24 July 2025
EMADOC-1700519818-2277028
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Invented name: Sirturo

International non-proprietary name: Bedaquiline

Procedure No. EMA/VR/0000249065

Marketing Authorisation Holder (MAH): Janssen Cilag International

Note

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands

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List of abbreviations

Abbreviation	Description of abbreviated term
AE	adverse event
AESI	adverse event of special interest
AFB	acid-fast bacilli
ALT	alanine aminotransferase
AM	amikacin
AR	adverse reaction
AST	aspartate aminotransferase
ATP	adenosine 5'-triphosphate
AUC_{168h}	area under the plasma concentration-time curve from time of administration to 168 hours (total of 3 doses)
AUC_{xh}	area under the plasma concentration-time curve from the time of dose administration up to *x* hours postdose
BDLLfx	bedaquiline, delamanid, linezolid, and levofloxacin
BDLLfxC	bedaquiline, delamanid, linezolid, levofloxacin, and clofazimine
BDQ	bedaquiline
BLLfxCZ	bedaquiline, linezolid, levofloxacin, clofazimine, and pyrazinamide
BLMZ	bedaquiline, linezolid, moxifloxacin, and pyrazinamide
BPaL	bedaquiline, pretomanid, and linezolid
BPaLM	bedaquiline, pretomanid, linezolid, and moxifloxacin
BR	background regimen
BW	body weight
CFZ	clofazimine
CM	capreomycin
CS	cycloserine
CSR	clinical study report
CXR	chest X-ray
CYP	cytochrome P450
DBP	diastolic blood pressure
DLM	delamanid
DR	drug resistant
DS	drug susceptible
DST	drug susceptibility testing
ECG	electrocardiogram
EMA	European Medicines Agency
EU	European Union
GM	geometric mean
HIV	human immunodeficiency virus
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
INH	isoniazid
IQR	interquartile range
ITT	intention-to-treat
KM	kanamycin
LFX	levofloxacin

LOAEL	lowest-observed-adverse-effect-level
LZD	linezolid
M. tuberculosis	*Mycobacterium tuberculosis*
M2	*N*-monodesmethyl metabolite of BDQ
MDR	multidrug resistant
MedDRA	Medical Dictionary for Regulatory Activities
MGIT	Mycobacteria Growth Indicator Tube
MIC	minimal inhibitory concentration
mITT	modified intention-to-treat
NOAEL	no-observed-adverse-effect-level
Pa	pretomanid
PIP	Pediatric Investigation Plan
PK	pharmacokinetic(s)
popPK	population pharmacokinetics
pre-XDR	pre-extensively drug-resistant
PZA	pyrazinamide
qd	once daily
QTc	QT corrected
RMP	rifampicin
RR	rifampicin resistant
SAE	serious adverse event
SBP	systolic blood pressure
SMQ	Standard MedDRA Queries
STREAM	Standardized Treatment Regimen of Anti-TB drugs for patients with MDR-TB
TB	tuberculosis
TEAE	treatment-emergent adverse event
tiw	three times per week
ULN	upper limit of normal
US	United States
WHO	World Health Organization
XDR	extensively drug-resistant

Definition of terms

AFB smear	A positive AFB smear indicates a possible mycobacterial infection. However, a culture and identification of the grown isolate must be performed to confirm a diagnosis.
AFB-evaluable participant	Participant identified as MGIT-evaluable and who in addition has a positive AFB smear result at baseline (or screening if baseline is missing/negative) and at least one postbaseline AFB smear result available.
Baseline BR	Defined as all BR anti-TB drugs that the participant is taking during the interval from first intake of BDQ +14 days after the first intake.
BDQ Treatment Phase	For safety and TB treatment outcome analyses, defined for each participant as the period from the first BDQ intake to the last BDQ intake +1 week.
Clinical (microbiology) sample	Expectorated sputum, gastric aspirates, nasopharyngeal aspirates, oral swabs or other respiratory (e.g., hypertonic saline induced sputum) and non-respiratory samples (e.g., lymph node aspiration, stool specimens, urine sample) that allow diagnosis of TB in children.
Confirmed AFB smear conversion	For AFB-evaluable participant: defined as two consecutive negative AFB smears (sputum or other clinical sample) at least 25 days apart and with the last AFB smear sample collected within the analysis visit window of interest (Week 24/Week 120). All intermediate AFB smears must be negative as well (intermittent missing smear results are not taken into account).
Confirmed culture conversion	For MGIT-evaluable participant: defined as 2 consecutive negative MGIT cultures (sputum or other clinical sample) at least 25 days apart and with the last MGIT culture result within the analysis visit window of interest (Week 24/Week 120). All intermediate MGIT cultures must be negative as well (intermittent missing/contaminated cultures are not taken into account).
Confirmed MDR-TB	Defined as clinical evidence of TB disease (i.e., at least one of the following signs or symptoms: persistent cough, weight loss, or failure to thrive, persistent unexplained fever, night sweats, persistent unexplained lethargy or reduced playfulness, enlarged lymph node, or the presence of any of the following in the neonate: pneumonia, unexplained hepatosplenomegaly, or sepsis-like illness; imaging [e.g., CXR, CT scan, ultrasound] or other assessment [e.g., immunological] results consistent with pulmonary or non-severe extrapulmonary TB disease); together with the detection of *M. tuberculosis* (either by culture or molecular probe) from a specimen collected up to 6 months prior to screening from the child with demonstration of genotypic (e.g., GeneXpert) or phenotypic resistance to at least RMP.
Discontinuation	3 types are defined: 1. Discontinuation of study drug (e.g., due to toxicity): participant can continue the BR and study procedures. 2. Discontinuation of study drug and study procedures: participant is followed-up for survival until 120 weeks postbaseline. 3. Withdrawal from the study: participant discontinues the study (including survival follow-up) prematurely, withdrawal of consent/assent.
DST	Used to determine the level of susceptibility or resistance of a *M. tuberculosis* isolate to an anti-TB drug. Results are reported as MIC (quantitative assessment; expressed as value in µg/mL) or as susceptible/resistant (qualitative assessment) to a critical concentration or based on the presence of mutations in the *pncA* gene known to cause resistance for PZA.
Favorable treatment outcome at Week 24 (Study TMC207-C211)	For analysis purposes, participant is classified as having a favorable treatment outcome at Week 24 if: Completed TB treatment (=24 weeks of BDQ): For the Week 24 analysis, participant is considered as having completed TB treatment if that participant does not prematurely and permanently discontinue BDQ treatment within the 24-week BDQ Treatment Phase AND The investigator's overall global assessment of TB (i.e., overall assessment of TB based on signs and symptoms and radiological improvement according to Consensus Statement [Seddon 2013]) at Week 24 has a result of "resolved" AND For confirmed and MGIT-evaluable MDR-TB participant, in addition, the participant has to meet microbiological criteria as defined per protocol.

Follow-up Phase	Defined for each participant as the period after completion of TB treatment BDQ + BR) starting from the end of the Overall Treatment Phase +1 day, up to study completion or discontinuation.
ITT analysis set	Includes all participants, regardless of their compliance with the protocol, who have at least 1 administration of BDQ.
Loading dose	BDQ 8 mg/kg qd for the first 2 weeks of BDQ treatment in Cohort 3.
Maintenance dose	BDQ 4 mg/kg tiw following 2 weeks of loading dose (qd) for the remaining 22 weeks of BDQ treatment in Cohort 3.
MDR-TB	TB due to infection with a strain of *M. tuberculosis* that is resistant to at least RMP and INH.
$MDR\text{-}TB_{H\&R}$	MDR-TB excluding pre-XDR- and XDR-TB.
MGIT-evaluable participant	Participant diagnosed with confirmed MDR-TB at screening and who has a positive MGIT culture at baseline (or screening if baseline is missing/ contaminated/negative) and at least one postbaseline MGIT culture result.
mITT analysis set	Subset of the ITT analysis set excluding those participants who do not have confirmed or probable MDR-TB.
Overall Treatment Phase (BDQ + BR)	For safety and TB treatment outcome analyses, defined for each participant as the period from the first BDQ intake to the last intake of any drug in the treatment regimen +1 week. The Overall Treatment Phase encompasses the BDQ Treatment Phase.
Phase 2b studies	Completed Phase 2b studies TMC207-C208 Stage 2 and TMC207-C209 in adult participants with MDR-TB.
Pre-XDR-TB	TB due to infection with a MDR strain of M. tuberculosis that is resistant either to at least one of the injectable second-line drugs (AM, KM, and CM) or to any fluoroquinolone, but not both.
Probable MDR-TB	Probable (clinically diagnosed) MDR-TB disease is defined as clinical evidence of TB disease (i.e., at least 1 of the signs or symptoms suggestive of TB disease, imaging or other assessment results consistent with pulmonary or non-severe extrapulmonary TB disease) AND eligible for MDR-TB treatment in accordance with local standard of care AND documented exposure to a source case with pulmonary MDR-TB based on a standardized questionnaire.
RR-TB	TB due to infection with a strain of *M. tuberculosis* that is resistant to at least RMP and susceptible to INH or INH DST is missing.
Source case	A person with contagious microbiologically confirmed pulmonary MDR-TB is considered a source case when meeting the criteria specified in the protocol.
Study drug	BDQ or TMC207.
Sustained clinical cure	Defined as having a favorable treatment outcome at Week 24 AND at Week 120 (or last visit for participants prematurely discontinuing study participation [=endpoint]).
TEAE	AE with onset after first administration of BDQ or that is a consequence of a pre-existing condition that has worsened since baseline.
Treatment-emergent definition for toxicity graded or non-graded abnormality	An abnormality (toxicity graded or non-graded abnormality based on normal [reference] ranges) is considered treatment-emergent if it is worse than the baseline abnormality. If the baseline abnormality is missing, the abnormality is always considered as treatment-emergent. A shift from "abnormally low" at baseline to "abnormally high" postbaseline (or vice versa) is also considered treatment-emergent.
Time to MGIT culture conversion	Calculated as the interval in days from the first administration of BDQ to the sputum or other clinical sampling date of the first of the 2 consecutive negative MGIT culture results collected at least 25 days apart.
XDR-TB	TB due to infection with an MDR strain of *M. tuberculosis* that is resistant to at least one of the injectable anti-TB drugs (AM, KM, and CM) as well as to any fluoroquinolone.

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 04 February 2025 an application for a variation.

The following variation was requested:

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

Extension of indication to include treatment of paediatric patients (2 years to less than 5 years of age and weighing at least 7 kg) with pulmonary tuberculosis (TB) due to Mycobacterium tuberculosis resistant to at least rifampicin and isoniazid, for SIRTURO, based on the Week 24 primary analysis from Cohort 3 (≥2 to <5 years of age) of Study TMC207-C211; this is an open-label, multicentre, single-arm study to evaluate pharmacokinetics, safety/tolerability, antimycobacterial activity and dose selection of bedaquiline in children (birth to <18 years) with multidrug-resistant-TB (MDR-TB). Long-term follow-up to Week 120 in participants of Cohort 1 (≥12 to <18 years of age) and Cohort 2 (≥5 to <12 years of age) have also been submitted. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 11.1 of the RMP has also been submitted. In addition, the Marketing authorisation holder (MAH) took the opportunity to update the list of local representatives in the Package Leaflet and introduce minor changes to the PI.

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

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision EMA/PE/0000181219 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP EMA/PE/0000181219 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

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

Scientific advice

The MAH did not seek Scientific Advice 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: Not applicable

Timetable	Actual dates
Submission date	04 February 2025
Start of procedure:	22 February 2025
Joint CHMP / PRAC Rapporteur's preliminary assessment report circulated on:	15 April 2025
PRAC outcome	08 May 2025
Joint Rapporteur's updated assessment report circulated on:	15 May 2025
Request for supplementary information on:	22 May 2025
MAH's responses submitted to the CHMP on:	10 June 2025
Joint Rapporteur's preliminary assessment report on the MAH's responses circulated on:	08 July 2025
Joint Rapporteur's updated assessment report on the MAH's responses circulated on:	17 July 2025
CHMP opinion:	24 July 2025

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

Tuberculosis (TB), an infectious disease caused by *Mycobacterium tuberculosis*, is a significant cause of morbidity and mortality worldwide. During more recent years the burden of TB resistant to first line therapy has increased rapidly and TB resistant to multiple anti-mycobacterial agents is now increasingly reported in all regions of the world. The incidence of rifampicin-resistant TB (RR-TB) and multi-drug-resistant TB (MDR-TB) 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.

State the claimed the therapeutic indication

This application is intended to broaden the currently approved indication for bedaquiline (BDQ) to include the paediatric patient population aged ≥2 to <5 years and to provide dosing recommendations for paediatric patients weighing ≥7 to <15 kg.

Epidemiology and risk factors, screening tools/prevention

An estimated 7.5 million children and adolescents aged <15 years become infected every year. Drug resistant TB remains a public health threat, with an estimated 25,000 to 32,000 children worldwide who develop RR/MDR-TB every year.

Clinical presentation, diagnosis and prognosis

Childhood TB disease is also often accompanied by or confused with important co-morbid conditions that may be reported as the primary illness or primary cause (e.g., acute bacterial pneumonia, HIV-related disease such as Pneumocystis carinii pneumonia, lymphoid interstitial pneumonia, or wasting, malnutrition, bacterial or viral meningitis). Estimated case-fatality ratios for MDR-TB in untreated children aged 0 to <5 years and children aged ≥5 to <15 years are 43.6% and 14.9%, respectively (Jenkins, 2017).

Late detection or difficulty establishing the diagnosis of TB is more common in younger children and occurs due to several factors: young children usually have paucibacillary TB which may not be detectable by available bacteriological tests; lack of a sensitive point-of-care diagnostic test; difficulties in collecting suitable respiratory samples for bacteriological confirmation; and misdiagnosis due to the overlap of nonspecific symptoms of TB with other common childhood diseases.

Management

The principles of MDR/XDR-TB treatment regimens used in children are similar to those of adults and the second-line treatments are generally used. RR/MDR-TB is treatable and curable by using second-line treatment but can be fatal without treatment. Second line treatment options, moreover, are often more toxic and expensive than first-line treatments used to treat drug susceptible (DS)-TB.

For patients aged ≥14 years with RR/MDR-TB without previous exposure to BDQ, pretomanid (Pa), and linezolid (LZD), the 2022 WHO guidelines (WHO Operational Handbook on TB Module 5 2022; Appendix 1) prioritize a 6-month BPaLM (bedaquiline, pretomanid, linezolid, and moxifloxacin) regimen for treatment of RR/MDR-TB.

In 2024, WHO recommended a new 6-month BDLLfxC (bedaquiline, delamanid, linezolid, levofloxacin, and clofazimine) regimen that expands the use of a 6-month regimen to adolescents and children of all ages with RR/MDR-TB without previous exposure to BDQ, delamanid (DLM), and LZD. The regimen may be initiated without delay in case of unknown fluoroquinolone (FQ) resistance at time of diagnosis and then continued with or without either levofloxacin (LFX) or clofazimine (CFZ) depending on FQ drug susceptible testing (DST) results.

Additional 9-month regimens are recommended by WHO as alternatives to longer (18-month) regimens in patients of all ages with RR/MDR-TB without previous exposure to BDQ, DLM, and LZD (defined as >1-month exposure) and in whom resistance to FQ has been excluded (WHO Rapid Communication for DR-TB 2024): BLMZ (bedaquiline, linezolid, moxifloxacin, and pyrazinamide), BLLfxCZ (bedaquiline, linezolid, levofloxacin, clofazimine, and pyrazinamide), and BDLLfxZ (bedaquiline, linezolid, levofloxacin, and pyrazinamide)).

The current WHO recommendation for the use of BDQ in children <6 years of age is conditional (very low certainty of evidence) and was based on preliminary data from Study P1108 (IMPAACT; n=12 for this age category).

The cumulative number of children aged 0 to 14 years with RR/MDR-TB who were reported as being enrolled on treatment from 2018 to 2022 was 21,600, only 19% of the 5-year target of 115,000 (WHO Global TB Report 2023).

2.1.2. About the product

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*) in adults and paediatric patients (5 years to less than 18 years of age and weighing at least 15 kg).

BDQ is marketed under the tradename Sirturo and is approved in more than 70 countries/territories worldwide.

BDQ 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 treatments. In vitro testing has shown bactericidal activity against 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.

There are two approved tablet formulations, a 100 mg strength approved for adults and children from 12 years of age and a 20 mg strength approved for children from 5 years of age.

The latter can be used for children from 2 years of age (≥7 to <15 kg). The 20 mg tablets are uncoated, white to almost white oblong tablet (12.0 mm long x 5.7 mm wide), with score line on both sides. The 20 mg strength contains the excipients silicified microcrystalline cellulose 147 mg, crospovidone 12.0 mg, colloidal anhydrous silica 6.0 mg, hypromellose 7.0 mg, polysorbate 20 0.04 mg and sodium stearyl fumarate 4.0 mg. The excipients are commonly used, and no safety issues are foreseen when used in children from 2 years of age.

The 20 mg tablets can be divided into two equal doses and for those not able to swallow the tablets whole/or divided it is possible to disperse them in water prior to administration with food. It is also possible to crush and mix the tablets with food to facilitate administration. Finally, the tablets can be administered via a feeding tube. These administration possibilities have already been approved for children from 5 years of age and are considered acceptable also for children from 2 years of age. The proposed handling to facility the administration of the tablets is sufficiently described in the product information.

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).

The study conducted in support of the sought paediatric extension (ongoing Phase 2, open label, single-arm Study TMC207-C211) was conducted in alignment with the agreed Paediatric Investigation Plan (EMA/PE/0000181219).

The MAH previously received CHMP Scientific Advice on aspects of the adult clinical development programme. The MAH does not indicate that any central or national Scientific Advice has been received specific to the paediatric development.

2.1.4. General comments on compliance with GCP

The MAH stated in the submission that the ongoing paediatric Phase 2 Study TMC207-C211 (conducted in the Philippines and South Africa) is conducted and reported in accordance with the ethical principles originating in the Declaration of Helsinki and in accordance with ICH GCP guidelines, applicable regulatory requirements, and in compliance with the respective protocols.

2.2. Non-clinical aspects

2.2.1. Introduction

The provided addendum to the non-clinical overview includes safety margins, but it does not include the overview of established non-clinical toxicity profiles. Some of the discussion below is based on the initial MAA for Sirturo.

2.2.2. Toxicology

The overview provides novel animal-to-human toxicological exposure margin estimates for BDQ and the major metabolite M2 (based on pharmacokinetic data from treated children ≥2 to <5 years of age). The following exposure margins were recalculated (refer also to the clinical PK section):

Species	Study Type (Study No.)	NOAEL / LOAEL Dose (mg/kg/day)	BDQ								M2							
			C_{max} (µg/mL)		AUC_{0-24h} (µg.h/mL)		C_{max} Animal/Human Ratio		AUC Animal/Human Ratio		C_{max} (µg/mL)		AUC_{0-24h} (µg.h/mL)		C_{max} Animal/Human Ratio		AUC Animal/Human Ratio	
			M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F
Rat	Repeat-dose juvenile toxicity (Mod4.2.3.5.4/TMC207-NC119 Study Report)	15 (NOAEL)	1.17	2.46	13.1	35.6	0.3	0.7	0.3	0.7	0.55	0.75	10.5	16.3	1.1	1.4	1.0	1.5
Rat	26-week repeat-dose toxicity (Mod4.2.3.2/TMC207-NC109 Study Report)	5 (LOAEL)	0.69	1.0	6.62	16.8	0.2	0.3	0.1	0.4	0.27	0.49	5.07	8.85	0.5	0.9	0.5	0.8
Dog	39-week repeat-dose toxicity (Mod4.2.3.2/TMC207-NC111 Study Report)	2 (NOAEL)	1.58	1.20	27.9	21.3	0.4	0.3	0.6	0.4	0.56	0.65	11.7	13.3	1.1	1.3	1.1	1.3
Human	Cohort 3[a] (Mod5.3.3.2/TMC207-C211 W24 Cohort 3 CSR)	NA	3.69		47.8		NA		NA		0.52		10.6		NA		NA	

2.2.3. Ecotoxicity/environmental risk assessment

An ERA for bedaquiline in line with the 2024 CHMP ERA GL was provided (including a secondary poisoning assessment which gave a RQ of 0.048x). While BDQ is not an environmental risk based on PEC/PNEC estimations (PECsw based on refined value of 0.006 ug/L, risk quotients or RQ or RCR < 1), it is a PBT substance. This is also noted in SmPC sections 5.3 and 6.6.

2.2.4. Discussion on non-clinical aspects

Non-clinical studies show that BDQ and M2 are medium to strong inducers of phospholipidosis in preclinical species at exposure levels not much in excess of expected clinical. Phospholipidosis or

phospholipidosis-like changes (e.g., microvacuolation, foamy macrophages, histiocytosis, swollen macrophages, histiocytic infiltrates) were reported in liver (rat, dog), skeletal muscle (rat), lung (mouse, rat, dog), spleen (dog), kidney (mouse), pancreas (mouse) and thymus (dog). Data from in vitro studies using human monocyte cell-line indicated that the phospholipidogenic potential was highest for the M2 metabolite followed by M3 and the parent compound. The relation of phospholipidosis, toxicity and impairment of organ function is not clear. Other BDQ and M2 non-clinical toxicity outcomes are degenerative changes (fundic glands) and necrosis in stomach (mouse, dog), degenerative, necrotic changes in striated muscles and heart (rat, dog), hypertrophy follicular epithelium in thyroid (rat), granulocytic infiltrates and necrosis of corpora lutea (rat), tubular atrophy in testes (dog), conjunctivitis and corneal opacities plus intolerance to bright light at high doses (dog), and renal basophilia/nephropathy (rat). The apparent very high potential for BDQ and M2 to accumulate in tissues/organs may also be a confounding factor when considering long term effects.

Assessment of paediatric data on non-clinical aspects

Safety margins were calculated for juvenile repeat-dose in rat with NOAEL 15 mg/kg/day, 39-week (9-month) repeat-dose dog with NOAEL at 2 mg/kg/day, and the lowest dose of 5 mg/kg/day in the 26-week (6-month) repeat-dose rat study. The exposure margins to human (child) Cmax and AUC levels were low: ranging from 0.1 to 0.7 for BDQ and 0.5 to 1.5 for M2 (refer also to the clinical PK section).

2.2.5. Conclusion on the non-clinical aspects

The provided non-clinical overview indicates that there are no animal-to-human exposure margins for the various toxic effects found in the toxicological studies. Among the known non-clinical toxic effects, there are none that emerge as a novel concern as compared to the previous approved age indications.

Considering the above data, bedaquiline is not expected to pose a risk to the environment.

2.3. Clinical aspects

2.3.1. Introduction

This application is intended to support the broadening of the currently approved indication for BDQ to include the paediatric patient population aged ≥2 to <5 years, based on the Week 24 primary analysis from Cohort 3 (≥2 to <5 years of age) of Study TMC207-C211 (data cut-off date of 09 May 2024), including subjects aged ≥2 to ≤5 years with confirmed or probably pulmonary MDR-TB, and to provide dosage recommendations for paediatric patients weighing ≥7 to <15 kg. This analysis was performed when the last of 15 participants enrolled in Cohort 3 had reached Week 24 or discontinued prematurely.

Furthermore, long-term follow-up to Week 120 in participants of Cohort 1 (≥12 to <18 years of age) and Cohort 2 (≥5 to <12 years of age) is completed and relevant safety and TB treatment outcome results are included. In addition, a literature review on BDQ use in paediatrics is provided.

The paediatric study TMC207-C211 is an open-label, multi-centre, single-arm, ongoing phase II study in children and adolescents 0 months to <18 years of age (in 4 different age cohorts). The primary objectives are to evaluate the safety and tolerability of bedaquiline over a 24-week treatment period in each age cohort and the PK of BDQ to provide guidance on dose selection for each of the age cohorts evaluated in this study.

GCP

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

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

2.3.2. Pharmacokinetics

The already approved age-appropriate 20 mg bedaquiline scored tablet formulation (G008) is intended to be used in paediatric patients (2 to under 18 years) weighing ≥7 kg.

The data from Cohort 3 of the paediatric study TMC207-C211 (week 24 data) is included in *Table 1* below.

Table 1 Tabulated Overview of Studies Included supporting the Use of Bedaquiline in paediatric subjects with Confirmed or Probable Multidrug-resistant Tuberculosis Infection

Type of Study	Study ID	Population	Number of Participants[a]	Dosage	Status
Phase 2					
Phase 2	TMC207-C211 (Cohort 1)	MDR-TB infected adolescents (≥12 to <18 years)	15	400 mg qd for 2 weeks, followed by 200 mg tiw for 22 weeks	Completed
	TMC207-C211 (Cohort 2)	MDR-TB infected children (≥5 to <12 years)	15	200 mg qd for 2 weeks, followed by 100 mg tiw for 22 weeks	Completed
	TMC207-C211 (Cohort 3, **new**)	MDR-TB infected children (≥2 to <5 years)	15	80 to 120 mg qd for 2 weeks, followed by 40 to 60 mg tiw for 22 weeks	Ongoing (primary Week 24 analysis complete)

BDQ=bedaquiline; ID=identifier; MDR-TB=multidrug-resistant tuberculosis; PK=pharmacokinetic(s); qd=once daily; RR/MDR-TB=rifampicin-resistant or multidrug-resistant tuberculosis; tiw=3 times per week.

a Participants who received BDQ and had evaluable PK samples.

Bioanalytical Methods

The bioanalytical method was not changed for the analysis of the PK samples collected in Cohort 3 compared to the previous cohort (i.e. method BA10946, procedure EMEA/H/C/002614/X/0036/G).

Target population

The PK in the target population was described using non-compartmental analysis and PopPK analysis with data from Cohort 3. 15 children ≥2 to <5 years received BDQ at a weight-based dosage (8 mg/kg once daily for 2 weeks followed by 4 mg/kg tiw for 22 weeks [rounded up or down to the closest 10-mg unit]). BDQ was administered as the commercial, age-appropriate 20-mg scored tablet (G008).

Blood samples for the determination of BDQ and M2 concentrations in plasma were collected throughout the 24-week open-label BDQ treatment phase. PK parameters were derived using non-compartmental methods for BDQ and M2 at Weeks 2 and 12. Week 12 and 24 data were used mainly for popPK analyses. PK parameters, including AUC168h, for BDQ were determined using NLME models.

Non-compartmental analysis

Methods

Individual PK parameters were determined using NCA for bedaquiline and M2. Cmax, Cmin, Tmax, and AUC24h were reported at Weeks 2 and 12, for all participants with valid PK observations. Additionally, AUC0-last, and Tlast were reported at Week 12. Cmin, Tmin, and t1/2 were reported at Week 24, for all participants with valid PK observations. These exposure metrics were tabulated with summary statistics.

Results

In Cohort 3, NCA-based PK parameters of BDQ and M2 were obtained at the end of the loading phase (Week 2) and during the maintenance phase (Week 12) (see Table 2 and Table 3).

Table 2 PK of BDQ in Cohort 3 (Children With MDR-TB, ⩾2 to <5 Years) (Study TMC207-C211)

	Mean±SD; t_{max}: Median (Range)		
Cohort 3: Children (≥2 to <5 Years)	**BDQ 8 mg/kg qd +BR Week 2 (Day 14) Loading Phase**	**BDQ 4 mg/kg tiw +BR Week 12 Maintenance Phase**	**BDQ 4 mg/kg tiw +BR Week 24 Maintenance Phase**
n	15[a]	15[b]	15[c]
t_{max}, h	6 (0-8)	6 (2-24)	-[d]
C_{min}, ng/mL	863±395	486±161	530±227
C_{max}, ng/mL	3,690±2,640	1,810±872	-[d]
AUC_{24h}, ng.h/mL	47,800±27,000	26,700±7,270	-[d]
$t_{1/2}$, h	-	-	2,020±654

AUC24h=area under the plasma concentration-time curve up to 24 hours postdose; BDQ=bedaquiline; BR=background regimen; Cmax=maximum plasma concentration; Cmin=minimum plasma concentration; MDR-TB=multidrug-resistant tuberculosis; N=number of participants; n=maximum number of participants with data; PK=pharmacokinetic(s); qd=once daily; tiw=3 times per week; SD=standard deviation; t1/2=elimination half-life; tmax=time to reach the maximum plasma concentration.

Note: Parameter values rounded to nearest whole number.

a N=14 for AUC24h.

b N=10 for AUC24h.

c N=11 for t1/2.

d At Week 24 only a trough sample (Cmin) was drawn. For calculation of BDQ exposure (AUC) at Week 24, population PK analysis was used

Table 3 PK of M2 in Cohort 3 (Children With MDR-TB, ⩾2 to <5 Years) (Study TMC207-C211)

	Mean±SD; t_{max}: Median (Range)		
Cohort 3: Children (≥2 to <5 Years)	**BDQ 8 mg/kg qd +BR Week 2 (Day 14) Loading Phase**	**BDQ 4 mg/kg tiw +BR Week 12 Maintenance Phase**	**BDQ 4 mg/kg tiw +BR Week 24 Maintenance Phase**
n	15[a]	15[b]	15
t_{max}, h	4 (0-8)	4 (0-24)	-[c]
C_{min}, ng/mL	313±113	146±47	155±77
C_{max}, ng/mL	516±235	228±84	-[c]
AUC_{24h}, ng.h/mL	10,600±4,690	4,480±1,410	-[c]

AUC24h=area under the plasma concentration-time curve up to 24 hours postdose; BDQ=bedaquiline; BR=background regimen; Cmax=maximum plasma concentration; Cmin=minimum plasma concentration; M2=N-monodesmethyl bedaquiline; MDR-TB=multidrug-resistant tuberculosis; N=number of participants; n=maximum number of participants with data; PK=pharmacokinetic(s); qd=once daily; tiw=3 times per week; SD=standard deviation; tmax=time to reach the maximum plasma concentration.

Note: Parameter values rounded to nearest whole number.

a N=14 for AUC24h.

b N=10 for AUC24h.

c At Week 24 only a trough sample (Cmin) was drawn.

The key PK parameters were:

- Week 2: mean BDQ AUC24h and Cmax of 47,800 ng.h/mL and 3,690 ng/mL, respectively, and mean M2 AUC24h and Cmax of 10,600 ng.h/mL and 516 ng/mL, respectively.
- Week 12: mean BDQ AUC24h and Cmax of 26,700 ng.h/mL and 1,810 ng/mL, respectively, and mean M2 AUC24h and Cmax of 4,480 ng.h/mL and 228 ng/mL, respectively.

Similar to the trend observed in the adult population and the previous cohorts in paediatrics, the mean AUC24h and Cmax for BDQ and M2 in children ≥2 to <5 years, at the per-protocol dose, were higher at the end of the loading phase compared to the maintenance phase. The BDQ AUC24h at Week 2 was 47,800 ng.h/mL versus 26,700 ng.h/mL at Week 12 and Cmax at Week 2 was 3,690 ng/mL versus 1,810 ng/mL at Week 12. For M2, AUC24h and Cmax at Week 2 were 10,600 ng.h/mL and 516 ng/mL, respectively, versus 4,480 ng.h/mL and 228 ng/mL, respectively, at Week 12.

Compared to adults in the Phase 3 STREAM Stage 2 study (who received a loading dose of 400 mg once daily for 2 weeks), BDQ mean AUC24h and Cmax in children ≥2 to <5 years were 1.15 and 1.21-fold higher, respectively, at Week 2. During the maintenance phase (Week 12), BDQ Cmax was 1.05-fold higher in children ≥2 to <5 years compared to adults in STREAM Stage 2.

Population pharmacokinetic analysis

A model-based analysis of BDQ and M2 was performed based on all available concentration data from the 15 children enrolled in Cohort 3.

Objectives

The objectives of the analysis were to:

- Validate the existing BDQ-M2 parent-metabolite model for children aged ≥2 to <5 years (Cohort 3) to confirm the suitability of the model to derive the model-based exposure metrics and support the dose selection.
- Determine the BDQ and M2 exposure metrics from the observed data in paediatric participants enrolled in Cohort 3 of Study TMC207-C211 and compare these with adult exposure metrics.

- Simulate BDQ and M2 exposures for a weight-banded dosage in the paediatric TB population weighing ≥7 to <15 kg and determine a dosage for the label resulting in similar exposure to those observed in adults at the recommended dosage (400 mg QD for the first 2 weeks, followed by 200 mg TIW for 22 weeks), i.e., the dosage that provides a GM BDQ AUC168h at Weeks 12 and 24 within the pre-specified 60 to 140% window around the adult GM BDQ AUC168,ss (86,400 to 201,000 ng·h/mL with the approved maintenance dosage of 200 mg TIW).

Data

The PK data used in this analysis were obtained from 15 paediatric participants enrolled in Cohort 3 (≥2 to <5 years of age), administered a loading dose of 8 mg/kg QD for 14 days followed by a maintenance dose of 4 mg/kg TIW for 22 weeks. Doses were rounded up or down to the closest 10-mg unit. Actual loading and maintenance doses ranged from 80 to 120 mg QD and from 40 to 60 mg TIW, respectively.

There were 386 BDQ and 386 M2 concentration records in Cohort 3.

A summary of baseline demographics for participants recruited in Cohort 3 is displayed in Table 4.

Table 4 Baseline Demographics for Cohort 3 of Study TMC207-C211

	Age (ys)	Weight (kg)	BSA (m^2)	eGFR (ml/min/1.73 m^2)	Albumin (g/L)	ALT (U/L)	AST (U/L)	BILI (umol/L)	Sex	Race
N	15	15	15	15	15	15	15	15	Male: 8	Black: 4
Missing	0	0	0	0	0	1	0	7	(53.3%)	(26.7%)
Mean	3.8	13.4	0.6	171	47	11.4	33.5	4.9	Female: 7	Asian: 11
SD	1	1.5	0	38.3	2.8	8.3	6.2	1.4	(46.7%)	(73.3%)
CV %	25.2	11	8.1	22.4	6	72.5	18.4	27.8		
Median	3.8	13.5	0.6	156.3	48	7.5	34	5.5		
Min	2	10.2	0.5	129.9	43	4	18	3		
Max	5.8	15.8	0.7	266.1	51	31	44	6		

ALT = alanine aminotransferase, AST = aspartate aminotransferase, BILI = bilirubin, BSA = body surface area, CV = coefficient of variation, eGFR = estimated glomerular filtration rate. N = number of participants, SD = standard deviation.

Individual concentration-time plots for BDQ and M2 following PK sampling at Weeks 2, 12, and 24 are displayed in Figure 1 and Figure 2.

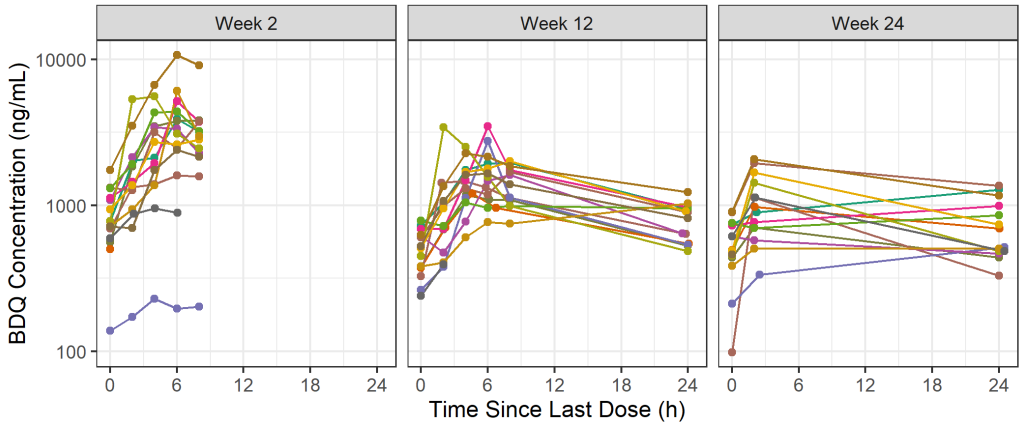

Figure 1 Individual BDQ Concentration-Time Profiles: Cohort 3 of Study TMC207-C211

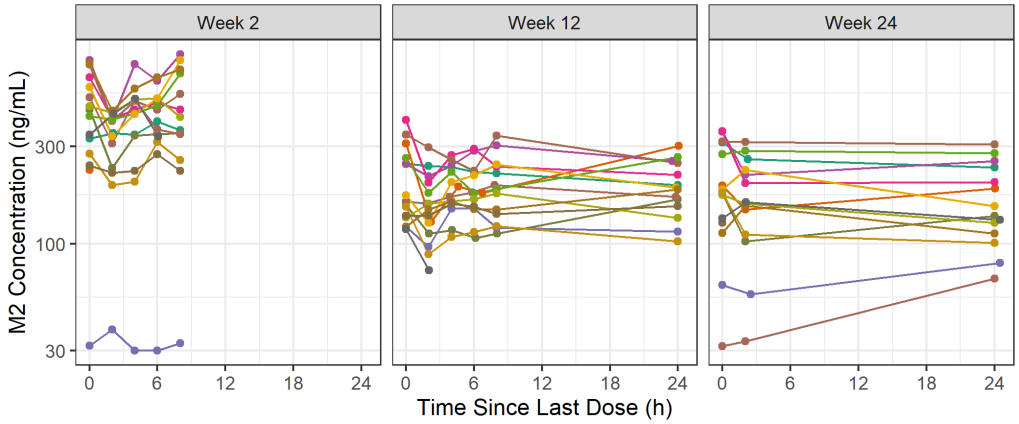

Figure 2 Individual M2 Concentration-Time Profiles: Cohort 3 of Study TMC207-C211

Mean (±SD) BDQ and M2 concentration-time profiles at Weeks 2, 12, and 24 were plotted versus time since last dose to compare the exposures obtained in Cohort 3 (paediatrics aged ≥2 to <5 years) with exposures previously obtained in Cohort 1 (adolescents aged ≥12 to <18 years) and Cohort 2 (paediatrics aged ≥5 to <12 years) (Figure 3 and Figure 4).

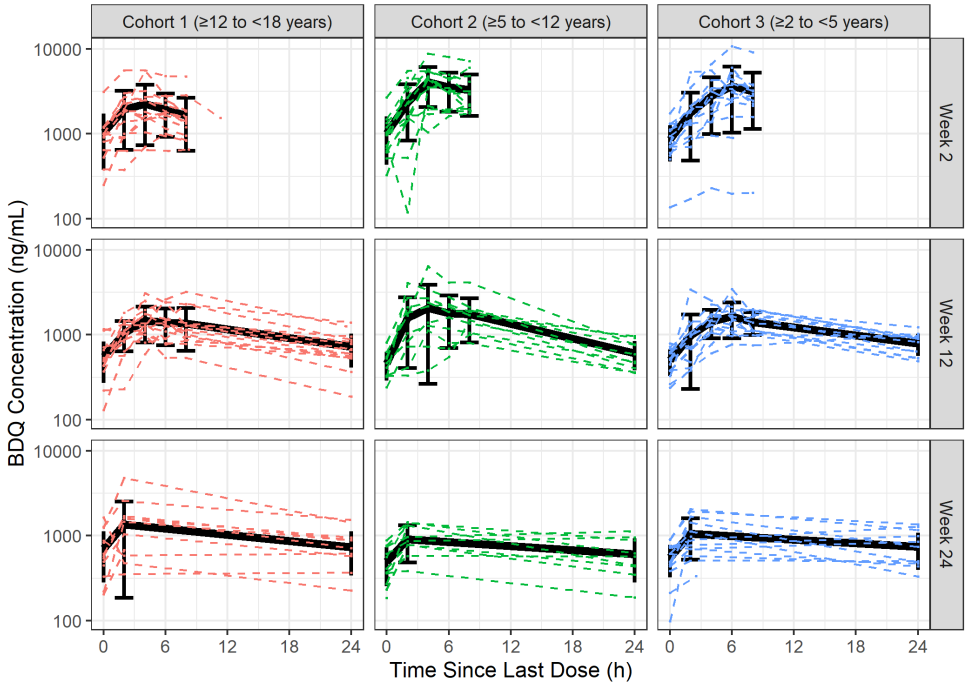

Figure 3 Mean (±SD) BDQ Concentration-Time Profiles from Study TMC207-C211. Dashed lines = individual profiles, solid lines and error bars = mean ± SD.

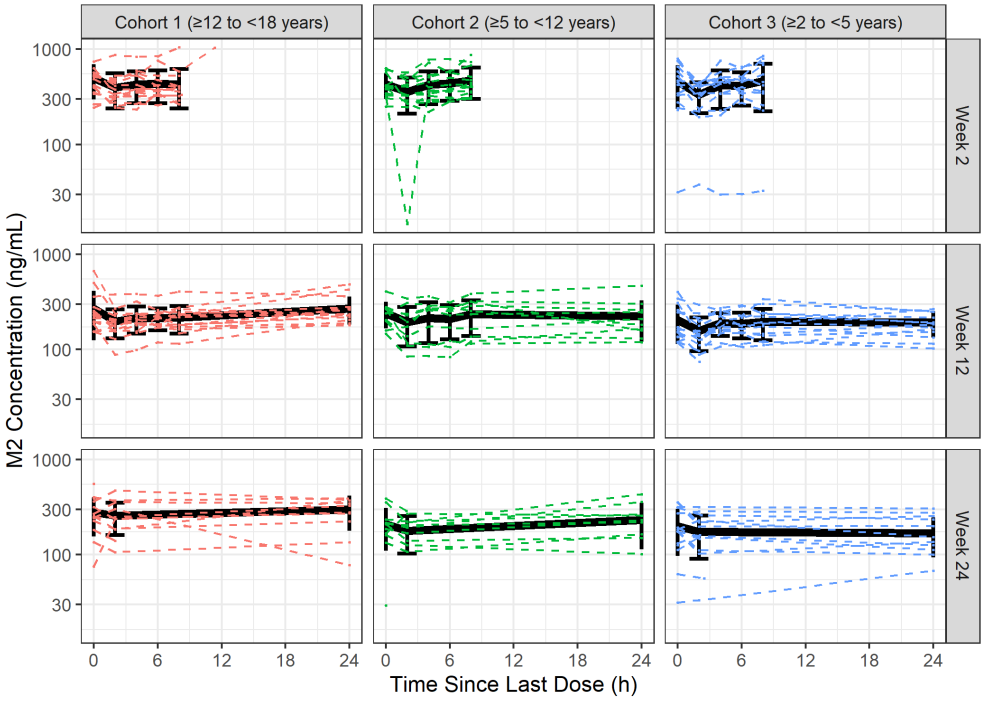

Figure 4 Mean (±SD) M2 Concentration-Time Profiles from Study TMC207-C211. Dashed lines = individual profiles, solid lines and error bars = mean ± SD.

Methods

The previously developed population PK model for BDQ and M2 in adults (procedure EMEA/H/C/002614/II/0056) was fitted to the PK data from study TMC207-C211, with population parameters fixed to the final estimates (MAXEVAL=0).

The prior population PK model was developed using data from 480 participants recruited in 9 clinical studies including healthy adults aged 18 to 55 years (n = 111, nPK = 1896), and adult patients aged 18 to 65 years with drug sensitive, multi-drug resistant, pre-extensively drug resistant, or extensively drug-resistant TB (n = 369, nPK = 3326).

The BDQ part of the previously developed BDQ-M2 parent-metabolite model consisted of a 4-compartment disposition model with a dual zero-order input (Figure 5) and was parameterised in terms of CL/F, apparent clearances between the central and the peripheral compartments (CLp1-3/F), apparent volume of distribution of the central (Vc/F), and peripheral compartments (Vp1-3/F). Other parameters included an ALAG1 dependent on formulation, a TLAG, D1, D2, FR1, and relative F dependent on study. For the simulations, F was assumed to be the 1.0, as per adult phase 2 studies (TMC207-TiDP13-C208, and TMC207-TiDP13-C209), with ALAG1 fixed to 0.480 hours (estimate for the solution) to allow for a conservative estimate of Cmax should dosage form modifications be required for younger children.

The M2 part of the previously developed BDQ-M2 parent-metabolite model was described by a two-compartment model with linear elimination. Parameters for the BDQ-M2 parent-metabolite model are presented in Table 5.

Although body size was not a covariate in the adult parent-metabolite model, to appropriately account for the age-related changes in body weight of children and adolescents, allometric scaling of WT on all BDQ and M2 clearance and volume parameters were included in the paediatric model as an exponent of 0.75 was used for clearance parameters and an exponent of 1.0 was used for volume parameters. Additionally, a CYP3A4 maturation function that describes the increase in CYP3A4 with age as a fraction of adult CYP3A4 abundance was applied to BDQ and M2 clearances under the assumption that BDQ and M2 is predominately eliminated by CYP3A4. While CYP3A4 enzyme maturation is expected to be completed by 2 years of age, the enzyme maturation factor was implemented to enable use of the population PK model for age <2 years (Cohort 4).

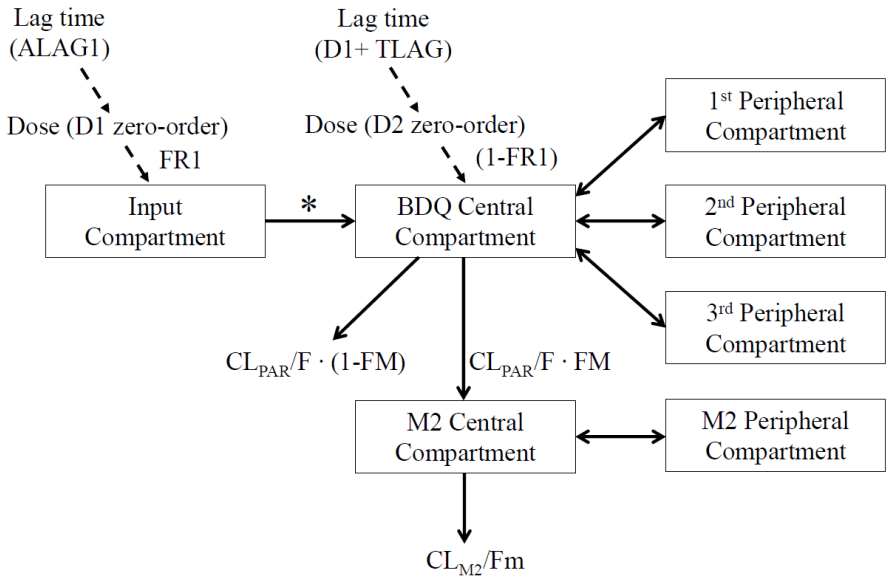

*Figure 5 Schematic of the Parent-Metabolite PK Model for BDQ and M2. ALAG1 = absorption lag-time for the first pathway, BDQ = bedaquiline, CLMET/F = apparent clearance for the metabolite, CLPAR/F = apparent clearance for the parent, D1 = duration of zero-order input into the first compartment, D2 = duration of zero-order input into the second compartment, F = bioavailability, Fm = fraction metabolized, FR1 = fraction of the dose absorbed via the first pathway, TLAG = absorption lag-time. *Rate parameter was fixed to 1000.*

Table 5 Parameter Estimates for the Parent-Metabolite PK Model for BDQ and M2

Parameter Name	Estimate Value (%RSE[a])	95%CI[a]
BDQ		
Apparent clearance (CL_{PAR}/F, L/h)	2.62 (4.4)	2.40 – 2.85
Effect of black race on CL_{PAR}/F and CL_{MET}/F	71.1 (13.4)	51.9 – 89.2
Effect of HVs or study C202 on CL_{PAR}/F[b]	45.0 (28.6)	23.9 – 72.6
Apparent central volume of distribution ($V_{c,PAR}$/F, L)	117 (8.0)	97 – 134
Effect of sex on $V_{c,PAR}$/F	-25.8 (35.9)	-42.7 – -6.2
Apparent clearance between the central and first peripheral compartment (CL_{p1}/F, L/h)	23.3 (6.8)	20.1 – 26.6
Apparent volume of distribution for the first peripheral compartment (V_{p1}/F, L)	124 (5.0)	113 – 137
Apparent clearance between the central and second peripheral compartment (CL_{p2}/F, L/h)	8.61 (3.8)	8.01 – 9.25
Apparent volume of distribution for the second peripheral compartment (V_{p2}/F, L)	2770 (5.6)	2466 – 3062
Apparent clearance between the central and third peripheral compartment (CL_{p3}/F, L/h)	3.35 (4.3)	3.11 – 3.68
Apparent volume of distribution for the third peripheral compartment (V_{p3}/F, L)	7670 (3.0)	7255 – 8166
Fraction of the dose absorbed via the first pathway[c] (FR1)	1.06 (11.9)	0.85 – 1.34
Duration of zero-order input for first absorption pathway (D1, h)	2.53 (4.0)	2.33 – 2.71
Absorption lag-time for the first pathway (solution) ($ALAG1_{solution}$, h)	0.48 (10.6)	0.38 – 0.59
Absorption lag-time for the first pathway (tablet) ($ALAG1_{tablet}$, h)[b]	0.921 (0.5)	0.911 – 0.930
Duration of zero-order input for second absorption pathway (D2, h)	2.31 (5.8)	2.07 – 2.60
Lag time for second absorption pathway (TLAG, h)[d]	0.815 (13.7)	0.525 – 0.989
Relative bioavailability for studies C208 and C209 (F)	1 Fixed	–
Relative bioavailability for studies 102 and C104 (F)[b]	1.49 (9.7)	1.23 – 1.82
Relative bioavailability for studies C109, C110, C111, C202, and TBC1003 (F)[b]	1.93 (5.3)	1.74 – 2.14
Fraction metabolized for patients with MDR-TB (FM_{TB})	0.542 (6.3)	0.468 – 0.605
Effect of HV on FM_{TB}[b,e]	0.481 (10.2)	0.381 – 0.574
M2		
Apparent clearance (CL_{MET}/F, L/h)	4.95 (6.9)	4.21 – 5.65
Apparent central volume of distribution ($V_{c,MET}$/F, L)	Fixed to $V_{c,PAR}$/F	–
Apparent clearance between the central and peripheral compartment ($CL_{p1,MET}$/Fm, L/h)	104 (15.7)	77 – 140
Apparent peripheral volume of distribution ($V_{p1,MET}$/Fm, L)	862 (6.7)	753 – 970
Pediatric covariates		
Effect of WT on all clearance parameters	0.75 Fixed	–
Effect of WT on all volume parameters	1.00 Fixed	–
CYP3A4 maturation half live (Weeks)	71 Fixed	–
Hill factor on CYP3A4 maturation function	3.9 Fixed	–
Between subject variability for CL_{PAR}/F (%)	44 (7.7)	40.8 – 47.4
Between subject variability for $V_{c,PAR}$/F (%)	71.1 (13.5)	61.1 – 81.3
Between subject variability for FR1 (%)	97 (16.1)	81.2 – 112.8
Between subject variability for F (%)	36.9 (7.4)	33.9 – 39.5
Between subject variability for CL_{MET}/F	45.3 (8.5)	41.4 – 48.8
Between subject variability for FM	27.9 (14.6)	24.1 – 31.8
Between subject variability for $CL_{p1,MET}$/Fm	158 (18.4)	124 – 183
Covariance for CL_{PAR}/F – CL_{MET}/F[f] (–)	0.181 (7.5)	0.152 – 0.207
Residual unexplained variaiblity for BDQ in HVs (%)[b]	23.9 (2.3)	23.5 – 24.5
Residual unexplained variaiblity for BDQ in Patients with MDR-TB (%)[b]	28.8 (1.9)	28.3 – 29.3

BDQ = bedaquiline, CI = confidence interval, HV = healthy volunteers, MDR-TB = multi-drug resistant Mycobacterium tuberculosis, RSE = relative standard error, RUV = residual unexplained variability, WT = total body weight. [a]Derived from sampling importance resampling (SIR). [b]Not applicable to the simulations for TMC207-C211. [c]Parameterized as FR1=(1+FR1). [d]Parameterized as ALAG2 = D1 + TLAG. [e]Fraction metabolized for healthy volunteers was parameterized as FMMDR-TB · (1 - 0:481). [f]Reported as covariance estimate. Correlation coefficients are 0.908 for CLPAR/F & CLMET/F, 0.652 for RUVBDQ,HV & RUVM2, and 0.492 for RUVBDQ,MDR-TB & RUVM2.

The following relationships were used to incorporate body weight and maturation on BDQ CL:

$$TVCL_i = TVCL \times \left(\frac{WT_i}{58}\right)^{\theta_{WT}} \times F_{CYP3A4}$$

where

$$F_{CYP3A4} = \frac{PMA^{3.9}}{71^{3.9} + PMA^{3.9}}$$

and PMA is post-menstrual age in weeks, calculated as post-natal age plus 40 weeks. A commonly used maturation function (Salem also known as updated Johnson) was used. The CYP3A4 maturation function predicted near full maturation by 2 years of age (data now shown).

Model evaluation included standard goodness-of-fit plots as well as visual predictive checks (VPCs).

Model-based exposure metrics for BDQ and M2 were derived on Weeks 2, 12 and 24. The individual predicted concentrations were derived for by fitting the previously developed population PK model scaled to paediatrics without population parameter re-estimation (MAXEVAL=0).

The exposure metrics were then tabulated and graphically compared to the simulated corresponding adult exposure for a dose of 400 mg QD for 14 days followed by 200 mg TIW for 22 weeks. Additionally, for BDQ, the GM AUC168h at Week 12 and 24 was compared to the 60% to 140% range for the adult GM AUC168h (i.e., 86,200 ng·h/mL to 201,000 ng·h/mL) at steady-state for a dose of 200 mg TIW.

Simulations

A dataset of virtual paediatric and adolescent participants was generated from two sources. For virtual participant aged <10 years, demographic data was generated from the WHO weight-for-age statistical tables. The lower expected weight for TB patients was accounted for by a correction factor based on the reference Svensson EM et al. Clinical Pharmacokinetics, 57(5):591–599, aug 2017.

To determine the optimal dosage to be used in the paediatric TB population weighing ≥7 to <15 kg, exposures following different weight-banded loading and maintenance dosing strategies were determined, splitting the body weight into 2 subgroups as per WHO recommendations (i.e., ≥7 to <10 kg and ≥10 to <15 kg). Time-varying body weight was considered in the simulations.

AUC168h at Weeks 12 and 24 was computed from the simulation. Evaluation of the dosage was based on achieving comparable BDQ exposure to adults at Weeks 12 and 24 (GM within 60 to 140% to adult reference, i.e., 86,200 to 201,000 ng·h/mL), with comparable variability.

Results

GOF plots developed by fitting the BDQ-M2 parent-metabolite model to the Cohort 3 data are displayed in Figure 6 and Figure 7. To evaluate the predictive performance of the model, VPCs for BDQ and M2 were conducted (see Figure 8 and Figure 9).

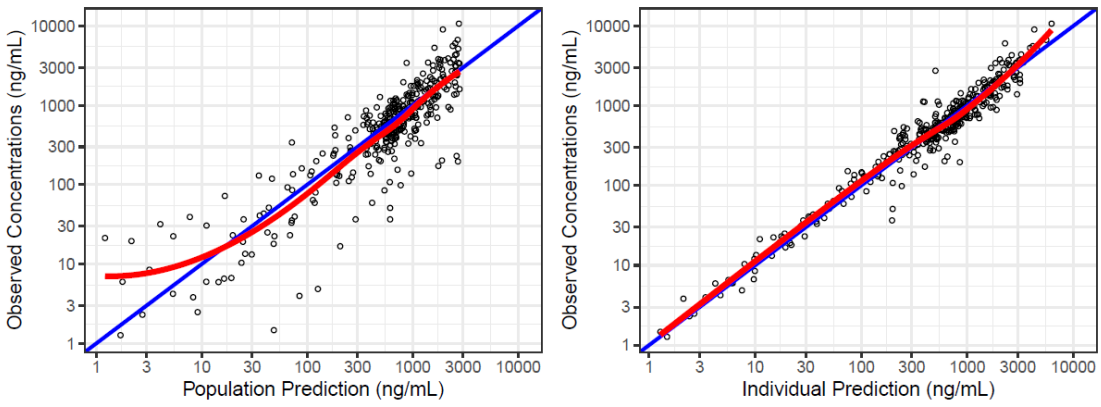

Figure 6 GOF Plots for BDQ: Cohort 3. The solid blue lines represent the line of unity and the solid red lines represent the locally weighted least-square regression based on the observations. Note: Log-log scale used.

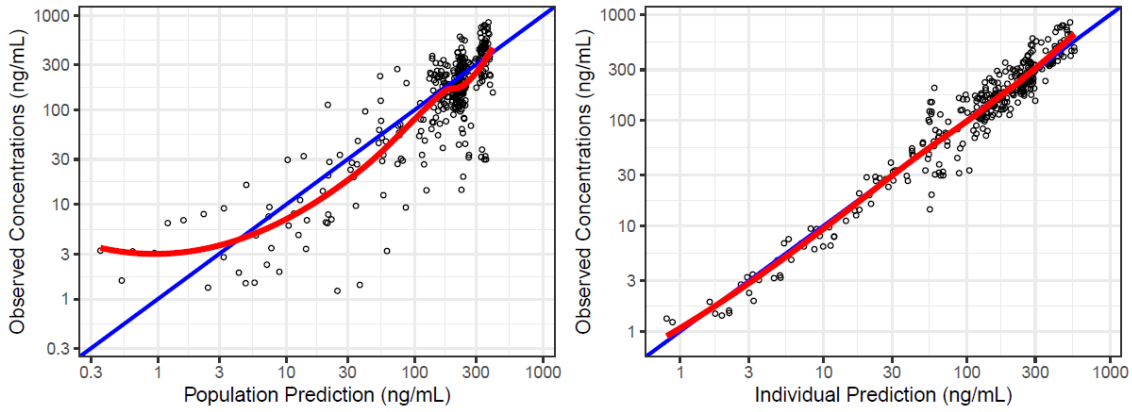

Figure 7 GOF Plots for M2: Cohort 3. The solid blue lines represent the line of unity and the solid red lines represent the locally weighted least-square regression based on the observations. Note: Log-log scale used.

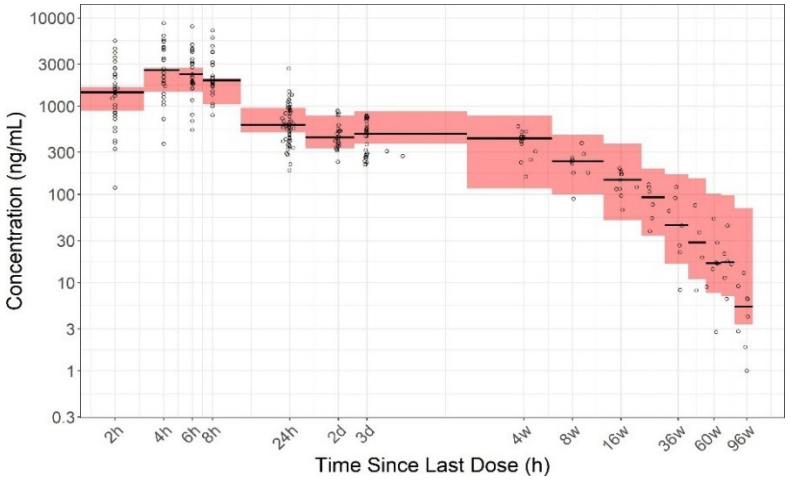

Figure 8 VPC for BDQ: Cohort 3. Open circles = individual observed, solid black line = observed median concentration, shaded red areas = 95% confidence interval around the model-predicted median. Note: Log-log scale is used.

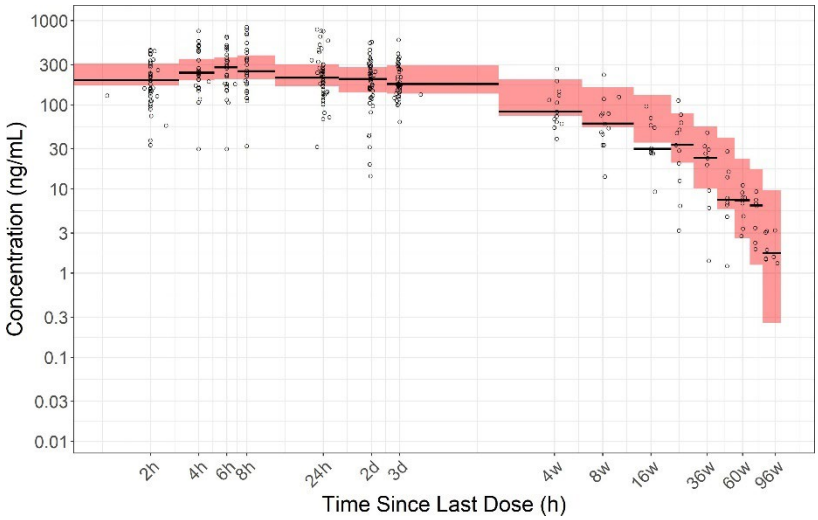

Figure 9 VPC for M2: Cohort 3. Open circles = individual observed, solid black line = observed median concentration, shaded red areas = 95% confidence interval around the model-predicted median. Note: Log-log scale is used.

Scatterplots of model-predicted Week 24 AUC168h for BDQ and M2 by body weight are displayed in Figure 10 and Figure 11.

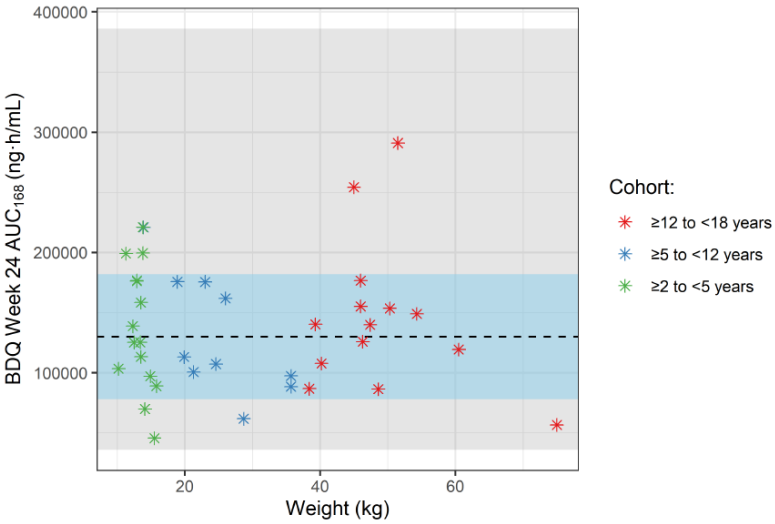

Figure 10 Week 24 Model-Predicted BDQ AUC168h by Weight. AUC168h = area under the plasma concentration-time curve from time of administration to 168 hours (total of 3 doses), Stars = model predicted AUC168h (red = Cohort 1, blue = Cohort 2, green = Cohort 3), dashed black line = the GM AUC168h at Week 24 from simulated adult data, grey shaded area = 95% PI for AUC168h at Week 24 from simulated adult data, blue shaded area = 60 to 140% of simulated adult GM AUC168h at Week 24.

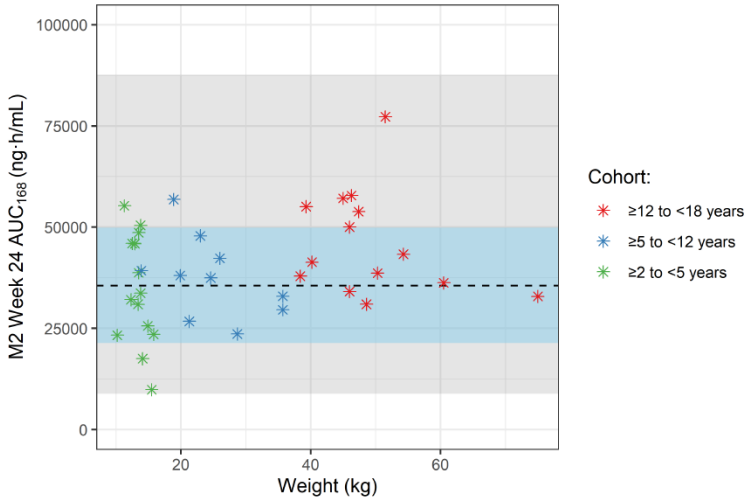

Figure 11 Week 24 Model-Predicted M2 AUC168h by Weight. AUC168h = area under the plasma concentration-time curve from time of administration to 168 hours (total of 3 doses), Stars = model predicted AUC168h (red = Cohort 1, blue = Cohort 2, green = Cohort 3), dashed black line = the GM AUC168h at Week 24 from simulated adult data, grey shaded area = 95% PI for AUC168h at Week 24 from simulated adult data, blue shaded area = 60 to 140% of simulated adult GM AUC168h at Week 24.

Simulations

The BDQ-M2 parent-metabolite model was used to simulate BDQ and M2 exposures in paediatric TB patients ≥2 years, including a WHO-aligned dosage where patients ≥7 to <10 kg were administered 80 mg QD/40 mg TIW and patients ≥10 to 15 kg were administered 120 mg QD/60 mg TIW (Table 6 and Figure 12). A low-dose scenario was also simulated (7-10kg: 60 mg QD/30 mg TIW, 10-15kg: 100 mg QD/50 mg TIW). The simulations included adults and older/heavier children for reference. The simulations showed that the WHO-aligned dosage resulted in >90% of patients 7-15 kg were within the adult reference range for BDQ AUC. Simulated AUC for M2 is shown in Figure 13.

Table 6 Simulated Pediatric BDQ Exposure: WHO-aligned Dosage

Week	Weight band	N	AUC* (ng·h/mL)				
			Mean	GM	Median	SD	95% PI
2	≥7 to <10 kg	1681	38600	35400	35500	16500	14700 – 79100
2	≥10 to <15 kg	2819	40600	37100	36900	18000	16300 – 83500
2	≥15 to <30 kg	1000	43800	40000	40600	19200	16800 – 90800
2	≥30 kg	1000	51000	46400	46600	22600	19500 – 110000
2	Adult Reference	1000	45000	39600	38500	25200	14000 – 109000
12	≥7 to <10 kg	1681	120000	105000	108000	63500	36700 – 276000
12	≥10 to <15 kg	2819	128000	112000	112000	70300	39600 – 308000
12	≥15 to <30 kg	1000	139000	122000	122000	72800	46000 – 322000
12	≥30 kg	1000	163000	144000	147000	82900	52100 – 364000
12	Adult Reference	1000	139000	119000	119000	83000	34600 – 355000
24	≥7 to <10 kg	1681	133000	115000	118000	75200	38200 – 319000
24	≥10 to <15 kg[†]	2470	145000	125000	125000	85800	41700 – 361000
24	≥15 to <30 kg	985	154000	133000	134000	86100	47500 – 371000
24	≥30 kg	1015	182000	158000	162000	97500	55300 – 435000
24	Adult Reference	1000	152000	130000	129000	93400	35900 – 386000
SS	≥7 to <10 kg	1681	145000	128000	129000	76700	48900 – 331000
SS	≥10 to <15 kg[†]	2470	164000	144000	143000	90300	53200 – 395000
SS	≥15 to <30 kg	985	177000	156000	156000	93200	57800 – 436000
SS	≥30 kg	1015	109000	95700	96400	59000	36700 – 277000
SS	Adult Reference	1000	144000	131000	127000	69600	53200 – 328000

AUC = area under the plasma concentration-time curve, GM = geometric mean, N = number of simulated participants, PI = prediction interval, SD = standard deviation, SS = steady state, *AUC at Week 2 refers to AUC24h, AUCs at Week 12 and 24 refer to AUC168h, and AUC at Week SS refers to AUC168,ss.

Paediatric patients who outgrow 15 kg at Week 12 are excluded from the Week 24 and steady-state summary statistics.

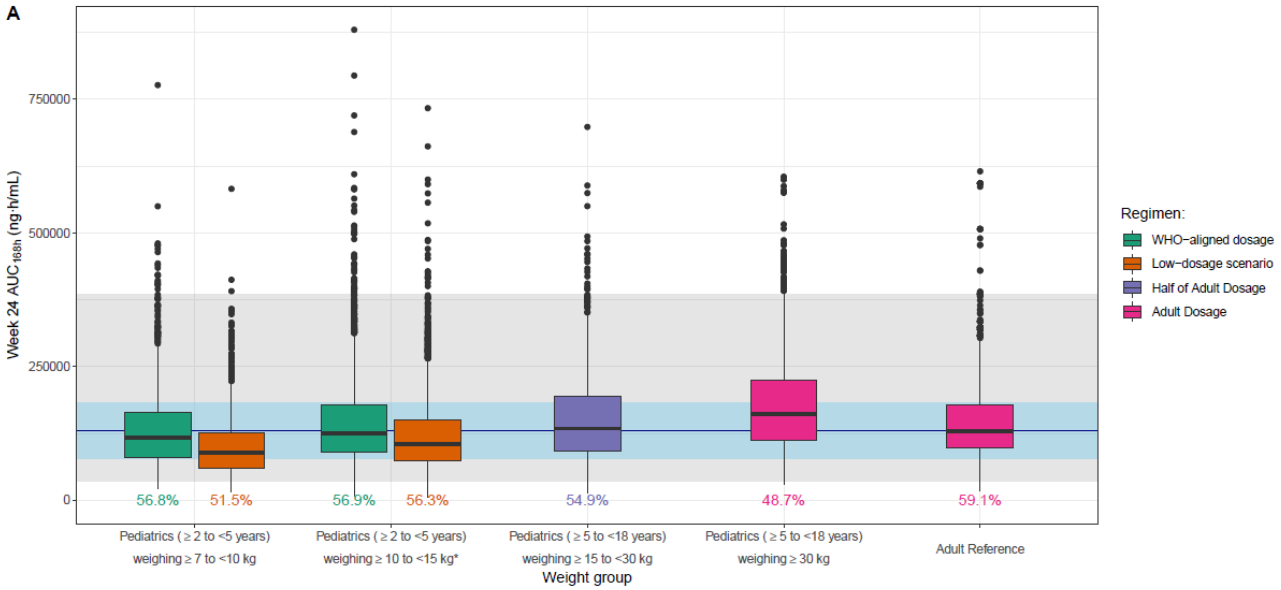

*Figure 12 Boxplots of Week 24 BDQ AUC168h Stratified by Age and Weight Band. AUC168h = area under the plasma concentration-time curve from time of administration to 168 hours (total of 3 doses), Thick solid line = median AUC, hinges = 25th & 75th percentiles (i.e., IQR), whiskers = 1:5 · IQR, dots = AUC outside the whiskers, grey shaded area = 95% PI for Week 24 AUC168h in adults, blue shaded area = 60 to 140% of GM of Week 24 AUC168h in adults, numbers = percentage of individual exposure within 60 to 140% of GM of predicted Week 24 AUC168h in adults. The adult reference AUC was predicted from the BDQ-M2 parent-metabolite model with the standard BDQ dose (400 mg QD for 2 weeks, followed by 200 mg TIW for 22 weeks). *Paediatric patients who outgrow 15 kg at Week 12 are excluded from the Week 24 and steady-state summary statistics.*

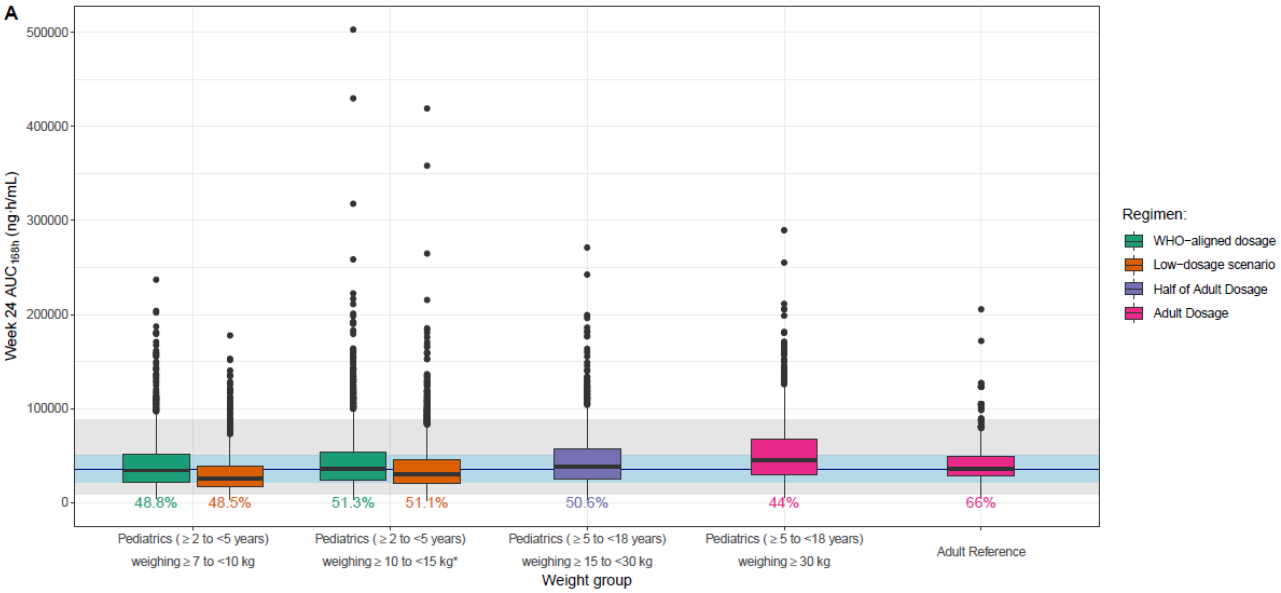

*Figure 13 Boxplots of Week 2 M2 AUC24h Stratified by Age and Weight Bands. AUC168h = area under the plasma concentration-time curve from time of administration to 168 hours (total of 3 doses), Thick solid line = median AUC, hinges = 25th & 75th percentiles (i.e., IQR), whiskers = 1.5 · IQR, dots = AUC outside the whiskers, grey shaded area = 95% PI for AUC in adults, blue shaded area = 60 to 140% of GM of AUC in adults, numbers = percentage of individual exposure within 60 to 140% of GM of predicted AUC in adults. The adult reference AUC was predicted from the BDQ-M2 parent-metabolite model with the standard BDQ dosage. *Paediatric patients who outgrow 15 kg at Week 12 are excluded from the Week 24 and steady-state summary statistics.*

2.3.3. PK/PD modelling

No apparent relationship between the PK of BDQ and TB treatment outcomes (favourable treatment outcome) could be derived for Cohort 3 of Study TMC207-C211 due to the small sample size.

Similarly, due to the low number of participants with significant QT prolongation or with elevated liver enzymes, no PK/PD analysis could be performed in terms of safety.

The highest exposure to BDQ (i.e. at the end of the loading phase), was not associated with any clinically relevant safety observations.

2.3.4. Discussion on clinical pharmacology

The benefit-risk in children ≥2 to <5 years is mainly based on a PK-bridging strategy with extrapolation of efficacy/safety from adults by means of exposure matching.

Bioanalysis of bedaquiline and M2 was performed using the same method as for Cohorts 1 and 2 of Study TMC207-C211 which is considered reasonable.

PK sampling was included with measurement of BDQ and the metabolite M2. The PK sampling schedule included collection of PK data on Weeks 2 and 12 and sparse PK data collection at Week 24. The Weeks 2 and 12 data allowed adequate calculation of the non-compartmental analysis-based exposure metrics AUC and Cmax. Cmin could be adequately determined at Weeks 2, 12 and 24. Standard non-compartmental analysis approaches were used, which is acceptable.

The main adult target exposure range for bedaquiline was defined as geometric mean AUC168h at Weeks 12 and 24 within the target range of 86200 to 201000 ng*h/mL. The 86200 to 201000 ng*h/mL target represents was 60% to 140% of the geometric mean steady-state AUC168h of 144000 ng*h/mL. The exposure matching was further supported by the following comparisons:

- The paediatric non-compartmental AUC24h at Weeks 2 and 12 for bedaquiline and M2 were compared with the corresponding adult AUC from the Phase 3 Study STREAM Stage 2
- The model-predicted paediatric AUC168h at Weeks 12, 24 and at steady-state were compared to the simulated mean and 95% prediction interval for adult AUC168h for bedaquiline and M2. The paediatric AUC was based on the observed dosing regimen
- The simulated paediatric AUC168h at Weeks 2, 12, 24 and at steady-state were compared to the simulated mean and 95% prediction interval for adult AUC168h for bedaquiline and M2. The paediatric AUC was based on the proposed dosing regimen (according to the SmPC)
- The observed PK concentrations vs time for bedaquiline and M2 for patients in Cohort 3 in Study TMC207-C211 were visually compared with observed PK concentrations for Cohorts 1 and 2

Overall, this is considered acceptable and allows adequate comparisons of both the central tendency and variability at relevant time-points. AUC is considered the most important exposure metric for extrapolating efficacy/safety for bedaquiline and is reasonable to use as the primary PK exposure metric for the exposure matching.

The non-compartmental analysis suggests that the PK exposure is within the range of the adult target exposure. This was further supported by the PopPK analysis, where individually predicted Week 24 exposures in paediatric patients in Cohort 3 were shown to have exposures within the adult target exposure range (a similar conclusion can be drawn from the Week 12 comparison). This generally supports adequate exposure matching. However, the observed PK data only covered a body weight

range down to 10 kg which means that these data on their own are not informative of the proposed posology in patients <10 kg. Furthermore, the studied posology (according to the Study TMC207-C211 protocol) is not identical to the proposed posology.

The PK data was analysed using PopPK modelling. In contrast to non-compartmental analyses, PopPK modelling can generally be used for simulations which can support dose recommendations for scenarios which has not been directly observed, including proposed doses in patients <10 kg (the smallest patient weighed 10 kg) and the fact that a (slightly) different posology is proposed compared to the dose listed in the Study TMC207-C211 protocol.

The applied PopPK model was based on a previously developed adult bedaquiline-M2 model which was assessed in procedure EMEA/H/C/002614/II/0056. The adult model was adapted by incorporating body weight using allometric scaling of clearance and volume terms with exponents fixed to literature values (0.75 for clearance terms and 1 for volume terms) and an age-based maturation function for the elimination.

The body weight relationship was normalized at 58 kg which is comparable to the mean body weight in the dataset used to develop the adult model of 54 kg. The maturation function was based on fixed parameter estimates from the literature and predicted complete maturation already at 2 years. Thus, the maturation function has no relevant impact for the current procedure from 2 years is the lowest age included in the dataset and the proposed indication only covers patients > 2 years.

The PopPK model was evaluated on the paediatric data from patients in Cohort 3 but no re-estimation was performed based on the paediatric data (i.e. MAXEVAL was set to 0). The model was evaluated using standard goodness-of-fit plots and using a VPC for all PK data in Cohort 3. Based on the provided results, the model gives acceptable description of the observed PK data for patients in Cohort 3. Of note, the adult PopPK model had a tendency to over-predict concentrations for M2 for adults in STREAM Stage 2 (procedure EMEA/H/C/002614/II/0056) which is a limitation of the applied model. However, this issue is not pursued further since the model gave acceptable description of the M2 PK-profile in Cohort 3 (Figure 9).

The PopPK model was used to perform simulations for the proposed dose patients in different weight groups, including patients 7-10 kg which has not been observed (min body weight in Cohort 3 was 10 kg). Since there are no observed data in patients 7-10 kg, the dose recommendation relies on full extrapolation. The simulations show that the AUC at steady-state in patients 7-10 kg at the proposed dose was within the adult exposure range. The simulations also showed that the Ctrough and Cmax at steady-state in patients 7-10kg at the proposed dose was within the adult exposure range.

The results in this report focus on PK-comparisons of bedaquiline and M2 at Week 24. Results were also provided for Weeks 2, 12 and at steady state which were in agreement with the Week 24 results in terms of exposure matching compared to adults.

The PopPK model is considered fit-for-purpose to extrapolate PK exposures below the observed body weight range (7-10 kg). The MAH demonstrated that the adult PopPK model gives an acceptable description of the body weight-PK relationship across different body weights in Study TMC207-C211 by providing pcVPCs stratified by body weight.

The proposed posology in patients 10-15 kg differ slightly from the dosing according to the Study TMC207-C211 protocol which is acceptable. The PopPK model simulations showed that the exposures in patients 10-15kg were within the adult target exposure range.

The formulation used in Cohort 3 of Study TMC207-C211 was G008 (20 mg tablet) which is the same formulation that was used when approving the use in paediatric patients down to 5 years and 15 kg. Thus, the already approved 20 mg tablet is appropriate to use also in patients down to 2 years.

Descriptive PK information is given in SmPC section 5.2 where the predicted Week 24 AUC168h has been added for paediatric patients weighing 7-15 kg which is acceptable. Of note, along with this addition, the MAH proposes a more condensed paediatric paragraph in Section 5.2 which is acceptable.

No relevant information on the exposure-response relationship for bedaquiline in Cohort 3 was provided. The MAH described that the sample size was too limited to adequately assess exposure-response and for the endpoints where exposure-response was explored, it was not possible to identify any relevant exposure-response trends. This is considered acceptable.

2.3.5. Conclusions on clinical pharmacology

PK-data were presented from 15 patients aged 2-5 years in Cohort 3 of Study TMC207-C211. The PK-data were analysed using non-compartmental analysis and using PopPK modelling. The data in patients >10 kg was adequately described and the proposed dosing regimen in patients 10-15 kg is acceptable. The posology in patients 7-10 kg is based on full extrapolation. The posology was supported by adequate PopPK-based simulations from a fit-for-purpose PopPK model.

2.4. Clinical efficacy

2.4.1. Main study

Study TMC207-C211: A Phase 2, Open-label, Multicenter, Single-arm Study to Evaluate the Pharmacokinetics, Safety, Tolerability and Anti-mycobacterial Activity of TMC207 in Combination with a Background Regimen (BR) of Multidrug Resistant Tuberculosis (MDR-TB) Medications for the Treatment of Children and Adolescents 0 Months to <18 Years of Age Who Have Confirmed or Probable Pulmonary MDR-TB

The data supporting the sought paediatric extension down to 2 years of age comes from Cohort 3 of the ongoing study TMC207-C211. Meanwhile, Week 24 results from completed Cohorts 1 and 2 have been submitted and assessed within earlier procedures (EMEA/H/C/002614/II/0033/G, EMEA/H/C/002614/X/0036/G).

Study Phase	Population	Age Cohorts	Participants Exposed to BDQ[a]	BDQ Dose	Cohort Status Reference
2	Adolescents and children with confirmed or probable pulmonary MDR-TB[b]	Cohort 1 (≥12 to <18 years)	15	400 mg qd in Weeks 1 and 2; 200 mg tiw in Weeks 3 to 24	Completed Week 24 and Week 120 analyses
		Cohort 2 (≥5 to <12 years)	15	200 mg qd in Weeks 1 and 2; 100 mg tiw in Weeks 3 to 24	Completed Week 24 and Week 120 analyses
		Cohort 3 (≥2 to <5 years)	**15**	**8 mg/kg qd in Weeks 1 and 2; 4 mg/kg tiw in Weeks 3 to 24**	**Completed Week 24 analysis**
		Cohort 4 (0 months to <2 years)	0	Age- and weight-based dosing	Enrolling

[a] At the data cutoff date of 09 May 2024.
[b] Including RR-TB.

Methods

Study participants

Paediatric participants of ≥2 to <5 years weighing at least 3 kg with confirmed or probable (clinically diagnosed or presumed) pulmonary and/or non-severe extrapulmonary MDR-TB, including XDR-TB infection, based on the case definitions of paediatric pulmonary and non-severe extrapulmonary TB as described in the international (WHO) guidelines and in accordance with the local standard of care, and who would initiate or had already begun MDR-TB treatment.

- Confirmed MDR-TB disease defined as clinical evidence of TB disease (i.e., at least 1 of the following signs or symptoms: persistent cough, weight loss, or failure to thrive, persistent unexplained fever, night sweats, persistent unexplained lethargy or reduced playfulness, enlarged lymph node, or the presence of any of the following in the neonate: pneumonia, unexplained hepatosplenomegaly, sepsis-like illness; imaging [e.g., CXR, CT scan, ultrasound] or other assessment [e.g., immunological] results consistent with pulmonary or non-severe extrapulmonary TB disease) together with the detection of M. tuberculosis (either by culture or molecular probe) from a clinical sample collected up to 6 months prior to screening from the participant with demonstration of genotypic (e.g., GeneXpert) or phenotypic resistance to at least RMP.
- Probable (clinically diagnosed) MDR-TB disease defined as clinical evidence of TB disease (i.e., at least 1 of the signs or symptoms suggestive of TB disease: persistent cough, weight loss, or failure to thrive, persistent unexplained fever, night sweats, persistent unexplained lethargy or reduced playfulness, enlarged lymph node, or the presence of any of the following in the neonate: pneumonia, unexplained hepatosplenomegaly, or sepsis-like illness; imaging [e.g., CXR, CT scan, ultrasound] or other assessment [e.g., immunological] results consistent with pulmonary or non-severe extrapulmonary TB disease);

  AND eligible for MDR-TB treatment in accordance with local standard of care;

  AND documented exposure to a source case with pulmonary MDR-TB based on a standardized questionnaire.

Treatments

Participants received BDQ at 8 mg/kg qd for 2 weeks followed by 4 mg/kg tiw for 22 weeks in combination with a BR. BDQ was administered using an age-appropriate oral tablet formulation (20-mg oral scored tablet, G008), administered with food. The dose of BDQ was rounded up or down to the nearest 10-mg unit and the actual administered dose ranged, from 80 to 120 mg qd for the first 2 weeks and from 40 to 60 mg tiw for the following 22 weeks.

After completion of BDQ treatment, as applicable, treatment with BR of a duration per the investigator's discretion continued, followed by a Follow-up Phase (starting 1 day after the end of the Overall Treatment Phase [BDQ+BR]) up until the Week 120 visit or premature study discontinuation.

Objectives

Primary:

• Safety and tolerability of BDQ over a 24-week treatment.

• PK of BDQ over a 24-week treatment period.

Secondary:

• TB treatment outcomes, including antimycobacterial activity of BDQ, over a 24-week treatment in confirmed or probable MDR-TB of BDQ.

• PK-PD relationships for safety and TB treatment outcomes over a 24-week treatment period.

• Adherence and palatability of the 100-mg oral tablet formulation and the age-appropriate 20-mg oral tablet formulation.

• Long-term safety, tolerability, and TB treatment outcomes of BDQ in combination with a BR of MDR-TB drugs in confirmed or probable MDR-TB over 120 weeks postbaseline.

Exploratory:

• BDQ MICs in isolates from positive cultures from children and adolescents with confirmed MDR-TB.

• Development of resistance to drugs used in the BR.

• BDQ and M2 penetration in CSF in children and adolescents without contraindications to lumbar puncture who require a lumbar puncture postbaseline as part of their standard of care.

Outcomes/endpoints

Safety: refer to Clinical safety section.

PK: refer to Pharmacokinetics section.

Efficacy:

• The proportion of participants with favourable treatment outcome at Week 24 and corresponding 95% CI was calculated, overall and by subgroup.

• The median time to MGIT culture conversion was to be estimated using the Kaplan-Meier method, if >3 confirmed and MGIT-evaluable MDR-TB participants were identified per age cohort.

• The median time to AFB smear conversion was to be estimated using the Kaplan-Meier method, if >3 MGIT-evaluable participants were identified per age cohort.

• The number and percentage of participants with anti-TB drug resistance at screening/baseline and postbaseline were tabulated for each anti-TB drug for which DST results were available.

Favourable treatment outcome includes positive outcome for all the following components: completion of TB treatment, the investigator's global TB assessment, and if available, microbiological assessment.

The investigator's global TB assessment is a clinical assessment based on the participant's condition including assessment of signs and symptoms of TB (resolved/partially resolved/not resolved) and the assessment of radiological improvement (yes/no).

TB treatment outcome can only be fully assessed in the Week 120 analysis following completion of TB treatment (BDQ + BR). TB treatment outcome results at Week 24 represent a preliminary assessment.

For antimycobacterial activity assessments, clinical samples were collected to assess the presence or absence of *M. tuberculosis* using MGIT cultures and AFB smears or any other available testing and to determine drug susceptibility using molecular assays and phenotypic DST.

In confirmed and MGIT-evaluable MDR-TB participants, DST was done at baseline (or screening if positive MGIT culture at baseline was not available) at the central microbiology laboratory and was only to be performed postbaseline on the last positive MGIT culture or in case of relapse/re infection.

Baseline extent of drug resistance of the M. tuberculosis strain (based on the 2013 WHO definitions) in confirmed MDR-TB participants with negative MGIT culture results at screening and baseline was based on DST results from clinical samples collected up to 6 months prior to screening. For probable MDR-TB participants, the DST results of the source case were used.

Palatability was listed and summarized descriptively per analysis visit, including Endpoint derived as last observation carried forward (LOCF).

Sample size

A total of 15 participants were to be enrolled in Cohort 3. This sample size was determined according to considerations for the primary PK objective.

The ITT analysis set used for safety includes all participants, regardless of their compliance with the protocol, who have at least 1 intake of BDQ.

The mITT analysis set used for efficacy is a subset of the ITT analysis set excluding those participants who do not have confirmed or probable MDR-TB (used for TB treatment outcome analyses).

Statistical methods

Efficacy outcomes were presented as descriptive statistics using the modified-Intention-To-Treat (mITT) analysis set. No inferential testing was planned and the study was not designed or powered for such.

Results

Recruitment

Participants in this study were screened at 4 sites in the Philippines (1 site), South Africa (2 sites), and Uganda (1 site).

Conduct of the study

Study initiation date: 4 May 2016

FPFV (Cohort 3): 25 Nov 2019

Last week 24 visit (Cohort 3): 9 May 2024 (database lock)

Major protocol deviations were noted in 3 of 15 participants in the ITT analysis set: rich PK sampling was not collected completely for 2 participants (for 1 participant at Week 2 and for 1 participant at Week 12) and for 1 participant, ECG and vital signs assessments were performed prior to ICF signing. The protocol deviations observed are not considered to affect the results or conclusions of the study.

Participant flow

In Cohort 3, a total of 15 participants were enrolled and treated with BDQ in combination with an individualized BR of anti TB drugs. At the time of the Week 24 analysis for Cohort 3 (database cut-off 09 May 2024), all 15 participants had reached the end of the BDQ Treatment Phase and were at varying stages of the study post-BDQ treatment phase (BR completed in 11 participants, ongoing in 4 participants, study discontinued by 1 participant; Week 120 visit completed by 6 participants).

One participant discontinued the study on Day 339 (Week 48) as the participant's caregiver was no longer willing to travel for follow-up visits after treatment completion.

Baseline data

The majority of participants in Cohort 3 were Asian (11 of 15 participants; all 11 participants enrolled in the Philippines). The remaining 4 participants were black and enrolled in South Africa. About half of the participants were male (8 of 15 participants). The median (range) age at screening was 3.8 (2.0 4.9) years, indicating participants have been enrolled over the entire age range of the cohort. The median (range) weight at baseline was 13.5 (10.2-15.8) kg.

Of the 15 participants in Cohort 3, 3 participants had confirmed MDR TB (all had MDR-TBH&R), including one participant who had a positive MGIT culture at screening (MGIT-evaluable). The remaining 12 participants had probable MDR-TB (6 had RR-TB, 5 had MDR-TBH&R, and 1 had XDR-TB; for all 12 participants based on source case DST). There were no AFB-evaluable participants. All participants were categorized as having "no cavitations or cavitations <2 cm" at baseline. None of the participants in Cohort 3 were HIV-co-infected. All 15 participants had received second-line anti-TB drugs prior to first administration of BDQ at Day 1.

The number of anti-TB drugs in the BR during the Overall Treatment Phase ranged from 4 to 6. The most frequently used anti-TB drugs in the baseline BR (i.e., the BR used during the first 2 weeks of the BDQ Treatment Phase) were similar to those used in the BDQ Treatment Phase and the Overall Treatment Phase and were also aligned with those anti-TB drugs used prior to the start of BDQ treatment (i.e., CFZ, LFX, LZD, and CS; all in at least 11 participants).

The most commonly reported TB-specific medical history disorders ongoing at screening included cough and TB (both in 14 of 15 participants), failure to thrive (in 12 of 15 participants), weight decreased (in 6 of 15 participants), and night sweats (in 5 of 15 participants).

Numbers analysed

All 15 participants enrolled in Cohort 3 were included in both the ITT and mITT analysis sets.

Outcomes and estimation

The median (range) total duration of the BDQ treatment was 24.0 (23.9 to 24.3) weeks.

During the BDQ loading phase (qd dosing), 2 participants missed doses for 1 and 2 days, respectively. The missed doses were not associated with any adverse events.

During the 2-week loading phase when BDQ was administered at 8 mg/kg qd in Cohort 3, median (range) compliance was 100.0% (90.9 to 100.6%). During the 22-week maintenance phase when BDQ was administered at 4 mg/kg tiw, median (range) compliance was 100.0% (95.0 to 137.9%).

After 24 weeks of treatment with BDQ in combination with an individualized BR, 4 of 15 (26.7%) participants in the mITT analysis set had a favourable treatment outcome. Radiologically, 13 of 15 participants had signs and symptoms "resolved" and 2 had signs and symptoms "partially resolved". None of the participants experienced a worsening in cavitation category at Week 24 compared to baseline.

All 4 participants with favourable treatment outcome at Week 24 were enrolled in South Africa. As all participants completed BDQ treatment and only one participant was MGIT evaluable, the Week 24 derivation of favourable treatment outcome is primarily driven by the investigator's global TB

assessment component. In South Africa, the investigator's global TB assessment was "resolved" for all 4 participants given that signs and symptoms had resolved, and radiological improvement was observed.

In the Philippines, the investigator's global TB assessment was "partially resolved" for all 11 participants, leading to the categorization of no favourable treatment outcome. The "partially resolved" assessment was made by the investigator, even though 5 of 11 participants had signs and symptoms resolved and radiological improvement observed (yes [n=4] or not applicable [n=1]). In addition, among these 5 participants, the only confirmed and MGIT-evaluable MDR-TB participant achieved MGIT culture conversion (microbiological criteria met = "resolved") by Week 4 (Day 29). The investigator clarified that all 11 participants from the Philippines were still ongoing on BR at the Week 24 visit, and the final overall TB treatment outcome assessment will be done at the end of TB treatment (BDQ + BR).

At the data cutoff date, all 7 participants (including the one confirmed and MGIT-evaluable MDR TB participant) who completed the Week 120 visit (6 participants) or discontinued study participation prematurely (1 participant), had a favourable treatment outcome at study end (i.e., Week 120 or premature study discontinuation). Three of the 7 participants reaching study end had sustained clinical cure as per-protocol definition of having a favourable treatment outcome at both Week 24 and study end. No participants died up to the data cutoff date of the Week 24 analysis.

The one confirmed and MGIT-evaluable MDR-TB participant achieved culture conversion by Week 4 (Day 29) with sustained MGIT culture conversion up to Week 120, indicating no relapse or reinfection. No emergence of resistance could be evaluated as this participant had negative MGIT cultures at all postbaseline timepoints up to Week 120.

Supportive data

The MAH took the opportunity to submit updated long-term (Week 120) efficacy data from Cohort 1 (adolescents ≥12 to <18 years of age) and Cohort 2 (children ≥5 to <12 years of age) of ongoing paediatric Phase 2 study TMC207 C211.

In the Week 120 analyses, 13 of 15 participants in Cohort 1 and 10 of 13 participants in Cohort 2 had a favourable TB treatment outcome. For all participants who achieved favourable treatment outcome at Week 24 (7 participants in Cohort 1 and 6 participants in Cohort 2), favourable treatment outcome was sustained up to the end of study (Week 120).

MGIT culture conversion was sustained up to the end of study (Week 120) for all MGIT-evaluable participants who achieved culture conversion at Week 24: in 7 participants in Cohort 1 (based on the updated Week 24 analysis) and 3 participants in Cohort 2.

Note that due to the addition of microbiological criterion #4 in protocol Amendment 5, TB treatment outcome at Week 24 was updated in the Week 120 analysis of Cohort 1. Compared to the initial Week 24 analysis, 1 more participant met the added culture conversion criterion, resulting in an updated Week 24 culture conversion rate of 87.5% (7 of 8 participants) for Cohort 1. Favourable treatment outcome remained unchanged and efficacy conclusions, which are anyway not pivotal but supportive, are unchanged.

2.4.2. Discussion on clinical efficacy

Design and conduct of clinical studies

The data supporting the sought paediatric extension down to 2 years of age come from Cohort 3 of the ongoing study TMC207-C211, a Phase 2, single-arm, open-label safety and PK study in paediatric participants, with 15 participants per age cohort.

Cohort 3 included 15 paediatric subjects ≥2-<5 years of age with confirmed or probable multidrug-resistant tuberculosis (MDR-TB) infection, who were enrolled and treated with BDQ at 8 mg/kg qd for 2 weeks followed by 4 mg/kg tiw for 22 weeks in combination with an individualized background regimen.

The primary objective was to evaluate the PK, safety and tolerability of BDQ over a 24-week treatment period in each age cohort and to provide guidance on dose selection for each of the age cohorts. The study is not designed or powered to evaluate efficacy beyond descriptive statistics for secondary efficacy endpoints. The submitted descriptive efficacy data comprise the Week 24 primary analysis. Moreover, formal treatment outcome is generally not considered possible to fully assess until Week 120. Thus, notwithstanding these limitations, the design of the study, including population, objectives and endpoints, was fit for purpose.

The majority of participants in Cohort 3 were Asian. About half of the participants were male. The median (range) age at screening was 3.8 (2.0 4.9) years. The median (range) weight at baseline was 13.5 (10.2-15.8) kg. The median (range) total duration of the BDQ treatment was 24.0 (23.9 to 24.3) weeks and compliance with study medication was very high.

Of the 15 participants in Cohort 3, 3 participants had confirmed MDR TB (all had MDR-TBH&R), including one participant who had a positive MGIT culture at screening (MGIT-evaluable). The remaining 12 participants had probable MDR-TB based on source case DST. There were no AFB-evaluable participants. Diagnosis and treatment outcome assessments differ in children versus adults due to the frequent paucibacillary nature of TB in paediatric patients and difficulties in obtaining the necessary samples for microbiology. It is therefore unsurprising that culture confirmation (MGIT culture results) of MDR-TB is only available for a limited number of participants.

All participants were categorized as having "no cavitations or cavitations <2 cm" at baseline. None of the participants in Cohort 3 were HIV-co-infected. The number of anti-TB drugs in the BR during the Overall Treatment Phase ranged from 4 to 6.

Efficacy data and additional analyses

After 24 weeks of treatment with BDQ in combination with an individualized BR, 4 of 15 (26.7%, all from South Africa) participants in the mITT analysis set had a favourable treatment outcome. In the Philippines, the investigator's global TB assessment (the main driver for the treatment outcome) of "partially resolved" was made for 11 patients, even though 5 of 11 participants had signs and symptoms resolved and radiological improvement observed. Radiologically, 13 of 15 participants had signs and symptoms "resolved" and 2 had signs and symptoms "partially resolved". None of the participants experienced a worsening in cavitation category at Week 24 compared to baseline.

At the data cutoff date, all 7 participants (including the one confirmed and MGIT-evaluable MDR TB participant) who completed the Week 120 visit (6 participants) or discontinued study participation prematurely (1 participant), had a favourable treatment outcome at study end (ie, Week 120 or premature study discontinuation). Three of the 7 participants reaching study end had sustained clinical cure as per-protocol definition of having a favourable treatment outcome at both Week 24 and study end. No participants died up to the data cutoff date of the Week 24 analysis.

The one confirmed and MGIT-evaluable MDR-TB participant achieved culture conversion by Week 4 (Day 29) with sustained MGIT culture conversion up to Week 120, indicating no relapse or reinfection.

No emergence of resistance could be evaluated as this participant had negative MGIT cultures at all postbaseline timepoints up to Week 120.

2.4.3. Conclusions on the clinical efficacy

Since it is fully endorsed that efficacy and safety can be extrapolated based on systemic exposure, the primary objective of study TMC207-C211 is to establish a dose in adolescence resulting in an exposure of BDQ similar to adults. While a dosage of 8 mg/kg qd for 2 weeks followed by 4 mg/kg tiw for 22 weeks was used in the paediatric clinical study, a simplified clinical posology is supported by popPK modelling.

2.5. Clinical safety

Introduction

Sirturo was first approved in the European Union in 2013 for use in adults. The indication was extended to adolescents aged 12 years in 2019 and further extended to paediatric patients from 5 years of age in 2021.

Known adverse reactions in the adult population are:

System Organ Class (SOC)	Frequency Category	ARs
Nervous system disorders	Very Common	Headache, dizziness
Gastrointestinal disorders	Very Common	Nausea, vomiting
	Common	Diarrhoea
Hepatobiliary disorders	Very Common	Transaminases increased
Musculoskeletal and connective tissue disorders	Very Common	Arthralgia
	Common	Myalgia
Investigations	Very Common	Electrocardiogram QT prolonged

Safety information collected from cohorts 1 and 2 of the study TMC207-C211 (i.e. 30 participants) did not indicate any difference between the paediatric population from 5 years of age compared to the adult population. Most common reactions in participants >5 years were hepatic reactions reported as reversible increases in ASAT/ALAT and hepatotoxicity.

Patient exposure

Study TMC207-C211 is a phase 2, open-label, multicentre, single-arm study to evaluate the pharmacokinetics, safety, tolerability and activity of BDQ in combination with a background regimen (BR) of MDR-TB medications in children and adolescents 0 months to <18 years of age. The data relevant for the variation (DLP: 09 May 2024) regards cohort 3 of the study; cohorts 1 and 2 have been assessed previously in earlier procedures.

Cohort 3 consists of 15 participants aged ≥2 to <5 years, who were administered 8 mg/kg once daily in weeks 1 and 2; 4 mg/kg three times per week in weeks 3 to 24. In this cohort, the most frequently used anti-TB treatments in the baseline regimen were similar to those used in the BDQ treatment phase and were also aligned with those anti-TB treatments used prior to the start of BDQ treatment (i.e., CFZ, LFX, LZD, and CS; all in at least 11 participants). The number of anti-TB treatments in the BR during the BDQ Treatment Phase ranged from 4 to 6.

The median (range) total duration of the BDQ treatment was 24.0 (23.9 to 24.3) weeks. The median (range) total duration of the BR up to the data cutoff date was 34.4 (24.1 to 60.1) weeks.

Per protocol, BDQ was administered together with an individualised BR. As the age-based cohorts in Study TMC207-C211 were opened and enrolled over a period of years, the treatments in the BR have differed between cohorts based on the evolving standard of care. Thus, the safety observations between cohorts may be influenced by the safety profiles of treatments in the BR. In Cohort 3, all participants received both CFZ and LZD in their BR. Less than half of the participants in Cohorts 1 and 2 received CFZ and LZD as part of their individualised BR.

Adverse events

A summary of AEs is presented in Table 3.

Table 7: Summary of Adverse Events; ITT (Study TMC207-C211 | Week 24 Primary Analysis, DB Cutoff 09MAY2024, Age Cohort: Cohort 3 [≥2 to <5 Years of Age])

Summary	TMC207 Treatment Phase	Overall Treatment Phase	Follow-up Phase
Analysis set: Intent-to-treat, N	15	15	11
Any adverse events	15 (100%)	15 (100%)	6 (54.5%)
Serious adverse events	0	0	0
AEs leading to death	0	0	0
AEs of at least grade 3	2 (13.3%)	2 (13.3%)	0
AEs of grade 4	0	0	0
AEs leading to permanent discontinuation of TMC207	0	0	NA
AEs leading to permanent discontinuation of BR*	1 (6.7%)	1 (6.7%)	NA

Key: NA=not applicable.
* This could be one or more anti-TB drugs included in BR.
The denominator for the percentage calculations is the total number of subjects in the ITT analysis set per phase.

All 15 participants experienced at least one AE during the BDQ Treatment Phase, including the following most frequently (in ≥10% of participants) reported events by Preferred Term: skin hyperpigmentation (46.7%; n=7), upper respiratory tract infection (40.0%; n=6), neutrophil count decreased (26.7%; n=4), vomiting (20.0%; n=3), bronchial hyperreactivity (20.0%; n=3), skin discoloration (20.0%; n=3), neutropenia (13.3%; n=2), and rash (13.3%; n=2).

Serious adverse event/deaths/other significant events

No deaths, SAEs, or AEs leading to permanent discontinuation of BDQ or temporary interruption of BDQ were reported up to the PLP of the Week 24 analysis.

During the BDQ Treatment Phase, 3 participants experienced AEs considered at least possibly related to BDQ by the MAH, none of which led to permanent discontinuation or temporary interruption of BDQ:

• One participant was reported with a Grade 1 AE of "insomnia". The event was considered possibly related to BDQ and BR, started on Day 2 and was considered resolved after a duration of 8 days while continuing BDQ treatment.

• Another participant was reported with a Grade 1 AE of "pruritus" and a Grade 1 AE of "rash". The event "pruritus" was considered possibly related to BDQ and BR by the MAH, started on Day 20, and

was considered resolved after a duration of 15 days while continuing BDQ treatment. The event of "rash" was considered very likely related to BDQ and BR by the MAH, started on Day 102, and was considered resolved after a duration of 31 days while continuing BDQ treatment.

• A third participant was reported with a Grade 1 of "ECG QT prolonged" (considered an AESI).

During the BDQ Treatment Phase, no Grade 4 AEs were reported. Two participants experienced a Grade 3 AE during the BDQ Treatment Phase. Neither of these events was assessed by the MAH as related to BDQ.

• One participant was reported with a Grade 3 AE of "amylase increased" (considered an AESI).

• Another participant was reported with a Grade 3 AE of "neutrophil count decreased".

None of these reported events were considered new safety concerns.

Adverse Events of Special Interest (AESIs)

AESIs as defined by the protocol are:

- QTcF measurement ≥500 ms while on treatment;
- ALT/AST ≥10 times ULN;
- ALT/AST ≥3 times ULN in the presence of total bilirubin >2 times the ULN;
- Any grade 3 or higher adverse event;
- Persistent haematuria.

Additionally, severe (grade 3) skin events (including severe skin reactions) are considered as AESIs due to that medications in the BR have been associated with rash.

Two participants experienced at least one AESI, as identified using MedDRA SMQs, during the BDQ Treatment Phase. None of them were assessed as related to BDQ by the MAH.

• One participant was reported with a treatment-emergent Grade 3 AE of "amylase increased". This participant already had a pre-treatment Grade 3 AE of "amylase increased" that resolved during the BDQ Treatment Phase (reported as starting on Day -1 and resolved on Day 29; considered not related to BDQ and possibly related to BR). The participant was receiving LFX, LZD, CFZ, and CS during the screening phase (all started 43 days prior to Day 1). The treatment-emergent Grade 3 AE of "amylase increased" was reported on Day 57. The event was considered not related to BDQ and possibly related to BR. No action was taken with BDQ administration, and no concomitant drugs were administered to treat the AE. Doses for LFX, LZD, and CFZ were decreased (but not for CS). No clinical symptoms of pancreatitis were reported. Pancreatic amylase evolved over time to a Grade 1 abnormality at Week 120 and the associated Grade 1 AE was not resolved at the last visit as indicated by the investigator.

The same participant was reported with a Grade 1 AE of "ECG QT prolonged" starting on Day 155. The maximum observed QTcF value during the study was 454 ms and the maximum observed increase from baseline was 47 ms (both observed on Day 155). The event was considered possibly related to BDQ and BR, but administration of BDQ and BR treatments was continued unchanged for this event. The AE of "ECG QT prolonged" was considered resolved after a duration of 24 days (i.e. 10 days after completion of BDQ treatment and while still receiving all BR treatments).

• Another participant experienced a Grade 2 AE of "conjunctivitis". The event started on Day 13 and was considered not related to BDQ and BR. The event was not accompanied by additional symptoms and considered resolved after a duration of 7 days while continuing BDQ treatment.

Laboratory findings

No Grade 4 treatment-emergent laboratory abnormalities were observed. Treatment-emergent Grade 3 laboratory abnormalities were observed during the BDQ Treatment Phase in 2 participants: "neutrophils and precursors decreased" (n=1) and "prothrombin time prolonged" (n=1).

The laboratory abnormality "neutrophils and precursors decreased" (grade ranged from 1 through 3) was observed in 6 of 15 participants during the BDQ Treatment Phase. All 6 participants had LZD in their BR, and neutropenia is a common adverse reaction of LZD. In addition, 4 of these 6 participants had a concurrent infection at the time of the event that could be a confounding factor. An AE of "neutropenia" or "neutrophil count decreased" was reported in all 6 participants (i.e. 2 and 4 participants, respectively). None of the AEs of "neutropenia" or "neutrophil count decreased" were considered by the MAH as related to BDQ and all but 1 were considered related to BR. The AEs were all Grade 1 and 2, except for 1 participant who experienced a Grade 3 AE of "neutrophil count decreased" with observed laboratory abnormality of Grade 3 "neutrophils and precursors decreased". The Grade 3 AE of "neutrophil count decreased" was considered not related to BDQ and BR but considered related to ongoing infections per the investigator. For 1 participant with a Grade 1 AE of "neutropenia", treatment with LZD was permanently discontinued due to the AE and for 2 participants with an AE of "neutrophil count decreased" (one Grade 1 and one Grade 2), LZD treatment was temporarily interrupted due to the AE. No other AEs related to white blood cell abnormalities were reported.

Review of the treatment-emergent non-graded laboratory abnormalities revealed no clinically significant findings.

Laboratory Parameters of Interest

· One participant had pancreatic amylase ≥2x ULN during the BDQ Treatment Phase (i.e., participant with the Grade 3 AE of "amylase increased").

· None of the participants met the laboratory criteria for Hy's law. None of the participants had ALT/AST ≥10x ULN, creatine kinase ≥10x ULN, or persistent haematuria.

Vital Signs, Electrocardiograms, Physical Findings, and Other Observations Related to Safety

Mean pulse rate decreased over time during the BDQ Treatment Phase; mean respiratory rate and mean supine SBP and DBP remained stable over time during the BDQ Treatment Phase. Most participants had fluctuations in body weight from visit to visit during the BDQ Treatment Phase, but no AEs related to weight decreased were reported. No vital signs-related AEs were reported.

Mean absolute values in QTcF increased over time during the BDQ Treatment Phase, yet no participants were observed to have a QTcF value >460 ms at any timepoint during the BDQ Treatment Phase. During the BDQ Treatment Phase, one participant had a worst treatment-emergent QTcF increase from baseline of >60 ms with no AE of "ECG QT prolonged" reported. Two ECG related AEs were reported during the BDQ Treatment Phase: one Grade 1 AE of "ECG QT prolonged" and one Grade 1 AE of "atrioventricular block first degree", which was considered not related to BDQ and BR and resolved after a duration of 267 days.

Post-baseline physical examination abnormalities during the BDQ Treatment Phase for participants with normal baseline findings were observed in at most 2 of 15 participants per body system category per timepoint except for treatment-emergent abnormalities for the body system "skin". Overall, 11 participants were reported to have treatment-emergent skin abnormalities of which most were related to skin discoloration or hyperpigmentation reactions. The majority of these 11 participants were also

reported with an AE of "skin discoloration" or "skin hyperpigmentation" during the BDQ Treatment Phase. All of these events were Grade 1. None of these events with discoloration of the skin were considered related to BDQ and all were considered related to BR. All 10 participants with reported AEs used CFZ in their BR. CFZ can cause skin discoloration /hyperpigmentation as well as discoloration of conjunctivae, tears, sweat, sputum, urine, and faeces in 75 to 100% of patients.

Adverse Drug Reactions

The applicant's causality assessment of ADRs for BDQ was based on prior controlled studies in adults. The most common ADR observed for Cohort 3 during the BDQ treatment phase was "vomiting" in 3 of 15 participants. Other ADRs were observed in 1 participant each during the BDQ Treatment Phase: "ECG QT prolonged" and "arthralgia". ADRs of "hepatotoxicity" or "transaminases increased" were not reported.

No new ADRs with BDQ were identified during the study up to the data cutoff date of the Week 24 analysis of Cohort 3.

Post marketing experience

Based on the 20,524,487 g distributed worldwide from launch to 31 August 2024, the estimated cumulative post marketing exposure to BDQ is 1,092,795 completed treatment courses. This number is including 2,134 completed paediatric treatment courses.

The MAH has reviewed all safety information related to use in paediatric patients in interval periodic benefit-risk evaluation reports and no safety issue has been identified in children <5 years of age.

2.5.1. Discussion on clinical safety

After 24 weeks of treatment with BDQ in combination with an individualized BR, 15 of 15 (100%) participants in the mITT analysis reported at least one AE. Most common events were skin hyperpigmentation, upper respiratory tract infection, neutrophil count decreased, vomiting, bronchial hyperreactivity, skin discoloration, neutropenia, and rash. None of the events were reported as serious. Skin hyperpigmentation has not been reported previously with BDQ, however all participants that reported the event had clofazimine in their BR. Clofazimine is known to cause hyperpigmentation and discoloration, thus these adverse reactions can reasonably be attributed to clofazimine rather than BDQ.

Three AESIs were reported in two participants, one participant reported increased ECG QT interval and increased amylase grade 3, and one participant reported conjunctivitis grade 3. The maximum increase in QT interval was 46 ms above baseline, 456 ms in total, and resolved within 10 days of completed BDQ treatment. The increase was considered related to BDQ. Increase in amylase was not considered related to BDQ. No deaths or discontinuations of BDQ were reported.

2.5.2. Conclusions on clinical safety

Data from cohort 3 adds information on safety of BDQ from 15 paediatric patients. While data is limited, no new safety information was identified in the review of reports of adverse events or scientific literature. No deaths or discontinuations of treatment were reported. No new safety concerns were identified based on the submitted data.

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 an updated RMP version with this application. The (main) proposed RMP changes were the following:

Product Overview Dosage Section

Addition of new recommended dosage for paediatric patients 2 years to less than 18 years of age:

- weighing ⩾7 kg to <10 kg
- weighing ⩾10 kg to <15 kg

Clinical trial exposure

Creation of new exposure tables presenting data from the Week 24 primary analysis of TMC207-C211 Cohort 3 (children ⩾2 to <5 years).

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 11.1 is acceptable.

2.7. Update of the Product information

The CHMP adopted a new indication (section 4.1) and the updated indication is now as follows:

"SIRTURO is indicated for use as part of an appropriate combination regimen in adult and paediatric patients (~~5~~**2** years to less than 18 years of age and weighing at least ~~15~~**7** kg) with pulmonary tuberculosis (TB) due to Mycobacterium tuberculosis resistant to at least rifampicin and isoniazid. Consideration should be given to official guidance on the appropriate use of antibacterial agents."

As a consequence of this new indication, sections 4.2, 4.8, 5.1 and 5.2 of the SmPC have also been updated. The Package Leaflet (PL) has been updated accordingly.

In addition, the list of local representatives in the PL has been revised and minor changes have been introduced in the product information.

2.7.1. User consultation

No justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH. However, the changes to the package leaflet are minimal and do not require user consultation with target patient groups.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

DR-TB in children is a serious and life-threatening disorder with only few treatment options. Routine surveillance data on MDR-TB among children are not available globally. Approximately 3% of children with TB are estimated to have MDR-TB. Global estimates of the burden of MDR-TB in children range from 25,000 to 32,000 incident cases annually. MDR-TB is an orphan disease in EU and USA.

The principles of MDR/XDR-TB treatment regimens used in children are similar to those of adults, requiring use of second-line drugs that are often more toxic and more expensive than first line options. The need for new therapeutic options to treat MDR-TB remains high. BDQ represents a valuable therapeutic treatment option with advantages in safety profile over authorised injectable (aminoglycoside) and other second-line agents.

BDQ has been authorised in adult subjects only since 2014 and is currently approved in paediatric patients ≥5 years old for combination regimen for pulmonary multidrug-resistant tuberculosis (MDR-TB). This application concerns an extension of indication for Sirturo to also include treatment of paediatric patients (2 years to less than 5 years of age and weighing at least 7 kg) with pulmonary TB due to Mycobacterium tuberculosis resistant to at least rifampicin and isoniazid.

3.1.2. Available therapies and unmet medical need

The principles of MDR/XDR-TB treatment regimens used in children are similar to those of adults, requiring use of second-line drugs that are often more toxic and more expensive than first line options.

BDQ has been authorised in adult subjects only since 2014 and was approved in paediatric patients ≥5 years old for combination regimen for pulmonary MDR-TB.

In 2022, new guidelines and an operational handbook have been developed by the WHO to better manage TB in children and adolescents. Based on currently available safety and efficacy data, the 2022 WHO guidelines prioritize a 6-month BPaLM regimen for treatment of RR/MDR-TB in patients aged ≥14 years. In 2024, WHO recommended a new 6-month BDLLfxC regimen that expands the use of a 6-month regimen to adolescents and children of all ages. Additional 9-month regimens (BLMZ, BLLfxCZ, and BDLLfxZ) are recommended by WHO as alternatives to longer (18-month) regimens in patients of all ages with RR/MDR-TB.

3.1.3. Main clinical studies

This application is based on the results from the study TMC207-C211, which is a clinical phase 2, still ongoing, multicentre, single arm, open-label study including four different cohorts which are based on age group. This application is supported by the Week 24 analysis of Cohort 3, which has completed enrolment. The primary objective was to evaluate the PK, safety and tolerability of BDQ over a 24-week treatment period in each age cohort and to provide guidance on dose selection for each of the age cohorts. This small, single-arm study is not designed to support direct inferences of efficacy, which was a secondary objective and is presented descriptively.

Cohort 3 included 15 paediatric subjects ≥2-<5 years of age with confirmed or probable MDR-TB infection, which were enrolled and treated with BDQ in combination with an individualized background regimen. These paediatric subjects received weight-based dosage (8 mg/kg once daily for 2 weeks

followed by 4 mg/kg tiw for 22 weeks [rounded up or down to the closest 10-mg unit]) using the commercial, age-appropriate 20-mg scored tablet (G008).

Efficacy assumptions in the paediatric population are based on extrapolation from the adult population via PK bridging.

3.2. Favourable effects

The PK analyses included data from all 15 patients in cohort 3 which included the PK-sampling of bedaquiline and M2 at Weeks 2 and 12 as well as sparse PK sampling at Week 24.

The PK-data were analysed using non-compartmental analyses separately for each week with PK-sampling. A comparison to corresponding adult PK exposures showed that the PK exposures following the studied posology were comparable between adults and children aged 2-5 years.

The PK-data were also analysed using PopPK modelling which included 386 BDQ and 386 M2 concentration from the 15 patients in Cohort 3. The simulations from the PopPK model of the proposed posology showed that the average exposures for the proposed posology in patients aged 2-5 years with body weight of 7-15kg are comparable to adults. The paediatric exposures were within the adult target exposure range.

Descriptive efficacy results were favourable in terms of treatment response. All participants in Cohort 3 had a "resolved" or "partially resolved" investigator's global TB assessment at Week 24. At the data cutoff date, all 7 participants that reached Week 120 or discontinued prematurely had a favourable treatment outcome at study end, including one MGIT-evaluable participant achieved who culture conversion by Week 4 (Day 29) with sustained MGIT culture conversion up to Week 120.

Updated data for Cohorts 1 and 2 show that favourable treatment outcome was sustained up to the end of the study (Week 120) for all participants who achieved favourable treatment outcome at Week 24. MGIT culture conversion was sustained until end of study for all participants who achieved culture conversion at Week 24 in these cohorts.

3.3. Uncertainties and limitations about favourable effects

The PK analyses have the limitation that observed PK data were only available from patients weighing >10 kg whereas a posology is sought in patients ≥7 kg. This implies extrapolation supported only by PopPK-based simulations for patients <10 kg. The MAH provided adequate PopPK simulations to support the proposed dose. The PopPK model is considered fit-for-purpose for supporting extrapolation outside the observed body weight range.

With regard to efficacy outcomes, treatment outcome is not considered possible to assess fully until Week 120, and in this report only data from primary Week 24 analysis is available for Cohort 3. More importantly, this small, single-arm study aims to support extrapolation of efficacy and safety to paediatric patients through PK bridging, which is generally accepted for this condition. Standalone conclusions on efficacy and safety in this age group 2 to < 5 years of age cannot be made on the basis of the descriptive efficacy data.

3.4. Unfavourable effects

All participants reported at least one adverse event, none of them serious. Two participants reported Grade 3 events (amylase increased and neutrophil count decreased, respectively). Two participants reported three AESIs: amylase increased (grade 3), QT prolongation (454ms, increased 47ms from baseline), and conjunctivitis grade 2.

None of the subjects met the criteria of Hy´s law. None of the participants had ALT/AST ≥10x ULN, creatine kinase ≥10x ULN, or persistent haematuria. None of the participants discontinued the study due to reported AEs. No participants died.

It should be noted that all reported AEs in this limited study are already known based data provided from the adult studies. No new safety issue has been detected.

3.5. Uncertainties and limitations about unfavourable effects

This is a limited study consisting of 15 paediatric subjects, and the data provided is complete up to Week 24 but not up to Week 120 for all participants.

All subjects were treated with 3-5 other medicines, some of them with potential to cause hepatotoxicity and skin reactions. It might therefore be challenging to evaluate whether BDQ only was associated with the observed AEs or if it was a result of treatment with the background regimen and/or BDQ.

3.6. Effects Table

Table 8. Effects Table for bedaquiline in treatment of MDR-TB (data cut-off: 09 May 2024).

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
PK BDQ 10-15 kg	Geometric mean (%CV) model-predicted AUC_{168h} at Week 24	ng·h/mL	126000 (37.9%)	Adult reference range: 86200 to 201000 ng·h/mL	The model-predicted W24 results agree with simulated and non-compartmental analysis results at Weeks 2, 12 and at steady state. The exposure for The model-predicted exposure is based on the studied posology which is slightly different from the proposed posology.	Study TMC207-C211 Cohort 3
PK BDQ 7-10 kg	Geometric mean (SD) PopPK simulated	ng·h/mL	115000 (75200)	Adult reference range: 86200 to	There are no observed PK data in patients <10 kg. The PopPK model is considered fit-for-	Simulations from the PopPK model (see

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
	AUC_{168h} at Week 12			201000 ng·h/mL	purpose for extrapolating PK in patients ≥7kg. The W24 results agree with simulated results at Weeks 2, 12 and at steady state.	Report 272949)
Efficacy: Favourable treatment outcome	Week 24 interim analysis	N (%)	4/15 (26.7%)	N/A	Final tx outcome can only be assessed at Week 120. Descriptive statistics.	Study TMC207-C211 Cohort 3
Efficacy: Radiological improvement	Week 24 interim analysis	N (%)	10/15 (66.7%)	N/A		
Efficacy: Resolution of signs and symptoms	Week 24 interim analysis	N (%)	13/15 (86.7%)	N/A		
Efficacy: Negative culture	Week 24 interim analysis	N	1/1	N/A		
Unfavourable Effects						
Known ADRs: vomiting, QTc prolonged, Arthralgia	Week 24 interim analysis	N (%)	3/15 (20%), 1/15, 1/15 (6.7%)	SmPC: *Very common*		Study TMC207-C211 Cohort 3

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The need for new therapeutic options to treat MDR-TB remains high. BDQ represents a valuable therapeutic treatment option with advantages in safety profile over authorised injectable (aminoglycosides) and other second-line agents.

The efficacy of BDQ in combination therapy for MDR-TB has previously been established from pivotal clinical studies in adults. This extension of indication application to include the paediatric population

(from 2 to 5 years) for the treatment of MDR-TB relies on extrapolation of clinical efficacy and safety, which requires demonstration of comparable plasma exposures in children to those in adults (i.e. exposure matching).

To this end, PK data and resulting analyses are pivotal to this submission. A limitation is that the observed PK data were only available from patients weighing >10 kg whereas a posology is sought in patients ≥7 kg. This implies extrapolation supported only by PopPK-based simulations for patients <10 kg. The MAH provided adequate PopPK simulations to support the proposed dose. The PopPK model is considered fit-for-purpose for supporting extrapolation outside the observed body weight range.

The proposed posology in patients >10 kg is acceptable since this is within the observed body weight range and the provided PK analyses showed that the exposure of both the observed and proposed posology in patients >10 kg is comparable to adults.

The descriptive efficacy data observed at the Week 24 analysis for Cohort 3, as well as updated long-term Week 120) efficacy data for Cohorts 1 and 2 provided with this submission, have their limitations but indicate favourable outcomes.

Within this application, whilst acknowledging the very limited size of the new safety dataset, no new ADRs for BDQ has been identified in paediatric subjects and the reported AEs are in line with the ones that are known from studies in adult subjects.

3.7.2. Balance of benefits and risks

The balance of benefits and risk for the extension of indication of treatment of MDR-TB to include patients aged 2 years and older and weighing 7 kg is considered positive.

3.8. Conclusions

The overall B/R of Sirturo is positive.

4. Recommendations

Outcome

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

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

Extension of indication to include treatment of paediatric patients (2 years to less than 5 years of age and weighing at least 7 kg) with pulmonary tuberculosis (TB) due to Mycobacterium tuberculosis resistant to at least rifampicin and isoniazid, for SIRTURO, based on the Week 24 primary analysis from Cohort 3 (≥2 to <5 years of age) of Study TMC207-C211; this is an open-label, multicentre, single-arm study to evaluate pharmacokinetics, safety/tolerability, antimycobacterial activity and dose selection of bedaquiline in children (birth to <18 years) with multidrug-resistant-TB (MDR-TB). Long-term follow-up to Week 120 in participants of Cohort 1 (≥12 to <18 years of age) and Cohort 2 (≥5 to <12 years of age) have also been submitted. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated.

The Package Leaflet is updated in accordance. Version 11.1 of the RMP has also been approved. In addition, the Marketing authorisation holder (MAH) took the opportunity to update the list of local representatives in the Package Leaflet and introduce minor changes to the PI.

The variation leads to amendments to the annexes I and IIIB and to the Risk Management Plan (RMP).

Amendments to the marketing authorisation

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

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan EMA/PE/0000181219 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

Similarity with authorised orphan medicinal products

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