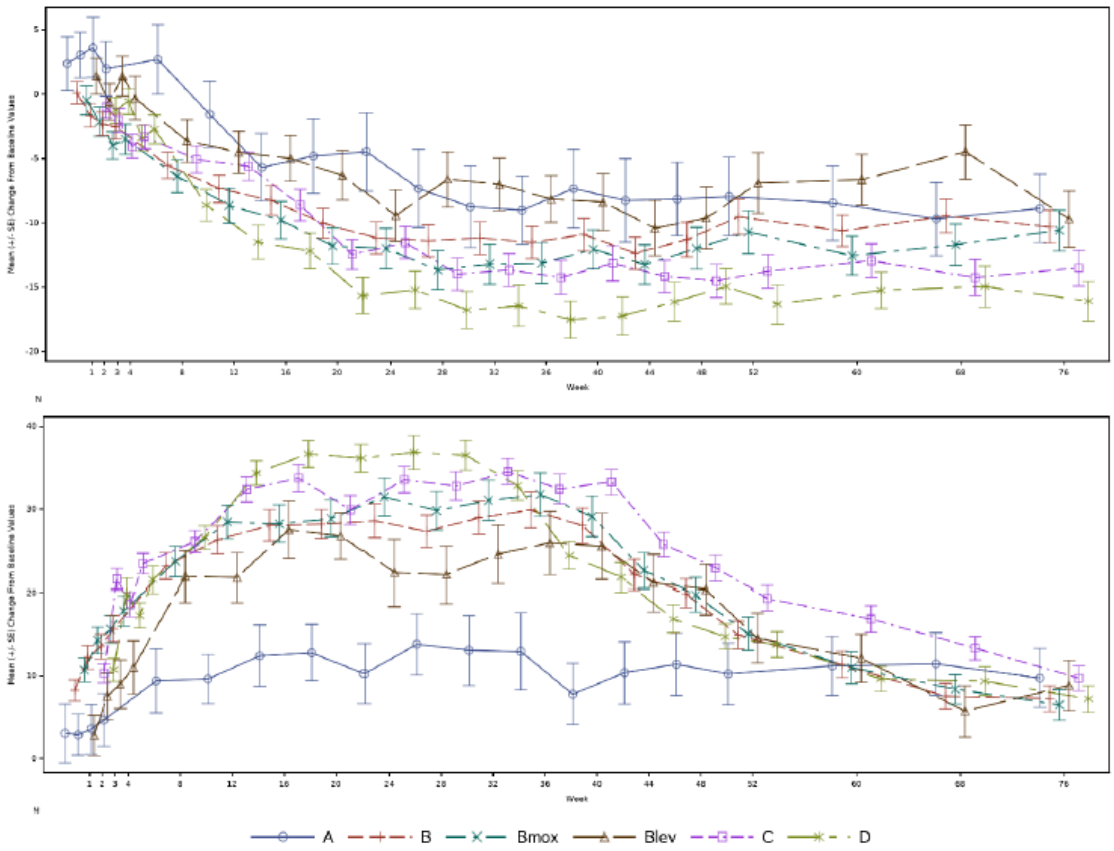
ECG Parameters Over Time

No sustained or clinically relevant changes over time were observed for mean PR duration, QRS duration, and RR duration during the study and across the different regimens.

A gradual decrease from baseline in heart rate over the first 24 weeks of treatment (4.5 bpm, 11.2 bpm, [12.0 bpm, 9.4bpm,] 11.5 bpm, and 15.2 bpm in Regimens A, B, [B_{mox}, B_{lev},] C, and D, respectively) was noted for all regimens.

Furthermore, for all regimens, the mean QTcF values gradually increased from baseline over the first 10-14 weeks, until a plateau was reached (Table 60, Figure 35). Maximum mean increases from baseline reached:

- 13.8 ms for Regimen A (Week 28)
- 29.9 ms for Regimen B (comparator) (Week 36)
- 31.8 ms for Regimen B_{mox} (comparator including moxifloxacin) (Week 36)
- 27.5 ms for Regimen B_{lev} (comparator including levofloxacin) (Week 16)
- 34.5 ms for Regimen C (bedaquiline) (Week 32)
- 36.9 ms for Regimen D (Week 24)



Key:SE=standard error, Blev=Regimen B with levofloxacin, Bmox=Regimen B with moxifloxacin.
Note: Visits: Windowed analysis visits such that only one assessment per participant per analysis visit is included in summary over time.
Note: Regimen B_{mox} participants randomized under protocol prior to v8.
Note: Regimen B_{lev} participants randomized under protocol v8 onwards.
Note: N is the number of participants with nonmissing values.
Note: Standard error is not estimable when N=1.

Modified based on Attachment GSFECG9902

Figure 35: Changes from baseline over time for heart rate (bpm) (Top) and QTcF (ms) (Bottom); safety analysis set (Study TMC207TBC3007)

Table 60: Summary of actual values and changes from baseline over time for QTcF (ms); Safety analysis set (Study TMC207TBC3007)

	A	B	Bmox	Blev	C	D
Safety Analysis Set	32	202	140	62	211	143
Baseline						
N	32	202	140	62	211	143
Mean (SD)	399.1 (24.96)	400.9 (21.72)	396.7 (20.73)	410.4 (21.10)	398.3 (20.98)	393.9 (20.12)
Week 8						
N	32	198	136	62	201	141
Mean (SD)	408.5 (29.05)	424.0 (26.31)	420.3 (25.91)	432.3 (25.51)	424.7 (24.24)	420.0 (20.69)
Mean CFB (SD)	9.4 (21.83)	23.1 (22.36)	23.7 (21.65)	21.9 (24.00)	26.1 (18.67)	26.6 (17.06)
Week 12						
N	32	195	133	62	201	142
Mean (SD)	408.8 (21.48)	427.6 (27.57)	425.5 (28.42)	432.1 (25.28)	430.9 (24.04)	427.9 (19.17)
Mean CFB (SD)	9.6 (16.72)	26.3 (23.62)	28.4 (23.66)	21.8 (23.06)	32.4 (21.86)	34.4 (17.74)

Table 61: Summary of actual values and changes from baseline over time for QTcF (ms); Safety analysis set (Study TMC207TBC3007)

	A	B	Bmox	Blev	C	D
Week 16						
N	31	195	133	62	201	141
Mean (SD)	411.4 (22.88)	428.8 (28.13)	424.5 (28.61)	437.9 (24.93)	432.4 (26.39)	430.2 (23.59)
Mean CFB (SD)	12.5 (20.69)	28.0 (26.35)	28.3 (26.07)	27.5 (27.15)	33.7 (23.67)	36.7 (18.95)
Week 24						
N	32	194	133	61	196	139
Mean (SD)	409.4 (23.73)	429.6 (30.47)	428.1 (30.27)	432.9 (30.90)	432.2 (26.31)	430.4 (24.07)
Mean CFB (SD)	10.3 (20.54)	28.6 (28.54)	31.5 (26.85)	22.4 (31.24)	33.6 (22.34)	36.9 (24.08)
Week 28						
N	31	192	130	62	197	138
Mean (SD)	413.1 (20.74)	428.3 (28.67)	426.4 (29.05)	432.5 (27.63)	431.2 (27.76)	430.0 (22.58)
Mean CFB (SD)	13.8 (20.55)	27.3 (26.92)	29.8 (26.59)	22.1 (27.07)	32.8 (24.25)	36.5 (21.13)
Week 32						
N	32	184	124	60	197	139
Mean (SD)	412.2 (24.44)	429.9 (30.13)	427.3 (32.37)	435.1 (24.28)	433.1 (24.48)	426.3 (23.95)
Mean CFB (SD)	13.1 (23.81)	28.9 (27.21)	31.1 (27.02)	24.6 (27.29)	34.5 (21.87)	32.8 (21.31)
Week 36						
N	32	182	124	58	190	136
Mean (SD)	412.1 (30.29)	430.5 (31.38)	428.1 (32.60)	435.7 (28.15)	430.7 (28.47)	417.9 (24.57)
Mean CFB (SD)	12.9 (26.29)	29.9 (29.22)	31.8 (29.24)	25.9 (29.03)	32.4 (24.68)	24.4 (19.50)
Week 40						
N	32	179	124	55	189	135
Mean (SD)	406.9 (27.30)	428.7 (30.26)	425.5 (31.46)	435.9 (26.20)	431.6 (25.56)	415.7 (24.43)
Mean CFB (SD)	7.8 (21.08)	28.0 (28.29)	29.1 (27.75)	25.5 (29.58)	33.3 (21.55)	21.8 (20.09)
Week 44						
N	32	181	125	56	183	135
Mean (SD)	409.5 (27.92)	422.5 (28.23)	418.6 (28.65)	431.3 (25.39)	424.7 (25.28)	410.7 (23.26)
Mean CFB (SD)	10.4 (21.16)	22.1 (24.38)	22.6 (23.89)	21.1 (25.63)	25.7 (20.34)	16.9 (19.11)
Week 132						
N	4	18	17	1	22	21
Mean (SD)	398.3 (10.14)	406.5 (21.13)	405.5 (21.31)	424.0 (NE)	408.9 (26.34)	398.1 (15.86)
Mean CFB (SD)	19.3 (21.12)	16.1 (19.79)	14.1 (18.56)	49.0 (NE)	21.9 (26.19)	11.0 (18.18)

Note: Visits: Windowed analysis visits such that only one assessment per participant per analysis visit is included in summary over time.
Note: Regimen Bmox participants randomized under protocol prior to v8.
Note: Regimen Blev participants randomized under protocol v8 onwards.
Note: N is the number of participants with nonmissing values.
Modified based on Attachment TSFECG01 and Attachment TSFECG02

For participants in Regimen C (bedaquiline) and Regimen D enrolled at sites that had been preselected for the PK substudy, ECG values were closely monitored at PK visits (pre-dose and 4 hours post-BDQ intake). For these participants, across all visits in the Safety Analysis Set, no relevant changes between pre-dose and 4 hours post-dose were observed for mean heart rate, mean PR duration, QRS duration, QT duration, QTcF, QTcB, and RR duration.

The CHMP noted that heart rate gradually decreased from baseline over the first 24 weeks of treatment in all regimens and to a comparable degree in Regimens B (comparator) and C (bedaquiline) (4.5 bpm, 11.2 bpm, [12.0 bpm, 9.4 bpm,], 11.5 bpm, and 15.2 bpm in Regimens A, B, [B_{mox}, B_{lev},] C, and D, respectively). The mean QTcF values gradually increased from baseline over the first 10-14 weeks, until a plateau was reached. Maximum mean increases from baseline reached with values comparable values for Regimens B (comparator) and C (bedaquiline) (29.9 ms for Regimen B (comparator) (Week 36), 31.8 ms for Regimen B_{mox} (comparator including moxifloxacin) (Week 36); 34.5 ms for Regimen C (bedaquiline) (Week 32)). Thus, the CHMP did not identify any major differences between Regimens B (comparator) and C (bedaquiline).

Individual Abnormalities in ECG Parameters

QTcF

QTcF Abnormalities in All Participants Overall

Table 62 Tabulation of worst QTcF values/change from baseline (ms) categorization in the analysis treatment phase; safety analysis set (Study TMC207TBC3007)

	A	B	Bmox	Blev	C	D
Safety Analysis Set	32	202	140	62	211	143
Worst QTcF						
N	32	202	140	62	211	143
<450	23 (71.9%)	94 (46.5%)	75 (53.6%)	19 (30.6%)	92 (43.6%)	78 (54.5%)
>=450-<480	6 (18.8%)	70 (34.7%)	41 (29.3%)	29 (46.8%)	77 (36.5%)	43 (30.1%)
>=480-<500	1 (3.1%)	23 (11.4%)	13 (9.3%)	10 (16.1%)	31 (14.7%)	17 (11.9%)
>=500	2 (6.3%)	15 (7.4%)	11 (7.9%)	4 (6.5%)	11 (5.2%)	5 (3.5%)
Worst QTcF change from baseline						
N	32	202	140	62	211	143
<30	19 (59.4%)	33 (16.3%)	23 (16.4%)	10 (16.1%)	25 (11.8%)	13 (9.1%)
>=30-<60	9 (28.1%)	95 (47.0%)	67 (47.9%)	28 (45.2%)	95 (45.0%)	74 (51.7%)
>=60	4 (12.5%)	74 (36.6%)	50 (35.7%)	24 (38.7%)	91 (43.1%)	56 (39.2%)

Note: For worst QTcF, N is the number of participants with nonmissing values.
Note: For worst QTcF change from baseline, N is the number of participants with nonmissing values at both baseline and the specified timepoint.
Note: Visits: Windowed analysis visits such that only one assessment per participant per analysis visit is included in summary over time.
Note: Worst: Highest postbaseline averaged triplicate value (scheduled or unscheduled) emerging during the Analysis Treatment Phase.
Note: Regimen B_{mox} participants randomized under protocol prior to v8.0
Note: Regimen B_{lev} participants randomized from protocol v8.0 onwards.
Note: Analysis Treatment Phase: From date of randomization to date of last dose of any anti-TB drugs (including treatment extension and/or retreatment for relapse) +7 days.
Modified based on Attachment TSFECG03_OVERALL and Attachment TSFECG04_OVERALL

The CHMP noted that the worst (highest) QTcF values ≥500 ms were observed in 6.3%, 7.4%, 5.2%, and 3.5% of participants in Regimens A, B, C, and D, respectively, and were, thus, roughly comparable between treatment group B and C (bedaquiline) (risk of first QTcF ≥500 ms: hazard ratio of 1.43 [95% CI: 0.66,3.11]). The proportion of participants with worst (highest) QTcF values ≥480 ms to<500 ms was 3.1%, 11.4%, 14.7%, and 11.9% in Regimens A, B, C, and D, respectively, and thus, also here roughly comparable between Regimen B (comparator) and Regimen C (bedaquiline). The CHMP noted that 'QT prolonged' is already included in sections 4.4. and 4.8 of the SmPC.

QTcF Abnormalities by Subgroups

By HIV status and CD4 count, overall, similar incidences in worst (highest) QTcF values and QTcF change from baseline were observed across the strata during the Treatment Phase and Follow-up Phase. Any observed differences should be interpreted with caution due to the low sample sizes for

HIV-positive participants. Note that, of the 60 HIV-positive participants in BDQ-containing Regimens C and D, 1 participant in Regimen D had a QTcF value ≥500 ms during the Treatment Phase

By sex during the Treatment Phase, the following differences between the strata were observed for Regimens B, C, and D:

- the proportion of participants with worst (highest) QTcF values ≥480 ms to <500 ms was higher in females (14/81 [17.3%], 14/79 [17.7%], and 10/59 [16.9%] in Regimens B, C, and D, respectively) compared with males (9/121 [7.4%], 17/132 [12.9%], and 7/84 [8.3%], respectively)
- the proportion of participants with worst (highest) QTcF change from baseline ≥30 ms to <60 ms was lower in females in Regimen B (comparator) (31/81 [38.3%]) and Regimen D (23/59 [39.0%]) compared with males (64/121 [52.9%] and 51/84 [60.7%], respectively)

The CHMP noted that for HIV status and CD4 count, overall, similar incidences in worst (highest) QTcF values and QTcF change from baseline were observed across the strata during the Treatment Phase and Follow-up Phase. A trend towards higher QTcF values was observed in women in all treatment regimens. It is an established fact that sex impacts the QTc interval, which is longer in females.

ECG-related and Cardiac Disorders Adverse Events

The table below lists all reported ECG-related AEs from the Investigations SOC and all AEs from the Cardiac Disorders SOC during the Treatment Phase (Table 63).

Table 63 ECG-related and Cardiac Disorders adverse events in the analysis treatment phase, by body system and preferred term; safety analysis set (Study TMC207TBC3007)

MedDRA System Organ Class Dictionary-derived Term	A	B	C	D
Safety Analysis Set	32	202	211	143
Any adverse event, n(%)	32(100%)	197(97.5%)	206(97.6%)	142(99.3%)
Investigations	22(68.8%)	156(77.2%)	172(81.5%)	110(76.9%)
Electrocardiogram QT prolonged	7(21.9%)	113(55.9%)	128(60.7%)	80(55.9%)
Electrocardiogram PR prolongation	0	0	0	1(0.7%)
Electrocardiogram PR shortened	0	0	1(0.5%)	0
Electrocardiogram ST segment elevation	0	1(0.5%)	0	0
Electrocardiogram T wave abnormal	0	0	0	1(0.7%)
Cardiac disorders	5(15.6%)	43(21.3%)	46(21.8%)	25(17.5%)
Palpitations	3(9.4%)	13(6.4%)	21(10.0%)	7(4.9%)
Bradycardia	0	9(4.5%)	5(2.4%)	4(2.8%)
Sinus tachycardia	2(6.3%)	6(3.0%)	7(3.3%)	3(2.1%)
Tachycardia	1(3.1%)	3(1.5%)	8(3.8%)	5(3.5%)
Angina pectoris	0	6(3.0%)	2(0.9%)	3(2.1%)
Sinus bradycardia	0	3(1.5%)	3(1.4%)	4(2.8%)
Arrhythmia	0	5(2.5%)	2(0.9%)	1(0.7%)
Atrioventricular block first degree	0	2(1.0%)	3(1.4%)	0
Sinus arrhythmia	0	2(1.0%)	1(0.5%)	0
Extrasystoles	0	1(0.5%)	0	1(0.7%)
Ventricular extrasystoles	0	2(1.0%)	0	0
Acute coronary syndrome	0	0	1(0.5%)	0
Arrhythmia supraventricular	0	1(0.5%)	0	0
Atrioventricular block	0	0	1(0.5%)	0
Cardiac failure congestive	0	0	1(0.5%)	0
Cyanosis	0	1(0.5%)	0	0
Myocardial infarction	0	0	0	1(0.7%)
Supraventricular extrasystoles	0	0	1(0.5%)	0

Note: Participants are counted only once for any given event, regardless of the number of times they actually experienced the event.
Note: Number of participants in each regimen is used as denominator.
Note: Analysis Treatment Phase: From date of randomization to date of last dose of any anti-TB drugs (including treatment extension and/or retreatment for relapse) +7 days.
Note: Adverse events are coded using MedDRA v21.0.
Modified based on Attachment TSFAE02_TP

Four participants with an AE of Electrocardiogram QT prolonged discontinued BDQ (3 in Regimen C (bedaquiline) and 1 in Regimen D). Together with decreasing QTcF values after treatment and the lower proportion of participants with QTcF ≥500 ms in the Follow-up Phase compared to the Treatment Phase, this illustrates the reversibility of the QTcF prolongation.

There were 2 cases of sudden death: 'Sudden death' during the Treatment Phase in 1 participant in Regimen B (comparator) and 'Sudden cardiac death' during the Follow-up Phase in 1 participant in Regimen C (bedaquiline), considered unrelated to BDQ or other anti-TB drugs in the regimen by the investigator. However, all recorded QTcF values remained <500 ms in both participants.

The CHMP noted that no AEs coding to the PT of Torsade de Pointes were reported.

Visual Acuity and Colour Tests

Visual acuity (using a Tumbling 'E' chart) and colour tests (using Ishihara colour plates) were performed at timepoints indicated in the Assessment Schedule and at other timepoints in case of symptoms.

During the Treatment Phase, there were no clinically relevant values or changes in visual acuity over time and between the different regimens. Mean values were normal and ranged between 2.4-14.0 for left eye, 2.4-22.5 for right eye across regimens. No important changes were evident between mean values at baseline vs EOT for each regimen.

During the Treatment Phase, there were no clinically relevant values or changes in colour test over time and between the different regimens. The median value ranged between 0.0 and 1.5 (range: 0 [best score] to 17 [worst score]).

The CHMP noted that during the Treatment Phase, there were no clinically relevant values or changes in visual acuity seen over time and between the different regimens.

Safety in special populations

HIV

Disposition

In the ITT Analysis Set, in the subset of HIV-positive participants, most participants completed the study. Overall, 12/97 (12.4%) participants prematurely terminated study participation before the Week 132 visit. Overall, 5 HIV-positive participants died during the study: 0/6 (0%), 4/31 (12.9%), 1/34 (2.9%), and 0/26 (0%) participants in Regimens A, B, C, and D, respectively.

HIV Viral Load

Table 64 Qualitative Summary of viral load over time in HIV+ participants on ART; Safety analysis set (study TMC207TBC3007)

	A	B	Bmox	Blev	C	D
Safety Analysis Set	32	202	140	62	211	143
Baseline						
N	2	20	16	4	22	12
<400 copies/mL	2 (100.0%)	17 (85.0%)	13 (81.3%)	4 (100.0%)	19 (86.4%)	11 (91.7%)
>=400 copies/mL	0	3 (15.0%)	3 (18.8%)	0	3 (13.6%)	1 (8.3%)
At EOT						
N	2	20	16	4	22	12
<400 copies/mL	2 (100.0%)	8 (40.0%)	6 (37.5%)	2 (50.0%)	16 (72.7%)	12 (100.0%)
>=400 copies/mL	0	6 (30.0%)	6 (37.5%)	0	6 (27.3%)	0
Not available	0	6 (30.0%)	4 (25.0%)	2 (50.0%)	0	0
Last postbaseline						
N	2	20	16	4	22	12
<400 copies/mL	2 (100.0%)	14 (70.0%)	11 (68.8%)	3 (75.0%)	20 (90.9%)	10 (83.3%)
>=400 copies/mL	0	6 (30.0%)	5 (31.3%)	1 (25.0%)	2 (9.1%)	2 (16.7%)

Note: N is the number of HIV+ participants on ART at baseline with a baseline and at least 2 postbaseline viral load assessments. Percentage was calculated relative to N.
Note: Viral load assessments below limits of quantification/detection included in <400 copies/mL category.
Modified based on Attachment TSFLAB99090NART

HIV CD4 Cell Count

For HIV-positive participants who were on ART at baseline, baseline CD4 cell count was ≥350 cells/mm³ in 1/2 (50.0%) participants in Regimen A, 12/23 (52.2%) in Regimen B (comparator), 15/24 (62.5%) in Regimen C (bedaquiline), and 8/12 (66.7%) in Regimen D.

At Week 132, the majority of HIV-positive participants on ART with available results in Regimens B (4/5 [80.0%]) and C (bedaquiline) (7/8 [87.5%]), and all (3/3 [100%]) participants with available results in Regimen D had a CD4 cell count ≥350 cells/mm³.

Adverse events

Table 65: Summary of Adverse Events by treatment and/or follow-up phase HIV+ participants; Safety analysis set (study TMC207TBC3007)

	A	B	C	D
Safety Analysis Set	6	31	34	26
Overall (analysis treatment + follow-up phase)				
Any AEs	6 (100.0%)	30 (96.8%)	34 (100.0%)	26 (100.0%)
SAEs	2 (33.3%)	11 (35.5%)	6 (17.6%)	6 (23.1%)
Treatment-related SAEs[a]	2 (33.3%)	5 (16.1%)	1 (2.9%)	4 (15.4%)
AEs leading to death[b]	0	4 (12.9%)	1 (2.9%)	0
AEs of at least Grade 3	5 (83.3%)	20 (64.5%)	18 (52.9%)	18 (69.2%)
AEs of Grade 4	2 (33.3%)	7 (22.6%)	3 (8.8%)	9 (34.6%)
SAEs leading to permanent discontinuation of BDQ	0	0	0	0
SAEs leading to permanent discontinuation of other anti-TB drugs	1 (16.7%)	2 (6.5%)	0	1 (3.8%)
Analysis treatment phase				
Any AEs	6 (100.0%)	29 (93.5%)	34 (100.0%)	26 (100.0%)
SAEs	2 (33.3%)	9 (29.0%)	6 (17.6%)	5 (19.2%)
Treatment-related SAEs[a]	2 (33.3%)	5 (16.1%)	1 (2.9%)	4 (15.4%)
AEs leading to death[b]	0	2 (6.5%)	1 (2.9%)	0
AEs of at least Grade 3	5 (83.3%)	18 (58.1%)	18 (52.9%)	15 (57.7%)
AEs of Grade 4	1 (16.7%)	6 (19.4%)	2 (5.9%)	5 (19.2%)
SAEs leading to permanent discontinuation of BDQ	0	0	0	0
SAEs leading to permanent discontinuation of other anti-TB drugs	1 (16.7%)	1 (3.2%)	0	1 (3.8%)
Analysis follow-up phase				
Any AEs	6 (100.0%)	24 (77.4%)	30 (88.2%)	24 (92.3%)
SAEs	0	3 (9.7%)	1 (2.9%)	1 (3.8%)
Treatment-related SAEs[a]	0	0	0	0
AEs leading to death[b]	0	2 (6.5%)	0	0
AEs of at least Grade 3	1 (16.7%)	5 (16.1%)	4 (11.8%)	7 (26.9%)
AEs of Grade 4	1 (16.7%)	1 (3.2%)	2 (5.9%)	5 (19.2%)

[a]SAE is categorized as related if assessed by the investigator as possibly, probably, or definitely related to study drug.
[b]AEs leading to death are based on AE outcome of fatal.
Note: Number of participants in each regimen is used as denominator.
Note: AE grades are based on DAIDS criteria.
Note: Analysis Treatment Phase: From date of randomization to date of last dose of any anti-TB drugs (including treatment extension and/or retreatment for relapse) + 7 days.
Note: Analysis Follow-up Phase: From end of Analysis Treatment Phase to last participant contact (scheduled or unscheduled, or other contact eg, phone call).
Note: A participant in Regimen C with an SAE of Vomiting had an erroneously reported action taken with BDQ of "permanent discontinuation", as reported by the investigator on CRF Form 9b (Serious Adverse Event [SAE] Report). However, it was subsequently established that this participant completed the BDQ course (see Section 3.7.8.9 for details). In addition, AEs leading to BDQ discontinuation were identified through programmatic and medical review. The identified 20 participants (see Section 5.2.2.7) do not include the aforementioned participant with an SAE of Vomiting.
Modified based on Attachment TSFAE9901hivpos

The CHMP noted that no safety concerns regarding the AE profile were observed in HIV-positive patients.

Safety related to drug-drug interactions and other interactions

Bedaquiline was safely co-administered with antiretrovirals. See also Pharmacokinetics section.

Discontinuation due to adverse events

Discontinuations of BDQ Due to AEs During the Treatment Phase

In total, 13 participants experienced at least 1 AE from the Investigations SOC in temporal association with BDQ discontinuation. One event, Amylase increased in Regimen D, was serious. None had a fatal outcome:

- Amylase increased (1 participant each in Regimens A and D)
- AST increased (3 participants in Regimen C (bedaquiline))
- Electrocardiogram QT prolonged (3 participants in Regimen C (bedaquiline) and 1 in Regimen D)
- Hepatic enzyme increased (3 participants in Regimen C (bedaquiline) and 1 in Regimen D)

Six SAEs had a fatal outcome:

- Pulmonary tuberculosis (1 participant each in Regimens C and D)
- Respiratory failure (1 participant in Regimen C (bedaquiline))
- Respiratory distress (1 participant in Reg B_{mox}; BDQ received as part of salvage regimen)
- Acute coronary syndrome (1 participant in Regimen C (bedaquiline))
- Neuroglycopenia (1 participant in Regimen C (bedaquiline))

Adverse Events Leading to Change of Regimen

AEs leading to a change in treatment regimen were reported for 14/32 (43.8%) participants in Regimen A, 73/202 (36.1%) in Regimen B (comparator), 44/211 (20.9%) in Regimen C (bedaquiline), and 27/143 (18.9%) in Regimen D (unadjusted analysis). The adjusted proportion of participants with a change in treatment regimen due to AEs was notably lower in Regimen C (bedaquiline) (20.8%) compared with Regimen B (comparator) (36.2%), with an adjusted difference in proportions of 15.3% (95% CI: 6.8%,23.9%).

A change in treatment regimen was preceded by an SAE in 4/32 (12.5%), 13/202 (6.4%), 8/211 (3.8%), and 4/143 (2.8%) participants in Regimens A, B, C, and D, respectively.

For the following secondary comparisons, notable differences in the adjusted proportion of participants with a change in treatment regimen due to AEs were observed:

- Lower proportion in Regimen D vs Regimen B (comparator)*: 27/143 (19.0%) vs 48/140 (34.3%); adjusted difference in proportions of 15.4% (95% CI: 5.2%,25.5%)
- Lower proportion in Regimen C (bedaquiline)* vs Regimen B_{mox} (comparator including moxifloxacin): 28/144 (19.4%) vs 48/140 (34.3%); adjusted difference in proportions of 14.8% (95% CI: 4.7%,25.0%)
- Lower proportion in Regimen C (bedaquiline)* vs Regimen B_{lev} (comparator including levofloxacin): 16/67 (23.9%) vs 25/62 (40.3%); adjusted difference in proportions of 16.4% (95% CI: 0.5%,32.4%)

Post-marketing experience

Based on the total distribution of 15,082 kg of finished product from launch to 31 May 2023, the estimated cumulative post-marketing exposure to BDQ is 802,993 completed treatment courses.

2.5.1. Discussion on clinical safety

The Safety Analysis Set included all randomised participants (588) who had received at least 1 dose of treatment. Safety data were collected up to the end of the study (i.e., Week 132 or discontinued earlier) for all participants.

Almost all participants reported an AE during the treatment in all treatment arms and 37.5%, 68.8%, 71.1%, and 84.6% in the four study arms reported AEs during the follow up phase, AE frequencies were, thus, comparable between study arm B (comparator) and C (bedaquiline).

The most frequent PTs were QT prolongation, nausea, vomiting, arthralgia, pruritus and blood uric acid increases. Regimen B (comparator) and C (bedaquiline) where roughly comparable regarding frequencies in most of the mentioned PTs.

Frequencies of some PTs not previously identified as ADRs for BDQ were numerically slightly higher in Regimen C (bedaquiline) as compared to B. The MAH was asked to further discuss the possibility of a causal relationship between any of hyperkalaemia, dysglycaemia, skin discoloration, rash, and pruritis with BDQ. The totality of pre-clinical and clinical data for bedaquiline indicates neither disproportionate occurrence of such events in association with BDQ nor any reason to suspect a causal relationship**.** In summary, no new safety issues were identified.

The rate of AEs of at least Grade 3 was similar across regimens (62.5%, 51.0%, 53.1%, and 49.7% in Regimens A, B, C and D, respectively) with similar adjusted proportions between Regimen B (comparator) and Regimen C (bedaquiline) (adjusted difference in proportions: -2.0% [95% CI: -11.5%,7.5%]).

21.9%, 15.3%, 14.2%, and 13.3% of participants in Regimens A, B, C, and D, respectively, reported SAEs. Rates were, thus, roughly comparable between regimen B (comparator) and C (bedaquiline) and lower than in Regimen A. SAEs considered related to BDQ were in Regimen C (bedaquiline) Vomiting in 2 participants and Drug-induced liver injury in 1 participant. These terms are reflected in sections 4.4 and 4.8 of the SmPC.

At least one serious AESI was reported for 2/32 (6.3%), 6/202 (3.0%), 3/211 (1.4%), and 2/143 (1.4%) participants, respectively. There were no detected cases of torsade des pointes. QT prolongation is a well characterised side effect that is already reflected in sections 4.4 and 4.8 of the SmPC, which is considered sufficient.

Seven participants met the laboratory criteria for Hy's law (defined as an ALT or AST value of ≥3xULN and a corresponding total bilirubin of ≥2xULN), of which 3 were in Regimen B (comparator) and 3 in Regimen C (bedaquiline) during the Treatment Phase, and 1 in Regimen D during the Follow-up Phase (from Day 490). Thus, Regimen B (comparator) and C (bedaquiline) were comparable regarding the rate of this event. The possibility for liver toxic events and the possibility of elevated transaminases is adequately reflected in sections 4.4 and 4.8 of the SmPC. Data do not raise any new concerns.

The mean maximal QT prolongation in study arm C, which is the treatment regimen relevant for labelling, was 34.5 ms. This is due to the sum effect of several drugs increasing the QT interval. This risk is well known and subject to monitoring as per sections 4.4 and 4.8 of the SmPC. The study results do not raise any new concerns.

97 HIV-positive participants were included into the study, for whom concomitant ART was allowed. The mortality rate in HIV-positive participants was low and comparable to that in the overall study population. Similar incidences in worst (highest) QTcF values and QTcF change from baseline were

observed across the strata during the Treatment Phase and Follow-up Phase as for non-infected patients.

Overall, 21 participants died during the study with 8/202 (4.0%) in Regimen B (comparator), 11/211 (5.2%) in Regimen C (bedaquiline), and 2/143 (1.4%) in Regimen D. No participants did in Regimen A. The difference in the fatal rate between Regimen B (comparator) and C (bedaquiline) was statistically not significant (p-value=0.551), with an adjusted difference in proportions of -1.2% (95% CI: -5.2%,2.8%). The patterns of death / causes of death do not raise any specific safety concerns.

The MAH proposed to remove the warnings on mortality that were instituted in the SmPC. This was due to uncertainties about mortality at the time of approval, given the small size of the safety database. The present expanded safety database is not indicative of any specific concern about excess deaths when bedaquiline is part of the TB treatment regimen. Therefore, the MAH proposal is acceptable.

2.5.2. Conclusions on clinical safety

The STREAM Stage 2 study forms a considerable addition to the overall safety database for BDQ. The relevant BDQ containing regimen without an aminoglycoside, was similarly tolerated as regimens not comprising BDQ. Overall, mortality was roughly similar. No new safety concerns are raised.

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. Risk management plan

The MAH submitted a revised RMP version 10.2 with this application. The (main) proposed RMP changes are the following:

Details of this RMP Submission	
Version Number	10.2
Rationale for submitting an updated RMP:	This EU-RMP is updated to align the indication with the Summary of Product Characteristics (SmPC). In addition, due to the completion of the STREAM Stage 2 trial, this has been removed as an additional pharmacovigilance activity and as a post-authorisation efficacy study. Based on the data from this trial and cumulative evidence, all important potential risks and missing information have been removed.
Summary of significant changes in this RMP:	Update of the indication to align with the SmPC. <u>Safety concerns</u> Update of clinical trial exposure to include data from the STREAM Stage 2 trial. Removal of the following from the list of safety concerns: • Important potential risks: 'Severe hepatotoxicity', 'Pancreatitis', 'Myopathy', and 'Myocardial injury'.

	• Missing information: 'Long-term effects of bedaquiline treatment on mortality', 'Use in patients using potent inhibitors of drug metabolising enzymes', and 'Prolonged treatment duration'. • Electrocardiogram QT prolonged • Increased transaminases <u>Pharmacovigilance Plan</u> Removal of the completed STREAM Stage 2 trial. <u>Post-authorisation efficacy plan</u> Removal of the completed STREAM Stage 2 trial as a Specific Obligation.

Specifically, the list of safety concerns is updated from:

Table SVIII.1:Summary of Safety Concerns

Important Identified Risks	Electrocardiogram QT prolonged
	Increased transaminases
Important Potential Risks	Severe hepatotoxicity
	Pancreatitis
	Myopathy
	Myocardial injury
Missing Information	Long-term effects of bedaquiline treatment on mortality
	Use in patients using potent inhibitors of drug-metabolising enzymes
	Prolonged treatment duration

To:

Table SVIII.1:Summary of Safety Concerns

Important Identified Risks	None
Important Potential Risks	None
Missing Information	None

The suggested changes to the RMP are acceptable.

2.7. Overall conclusion on the RMP

The changes to the RMP and the changes to the conditions and obligations of the marketing authorisation are acceptable. The CHMP endorsed the Risk Management Plan version 10.2.

2.8. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.5, 4.8, 4.9, 5.1, 5.2 and 5.3 of the SmPC have been updated. The Labelling and the Package Leaflet have been updated accordingly. In addition, section E of Annex II has also been updated to reflect fulfilment of the last outstanding

Specific Obligation. Furthermore, the PI is brought in line with the latest QRD template version 10.3.

2.8.1. 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 changes to the package leaflet are minimal and do not require user consultation with target patient groups.

2.8.2. Additional monitoring

Pursuant to Article 23(3) of Regulation No (EU) 726/2004, Sirturo (bedaquiline) is removed from the additional monitoring list as more than five years have passed after the Union reference date and all specific obligations have been fulfilled.

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

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

In 2021, TB caused an estimated 1.4 million deaths among HIV-negative people and an additional 187,000 deaths among HIV-positive people. In 2021, the estimated proportion of people with TB who had RR/MDR-TB was 3.6% among new cases and 18% among those previously treated.

3.1.2. Available therapies and unmet medical need

Sirturo is presently approved for patients with multi-drug resistant TB that cannot constitute an effective treatment regimen with other agents.

By MDR-TB is meant tuberculosis resistant to the two key front-line agents, rifampicin and isoniazid. RR-TB means TB resistant only to rifampicin.

Treatment guidelines for MDR-TB have evolved substantially in the past 2 decades to include fewer drugs per regimen, relatively shorter (6-9 month versus ≥18 month) regimens and injectable-sparing regimens (all-oral regimens) due to the comparatively problematic safety profile (most notably the risk of irreversible hearing loss) and cumbersome administrative regimen of aminoglycosides.

Currently, BDQ is recommended by WHO as part of first-line regimens in rifampicin resistant (RR) and MDR-TB, including the 6-month all-oral BPaLM or BPaL regimen as well as 9-month or longer treatment regimens. Thus, the treatment community has already embraced Sirturo for the presently sought extension of indication, which covers all TB resistant to both rifampicin and isoniazid.

3.1.3. Main clinical studies

The STREAM Stage 2 was a Phase III, open-label, multicentre, active-controlled, randomised trial conducted to evaluate the efficacy and safety of Sirturo co-administered with other oral anti-TB drugs for 40 weeks in patients with sputum smear-positive pulmonary TB caused by M. tuberculosis that was resistant to at least rifampicin, but not second-line injectable agents or fluoroquinolones.

Thus, the study population contained patients with RR and MDR-TB, but not pre-XDR or XDR TB, where there is also resistance to fluoroquinolones and possibly also other agents.

This study was subject to multiple protocol amendments. Ultimately the key comparison was between bedaquiline for 40 weeks (group B) versus 16 weeks of an aminoglycoside (kanamycin or amikacin) (group C) within the framework of the so-called Bangladesh regimen:

- Group B (N=202), a 40-week control treatment of moxifloxacin or levofloxacin, clofazimine, ethambutol, pyrazinamide, supplemented by injectable kanamycin, high-dose isoniazid, and prothionamide in the first 16 weeks (intensive phase)
- Group C (N=211), a 40-week, all-oral treatment of bedaquiline, levofloxacin, clofazimine, ethambutol, and pyrazinamide, supplemented by high-dose isoniazid and prothionamide in the first 16 weeks (intensive phase)

The primary efficacy outcome measure was the proportion of patients with a favourable outcome at Week 76. A favourable outcome at Week 76 was defined as last 2 consecutive cultures negative and no unfavourable outcome. An unfavourable outcome at Week 76 encompassed clinically relevant changes in treatment, all-cause mortality, at least 1 of the last 2 culture results positive, or no culture results within the Week 76 window.

3.2. Favourable effects

In the primary mITT population, approximately 75% of patients were classified as MDR-TB (resistant to rifampicin and isoniazid) whereas 15% had RR-TB only resistant to rifampicin among key agents.

In this population, the proportion of participants with a favourable outcome in Group C (bedaquiline) (82.4%) was statistically superiority to that in Group B (aminoglycoside) (71.4%) at Week 76 (p=0.004).

The observed difference being almost entirely driven by fewer changes in (including extension or restart of) treatment regimen amongst participants in group C.

Further, in the mITT Analysis Set, the adjusted difference in proportions of participants with a favourable outcome at Week 132 between Regimen B (comparator) (69.2%) and Regimen C (bedaquiline) (78.2%) was -9.0% (95% CI: -17.5%, -0.6%).

In the subgroup of HIV-positive participants, the observed proportions of participants with a favourable outcome were 9/25 (36.0%) at both Weeks 76 and 132 in Regimen B (comparator) and 26/27 (96.3%) and 25/27 (92.6%) at Weeks 76 and 132, respectively, in Regimen C (bedaquiline). The reasons for unfavourable outcome at Week 76 amongst HIV-positive participants in Regimen B (comparator) were generally dominated by treatment regimen changes adding a second-line oral anti-TB drug (linezolid or bedaquiline)

The proportion of patients (mITT) with culture conversion at end of treatment was 90.8% in arm B and 95.5% in arm C. At week 76 microbiological response rates were 93.3% and 98.9% in arms B and C, respectively.

Median time to culture conversion (conversion status maintained) was 8.0 weeks (4.29 – 8.14) in Regimen B (comparator) and 4.1 weeks (4.14 – 4.43) in Regimen C (bedaquiline).

3.3. Uncertainties and limitations about favourable effects

The STREAM Stage 2 study protocol went through several major amendments while the study was open and enrolling, mostly in response to the changing clinical landscape and revisions to international treatment guidelines, to cease enrolment into Regimens A and D. The sample size was recalculated twice during the course of the open-label study.

Since there is no basis for an M1 (the contribution of aminoglycosides to sum regimen efficacy is not well defined), the study does not isolate the numerical contribution of bedaquiline to regimen efficacy. However, the results seen could not reasonably have been achieved with only the background regimen devoid of an aminoglycoside.

Other uncertainties arise due to the open-label set-up and the freedom to adjust individual treatment regimens at the discretion of the local investigator, rather than according to pre-specified criteria.

3.4. Unfavourable effects

The Safety Analysis Set included all randomised participants (588) who had received at least 1 dose of treatment. Safety data were collected up to the end of the study (i.e., Week 132 or discontinued earlier) for all participants.

Almost all participants reported an AE during the treatment in all treatment arms. The rate of AEs of at least Grade 3 was similar across regimens (51.0% and 53.1% in Regimens B and C)

15.3% and 14.2% of participants in Regimens B and C, respectively, reported SAEs.

The most frequent PTs were QT prolongation, nausea, vomiting, arthralgia, pruritus and blood uric acid increases. Regimen B (comparator) and C (bedaquiline) where roughly comparable regarding frequencies in most of the mentioned PTs (see the Effects Table 66).

Seven participants met the laboratory criteria for Hy's law (defined as an ALT or AST value of ≥3xULN and a corresponding total bilirubin of ≥2xULN), of which 3 were in Regimen B (comparator) and 3 in Regimen C (bedaquiline) during the Treatment Phase.

The mean maximal QT prolongation in study arm C, which is the treatment regimen relevant for labelling, was 34.5 ms. This is due to the sum effect of several drugs increasing the QT interval.

97 HIV-positive participants were included into the study, for whom concomitant ART was allowed. The mortality rate in HIV-positive participants was low and comparable to that in the overall study population. Similar incidences in worst (highest) QTcF values and QTcF change from baseline were observed across the strata during the Treatment Phase and Follow-up Phase as for non-infected patients.

Overall, 21 participants died during the study with 8/202 (4.0%) in Regimen B (comparator), 11/211 (5.2%) in Regimen C (bedaquiline). The difference in the fatal rate between Regimen B (comparator) and C (bedaquiline) was statistically not significant (p-value=0.551), with an adjusted difference in proportions of -1.2% (95% CI: -5.2%,2.8%).

3.5. Uncertainties and limitations about unfavourable effects

Overall, the study confirms the known adverse event profile of bedaquiline, with most of the reported side effects already being reflected in the product information.

3.6. Effects Table

Table 66: Effects Table for SIRUTO in the treatment of MDR-TB as part of a multi-drug regimen:

Effect	Short description	Treatment	Control	Uncertainties / Strength of evidence	References
Main favourable Effects (mITT population)					
Proportion with **favourable outcome**, Week 76 (*Primary analysis*)	**Favourable:** last 2 consecutive culture results negative. **Unfavourable:** death, regimen change, missing result.	**Regimen C (bedaquiline)** 82.4%	**Regimen B (comparator)** 71.4% -11.0% (-19.0% to -2.9%)	p-value NI <0.001 p-value sup. 0.004 Difference driven by changes in regimen (rather than positive culture result) in unblinded study with regimen changes permitted.	2.4.1.3.6. Outcomes and estimation Summary of clinical efficacy
Proportion with **culture conversion**, End of Treatment (*Secondary analysis*)	Last 2 consecutive negative cultures (collected at 2 separate visits assigned to separate analysis visits)	90.8% (85.6% - 94.3%)	95.5% (91.4% - 97.7%)		
Proportion with **culture conversion**, Weeks 76 (*Secondary analysis*)		93.2% (88.5% - 96.1%)	98.8% (96.0% - 99.7%)		
Median time to **culture conversion**		8.0 weeks (4.29 – 8.14 weeks	4.1 weeks (4.14 – 4.43 weeks)		
Unfavourable Effects					
QT prolongation	SMQ	**Regimen C (bedaquiline)** 60,7%	**Regimen B (comparator)** 56,4%	Already included in in section 4.8 of the SmPC	**Error! Reference source not found.**Clinical safety Summary of clinical safety
increase in transaminases	Preferred Term ALAT ASAT Hepatic enzyme increased Transaminases increased	 17,5% 19.0% 8.5% 1.4%	 19.8% 17.8% 4.5% 1.0%		
Nausea	PT	62.9%	54.0%		
Vomiting	PT	53.6%	61.9%		
Arthralgia	PT	44.5%	33.2%		
Myalgia	PT	4.3%	1.5%		
Hyperkalaemia	PT	5.2%	1.0%	Based on AE frequencies presented for Regimens C and B. Skin discoloration attributable to clofazimine (CFZ). No disproportionate occurrence in association with BDQ across totality of	
Rash	PT	13.3%	7.4%		
Pruritus	PT	26.5%	19.8%		
Skin discoloration	PT	9.0%	3.0%		
Hyperglycaemia	PT	8.5	3.0		
Hypoglycaemia	PT	5.2	3.5		

Effect	Short description	Treatment	Control	Uncertainties / Strength of evidence	References
				clinical data, nor grounds to suspect causal relationship with BDQ.	

Abbreviations: PT= Preferred Term, SMQ= Standardized MedDRA Query.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

At the time of approval, the main evidence for the efficacy of bedaquiline in the treatment of *M. tuberculosis* infection derived from the C208 study, in which patients with MDR- or pre-XDR pulmonary TB were randomised to receive bedaquiline or placebo as add on to an optimised background regimen.

This study clearly demonstrated the antimicrobial activity of bedaquiline, with a shorter time to sputum conversion and an increased cure rate.

However, the safety database was limited. There was a numerical excess in mortality in the bedaquiline arm, as well as concerns related to QT-prolongation and the impact of an increase in exposure, e.g., due to DDI with antiretrovirals.

This rendered an indication for patients with TB at least resistant to rifampicin and isoniazid, and who needed bedaquiline to compose an effective treatment regimen, due to intolerability or resistance to other agents.

Data were deemed non-comprehensive, and a CMA was instituted. The MAH was required to provide "additional efficacy and safety data" in comparison to a regimen not containing bedaquiline. The STREAM Stage 2 study was assigned as the specific obligation.

Due to an evolving treatment landscape, the open-label STREAM Stage 2 study underwent key protocol changes while underway. While this study is not a paradigm of methodological stringency, the reasons for key amendments are understood, and data considered interpretable in their regulatory and clinical context.

Ultimately, the key analysis was a comparison of bedaquiline as a substitute for the injectable aminoglycoside in the so-called Bangladesh regimen, in patients with rifampicin resistant, isoniazid susceptible, or MDR-TB. The primary objective of the study was to assess whether the proportion of participants with a favourable clinical efficacy outcome at Week 76.

The study had a non-inferiority design, with a 10% NIM. This is not based on the retention of a certain fraction of the efficacy of the aminoglycoside (a robust basis for an M1 is not available). Rather, it should be interpreted as representing an equivalence margin with respect to the usefulness of a regimen where oral bedaquiline replaces the aminoglycoside. This was accepted by the CHMP, since the antimicrobial efficacy of bedaquiline was not in doubt.

In the STREAM Stage 2 study, the time to sputum conversion was shorter in the bedaquiline arm. Moreover, the proportion of patients with culture conversion at week 76 was above 90% in the mITT population in both arms, with higher estimates in the bedaquiline arm. Thus, the antimicrobial efficacy of bedaquiline has been corroborated.

The study demonstrated statistical "non-inferiority" of the bedaquiline based regimen, as well as superiority with respect to "favourable clinical outcome", which was the primary endpoint. Superiority was driven by patients classified as having changed their allocated study intervention, which was more frequent in the control arm. While this was obviously not uninformed by treatment allocation, it reflects rational preferences with respect to adverse effects and convenience, as well as, possibly, lower antimicrobial efficacy of aminoglycosides compared to bedaquiline.

While STREAM Stage 2 was an open label study undergoing key protocol amendments, it is considered to have delivered evidence of the efficacy of the bedaquiline-based regimen in patients with MDR-TB. This is presently recommended by the WHO. Thus, efficacy data support the proposed extension of indication to all patients with TB that is resistant to at least both rifampicin and isoniazid.

However, deficiencies such as an unjustified NI margin, and superiority driven by patient management (change of treatment regimen) in an open label study, implies that it is not appropriate to accept a claim of statistical superiority or non-inferiority in section 5.1 of the SmPC. Rather, the nominal results in each arm should be presented.

With regards to safety, the study provides a randomised comparison of bedaquiline and aminoglycoside safety. Overall, the comparative safety profile here may be considered favourable. Qualitatively no new safety signals for bedaquiline were seen. The known safety issues, including hepatotoxicity and QT-prolongation were shown to be clinically manageable. Moreover, the study as provided more data to support the concomitant use of bedaquiline and standard antiretroviral treatment regimens.

Mortality rates were 8/202 (4.0%) in the aminoglycoside arm, and 11/211 (5.2%) in the bedaquiline arm. Most deaths were deemed likely due to tuberculosis. These data are reassuring with respect to concerns due to a numerical imbalance in deaths in the C208 study that was pivotal to conditional approval. These data, as well as the cumulative experience of bedaquiline use as followed per PSUR's, support the removal of the SmPC warnings of an "unexplained imbalance in deaths" in the small study that supported the initial approval of bedaquiline.

In summary, data from STREAM Stage 2 have addressed the outstanding uncertainties at the time of the granting of the conditional marketing authorisation. Data for Sirturo are now considered comprehensive, supporting the switch to a standard marketing authorisation no longer subject to specific obligations. Moreover, data support the MAH's proposed extension of indication to cover patients with pulmonary TB resistant to at least rifampicin and isoniazid.

3.7.2. Balance of benefits and risks

The demonstrated positive effects of bedaquiline as a treatment option for MDR-TB are considered to outweigh the negative effects.

3.7.3. Additional considerations on the benefit-risk balance

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

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

Description	Due date
The MAH will evaluate additional efficacy and safety data of bedaquiline in different treatment regimen compared to a regimen that does not include bedaquiline (confirmatory Phase III study) following an agreed protocol.	• Annual updates on study progress in the frame of annual renewal submissions • Final analysis - Clinical Study Report 4Q 2023

The MAH therefore took the opportunity of present type II variation to request the removal the outstanding specific obligation and the granting of a marketing authorisation in accordance with Article 14(1) of Regulation (EC) No 726/2004 ('marketing authorisation not subject to specific obligations').

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

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

3.8. Conclusions

The overall benefit-risk of Sirturo in the indication '*use as part of an appropriate combination regimen in adult and paediatric patients (5 years to less than 18 years of age and weighing at least 15 kg) with pulmonary tuberculosis (TB) due to Mycobacterium tuberculosis resistant to at least rifampicin and isoniazid*' is considered positive. The proposed changes to the product information are accepted.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends 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 - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II, IIIA and IIIB

Extension of indication (by removing the restriction limiting the use of Sirturo for patients for whom an effective treatment regimen cannot otherwise be composed for reasons of resistance or tolerability)

based on final results from study STREAM Stage 2; a multicentre, open-label, parallel-group, randomised, active-controlled study in participants aged 15 years or older with RR/MDR-TB to evaluate an investigational BDQ-containing, all-oral, 40-week regimen of anti-TB drugs (Regimen C) compared to an injectable-containing 40-week control regimen (Regimen B). Submission of the study fulfils SOB 007. As a consequence, sections 2, 4.1, 4.2, 4.4, 4.5, 4.8, 4.9, 5.1, 5.2 and 5.3 of the SmPC are updated. The Labelling and Package Leaflet are updated in accordance. A revised RMP version 10.2 has been approved. Furthermore, the PI is brought in line with the latest QRD template version 10.3.

The CHMP, having considered the application and having reviewed the data submitted by the marketing authorisation holder including the evidence concerning compliance with specific obligations, is of the opinion that the available data is comprehensive and supports the favourable benefit-risk balance of Sirturo, and that all specific obligations laid down in Annex II have been fulfilled.

Amendments to the marketing authorisation

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

The following specific obligation has been fulfilled and is therefore deleted from the Annex II to the Opinion:

Description	Due date
The MAH will evaluate additional efficacy and safety data of bedaquiline in different treatment regimen compared to a regimen that does not include bedaquiline (confirmatory Phase III study) following an agreed protocol.	• Annual updates on study progress in the frame of annual renewal submissions • Final analysis - Clinical Study Report 4Q 2023

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk management plan (RMP)

The Marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

In addition, an updated RMP should be submitted:

At the request of the European Medicines Agency;

Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0470/2022 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

Similarity with orphan medicinal products authorised at the start of the procedure

Sirturo was removed from the European Community (EC) register for orphan designated medicinal products on 7 March 2024.

The CHMP maintains by consensus its opinion that Sirturo is not similar to Deltyba, Dovprela and Granupas 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 'Product Name-H-C-Product Number-II-0056'