12 December 2019
EMA/982/2020
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

SIRTURO

International non-proprietary name: bedaquiline

Procedure No. EMEA/H/C/002614/II/0033/G

Note

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

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List of abbreviations

ADR	adverse drug reaction
AE	adverse event
AFB	acid-fast bacilli
ALT	alanine aminotransferase
AM	amikacin
AST	aspartate aminotransferase
ATP	adenosine 5'-triphosphate
AUCxh	area under the plasma concentration-time curve from the time of dose administration up to x hours post dose
AUClast	area under the plasma concentration-time curve from the time of dose administration to the time of the last quantifiable concentration
BDQ	bedaquiline
BR	background regimen
CFZ	clofazimine
CI	confidence interval
CM	capreomycin
Cmax	maximum plasma concentration
Cmin	minimum plasma concentration
CSR	clinical study report
CXR	chest X-ray
DB	database
DS(-TB)	drug-susceptible (tuberculosis)
DST	drug susceptibility testing
ECG	electrocardiogram
EMB	ethambutol
EU	European Union
FDA	Food and Drug Administration
HIV(-1/2)	human immunodeficiency virus (type 1/type 2)
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
INH	isoniazid

IQR	interquartile range
ITT	intent-to-treat
KM	kanamycin
LFX	levofloxacin
M. tuberculosis	Mycobacterium tuberculosis
M=F	Missing = Failure
M2	N-monodesmethyl metabolite of bedaquiline
MDR	multidrug-resistant
MDR(-TB)	multidrug-resistant (tuberculosis)
MDR-TBH&R	multidrug-resistant tuberculosis excluding pre-XDR and XDR (ie, resistant only to INH and RMP)
MDR-TBRR	rifampicin-monoresistant tuberculosis
MedDRA	Medical Dictionary for Regulatory Activities
MFX	moxifloxacin
MGIT	Mycobacteria Growth Indicator Tube
MIC	minimal inhibitory concentration
mITT	modified intent-to-treat
NTP	National Tuberculosis Program
PAS-C	para-aminosalicylic acid
PK	pharmacokinetic(s)
PopPK	population pharmacokinetic(s)
pre-XDR(-TB)	pre-extensively drug-resistant (tuberculosis)
PT	preferred term
PTO	prothionamide
PZA	pyrazinamide
qd	quaque die; once daily
QTcF	QT interval corrected for heart rate according to Fridericia
RMP	rifampin/rifampicin
SAE	serious adverse event
SCE	Summary of Clinical Efficacy
SCS	Summary of Clinical Safety
SMQ	Standardized MedDRA Queries
TB	tuberculosis

TBD	to be decided
tiw	three times per week
tmax	time to reach the maximum plasma concentration
TMC207	bedaquiline
ULN	upper limit of laboratory normal range
US	United States
WHO	World Health Organization
XDR(-TB)	extensively drug-resistant(tuberculosis)

1. Background information on the procedure

1.1. Type II group of variations

Pursuant to Article 7.2 of Commission Regulation (EC) No 1234/2008, Janssen-Cilag International NV submitted to the European Medicines Agency on 11 October 2018 an application for a group of variations.

The following variations were requested in the group:

Variations requested		**Type**	**Annexes affected**
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I
C.I.6.z	C.I.6.z - Change(s) to therapeutic indication(s) - Other variation	Type II	I and IIIB

Grouping of an Extension of Indication to include patients 12 years of age and older for SIRTURO and a Type II variation to change the safety information in Section 4.9 of the SmPC.

The extension of indication is supported by the Week 24 analysis of Cohort 1 (adolescent subjects aged ≥12 to <18 years) of Study TMC207-C211. Based on these data, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance.
An updated version of the RMP (version 3.2) was included in the submission.

SIRTURO, was designated as an orphan medicinal product EU/3/05/314 on 26 August 2005.

SIRTURO was designated as an orphan medicinal product in the following indication: treatment of tuberculosis.

The extended indication, which is the subject of this application, falls within the above-mentioned orphan designation.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0371/2016 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

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

Protocol assistance

The MAH did not seek Protocol Assistance at the CHMP.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Filip Josephson Co-Rapporteur: Ingrid Wang

Timetable	Actual dates
Submission date	11 October 2018
Start of procedure:	3 November 2018
CHMP Co-Rapporteur Assessment Report	20 December 2018
CHMP Rapporteur Assessment Report	21 December 2018
PRAC Rapporteur Assessment Report	21 December 2018
PRAC members comments	10 January 2019
PRAC Outcome	17 January 2019
CHMP members comments	27 January 2019
Updated CHMP Rapporteur(s) (Joint) Assessment Report	24 January 2019
Request for supplementary information (RSI)	31 January 2019
CHMP Rapporteur Assessment Report	29 April 2019
PRAC Rapporteur Assessment Report	29 April 2019
PRAC members comments	7 May 2019
PRAC Outcome	16 May 2019
CHMP members comments	20 May 2019
Updated CHMP Rapporteur Assessment Report	21 May 2019
Request for supplementary information (RSI)	29 May 2019
CHMP Rapporteur Assessment Report	20 August 2019
PRAC Rapporteur Assessment Report	20 August 2019
PRAC members comments	28 August 2019
PRAC Outcome	5 September 2019
CHMP members comments	9 September 2019
Updated CHMP Rapporteur Assessment Report	12 September 2019
Request for supplementary information (RSI)	19 September 2019
CHMP Rapporteur Assessment Report	2 October 2019
CHMP members comments	7 October 20190
Updated CHMP Rapporteur Assessment Report	10 October 2019
Request for supplementary information (RSI)	17 October 2019
CHMP Rapporteur Assessment Report	21 November 2019
CHMP members comments	02 December 2019
Updated CHMP Rapporteur Assessment Report	n/a
Opinion	12 December 2019

2. Scientific discussion

2.1. Introduction

Bedaquiline (SIRTURO) received a conditional approval in the EU in March 2014 and is "indicated for use as part of an appropriate combination regimen for pulmonary multidrug-resistant tuberculosis (MDR-TB) in adult patients (≥18 years of age) when an effective treatment regimen cannot otherwise be composed for reasons of resistance or tolerability".

Within this application the MAH has provided clinical data to include adolescents from 12 years of age in the indication. Adolescent subjects received the adult dosing regimen (400 mg QD for 14 days, followed by 200 mg TIW for 22 weeks) using the already approved adult 100 mg tablet. No new quality data and no new non-clinical data, apart from an updated environmental risk assessment, have been submitted in this application, which is considered acceptable by CHMP.

2.2. Quality aspects

This application does not include any specific quality variation application and the already approved formulation, 100 mg tablet for adults, is proposed for the paediatric population from 12 years of age. The tablets are uncoated, round biconvex tablet, 11 mm in diameter. The tablets contain the excipients cellulose, microcrystalline 82.2 mg, croscarmellose sodium 23.0 mg, hypromellose 8.0 mg, lactose monohydrate 152.9 mg, magnesium stearate 4.6 mg, maize starch 66.0 mg, polysorbate20 1.0 mg and silica colloidal anhydrous 1.4 mg.

Suitability of the formulation for the paediatric population from 12 years of age.

Since the variation concerns introduction of a paediatric population, the suitability of the proposed formulation in the proposed age group should have in principle been addressed, in line with the Guideline on pharmaceutical development of medicines for paediatric use EMA/CHMP/QWP/805880/2012 Rev.2. No such justification has been provided, but CHMP agreed that this was acceptable, since the proposed adult formulation only contains commonly used excipients in amounts for which no safety issues are foreseen in the proposed target age group. CHMP agreed therefore that the proposed adult formulation is considered acceptable from a quality point of view.

2.3. Non-clinical aspects

As the current application is a grouping of variations that includes a paediatric extension of the approved indication for Sirturo, the application included in the submission a full revised environmental risk assessment (ERA), including Phase I and Phase II, tier A and B studies. This ERA report differs from the previous report submitted at the time of the initial approval in 2014 only in the prevalence data used to calculate the Fpen, and consequently these data were assessed.

2.3.1. Ecotoxicity/environmental risk assessment

At the time of the initial approval, the substance bedaquiline was classified as a PBT (persistence, bioaccumulation, toxicity) substance.

PBT-assessment			
Parameter	Result relevant for conclusion		Conclusion
Bioaccumulation	log Kow /Dow	pH 3: 2.93	Not B
	BCF	1433 and 2049	B
Persistence	DT50 or ready biodegradability	Freshwater DT50: 2.7 days Sediment DT50: 257 days	P

Toxicity	NOEC	Algae: 0.77µg/L Daphnia: 4.7 µg/L Fish: 4.1 µg/L	T
PBT-statement :	The compound is considered as PBT		

As already mentioned, the revised ERA is based on updated prevalence data used to calculate the Fpen. During the assessment the MAH was asked by CHMP to provide the predicted environmental concentration in surface water (PECsurfacewater) with a percentage of market penetration (Fpen) taking into account regional differences and using the most conservative prevalence values of the disease in the EU and to recalculate the Fpen using both the prevalence data for the pediatric and the adult population In addition, the MAH was requested to complete the risk assessment for sediment (phase II, Tier B), according to the EMA guideline, and to provide the test report from the study on Anabaena flosaquae.

In the algal growth inhibition test with Cyanobacterium Anabaena flosaquae, bedaquiline had no apparent toxic effect during the 72-hour test period up to and including the highest concentration (0.78 µg/L).

Calculation and refinement of $PEC_{surfacewater}$

$PEC_{surfacewater}$ using an unrefined Fpen and using a bedaquiline dose of 400mg/day, is 2 µg/L.

The $PEC_{surfacewater}$ is refined using an estimation for the market penetration of the product, taking account of the sales forecast.

According to the MAH, using an estimation of the use of 314.5 kg/year in the EU (2018-2023 and 512.700 million inhabitants in EU), an Fpen of 0.0000042 (= 0.00042%) can be calculated, resulting in a PECsurfacewater of 0.00084 µg/L.

During the treatment period of 6 months, 18,800 mg are consumed per patient. This results in a total volume of 314.347 kg bedaquiline on the EU-market including both adult and paediatric patients.

Using this PECsurfacewater to calculate risk quotients (ratio PECsurfacewater/PNECwater is below 1; 0.00084 µg/L / 0.077 µg/L), no risk is identified for any of the compartments, but since the substance is a PBT, the following wording is included in the product information:

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

2.3.2. Discussion on non-clinical aspects

Apart from the updated ERA, no additional non-clinical data were submitted, which was considered acceptable by CHMP.

2.3.3. Conclusion on the non-clinical aspects

CHMP agreed that the updated data submitted for assessment in this application do not lead to a significant increase in environmental exposure further to the use of bedaquiline.

Considering the above data, bedaquiline should be used according to the precautions stated in the SmPC in order to minimize any potential risks to the environment.

2.4. Clinical aspects

2.4.1. Introduction

GCP

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

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

- Tabular overview of clinical studies

Tabulated Overview of Studies Supporting the Use of Bedaquiline in Pediatric Subjects With Confirmed or Probable Multidrug-resistant Tuberculosis Infection

Study (Phase, Status)	Treatment	Number of Subjects	Primary Endpoint
Pediatric subjects with confirmed or probable multidrug-resistant tuberculosis			
TMC207-C211 (Phase 2, ongoing)	**Cohort 1** (≥12 to <18 years) - BDQ[a] 400 mg qd for first 14 days - BDQ[a] 200 mg tiw (intakes at least 2 days apart) for following 22 weeks (ie, the adult dose regimen).	Enrolled N=15	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 evaluated in this study.
	Cohort 2[b] (≥5 to <12 years) - BDQ[c] 200 mg qd for first 14 days - BDQ[c] 100 mg tiw (intakes at least 2 days apart) for following 22 weeks.	Enrolled N=15[d]	
	Cohort 3[b] (≥2 to <5 years) Dose TBD based on Cohort 2 data[c]	Planned N= up to 15	
	Cohort 4[b] (0 months to <2 years) Dose TBD based on Cohort 2 and 3 data[c]	Planned N= up to 15	
Healthy adult subjects			
TMC207TBC1002 (Phase 1, final)	- BDQ 100 mg single dose as one 100-mg tablet[a] - BDQ 100 mg single dose as five 20-mg tablets - BDQ 100 mg single dose as 5 grams of granules containing 20 mg/g oral granulate	Enrolled N=36	Assess the relative bioavailability of BDQ after single-dose administration of 100 mg of BDQ as 20-mg tablets or granules using a 100-mg tablet formulation as the reference, with and without food.

BDQ = bedaquiline; CSR = clinical study report; CO = Clinical Overview; N = number of subjects; PK = pharmacokinetics; qd = once daily; SCE = Summary of Clinical Efficacy; SCS = Summary of Clinical Safety; TBD = to be decided; tiw = three times per week; TMC207 = bedaquiline.

[a] Bedaquiline oral tablet formulation was used, containing 100 mg bedaquiline per tablet (ie, the registered adult tablet, F001).

[b] Not in scope of this addendum to the CO.

[c] An age-appropriate oral formulation is/will be used in Cohorts 2, 3, and 4 (scored 20-mg tablet) containing 20 mg bedaquiline per tablet.

[d] Data on file.

2.4.2. Clinical Pharmacology aspects

Special populations

Data from the cohort 1 in the Phase 2 Study TMC207-C211 (open-label, single-arm study), including 15 adolescent subjects (≥12 to <18 years of age) are included in the pharmacokinetic analysis to support the extension of indication to include adolescent patients from 12 years of age.

The aim was to match the plasma exposure of bedaquiline in adolescent patients to the 60% – 140% range for the adult geometric mean AUC168h (86.200 ng*hr/mL – 201.000 ng*h/mL) at steady-state for a dose of 200 mg three times per week. The AUC168h at steady-state (144 ng*h/mL) is the geometric mean of an adult patient database sampled from the adult Phase 2 data used to develop the POP-PK model. This

geometric mean is close to the observed AUC168hfor a typical black subject (142 ng*h/mL) that was shown to be efficacious in the adult Phase 2b studies TMC207-C208 and TMC207-C209.

In addition, pharmacokinetic data from three subjects from cohort 2 (≥5 to <12 years of age) were provided. These subjects received a scored 20-mg tablet formulation. Moreover, the results from a Phase 1 Study TMC207TBC1002, performed to assess the relative bioavailability of bedaquiline following single-dose administration of 2 paediatric formulations (one of these being the 20-mg tablet given to cohort 2) in healthy adult subjects was also provided in this submission.

CHMP agreed that the MAH aim to match the exposure of bedaquiline in adolescent patients to the 60% – 140% range for the adult geometric mean AUC168h (86.200 ng*hr/mL – 201.000 ng*h/mL) based on the geometric mean of a virtual adult patient database is acceptable. Despite the fact that data from cohort 2 (children aged ≥5 to <12 years of age) and from Study TMC207TBC1002 were out of the scope of this application, these data are briefly summarised in this report.

2.4.2.1. Methods – analysis of data submitted

Analytical method

The liquid chromatographic-mass spectrometry/mass spectrometry (LC-MS/MS) bioanalytical method used for combined determination of bedaquiline and M2 in plasma in the original submission (PBRL-RD-780) was updated and validated for human lithium-heparin plasma samples in analytical method BA10375 (including evaluation of the additional stability of bedaquiline and M2 in stock solutions and in spiked human lithium-heparin plasma samples). The method was subsequently revalidated in analytical method BA10946 due to transfer of the method from an API3000 MS/MS system to an API5500 MS/MS system, and also to accommodate a reduction in the assay sample volume. In addition, a partial validation to the use of human Na-heparin plasma was done.

The method BA10946 was used for bioanalysis of samples from the clinical study TMC207-C211.

Table 1. Bioanalytical method for Bedaquiline and M2: Validation Parameters and Results for analytical Methods VA10375 and BA10946

Validation Parameters	BA10375		BA10946	
	Bedaquiline	M2 (R405786)	Bedaquiline	M2 (R405786)
Laboratory	PRA Health Sciences		PRA Health Sciences	
Matrix	Human lithium-heparin plasma (unless stated otherwise)		Human lithium-heparin plasma	
Lower limit of quantification (ng/mL)	-	-	1.00	1.00
Calibration range (ng/mL)	1.00 - 2,000	1.00 - 2,000	1.00 - 2,000	1.00 - 2,000
Regression parameters	-	-	Correlation coefficient: 0.9974 to 0.9991	Correlation coefficient: 0.9994 to 0.9996
Overall bias (%) [a]	1.00 ng/mL: -2.3 3.00 ng/mL: -0.4 100 ng/mL: -1.7 1,600 ng/mL: -7.0	1.00 ng/mL: 0.7 3.00 ng/mL: -1.6 100 ng/mL: 1.1 1,600 ng/mL: -3.3	1.00 ng/mL: 4.4 3.00 ng/mL: -1.7 100 ng/mL: -0.7 1,600 ng/mL: 1.8	1.00 ng/mL: 8.6 3.00 ng/mL: -0.1 100 ng/mL: 1.3 1,600 ng/mL: 4.4
Total precision (%) [b]	1.00 ng/mL: 12.0 3.00 ng/mL: 5.1 100 ng/mL: 3.7 1,600 ng/mL: 4.1	1.00 ng/mL: 16.2 3.00 ng/mL: 4.4 100 ng/mL: 3.9 1,600 ng/mL: 2.9	1.00 ng/mL: 4.3 3.00 ng/mL: 3.2 100 ng/mL: 3.2 1,600 ng/mL: 3.2	1.00 ng/mL: 6.8 3.00 ng/mL: 2.7 100 ng/mL: 3.4 1,600 ng/mL: 4.9
Maximum number of samples	189	189	122	122
Quality control samples	Within criteria	Within criteria	Within criteria	Within criteria
Accuracy and precision (up to 10-fold diluted validation samples)	10.0 - 20,000 ng/mL	10.0 - 20,000 ng/mL	-	-
Selectivity	Within criteria	Within criteria	Within criteria	Within criteria
Effect of plasma hemolysis	Within criteria	Within criteria	-	-
Matrix variability (bias [%]/precision [%])	1.00 ng/mL: 0.0/13.1	1.00 ng/mL: -11.8/8.5	1.00 ng/mL: 4.0/3.3	1.00 ng/mL: -0.3/5.1
Relative matrix factor (range/%CV)	-	-	3.00 ng/mL: 0.959 to 1.06/3.6 1,600 ng/mL: 0.979 to 1.02/1.6	3.00 ng/mL: 0.955 to 1.03/3.1 1,600 ng/mL: 0.937 to 1.01/2.9
Matrix effect in lipemic plasma	-	-	Within criteria	Within criteria
Matrix effect	3.00 ng/mL: within criteria 1,600 ng/mL: within criteria	3.00 ng/mL: within criteria 1,600 ng/mL: within criteria	-	-
Recovery of analyte (%)	3.00 ng/mL: 79.6 100 ng/mL: 84.2 1,600 ng/mL: 74.2	3.00 ng/mL: 97.1 100 ng/mL: 116.6 1,600 ng/mL: 109.3	3.00 ng/mL: 88.3 100 ng/mL: 89.5 1,600 ng/mL: 87.9	3.00 ng/mL: 84.2 100 ng/mL: 89.3 1,600 ng/mL: 86.5
Recovery internal standard (%)	50.0 ng/mL: 112.8	50.0 ng/mL: 85.3	50.0 ng/mL: 98.5	60.8 ng/mL: 91.8
Carry-over (contribution of analyte in blank matrix)	Within criteria	Within criteria	Within criteria	Within criteria
Stock solution stability (bedaquiline: 1.00 mg/mL; M2: 0.100 mg/mL)	Room temperature: 18 hours; Refrigerator (+4°C): 31 days	Room temperature: 18 hours; Refrigerator (+4°C): 182 days	Room temperature: 24 hours; Refrigerator (+4°C): 10 days	Room temperature: 18 hours; Refrigerator (+4°C): 182 days
Processed sample stability	-		+10°C: 97 hours	
Re-injection reproducibility	+10°C: 137 hours (original curve), +10°C: 137 hours (reinjected curve)		+10°C: 99 hours (original curve), +10°C: 99 hours (reinjected curve)	
Spiked human lithium-heparin plasma	Room temperature: 26 hours 5 freeze/thaw cycles (-20°C and -70°C)		-	
Spiked human lithium-heparin blood	Melting ice: 2 hours (incubation for 30 minutes at 37°C, followed by storage at 0°C for 10 minutes) Room temperature: 2 hours (incubation for 30 minutes at 37°C)		-	
Long term stability in human lithium-heparin plasma	-20°C: 410 days -70°C: 714 days		-	
Autosampler stability	+10°C: 119 hours	+10°C: 120 hours	-	
Partial validation for sodium-heparin plasma				
Within-run bias (%) [a]	1.00 ng/mL: 6.9 3.00 ng/mL: 4.4 100 ng/mL: 0.4 1,600 ng/mL: -8.9	1.00 ng/mL: -12.1 3.00 ng/mL: -9.3 100 ng/mL: 1.0 1,600 ng/mL: -7.0	-	
Total precision (%) [b]	1.00 ng/mL: 6.6 3.00 ng/mL: 2.1 100 ng/mL: 1.9 1,600 ng/mL: 2.3	1.00 ng/mL: 9.6 3.00 ng/mL: 4.3 100 ng/mL: 4.2 1,600 ng/mL: 3.1	-	

CV=coefficient of variation.
[a] Bias (accuracy) within criteria between -15.0% and +15.0% (-20.0% and +20.0% for the lowest concentration).
[b] CV (precision) within criteria if <15% (<20% for the lowest concentration) for BA10375 and if ≤15% (≤20% for the lowest concentration) for BA10946.

CHMP agreed that the performance of the analytical method was satisfactory according to the validation report. It was noted that an interim bioanalysis report with information on the in-study validation for study TMC207-C211 (as the study is ongoing) was provided and was considered satisfactory.

Dosing

The subjects in cohort 1 (adolescent subjects ≥12 to <18 years of age) received 400 mg once daily (qd) for the first 14 days, followed by bedaquiline 200 mg three times per week (tiw) with intakes at least 2 days (48 hours) apart for 22 weeks (i.e., the adult dose and dose regimen). The subjects received the commercial 100-mg oral tablet (F001).

Sampling

Rich PK data collection was performed at week 2 (pre-dose (time 0), and at 2, 4, 6 and 8 hours post dose) and week 12 (time points not presented). At Week 24 only a trough sample (Cmin) was drawn.

Non-compartmental analysis

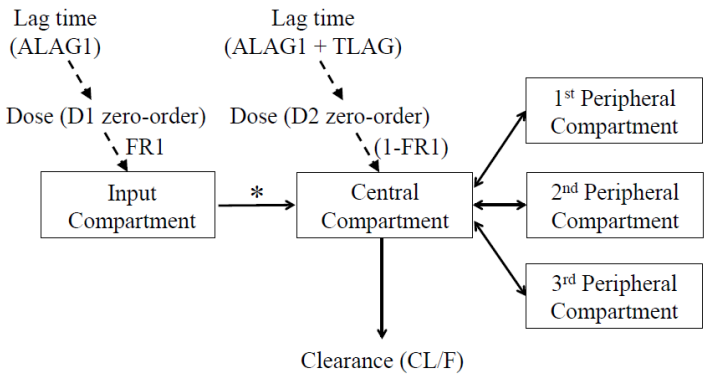
All PK parameters (tmax, Cmin, Cmax, AUC24h) were calculated using conventional non-compartmental methods (using WinNonlin, Microsoft Excel) using actual times of blood sampling, unless otherwise stated in the clinical study report.

Population Pharmacokinetics

All model-based analyses presented used a previously developed population PK model developed across 9 adult clinical studies in both healthy volunteers and patients.

The PK model previously developed for TMC207 was a 4-compartment disposition model with dual zero-order input (Figure 1). Two demographic covariates were included in the model. These were an increase in CL/F of 52.0% for subjects of Black race when compared to subjects of other races, and a decrease in Vc/F of 15.7% for females when compared to males. Residual unexplained variability (RUV) was estimated to be 20.6%. Parameters for the TMC207 PK model are presented in Table 2.

Figure 1. Schematic Diagram of the TMC207 Population PK Model



*Rate parameter fixed to 1000. D1 & D2, duration of dose into the input and central compartments, respectively; FR1, fraction of dose into the input compartment.

To appropriately account for the age-related changes in children and adolescence, allometric scaling of clearance and volume parameters based on total body weight (WT) was included, and fixed to 0.75 and 1, respectively.

Maximum a posteriori estimates of individual PK parameters were determined for each subject and then used to simulate concentrations. Exposure metrics (AUC168h) at week 12 and week 24 were then derived from the simulated concentrations using non-compartmental methods. Additionally, AUC24h at Weeks 12 was computed from the simulations and graphically compared to the observed AUC24h.

Table 2. Parameter Estimates for the TMC207 Population PK Model

Parameter		Parameter Estimate	Parameter SEE (CV%)	BSV Estimate (CV%)	BSV SEE (CV%)
CL/F (L/hr)	θ_1	2.78	5.1	50.4	12.3
V_c/F (L)	θ_2	164	5.0	39.1	15.6
CL_{p1}/F (L/hr)	θ_3	11.8	7.6		
V_{p1}/F (L)	θ_4	178	8.1		
CL_{p2}/F (L/hr)	θ_5	8.03	4.9		
V_{p2}/F (L)	θ_6	3010	9.0		
CL_{p3}/F (L/hr)	θ_7	3.58	9.0		
V_{p3}/F (L)	θ_8	7350	5.8		
FR1 (%)	$\theta_9/(1+\theta_9)$	58.5	11.1*	113	15.9
D1 (hr)	θ_{10}	2.22	1.0		
TLAG (hr)	θ_{11}	1.48	3.2		
D2 (hr)	θ_{12}	1.48	3.2		
ALAG1 solution (hr)	θ_{13}	0.541	5.7		
ALAG1 tablet (hr)	θ_{14}	0.917	0.6		
Study R207910-CDE102 or TiDP13-C104 on F	θ_{15}	1.51	7.5		
Other Studies on F**	θ_{16}	2.03	4.7		
Increase in CL with Black race (%)	θ_{17}	52.0	21.2		
Decrease in V_c with female sex (%)	θ_{18}	-15.7	42.5		
Increase in CL for healthy volunteers or C202 (%)	θ_{19}	37.5	35.2		
Between-subject variability on F	η_F			39.6	9.3
RUV (CV%)		20.6	3.3		
RUV on TiDP13-C208 or TiDP13-C209 (CV%)		27.7	3.2		
Correlation CL/V_c		0.407			

*On estimate of θ_9 (=1.41)
**Refers to studies TMC207-TiDP13-C109, TMC207-TiDP13-110, TMC207-TiDP13-111, TMC207-TiDP13-202 and TMC207-TBC1003

CHMP noted during the assessment that the demographics of the population included in the model development step was not presented, and asked for further clarification as to how well the model predicted the data that were used for model development and as to whether it was the model that was used to simulate the target mean AUC0-168h in adults.

The MAH has presented plots after the MAP analysis with the already developed model and demographics of the paediatric patient population. In the original application (EMEA/H/C/2614) the model presented appears to be the same as used in this application. The model predicted the adult healthy and patient data adequately.

The goodness-of-fit plots for the paediatric population did not show any large trends, although some high concentrations were slightly underpredicted. The visual predictive check plot, showing observed and predicted concentrations at week 12, indicates that the model predicts the data adequately.

The MAH has confirmed that this model was the one used to simulate the target mean area under the plasma concentration-time curve from the time of dose administration up to 168 hours post-dose (AUC168h) in adults at steady-state.

2.4.2.2. Results

Sampling

Primarily sparse PK sampling (Ctrough) has been performed. Rich PK data collection was performed at week 2 (day 14) and week 12. For 7 subjects the PK sampling was performed on Day 15 (first day of maintenance dose) instead of Day 14. At Week 24 only a trough sample (Cmin) was drawn. One subjects prematurely discontinued the study prior to week 24 PK sampling. Two additional subjects were not included in the week 24 analysis as they had their minimum plasma concentration (Cmin) sample taken 48 hours post-dose instead of 24 hours post-dose. Due to this deviation, the Cmin of both subjects were excluded from the summary statistics.

All pre-treatment/pre-dose samples were below limit of quantification, and one sample was found to be below limit of quantification post-dose. These samples were excluded from the analysis.

Study population

In Cohort 1 of the Clinical Pharmacology Study TMC207-C211, 15 adolescent subjects (≥12 to <18 years of age) with confirmed or probable pulmonary multidrug-resistant tuberculosis were enrolled. The median age at screening was 16 years (range: 14 to 17 years) and the median body mass index was 17.90 kg/m2 (range: 15.6 to 27.9 kg/m2). The majority of the 15 subjects were girls (12 subjects [80.0%]) and black (8 subjects [53.3%]). Eleven subjects (73.3%) had confirmed multidrug-resistant tuberculosis; the remaining 4 subjects (26.7%) were diagnosed with probable multidrug-resistant tuberculosis.

Table 3. Summary of Subject Demographics: Cohort 1

	Age (years)	Weight (kg)	Height (cm)	Sex	Race
N	15	15	15	Female: 12	Asian: 2
Mean	15.7	48.9	160	(80%)	(13.3%)
SD	1.29	9.01	8.44	Male: 3	Black/African American: 8
CV%	8.24	18.4	5.27	(20%)	(53.3%)
Median	16	46.2	157		White: 5
Min	14	38.4	150		(33.3%)
Max	17	75	175		

Non-compartmental analysis

The PK of bedaquiline and the metabolite M2 after multiple-dose administration in adolescent subjects with MDR-TB in Study TMC207-C211 compared to previously reported data on the multiple-dose PK of bedaquiline administered as the same formulation and at the same dose in adult subjects with MDR-TB in Study TMC207-C208 is presented in Table 4 and Table 5.

Non-compartmental analysis was used to derive PK parameters for observed bedaquiline and M2 at Weeks 2, 12, and 24. The increase in the observed mean Cmin (≈ 42%) between Weeks 12 and 24 (Cohort 1) indicates bedaquiline has not reached steady-state by Week 12. The elimination half-life of bedaquiline was reliably determined for one subject in Cohort 1 at 2110 hours (≈ 12.6 weeks). There is a difference of M2 exposure at Week 24 between adolescents and adults. This is likely caused an unexpected low value for M2 at this time point in adults.

Table 4. Across-Study Summary of PK of Bedaquiline in Plasma after Multiple-Dose Administration of Bedaquiline as the Commercial 100-mg Tablet (F001) in Subjects with MDR-TB (Studies TMC207-C211 [Current Submission] and TMC207-C208 [Previous Submission])

	Mean±SD; t_{max}: Median (Range)						
	400 mg qd			200 mg tiw			
Parameter	TMC207-C208 (Stage 1) Week 2 Adults	TMC207-C208 (Stage 2) Week 2 Adults	TMC207-C211 Week 2 Adolescents	TMC207-C208 (Stage 1) Week 8 Adults	TMC207-C211 Week 12 Adolescents	TMC207-C208 (Stage 2) Week 24 Adults	TMC207-C211 Week 24 Adolescents
n	21	30	6	18	15	19	12
t_{max}, h	5.97 (2.97-8.00)	5.00 (2.33-6.17)	2 (2-8.25)	5.03 (2.75-8.33)	4 (2-8)	5.05 (3.07-6.77)	-
C_{min}, ng/mL	955.7±556.7	727.9±256.6	1,220±1,010	620.2±466.3	544±263	355.2±169.5	774±420
C_{max}, ng/mL	3,270±1,144	2,763±1,185	2,310±1,770	1,659±722	1,800±736	1,267±435	-
AUC_{24h}, ng.h/mL	42,500±16,810	32,960±12,720	39,100±32,600	-	26,300±10,300	-	-
AUC_{48h}, ng.h/mL	-	-	-	43,370±25,740		28,010±9,408	-

AUC_{xh}=area under the plasma concentration-time curve up to x hours post dosing; C_{max}=maximum plasma concentration; C_{min}=minimum plasma concentration; n=maximum number of subjects with data; qd=once daily; tiw=3 times per week; t_{max}=time to reach the maximum plasma concentration.
In Study TMC207-C208 Stage 1, subjects with MDR-TB were treated with bedaquiline 400 qd and BR for 2 weeks followed by bedaquiline 200 mg tiw and BR for a further 6 weeks. In Study TMC207-C208 Stage 2, had the same treatment as Stage 1 but with a 22 week dose period rather than 6 weeks.

There is an observed apparent difference of M2 exposure at Week 24 between adolescents and adults. This is likely caused by (1) taking only a single sample and, more likely, (2) an unexpected low value for M2 at this time point in adults.

Table 5. Across-Study Summary of PK of M2 in Plasma after Multiple-Dose Administration of Bedaquiline as the Commercial 100-mg Tablet (F001) in Subjects with MDR-TB (Studies TMC207-C211 [Current Submission] and TMC207-C208 [Previous Submission])

	Mean±SD; t_{max}: Median (Range)						
	400 mg qd			200 mg tiw			
Parameter	TMC207-C208 (Stage 1) Week 2 Adults	TMC207-C208 (Stage 2) Week 2 Adults	TMC207-C211 Week 2 Adolescents	TMC207-C208 (Stage 1) Week 8 Adults	TMC207-C211 Week 12 Adolescents	TMC207-C208 (Stage 2) Week 24 Adults	TMC207-C211 Week 24 Adolescents
n	21	30	6	18	15	19	12
t_{max}, h	6.0 (0-24.2)	6.15 (1.1-24.2)	0 (0-8)	6.99 (0-48.0)	24 (0-24)	12.1 (5.0-48.1)	-
C_{min}, ng/mL	339.3±141.5	331.6±121.7	406±172	217.4±119.3	188±62	120.3±56.98	256±137
C_{max}, ng/mL	450.4±167.3	467±157	574±247	300.7±143.2	297±133	178±70.7	-
AUC_{24h}, ng.h/mL	9,378±3,568	9,217±3,151	11,700±4,830	-	5,620±1,580	-	-
AUC_{48h}, ng.h/mL	-	-	-	12,240±6,665	-	7,270±2,532	-

AUC_{xh}=area under the plasma concentration-time curve up to x hours post dosing; C_{max}=maximum plasma concentration; C_{min}=minimum plasma concentration; n=maximum number of subjects with data; qd=once daily; tiw=3 times per week; t_{max}=time to reach the maximum plasma concentration.
In Study TMC207-C208 Stage 1, subjects with MDR-TB were treated with bedaquiline 400 qd and BR for 2 weeks followed by bedaquiline 200 mg tiw and BR for a further 6 weeks. In Study TMC207-C208 Stage 2, had the same treatment as Stage 1 but with a 22 week dose period rather than 6 weeks.

Population pharmacokinetics

The mean model predicted AUC_{168h} values for Cohort 1 was at Week 12 for Cohort 1 was 127000 ng*hr/mL, and 145000 ng*hr/mL at Week 24. The increase in exposure observed between Weeks 12 and 24 indicates bedaquiline has not reached steady-state at Week 12, and a model based analysis determined an average ratio of AUC_{168h} at Week 24:AUC_{168h} at steady-state of approximately 0.82. It is estimated that the adolescent population in Cohort 1 has reached ~73% of steady-state at Week 12 and ~82% at Week 24. The same estimates for adults are ~68% of steady-state at Week 12 and ~78% at Week 24. Thus, in comparison to adults, adolescents will reach steady-state sooner.

The mean model predicted AUC_{168h} values at Week 12 and 24 were contained within 60% – 140% of the adult AUC_{168h} geometric mean at steady-state (86200 ng*hr/mL – 201000 ng*hr/mL).

The mean a posteriori PK parameter estimates for Cohort 1 are comparable to the adult population PK parameters. The η shrinkage on apparent clearance (CL/F) was 23.1%, indicating the model-based estimates of exposure will be slightly shrunk towards the population average.

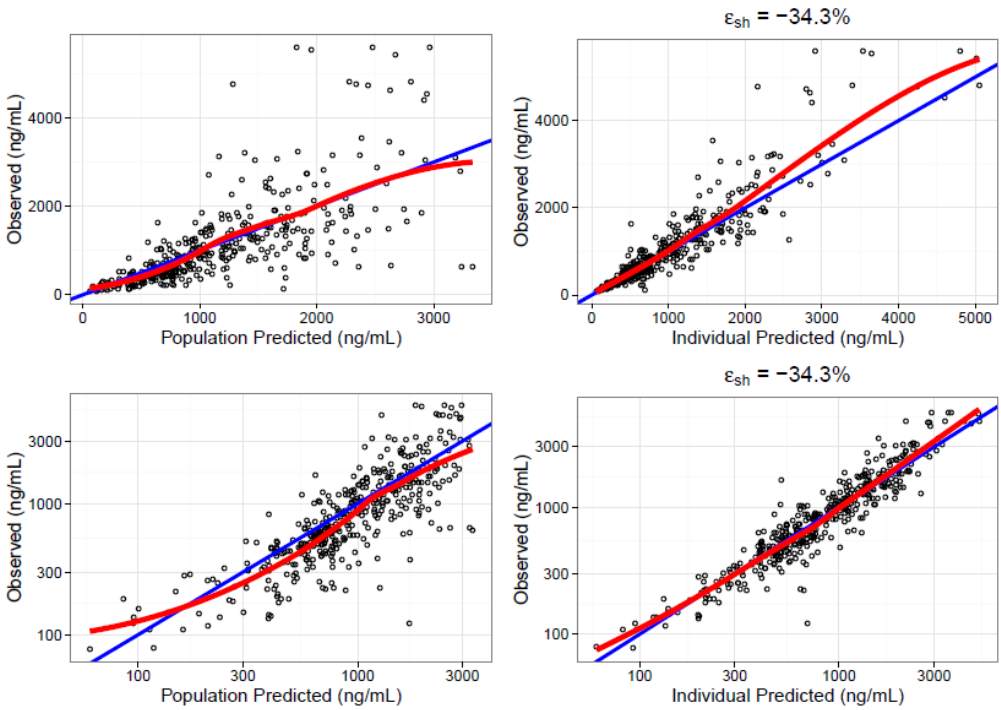
Table 6. Bedaquiline MAP PK Parameters for Subjects Recruited in Study TMC207-C211 Cohort 1

Cohort	ID	CL/F (L/hr)	V_2/F (L)	Q_3/F (L/hr)	Q_4/F (L/hr)	Q_5/F (L/hr)	V_3/F (L)	V_4/F (L)	V_5/F (L)	FR_1 (%)	F_1 (%)	F_2 (%)
1	1	2.15	101	8.81	6	2.67	121	2040	4980	44	28.1	35.9
	2	2.4	87.6	9.93	6.76	3.01	141	2390	5840	65.4	46.6	24.7
	3	1.9	65.7	8.66	5.89	2.63	118	1990	4870	22.2	7.47	26.2
	4	3.39	72.9	9.95	6.77	3.02	142	2400	5850	66.6	74	37.2
	5	5.06	104	14.3	9.74	4.34	230	3890	9500	80.9	40.9	9.69
	9	3.44	210	10.6	7.24	3.23	155	2620	6400	77.4	65.5	19.1
	10	4.77	217	10.1	6.9	3.08	145	2460	6010	69.5	61.5	27
	12	4.42	108	9.85	6.7	2.99	140	2370	5780	61.5	62.3	39.1
	17	1.29	115	9.75	6.64	2.96	138	2340	5700	57.7	53.8	39.5
	18	2.28	74	9.92	6.75	3.01	141	2390	5830	75.1	60.2	20
	19	4.4	86.8	10.6	7.22	3.22	154	2610	6370	80.3	102	25
	20	4.32	121	11.8	8.03	3.58	178	3010	7350	70.4	71.1	30
	21	3.42	107	11.2	7.65	3.41	167	2820	6890	82.2	77.2	16.7
	22	1.58	227	8.96	6.1	2.72	123	2090	5090	40.7	19.7	28.7
	23	3.77	164	10.8	7.35	3.27	158	2670	6530	68.6	141	64.7
	N	15	15	15	15	15	15	15	15	15	15	15
	Mean	3.24	124	10.4	7.05	3.14	150	2540	6200	64.1	60.8	29.6
	SD	1.23	54.1	1.39	0.949	0.423	27.6	467	1140	16.9	32.7	13
	Min	1.29	65.7	8.66	5.89	2.63	118	1990	4870	22.2	7.47	9.69
	Median	3.42	107	9.95	6.77	3.02	142	2400	5850	68.6	61.5	27
	Max	5.06	227	14.3	9.74	4.34	230	3890	9500	82.2	141	64.7
	CV%	37.9	43.7	13.5	13.5	13.5	18.4	18.4	18.4	26.4	53.8	43.8
	Geometric Mean	2.99	115	10.3	6.99	3.12	148	2500	6110	61.2	50.7	27.1

All data are reported to 3 significant digits. FR1 = fraction of dose absorbed via the first absorption pathway, F1 = relative bioavailability via the first absorption pathway, F2 = relative bioavailability via the second absorption pathway, total relative bioavailability = F1 + F2.

The adequacy of using the adult population pharmacokinetic (POPPK) model to describe the individual pharmacokinetic (PK) profiles of bedaquiline was assessed based on multiple diagnostic plots, i.e., DV vs PRED (observations vs predictions) and DV vs IPRED (observations vs individual predictions) (see following figure). The axes for the top plots are on a linear scale while the axes for the bottom plots are on a semilogarithmic scale.

Figure 2. Goodness-of-fit plots for the Bedaquiline Model

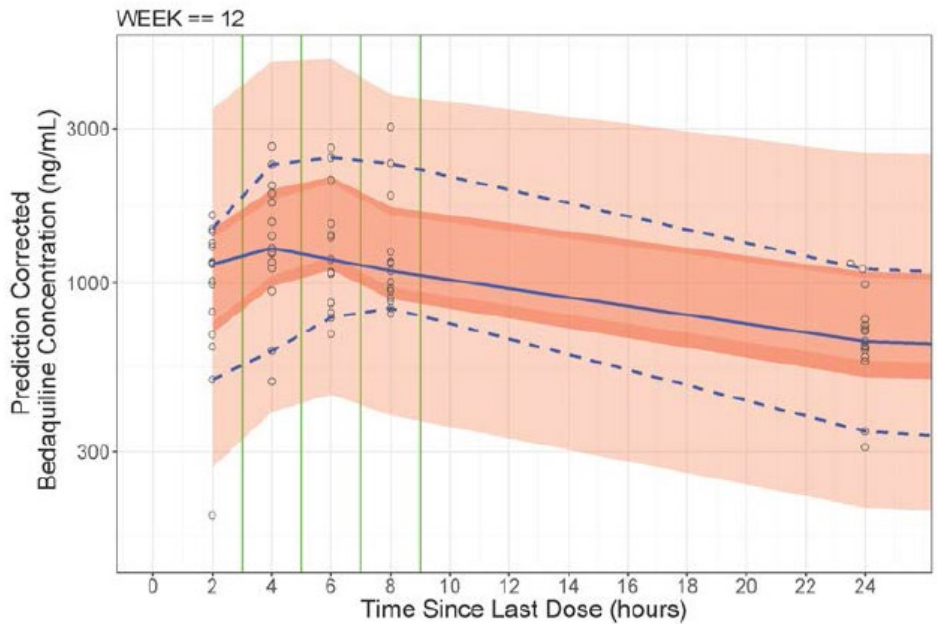


The solid blue lines represent the line of unity, the solid red lines represent the trend in the data (Loess smooth), and ε_{sh} shows shrinkage for the residual variability. The axis for the plots on the bottom is on the log scale.

These diagnostic plots show a normal random scatter around the line of identity and indicate the absence of significant bias.

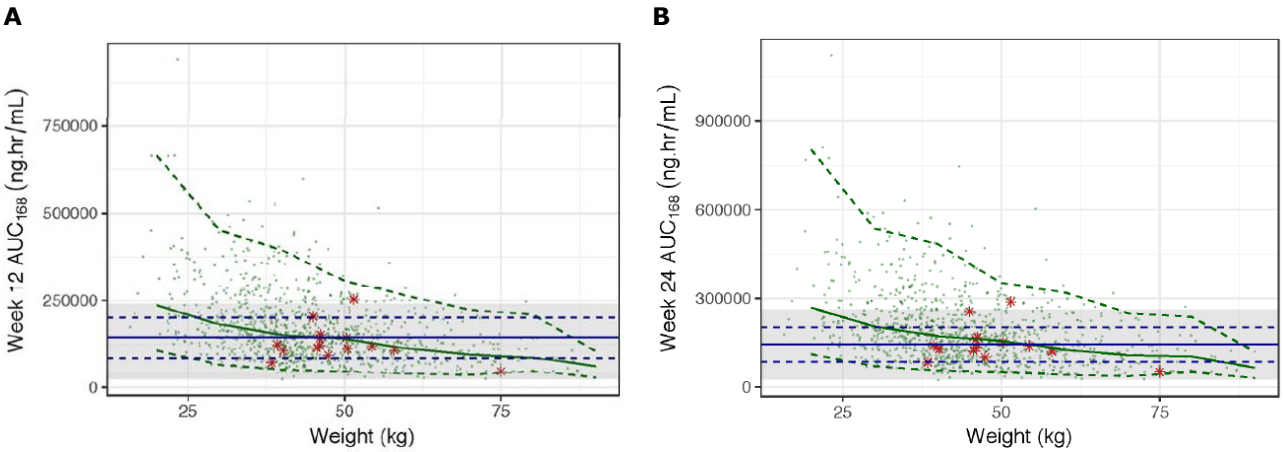
In addition, a prediction-corrected visual predictive check (pcVPC) for the PK data sampled at Week 12 in Cohort 1 of Study C211 over a 24-hour time period has been created (see following figure).

Figure 3. pcVPC for Bedaquiline in Cohort 1 at week 12 (study C211)



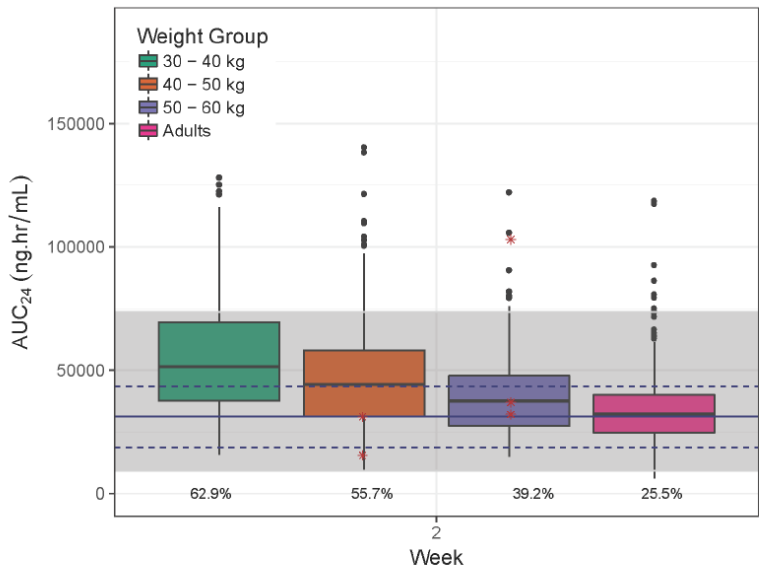
To investigate the appropriateness of the doses used in Cohort 1, AUC168h was determined following the current loading and maintenance dosing strategies. 1000 subjects in each cohort were sampled from the virtual paediatric subject database.

Figure 4. Week 12 (A) and Week 24 (B) Model Predicted and Simulated Bedaquiline AUC168h by WT: Cohort 1 including the 60-140% of the geometric mean Adult exposure



Green solid line = the median of simulated AUC_{168h} in adolescents at Week 12 or Week 24; green dashed lines = 2.5th and 97.5th percentiles of simulated Week 12 or Week 24 AUC_{168h} in adolescents; blue solid line = geometric mean AUC_{168h} in adults at steady-state; blue dashed lines = 60-140% range of geometric mean AUC_{168h} in adults at steady-state; red stars = Week 12 and Week 24 model-predicted AUC_{168h} for Cohort 1 of Study C211; grey area = 95% range for AUC_{168h} at Week 12 or Week 24 in adults.

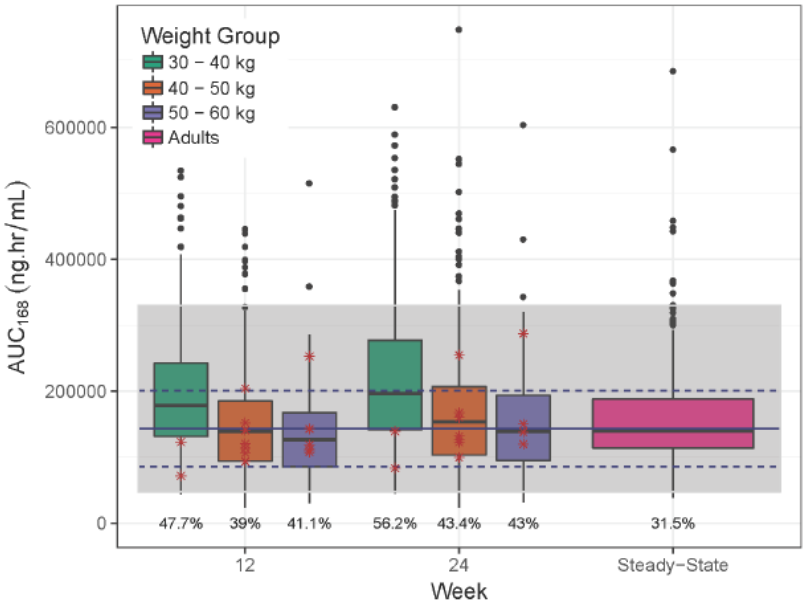
Figure 5. Boxplots Presenting the percentage of Simulated Subjects that fall outside the adult target exposure (AUC24h in Adults at week 2) at week 2, per weight group



Grey area = 95% range of AUC_{24h} in adults at Week 2; solid blue line = geometric mean AUC_{24h} in adults at Week 2; dashed blue lines = 60-140% of geometric mean AUC_{24h} in adults; red stars = model-predicted individual AUC_{24h} at Week 2 for Cohort 1 of Study C211.
The percentage of subjects outside the 60-140% range is depicted below each weight band for the adolescents in each weight category, as well as for the adult population.

The median value for every weight group falls within the 60-140% range of the geometric mean in adults. Although the simulations show an increased percentage of subjects with a lower body weight (ie, 30-40 kg) above this range, the individually predicted AUC168h at Week 12 for the 2 subjects from Cohort 1 with a weight within the 30-40 kg range (i.e., 39.3 and 38.4 kg) do not indicate an AUC168h at the higher end of the exposure range.

Figure 6. Boxplots presenting the percentage of Simulated Subjects that fall outside the adult target exposure (AUC168h in Adults at steady-state) at week 12 and week 24, per weight group



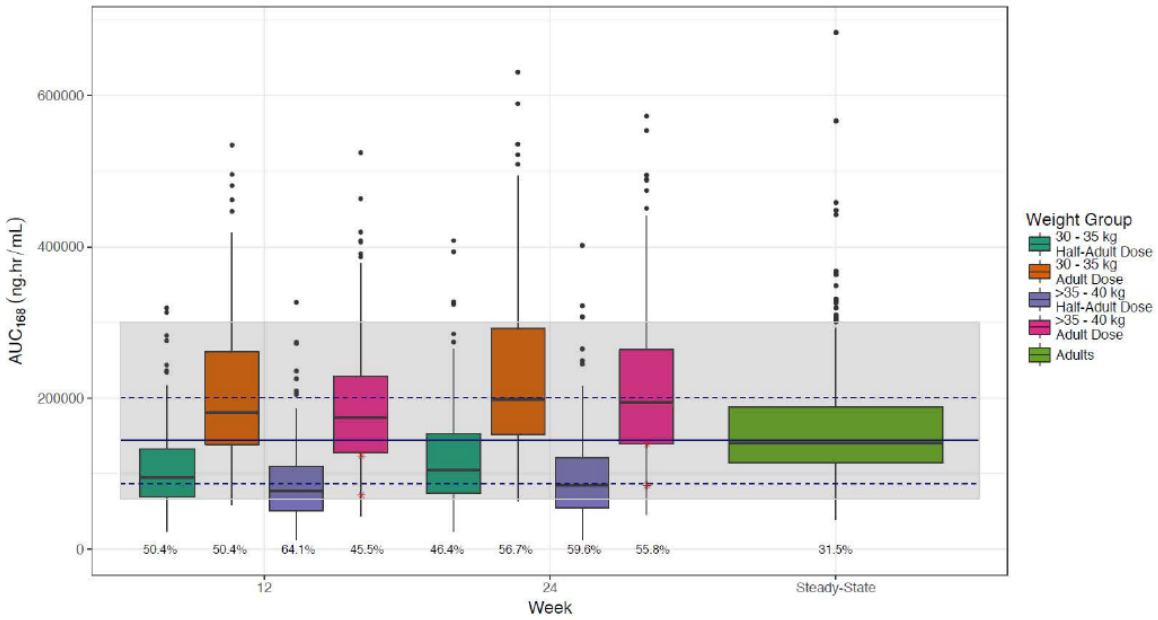
Grey area = 95% range of AUC_{168h} in adults at steady-state; solid blue line = geometric mean AUC_{168h} in adults at steady-state; dashed blue lines = 60-140% of geometric mean AUC_{168h} in adults; red stars = model-predicted individual AUC_{168h} at Week 12 and Week 24 for Cohort 1 of Study C211.
The percentage of subjects outside the 60-140% range is depicted below each weight band for the adolescents in each weight category, as well as for the adult population.

The boxplots per weight group show that the median value for every weight group falls within the 60-140% range of the geometric mean in adults. Although the simulations show an increase in the percentage of subjects that fall above this range with a lower body weight (i.e., 30-40 kg), the individually predicted AUC168h at Week 12 for the 2 subjects from Cohort 1 with a weight within the 30-40 kg range (i.e., 39.3 and 38.4 kg) do not indicate an AUC168h at the higher end of the exposure range.

Table 7. Percentage of Simulated Subjects That Fall Outside the Adult Target Exposure at Week 12 and Week 24, per Weight Group

	Week 12			Week 24		
Range Simulated Subjects	30-40 kg (n=283)	40-50 kg (n=316)	50-60 kg (n=158)	30-40 kg (n=283)	40-50 kg (n=316)	50-60 kg (n=158)
<60% adult geometric mean	8.8% (n=25)	18.7% (n=59)	25.3% (n=40)	7.4% (n=21)	15.2% (n=48)	19.6% (n=31)
60-140% adult geometric mean	52.3% (n=148)	61.1% (n=193)	58.9% (n=93)	43.8% (n=124)	56.6% (n=179)	57% (n=90)
>140% adult geometric mean	38.9% (n=110)	20.3% (n=64)	15.8% (n=25)	48.8% (n=138)	28.2% (n=89)	23.4% (n=37)

Figure 7. Simulated Bedaquiline AUC168h in the Adolescent Population at week 12 (left), Week 24 (middle), and the Bedaquiline AUC168h in the Adult Population (right), for the subgroups 30-35 kg and >35-40 kg Given the Proposed Dose and Half of the Proposed Dose



Red stars: Observed AUC_{168h} values in Cohort 1.
The percentage below each boxplot indicates the percentage of simulated values that are outside the 60 to 140% range (sum of subjects <60% and subjects >140%).

Table 8. Percentage of Simulated Subjects That Fall Within and Outside the Adult Target Exposure at Weeks 12 and 24 per Weight Group (30-35 kg and >35-40 kg) Given the Proposed Dose and Half of the Proposed Dose

	Week 12 30-35 kg Adult Dose	Week 12 30-35 kg ½ Adult Dose	Week 12 >35-40 kg Adult Dose	Week 12 >35-40 kg ½ Adult Dose	Week 24 30-35 kg Adult Dose	Week 24 30-35 kg ½ Adult Dose	Week 24 >35-40 kg Adult Dose	Week 24 >35-40 kg ½ Adult Dose
Range	(n=127)	(n=127)	(n=156)	(n=156)	(n=127)	(n=127)	(n=156)	(n=156)
<60% Adult GM	8.7% (n=11)	42.5% (n=54)	9% (n=14)	59.6% (n=93)	7.1% (n=9)	34.6% (n=44)	7.7% (n=12)	53.2% (n=83)
60-140% Adult GM	49.6% (n=63)	49.6% (n=63)	54.5% (n=85)	35.9% (n=56)	43.3% (n=55)	53.5% (n=68)	44.2% (n=69)	40.4% (n=63)
>140% Adult GM	41.7% (n=53)	7.9% (n=10)	36.5% (n=57)	4.5% (n=7)	49.6% (n=63)	11.8% (n=15)	48.1% (n=75)	6.4% (n=10)

GM = geometric mean

CHMP noted that the MAH has compared the simulated exposure in adults with model-based predictions of individual bedaquiline using all available concentration data from cohort 1. The geometric mean AUC168h at week 12 were within the AUC168h,ss ±40%. CL/F showed moderate inter-individual variability (CV% ~38%). No PK data are available for subjects aged 12-13 years.

Model-based predicted concentrations and goodness-of-fit plots have been provided. Eta shrinkage was moderate to high (~34%). The η shrinkage on apparent clearance (CL/F) was moderate at 23.1%. The goodness-of-fit plots for the paediatric population do not show any large trends. The visual predictive check plot, showing observed and predicted concentrations at week 12, indicates that the model predicts the data adequately.

The MAH has presented predicted AUC168h at week 12 and 24 for the Cohort 1-population. An increase in exposure is observed between Weeks 12 and 24. At week 12 it is predicted that 68% of adults and 73% of adolescent have reached steady state. The adolescent, in comparison to adults, will reach steady-state sooner.

The weight stratified boxplots of exposure at week 2 shows that the subjects of lowest weight are outside the 60-140% range, 61% of subjects are predicted to have an exposure >140% of adult geometric mean. However, the exposure is below the observed exposure during the maintenance phase. The week 12 and 24 weight-stratified boxplots show that a high number of adolescent subjects weighing 30-40 kg are outside the adult target exposure (60-140%), although the median is within the adult target exposure. If the weight bands were narrower the subjects <35 kg could have a median outside the adult target range. No exposure-response relationship was found for bedaquiline in the adult program.

Comparison of the proposed doses to the doses resulting from allometric scaling shows that 600 mg for the 30 to 40 kg body weight range will give an exposure higher than the 140% of adult geometric mean. The adolescent week 12 weight-stratified AUC168h exposure shows that a relatively high number of subjects weighing 30-40 kg are outside the adult target exposure (60-140%), however the median is within the adult target exposure.

Even though there is a theoretical risk of overexposure with the adult dose in subjects weighing 30-40 kg which could increase the risk for AEs such as increased liver transaminases and prolonged QT-interval, CHMP agreed that underexposure is from a clinical point of view considered a more direct and well defined risk, as this may result in treatment failure with subsequent emergence of resistance due to the risk for lack of efficacy. Furthermore, a more granular dose adjustment than the one presently investigated, is not considered practically feasible.

2.4.2.3. Relative bioavailability study TMC207TBC1002

Phase 1, open-label, randomised, 3-way crossover study in three panels of healthy, adult subjects (N=36) to assess the relative bioavailability of 100 mg bedaquiline after single-dose administration of two paediatric formulations (water dispersible 20 mg tablets [G003] or 20 mg/g granules [G004]) vs. the approved tablet formulation (F001), with and without food (standardised regular-fat yoghurt and standardised breakfast). A washout period of four weeks was considered sufficient. Taste testing of the bedaquiline formulations was performed by means of questionnaires. Safety and tolerability were evaluated throughout the study.

For all three formulations, bedaquiline C_{max} and AUC_{72h} were increased after intake with a standardised breakfast compared to intake with standardised regular-fat yoghurt and after fasted conditions. Pre-dose concentrations were not higher than 5% of Cmax. Tmax was 4-5 hours for all formulations in the fed state, and ~6 hours in the fasted condition.

Bioequivalence (BE) for both the paediatric formulations were shown at fed conditions (standardised breakfast) compared to the 100 mg tablet. The BE acceptance criteria were not met for the granules at the fed condition (standardised regular-fat yoghurt); Cmax and AUC LS mean ratios were 119.75 (90%CI 107.22-133.71) and 117.61 (109.72-126.07). For the dispersible tablet (standardised regular-fat yoghurt), the acceptance criteria were met, however upper bound CI for C_{max} was close to 125 (LS means ratio 111.93, 90%CI 100,23-124.99). The BE acceptance criteria were not met for neither the dispersible tablets nor the granules in the fasted condition.

2.4.3. Discussion on clinical pharmacology

Data from 15 adolescent subjects age 14 to 17 years of age were included in the pharmacokinetic analysis to support of the extension of indication to include adolescent patients from 12 years of age with the dosing regimen of 400 mg once daily (q,d,) for the first 14 days, followed by bedaquiline 200 mg three times per

week (t,I,w,) with intakes at least 2 days (48 hours) apart for 22 weeks. The aim was to match the exposure of bedaquiline in adolescent patients to the 60% – 140% range for the adult geometric mean AUC168h (86.200 ng*hr/mL – 201.000 ng*h/mL) at steady-state for a dose of 200 mg three times per week.

The model used in this application is the same as the model presented in the original NCE application (EMEA/H/C/2614). This model was used to simulate the adult target mean area under the plasma concentration-time curve from the time of dose administration up to 168 hours post-dose (AUC168h) in adults at steady-state. Model-based predicted concentrations and goodness-of-fit plots have been provided. Eta shrinkage was moderate to high (~34%). The η shrinkage on apparent clearance (CL/F) was moderate at 23.1%. The goodness-of-fit plots for the paediatric population do not show any large trends. The visual predictive check plot, showing observed and predicted concentrations at week 12, indicates that the model predicts the data adequately.

The marketing authorisation holder has compared the simulated exposure in adults with model-based predictions of individual bedaquiline using all available concentration data from cohort 1. The weight stratified boxplots of exposure at week 2 shows that 61% of the subjects of lowest weight are predicted to have an exposure >140% of adult geometric mean. However, the exposure is below the predicted concentrations in adults at steady state. The week 12 and 24 weight-stratified boxplots show that a high number of adolescent subjects weighing 30-40 kg are outside the adult target exposure (60-140%), however the median is within the adult target exposure. No exposure-response relationship was found for bedaquiline in the adult program. Comparison of the proposed doses to the doses resulting from allometric scaling shows that 600 mg for the 30 to 40 kg body weight range will give an exposure that is to some extent higher than the 140% of adult geometric mean.

Even though there is a theoretical risk of overexposure with the adult dose in subjects weighing 30-40 kg which could increase the risk for AEs such as increased liver transaminases and prolonged QT-interval, underexposure is from a clinical point of view considered a more direct and well defined risk, as this may result in treatment failure with subsequent emergence of resistance due to the risk for lack of efficacy. Furthermore, a more granular dose adjustment than the one presently investigated, is not considered practically feasible.

Given the life-threatening nature of TB infection, and the medical need for bedaquiline in the target population of patients with MDR-TB, CHMP agreed that it acceptable to administer the adult dose to children ≥12 years of age weighing ≥30 kg, taking into account the potential risk of increased AE. It is to be noted that the SmPc contains information about monitoring QTc and transaminases; in addition, a specific warning for adolescents weighing between 30 and 40 kg was added to section 4.4. of the PI. CHMP considered this was appropriate, due to the existing incertitude and in view of the potential life-threatening adverse events.

2.4.4. Conclusions on clinical pharmacology

The CHMP considered that this Application was approvable from the clinical pharmacology perspective.

2.5. Clinical efficacy

2.5.1. Main study

Study TMC207-C211: A Phase 2, Open-label, Multicentre, 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

Study design

The MAH has submitted results from cohort 1 in the still ongoing phase 2 study TMC207-C211. This cohort aimed to include 15 subjects at the age of ≥12 to <18 years of age.

Study TMC207-C211 is a single-arm, open-label study with PK and safety as primary objectives and is not designed to determine efficacy. The treatment schedule for BDQ was as follows: BDQ 400 mg once daily for the first 14 days, thereafter BDQ 200 mg three times a week (intakes at least 2 days apart) for 22 weeks, which is similar to the adult dose regimen.

The evaluation of clinical treatment outcome of bedaquiline for the treatment of pulmonary MDR-TB in adolescent subjects aged ≥12 to <18 years, is based on the Week 24 interim analysis for Cohort 1, conducted to assess the primary study objectives of PK and safety at this time point. As a result, the term "treatment outcome at Week 24" is used to describe the available interim data on treatment outcome.

The subjects were enrolled and treated with bedaquiline (BDQ) in combination with an individualized background regimen (BR). Unlike the clinical studies performed in adult subjects that enrolled only subjects with confirmed tuberculosis (TB) disease, Cohort 1 of Study TMC207-C211 included adolescent subjects who had confirmed or probable pulmonary MDR-TB and who would initiate or had already begun MDR-TB treatment within 8 weeks prior to baseline.

The diagnosis was based upon microbiological, clinical, radiological, epidemiological and immunological assessments in accordance with standard pediatric TB practice and national and international guidelines. The case definitions of pediatric pulmonary TB included: 1) a chest X-ray (CXR) consistent with intrathoracic TB required from all subjects and 2) a questionnaire to improve specificity of the source contact. Exposure to a source case with MDR-TB was documented at screening, since studies consistently have shown that children presenting with TB often have had a contact that has been diagnosed with TB.

Tuberculosis disease status at screening was evaluated by using Interferon Gamma Release Assay (IGRA) or Diaskin, if no positive IGRA or Diaskin test result was available within 2 months before screening.

Endpoints

The primary objective of this study is PK which is discussed in the previous section.

Final disease outcome at Week 120 in Study TMC207-C211 is classified as either favorable or unfavorable, based on the availability of screening and post baseline culture data.

For the Week 24 interim analysis, a subject is classified as having a favorable treatment outcome if he or she completes the overall prescribed TB treatment at Week 24 and the investigator´s global TB assessment is that signs and symptoms have resolved within the Week 24 window, and in addition the subject falls in 1 of the 3 categories:

a. Have confirmed culture conversion for subjects with evaluable microbiology samples in the Week 24 window.

b. Have completed TB treatment at Week 24 and have signs and symptoms resolved for subjects with no or only a single post baseline sputum sample available.

c. Have the last 2 cultures negative for MDR-TB within the analysis window and have completed overall prescribed TB treatment at Week 24 for subjects with at least the last 2 acceptable post baseline sputum samples available but unable to produce sputum up to the Week 24 window.

Statistical analysis

The clinical treatment outcome endpoint was comprised of clinical and radiological improvement, survival and evaluation of *M. tuberculosis* on serial microbiology specimen sample culture examinations, the following analysis were performed:

- The proportion of subjects with favorable treatment outcome and corresponding 95% confidence intervals (CIs) were calculated, for overall subjects and by subgroup.
- The time to AFB smear conversion and to culture conversion (overall and by baseline drug resistance) was estimated and graphically displayed by Kaplan-Meier plots.
- The number and percentage of subjects with drug resistance at screening or baseline was tabulated for each anti-TB drug for which DST results were available.

Several subgroup analyses were performed.

Demographic data

Table 9. Demographic Data in Cohort 1 (12 to <18 Years of Age); ITT (Study TMC207-C211| Interim Analysis, DB Cutoff 14NOV2017)

	TMC207/BR
Analysis Set: Intent-to-treat, N	15
Sex, n (%)	
N	15
Female	12 (80.0%)
Male	3 (20.0%)
Age (years)	
N	15
Mean (SD)	15.7 (1.29)
Median	16.0
Min; Max	(14; 17)
Race, n (%)	
N	15
Asian	2 (13.3%)
Black	8 (53.3%)
White	5 (33.3%)
Height (cm)	
N	15
Mean (SD)	160.01 (8.440)
Median	157.20
Min; Max	(150.0; 175.0)
Weight (kg)	
N	15
Mean (SD)	48.93 (9.006)
Median	46.20
Min; Max	(38.4; 75.0)
Body mass index (kg/m²)	
N	15
Mean (SD)	19.11 (3.116)
Median	17.90
Min; Max	(15.6; 27.9)
Country, n (%)	
N	15
Philippines	2 (13.3%)
Russian Federation	5 (33.3%)
South Africa	8 (53.3%)

Of the 15 subjects, 11 (73.3%) subjects had confirmed MDR-TB and 4 (26.7%) subjects had probable MDR-TB (based on source case DST) at baseline. Of the 11 subjects with confirmed MDR-TB: Six (40.0%) subjects were infected with an MDR-TBH&R *M. tuberculosis* strain. Four (26.7%) subjects were infected with an MDR-TBRR *M. tuberculosis* strain. One (6.7%) subject was infected with an XDR-TB *M. tuberculosis* strain.

Previous anti-TB treatment

All 15 subjects had used anti-TB medication previously. The use of second-line drugs had to be limited to the 8-week period prior to baseline. The most frequently used previous anti-TB medications (in more than 9 of 15 subjects) were LFX (in 14 [93.3%] subjects), PZA (in 13 [86.7%] subjects), KM (in 11 [73.3%] subjects) and EMB (in 10 [66.7%] subjects). Previous use of INH and RMP was reported for 7 of 15 (46.7%) subjects and 1 of 15 (6.7%) subjects respectively.

Background regimen (BR)

Table 10. Background Regimen at Baseline in Cohort 1 (12 to <18 Years of Age); ITT (Study TMC207-C211| Interim Analysis, DB Cutoff 14NOV2017)

	TMC207/BR
Analysis set: Intent-to-treat, N	15
Any use of background TB drug treatment, n (%)	15 (100.0%)
Aminoglycosides	13 (86.7%)
Amikacin sulfate	1 (6.7%)
Kanamycin	12 (80.0%)
Fluoroquinolones	15 (100.0%)
Levofloxacin	15 (100.0%)
Miscellaneous anti-TB drugs	15 (100.0%)
Cycloserine	3 (20.0%)
Ethambutol	8 (53.3%)
Ethionamide	8 (53.3%)
Isoniazid	7 (46.7%)
PAS-C	3 (20.0%)
Prothionamide	5 (33.3%)
Pyrazinamide	13 (86.7%)
Terizidone	8 (53.3%)
Combinations	
Amikacin sulfate + ethambutol + levofloxacin + pyrazinamide	1 (6.7%)
Cycloserine + kanamycin + levofloxacin + PAS-C + pyrazinamide	1 (6.7%)
Cycloserine + kanamycin + levofloxacin + prothionamide + pyrazinamide	1 (6.7%)
Cycloserine + levofloxacin + prothionamide + pyrazinamide	1 (6.7%)
Ethambutol + ethionamide + isoniazid + kanamycin + levofloxacin + PAS-C + pyrazinamide	1 (6.7%)
Ethambutol + ethionamide + isoniazid + kanamycin + levofloxacin + pyrazinamide + terizidone	4 (26.7%)
Ethambutol + ethionamide + kanamycin + levofloxacin + pyrazinamide + terizidone	1 (6.7%)
Ethambutol + kanamycin + levofloxacin + prothionamide	1 (6.7%)
Ethionamide + isoniazid + kanamycin + levofloxacin + pyrazinamide + terizidone	2 (13.3%)
Kanamycin + levofloxacin + prothionamide + pyrazinamide	1 (6.7%)
Levofloxacin + PAS-C + prothionamide + terizidone	1 (6.7%)

The denominator for the percentage calculations is the total number of subjects in the ITT population.
Background Regimen at Baseline: all BR drugs that overlap with the interval [First intake of TMC207, First intake of TMC207 + 14 days].

Results

Table 11. Treatment Duration in Cohort 1 (12 to <18 Years of Age); ITT (Study TMC207-C211| Interim Analysis, DB Cutoff 14NOV2017)

	TMC207 / BR	
	TMC207 Treatment	Background Regimen
Analysis set: Intent-to-treat, N	15 (100.0%)	15 (100.0%)
Treatment duration (weeks)		
N	15	15
Mean (SD)	23.6 (1.14)	44.8 (18.90)
Median (Min; Max)	23.9 (20; 25)	42.0 (20; 78)

BR = background regimen; DB = database; ITT = intent-to-treat; N = number of subjects; max = maximum; min = minimum; SD = standard deviation, TMC207 = bedaquiline.
The denominator for the percentage calculations is the total number of subjects in the analysis set.
For ongoing subjects, duration (weeks) is calculated as: (data cutoff date-first intake date+1)/7.

Fifteen subjects were enrolled to the cohort 1 and treated with BDQ in combination with BR consisting of ant-TB drugs. Fourteen of 15 (93.3%) subjects in the ITT analysis set completed intake of bedaquiline as planned and were ongoing in the study at the time of the database cutoff date.

One of 15 (6.7%) subjects in the ITT analysis set discontinued the study prematurely. The subject had an XDR-TB infection and required treatment with CFZ (which was disallowed per protocol at that time). The subject was withdrawn from the study after the Week 16 visit and referred to the NTP for further management.

The youngest child included in the Cohort was 14 years old and the weight span was 38-73 kg, with a mean body weight of 49 kg.

Susceptibility

Susceptibility results for BDQ at baseline are available for 6 of 15 subjects; all strains were susceptible to BDQ according to the EUCAST breakpoint of S≤0.25 mg/L and R>0.25 mg/L.

Protocol deviations

Major deviations from the protocol were reported in 6/15 (40%) of the subjects:

Three subjects had a protocol deviation related to eligibility criteria

- One subject received BDQ despite not satisfy all selection criteria (ie, had ECG abnormality at screening: heart rate was 49 bpm and ECG interpretation were sinus bradycardia).
- One subject was enrolled while screening prothrombin time results were only available one day after baseline.
- One subject under legal guardianship was enrolled while it is not allowed per Russian law.

Two subjects had a protocol deviation related to disallowed medications

- One subject received disallowed concomitant medication (ie, MFX).
- One subject received medication in the BR in combination with bedaquiline that was disallowed per local protocol (i.e., AM; disallowed per Russian NTP guidelines).

Three subjects had a protocol deviation related to PK sampling:

- Three subjects had a rich PK sample collected on a day without BDQ administration.

According to the MAH these protocol deviations observed are not considered to affect the results or conclusions of the study.

Treatment compliance

During the 2-week loading dose phase when bedaquiline was administered at 400 mg qd in Cohort 1, 14 of 15 (93.3%) subjects were fully compliant.

During the 22-week maintenance dosing phase when bedaquiline was administered at 200 mg tiw, 9 of 15 (60.0%) subjects had a compliance of 100%.

Treatment outcome

After 24 weeks of treatment with bedaquiline in combination with BR, 7 of 15 subjects (46.7%, with a 95% CI of 22.3%; 72.6%) had a favorable treatment outcome. For 7 out of the 8 subjects without a favorable treatment outcome, the reason was `signs and symptoms not completely resolved per investigator's global TB assessment´.

Table 12. Culture Conversion Rate Categorization (Week 24 Analysis) (Primary M=F) in Cohort 1 (12 to <18 Years of Age); mITT (Study TMC207-C211| Interim Analysis, DB Cutoff 14NOV2017)

2.5.2. Discussion on clinical efficacy

Since it is fully endorsed that, based on similar biology between adolescents and adults, efficacy can be extrapolated based on systemic exposure, the primary objective is to establish a dose in adolescence resulting in an exposure of bedaquiline that is comparable to that observed in adults. CHMP has agreed during this assessment to the fact that the exposure of bedaquiline in adolescent patients generally falls within 60% – 140% range for the adult geometric mean AUC168h (86.200 ng*hr/mL – 201.000 ng*h/mL) at steady-state for the proposed dose of 200 mg bedaquiline three times per week.

CHMP agreed therefore that efficacy can be extrapolated from adults to adolescent patients (12 years to less than 18 years of age and weighing at least 30 kg).

2.5.3. Conclusions on the clinical efficacy

CHMP agreed that the extension of indication is approvable from the efficacy point of view.

2.6. Clinical safety

Introduction

The safety data consists of results from Week 24 interim analysis for Cohort 1 of Study TMC207-C211 (with database cutoff date 14 November 2017) in adolescent subjects (aged ≥12 to <18 years) with confirmed or probable multidrug-resistant tuberculosis (MDR-TB) infection.

Patient exposure

Table 13. Number of Subjects at Each Visit in Cohort 1 (12 to <18 Years of Age); ITT (Study TMC207-C211| Interim Analysis, DB Cutoff 14NOV2017)

	TMC207/BR	
	ITT	mITT
Overall Treatment Phase		
Baseline	15 (100.0%)	15 (100.0%)
Day 1	15 (100.0%)	15 (100.0%)
Week 2	15 (100.0%)	15 (100.0%)
Week 4	15 (100.0%)	15 (100.0%)
Week 6	15 (100.0%)	15 (100.0%)
Week 8	15 (100.0%)	15 (100.0%)
Week 12	15 (100.0%)	15 (100.0%)
Week 16	15 (100.0%)	15 (100.0%)
Week 20	15 (100.0%)	15 (100.0%)
Week 24	14 (93.3%)	14 (93.3%)
Week 28	11 (73.3%)	11 (73.3%)
Week 32	8 (53.3%)	8 (53.3%)
Week 40	8 (53.3%)	8 (53.3%)
Week 48	7 (46.7%)	7 (46.7%)
Week 60	4 (26.7%)	4 (26.7%)
Week 72	2 (13.3%)	2 (13.3%)

The denominator for the percentage calculations is the total number of subjects in the analysis population.

Adverse events

Table 14. Summary of Adverse Events in Cohort 1 (12 to <18 Years of Age); ITT (Study TMC207-C211| Interim Analysis, DB Cutoff 14NOV2017)

Category of Event, n(%)	TMC207 Treatment Phase	Overall Treatment Phase
Analysis set: Intent-to-treat, N	15	15
Any adverse events	14 (93.3%)	14 (93.3%)
Serious adverse events	2 (13.3%)	2 (13.3%)
AEs of at least grade 3	4 (26.7%)	4 (26.7%)
AEs of grade 4	1 (6.7%)	1 (6.7%)
AEs leading to permanent stop of bedaquiline	0	0
AEs leading to permanent stop of one or more BR drug	5 (33.3%)	5 (33.3%)

n: number of subjects with 1 or more events.

During the BDQ Treatment phase, 14 of 15 (93.3%) subjects experienced at least one AE, all illustrated in the table below.

Table 15. Adverse Events (Regardless of Severity and Drug Relatedness) Reported in More Than One Subject by Body System and Preferred Term in Cohort 1 (12 to <18 Years of Age); ITT (Study TMC207-C211| Interim Analysis, DB Cutoff 14NOV2017)

MedDRA System Organ Class Dictionary-derived Term	TMC207 Treatment Phase	Overall Treatment Phase
Analysis set: Intent-to-treat, N	15	15
Any adverse event, n (%)	14 (93.3%)	14 (93.3%)
Ear and labyrinth disorders	4 (26.7%)	4 (26.7%)
Hypoacusis	2 (13.3%)	2 (13.3%)
Tinnitus	2 (13.3%)	2 (13.3%)
Eye disorders	4 (26.7%)	5 (33.3%)
Eye pain	2 (13.3%)	2 (13.3%)
Eye pruritus	0	2 (13.3%)
Vision blurred	2 (13.3%)	2 (13.3%)
Gastrointestinal disorders	4 (26.7%)	4 (26.7%)
Nausea	2 (13.3%)	2 (13.3%)
General disorders and administration site conditions	2 (13.3%)	2 (13.3%)
Infections and infestations	8 (53.3%)	8 (53.3%)
Upper respiratory tract infection	2 (13.3%)	2 (13.3%)
Vulvovaginal candidiasis	2 (13.3%)	2 (13.3%)
Injury, poisoning and procedural complications	3 (20.0%)	3 (20.0%)
Investigations	5 (33.3%)	5 (33.3%)
Prothrombin time prolonged	3 (20.0%)	3 (20.0%)
Musculoskeletal and connective tissue disorders	7 (46.7%)	7 (46.7%)
Arthralgia	6 (40.0%)	6 (40.0%)
Nervous system disorders	2 (13.3%)	2 (13.3%)
Psychiatric disorders	2 (13.3%)	2 (13.3%)
Skin and subcutaneous tissue disorders	4 (26.7%)	5 (33.3%)
Acne	4 (26.7%)	4 (26.7%)
Rash	2 (13.3%)	2 (13.3%)

n: number of subjects with 1 or more events.

The most frequently reported AEs (in more than 2 of 15 subjects during the BDQ Treatment phase) were arthralgia (in 6 [40.0%] subjects), acne (in 4 [26.7%] subjects), and prothrombin time prolonged (in 3 [20.0%] subjects).

AEs possible related to BDQ

One subject experienced a grade 1 episode of nausea, and an episode of vomiting on Day 2 of treatment with BDQ (grade 1 that worsened to grade 2). Both events were considered at least possibly related to BDQ and the BR; and not or doubtfully related to TB infection. Treatment with BDQ and BR was temporarily interrupted due to the vomiting. The events resolved after 103 and 31 days, respectively, and did not reoccur after treatment restart.

AEs possible related to TB infection or BR

Two of 15 (13.3%) subjects experienced at least one AE possible related to TB infection during treatment phase (Increased blood uric acid, fatigue). At the overall treatment phase 2 subjects were reported with possible TB related AEs (Increased blood uric acid, fatigue, arthralgia, productive cough).

During the treatment phase of BDQ, 12 of 15 (80.0%) subjects experienced at least one AE considered related to the BR, those were consistent throughout the overall treatment phase. The most frequently reported AE considered related to the BR (in more than 2 of 15 subjects) was arthralgia (in 6 [40.0%] subjects).

Table 16. Adverse Events of at Least Grade 3 by Body System and Preferred Term in Cohort 1 (12 to <18 Years of Age); ITT (Study TMC207-C211| Interim Analysis, DB Cutoff 14NOV2017)

MedDRA System Organ Class Dictionary-derived Term	TMC207 Treatment Phase	Overall Treatment Phase
Analysis set: Intent-to-treat, N	15	15
Any adverse event of at least grade 3, n (%)	4 (26.7%)	4 (26.7%)
Investigations	4 (26.7%)	4 (26.7%)
Alanine aminotransferase increased	1 (6.7%)	1 (6.7%)
Aspartate aminotransferase increased	1 (6.7%)	1 (6.7%)
Blood bilirubin increased	1 (6.7%)	1 (6.7%)
Blood creatine phosphokinase increased	1 (6.7%)	1 (6.7%)
Prothrombin time prolonged	3 (20.0%)	3 (20.0%)

n: number of subjects with 1 or more events.

None of the grade 3 or 4 AEs were considered related to treatment with BDQ by the investigator.

None of the 15 subjects permanently discontinued treatment with BDQ due to AEs.

Table 17. Adverse Events of Special Interest by Grouped Term in Cohort 1 (12 to <18 Years of Age); ITT (Study TMC207-C211| Interim Analysis, DB Cutoff 14NOV2017)

SMQ Term, Sub-SMQ Terms and Dictionary-derived Term	TMC207 Treatment Phase	Overall Treatment Phase
Analysis set: Intent-to-treat, N	15	15
Any adverse event of interest, n (%)	5 (33.3%)	5 (33.3%)
No adverse event of interest, n (%)	10 (66.7%)	10 (66.7%)
Acute pancreatitis (SMQ)	1 (6.7%)	1 (6.7%)
Blood bilirubin increased	1 (6.7%)	1 (6.7%)
Drug-related hepatic disorders - comprehensive search (SMQ)	4 (26.7%)	4 (26.7%)
Liver related investigations, signs and symptoms (SMQ)	1 (6.7%)	1 (6.7%)
Alanine aminotransferase increased	1 (6.7%)	1 (6.7%)
Aspartate aminotransferase increased	1 (6.7%)	1 (6.7%)
Blood bilirubin increased	1 (6.7%)	1 (6.7%)
Liver-related coagulation and bleeding disturbances (SMQ)	3 (20.0%)	3 (20.0%)
Prothrombin time prolonged	3 (20.0%)	3 (20.0%)
Severe cutaneous adverse reactions (SMQ)	1 (6.7%)	1 (6.7%)
Conjunctivitis	1 (6.7%)	1 (6.7%)

n: number of subjects.

Serious adverse event/deaths/other significant events

Table 18. Treatment-emergent Graded Laboratory Abnormalities (Worst Grade) During the Treatment Phases in Cohort 1 (12 to <18 Years of Age); ITT (Study TMC207-C211| Interim Analysis, DB Cutoff 14NOV2017)

	TMC207 Treatment Phase	Overall Treatment Phase
Analysis set: Intent-to-treat, N	15	15
Chemistry		
Alanine Aminotransferase		
N	15	15
Grade 4	1 (6.7%)	1 (6.7%)
Amylase, Pancreatic		
N	15	15
Grade 1	1 (6.7%)	1 (6.7%)
Grade 2	2 (13.3%)	2 (13.3%)
Aspartate Aminotransferase		
N	15	15
Grade 1	0	1 (6.7%)
Grade 4	1 (6.7%)	1 (6.7%)
Creatinine		
N	15	15
Grade 1	2 (13.3%)	2 (13.3%)
Gamma Glutamyl Transferase		
N	15	15
Grade 2	1 (6.7%)	1 (6.7%)
Hyperbilirubinemia		
N	15	15
Grade 4	1 (6.7%)	1 (6.7%)
Hypercalcemia		
N	15	15
Grade 1	1 (6.7%)	1 (6.7%)
Hyperkalemia		
N	15	15
Grade 1	2 (13.3%)	2 (13.3%)
Hyperuricemia		
N	15	15
Grade 1	3 (20.0%)	3 (20.0%)
Grade 2	5 (33.3%)	5 (33.3%)
Hypoglycemia		
N	15	15
Grade 1	2 (13.3%)	3 (20.0%)
Hypokalemia		
N	15	15
Grade 1	6 (40.0%)	8 (53.3%)

Hypomagnesemia		
N	15	15
Grade 1	1 (6.7%)	1 (6.7%)
Hyponatremia		
N	15	15
Grade 2	5 (33.3%)	5 (33.3%)
Hematology		
Hemoglobin		
N	15	15
Grade 1	2 (13.3%)	2 (13.3%)
Grade 2	1 (6.7%)	1 (6.7%)
Neutrophils and Precursors		
N	15	15
Grade 1	2 (13.3%)	2 (13.3%)
Neutrophils, Segmented		
N	15	15
Grade 1	2 (13.3%)	2 (13.3%)
Prothrombin Time		
N	15	15
Grade 1	3 (20.0%)	4 (26.7%)
Grade 2	0	3 (20.0%)
Grade 3	2 (13.3%)	2 (13.3%)

Notes: Unscheduled time points, if any, are also considered in this display.
A toxicity is treatment-emergent if it is worse than the baseline.
If the baseline is missing, the toxicity is always considered as treatment-emergent.

During the BDQ Treatment phase, the following treatment-emergent grade 3 or 4 laboratory abnormalities were observed: grade 3 prothrombin time increased in 2 of 15 (13.3%) subjects and grade 4 ALT increased, AST increased, and hyperbilirubinemia (all in 1 of 15 [6.7%] subjects).

One of the 15 subjects met the laboratory criteria for Hy´s law on Study Day 95 (Week 14) (i.e., a peak ALT/AST of ≥3xULN and a peak total bilirubin of ≥2xULN). This subject, who weighted 45 kg, concurrently experienced the grade 4 SAEs alanine aminotransferase increased, aspartate aminotransferase increased and increased bilirubin in blood. The provided pharmacokinetic parameters showed that both AUC and C_{max} was higher than the median values of the subjects in the cohort, however, no extreme values of AUC or C_{max} was registered for this subject. These reported SAEs resolved after a duration of 28 days, after temporary discontinuation of all anti-TB medications the subject was restarted on bedaquiline with elimination of prothionamide (PTO) from the BR, and the treatment period of BDQ was completed without recurrence of liver enzyme elevation.

No deaths occurred up to the data-lock point at Week 24.

Laboratory findings

Electrocardiogram

Median absolute values in QTcF increased during the BDQ Treatment phase, which was apparent as of Week 2, with median increases from baseline of more than 10 ms observed at different time points from Week 2 to Week 24 (largest median change from baseline: 18.0 ms for QTcF at Week 24). After Week 24 (ie, after stopping TMC207 treatment), median absolute values in QTcF gradually decreased. Overall, 9 of 15 (60.0%) subjects had a QTC prolongation during the BDQ Treatment phase compared to baseline. One of 15 [6.7%] subjects were reported with a significant ECG abnormality, ie, significantly high HR (114 bpm at one time point).

Additional change proposed to section 4.9 of the Product Information

The current position of the American Academy of Clinical Toxicology and the European Association of Poisons Centres and Clinical Toxicologists is that there is lack of evidence that activated charcoal improves clinical outcomes following acute overdose and it is therefore of limited benefit to routinely administer activated charcoal as a management of poisoned subjects. Furthermore, the MAH has pointed on the risks associated with its administration (such as bowel obstruction, nausea, vomiting, headache, pulmonary aspiration), and the relatively small percentage of patients for whom presentation for treatment falls within the window (60 min) of potential utility for activated charcoal. Therefore, the MAH has proposed to remove the recommendation in section 4.9 of the SmPC to administer activated charcoal following bedaquiline overdose and to have this recommendation replaced by instructions to the prescriber to handle a possible case as clinically indicated and to contact a poison information center if such is available. CHMP agreed to the proposal.

2.6.1. Discussion on clinical safety

In this interim-analysis of a single-armed cohort including 15 adolescence treated with similar dose of BDQ as in the treatment regimen for adults, no safety issues not already described were reported. The similar exposure in adolescents and adults with the proposed dose further supports the fact that the safety profile in adolescents should not be different than the one observed in adult patients.

2.6.2. Conclusions on clinical safety

CHMP agreed that this extension of indication, as well as the grouped procedure as a whole is approvable from the safety perspective.

2.6.3. 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.

2.7. Risk management plan

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

The PRAC considered that the risk management plan version 4.0 is acceptable.

The MAH is reminded that, within 30 calendar days of the receipt of the Opinion, an updated version of Annex I of the RMP template, reflecting the final RMP agreed at the time of the Opinion should be submitted to h-eurmp-evinterface@emea.europa.eu.

The CHMP endorsed the Risk Management Plan version 4.0 with the following content:

Safety concerns

Important identified risks	Electrocardiogram QT prolonged
	Increased transaminases
Important potential risks	Severe hepatotoxicity
	Pancreatitis
	Myopathy
	Myocardial injury

	Development of drug resistance
Missing information	Long-term effects of bedaquiline treatment on mortality
	Use in patients with severe hepatic impairment
	Use in patients with severe renal impairment
	Use in elderly patients
	Use during pregnancy
	Use in nursing mothers
	Use in HIV-coinfected patients on antiretroviral therapy
	Use in patients using potent inhibitors of drug-metabolizing enzymes and transporters
	Prolonged treatment duration

Pharmacovigilance plan and risk minimisation measures

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Important Identified Risks		
Electrocardiogram QT prolonged	Routine risk minimization measures: • SmPC Section 4.4; • SmPC Section 4.5; • SmPC Section 4.8; • PL Section 4; • Recommendations for ECG monitoring, the use of SIRTURO in patients with 1 or more risk factors for QT interval prolongation, and the monitoring of electrolytes are included in SmPC Section 4.4; • Advice on the use of SIRTURO in patients developing clinically significant ventricular arrhythmia or a QTcF interval of >500 ms (confirmed by repeat ECG) is included in SmPC Section 4.4; • Recommendation to obtain an ECG if syncope occurs is included in SmPC Section 4.4; • Warnings regarding coadministration of SIRTURO with medicinal products that prolong the QT interval are included in SmPC Sections 4.4 and 4.5; • Recommendations for ECG (QT interval) monitoring in case of deliberate or accidental overdose are included in SmPC Section 4.9; • Warnings for patients who have had an abnormal heart reading (ECG) or heart failure, who have a personal or family history of a heart problem called "congenital long QT syndrome", or who faint are included in PL Sections 2 and 4; • Legal status: restricted medical prescription. Additional risk minimization measures: • None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None. Additional pharmacovigilance activities: • STREAM Stage 2 trial Final analysis – Clinical Study Report: 4Q 2023; • Multi-Country MDR-TB Disease Registry (TBC4002) Final study report: 2Q 2020.
Increased transaminases	Routine risk minimization measures: • SmPC Section 4.4; • SmPC Section 4.8; • SmPC Section 5.3; • PL Section 4; • Recommendations regarding the use of SIRTURO, including dose adjustments, in patients with mild,	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None. Additional pharmacovigilance activities: • STREAM Stage 2 trial

	moderate, or severe hepatic impairment are included in SmPC Sections 4.2 and 5.2; • Warnings regarding coadministration of SIRTURO with other hepatotoxic medicinal products and alcohol are included in SmPC Section 4.4; • Recommendation for liver function monitoring is provided in SmPC Section 4.4; • Recommendation on evaluation and actions to be taken in case of increased transaminases is provided in SmPC Section 4.4; • A warning for patients who have liver disease or drink alcohol on a regular basis is included in PL Section 2; • Legal status: restricted medical prescription. Additional risk minimization measures: • None.	Final analysis – Clinical Study Report: 4Q 2023; • Multi-Country MDR-TB Disease Registry (TBC4002) Final study report: 2Q 2020.
Important Potential Risks		
Severe hepatotoxicity	Routine risk minimization measures: • SmPC Section 4.4; • SmPC Section 4.8; • SmPC Section 5.3; • PL Section 4; • Recommendations regarding the use of SIRTURO, including dose adjustments, in patients with mild, moderate, or severe hepatic impairment are included in SmPC Sections 4.2 and 5.2; • Warnings regarding coadministration of SIRTURO with other hepatotoxic medicinal products and alcohol are included in SmPC Section 4.4; • Recommendation for liver function monitoring is provided in SmPC Section 4.4; • Recommendation on evaluation and actions to be taken in case of increased transaminases is provided in SmPC Section 4.4; • A warning for patients who have liver disease or drink alcohol on a regular basis is included in PL Section 2; • Legal status: restricted medical prescription. Additional risk minimization measures: • None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None. Additional pharmacovigilance activities: • STREAM Stage 2 trial Final analysis – Clinical Study Report: 4Q 2023; • Multi-Country MDR-TB Disease Registry (TBC4002) Final study report: 2Q 2020.

Pancreatitis	Routine risk minimization measures: • SmPC Section 5.3; • Legal status: restricted medical prescription. Additional risk minimization measures: • None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None. Additional pharmacovigilance activities: • STREAM Stage 2 trial Final analysis – Clinical Study Report: 4Q 2023; • Multi-Country MDR-TB Disease Registry (TBC4002) Final study report: 2Q 2020.
Myopathy	Routine risk minimization measures: • SmPC Section 4.8; • SmPC Section 5.3; • PL Section 4; • Legal status: restricted medical prescription. Additional risk minimization measures: • None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None. Additional pharmacovigilance activities: • STREAM Stage 2 trial Final analysis – Clinical Study Report: 4Q 2023; • Multi-Country MDR-TB Disease Registry (TBC4002) Final study report: 2Q 2020.
Myocardial injury	Routine risk minimization measures: • SmPC Section 5.3; • Legal status: restricted medical prescription. Additional risk minimization measures: • None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None. Additional pharmacovigilance activities: • STREAM Stage 2 trial Final analysis – Clinical Study Report: 4Q 2023; • Multi-Country MDR-TB Disease Registry (TBC4002) Final study report: 2Q 2020.
Development of drug resistance	Routine risk minimization measures: • SmPC Section 4.2; • SmPC Section 4.4; • SmPC Section 5.1; • PL Section 3; • Recommendations regarding the initiation and monitoring of SIRTURO treatment by a physician experienced in the management of MDR-TB are included in SmPC Section 4.2; • Recommendations regarding the use of SIRTURO in combination with at least 3 medicinal products to which the patient's isolate has been shown to be susceptible in vitro, or at least 4 medicinal products to which the patient's isolate is likely to be susceptible, are included in SmPC Section 4.2; • Recommendation regarding the selection of the appropriate combination regimen is included in SmPC Section 4.2; • Recommendation regarding the use of SIRTURO in an	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Drug resistance surveillance Additional pharmacovigilance activities: • STREAM Stage 2 trial Final analysis – Clinical Study Report: 4Q 2023; • Multi-Country MDR-TB Disease Registry (TBC4002) Final study report: 2Q 2020.

	appropriate combination regimen to prevent development of resistance to SIRTURO is included in SmPC Section 4.4; • A warning for patients that stop taking SIRTURO is included in PL Section 3; • Legal status: restricted medical prescription. Additional risk minimization measures: • None.	
Missing Information		
Long-term effects of bedaquiline treatment on mortality	Routine risk minimization measures: • SmPC Section 4.1; • SmPC Section 4.4; • SmPC Section 5.1;	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None.
	• Legal status: restricted medical prescription. Additional risk minimization measures: • None.	Additional pharmacovigilance activities: • STREAM Stage 2 trial Final analysis – Clinical Study Report: 4Q 2023; • Multi-Country MDR-TB Disease Registry (TBC4002) Final study report: 2Q 2020.
Use in patients with severe hepatic impairment	Routine risk minimization measures: • SmPC Section 4.2; • SmPC Section 4.4; • SmPC Section 5.2; • Recommendations regarding the use of SIRTURO, including dose adjustments, in patients with mild, moderate, or severe hepatic impairment are included in SmPC Sections 4.2 and 5.2; • Warnings regarding coadministration of SIRTURO with other hepatotoxic medicinal products and alcohol are included in SmPC Section 4.4; • Recommendation for liver function monitoring is provided in SmPC Section 4.4; • Recommendation on evaluation and actions to be taken in case of increased transaminases is provided in SmPC Section 4.4; • A warning for patients who have liver disease or drink alcohol on a regular basis is included in PL Section 2; • Legal status: restricted medical prescription. Additional risk minimization measures: • None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None. Additional pharmacovigilance activities: • None.
Use in patients with severe renal impairment	Routine risk minimization measures: • SmPC Section 4.2; • SmPC Section 5.2; • Recommendations regarding the use of SIRTURO, including dose adjustments, in patients with mild, moderate, or severe (CrCl <30 mL/min) renal impairment or end-stage renal disease are included in SmPC Section 4.2; • Legal status: restricted medical prescription. Additional risk minimization measures: • None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None. Additional pharmacovigilance activities: • None.
Use in elderly	Routine risk minimization measures:	Routine pharmacovigilance

patients	• SmPC Section 4.2; • SmPC Section 5.2; • Legal status: restricted medical prescription. Additional risk minimization measures: • None.	activities beyond adverse reactions reporting and signal detection: • None. Additional pharmacovigilance activities: • STREAM Stage 2 trial Final analysis – Clinical Study Report: 4Q 2023; • Multi-Country MDR-TB Disease Registry (TBC4002) Final study report: 2Q 2020.
Use during pregnancy	Routine risk minimization measures: • SmPC Section 4.6; • SmPC Section 5.3; • Recommendations regarding the use of SIRTURO during pregnancy are included in SmPC Section 4.6 and PL Section 2; • Legal status: restricted medical prescription.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None. Additional pharmacovigilance activities: • None.
	Additional risk minimization measures: • None.	
Use in nursing mothers	Routine risk minimization measures: • SmPC Section 4.6; • SmPC Section 5.3; • Recommendations regarding the use of SIRTURO during breast-feeding are included in SmPC Section 4.6 and PL Section 2; • Legal status: restricted medical prescription. Additional risk minimization measures: • None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None. Additional pharmacovigilance activities: • None.
Use in HIV-coinfected patients on antiretroviral therapy	Routine risk minimization measures: • SmPC Section 4.4; • SmPC Section 4.5; • Recommendations regarding coadministration of SIRTURO with antiretrovirals are included in SmPC Section 4.5; • A warning for patients who have HIV infection is included in PL Section 2; • Legal status: restricted medical prescription. Additional risk minimization measures: • None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None. Additional pharmacovigilance activities: • STREAM Stage 2 trial Final analysis – Clinical Study Report: 4Q 2023; • Multi-Country MDR-TB Disease Registry (TBC4002) Final study report: 2Q 2020.
Use in patients using potent inhibitors of drug-metabolizing enzymes and transporters	Routine risk minimization measures: • SmPC Section 4.4; • SmPC Section 4.5; • PL Section 2; • Warnings regarding coadministration of SIRTURO with moderate or strong CYP3A4 inducers and inhibitors are included in SmPC Section 4.4; • Legal status: restricted medical prescription. Additional risk minimization measures: • None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None. Additional pharmacovigilance activities: • STREAM Stage 2 trial Final analysis – Clinical Study Report: 4Q 2023; • Multi-Country MDR-TB Disease Registry (TBC4002)

		Final study report: 2Q 2020.
Prolonged treatment duration	Routine risk minimization measures: • SmPC Section 4.2; • PL Section 3; • Recommendations regarding the initiation and monitoring of SIRTURO treatment by a physician experienced in the management of MDR-TB are included in SmPC Section 4.2; • Recommendation regarding posology is included in SmPC Section 4.2; • Legal status: restricted medical prescription. Additional risk minimization measures: • None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None. Additional pharmacovigilance activities: • STREAM Stage 2 trial Final analysis – Clinical Study Report: 4Q 2023; • Multi-Country MDR-TB Disease Registry (TBC4002) Final study report: 2Q 2020.

2.8. Update of the Product information

The approved changes to the Product Information can be found in the attached approved Product Information.

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, and 5.2 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

In addition, changes related to section 4.9 of the SmPC have been introduced. The MAH proposal to delete the information in section 4.9 of the SmPC to administer activated charcoal following bedaquiline overdose and to have this recommendation replaced by instructions to the prescriber to handle a possible case as clinically indicated and to contact a poison information center if such is available was considered acceptable, since CHMP agreed that there was limited value of its administration in situations of acute overdose. The reworded recommendation in section 4.9 is considered acceptable by CHMP.

2.8.1. User consultation

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

2.8.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, SIRTURO (bedaquiline) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU and it is approved under a conditional marketing authorisation.

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

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Tuberculosis is a transmissible disease caused by *M. tuberculosis* that commonly affects the lungs but can also spread to other organs. In 2016, there were an estimated 10.4 million prevalent TB cases (range:

8.8-12.2 million) and approximately 1.7 million people (range: 1.5-1.9 million) died from this disease in 2016.

The WHO recommends a standard short course (6 months) regimen for the treatment of drug-sensitive tuberculosis (DS-TB). The regimen comprises 2 phases: a 2-month intensive phase during which 4 drugs are administered qd or tiw (isoniazid [INH], rifampicin [RMP], pyrazinamide [PZA], and ethambutol [EMB]), followed by a 4-month continuation phase, usually consisting of INH and RMP, the two most important drugs for treating DS-TB. It is recommended that TB medicines be administered under directly observed therapy (DOT).

The short course regimen described above cannot be used when drug resistance is present. MDR-TB is defined as disease caused by strains of *M. tuberculosis* that are resistant to at least RMP and INH. In 2016, worldwide, 4.1% (95% confidence interval [CI], 2.8-5.3%) of all new TB cases and 19.0% (95% CI, 9.8-27.0%) of previously treated TB cases are MDR (including rifampicin-monoresistant TB [MDR-TBRR]). In 2016, 490,000 new cases of MDR-TB were identified. Coverage of testing for RMP resistance is increasing but remains low (41% overall). Tuberculosis is the leading cause of death among people with human immunodeficiency virus (HIV) infection. Regions with the highest rates of TB coincide with regions with the fastest growing HIV epidemics. The MDR-TB burden largely falls on 3 countries (India, China and the Russian Federation) which together account for nearly half of the global cases.

In a recent publication, it was estimated that 1.8 million (1.2-3.0 million) adolescents and young adults aged 10-24 years developed TB in 2012. In 2016, the WHO estimated that globally there were 1.04 million TB cases among children (under 15 years of age) and 253,000 TB deaths, 10% of the global totals, respectively.46 In high-burden settings, paediatric TB may comprise even up to 15 to 20% of the total disease burden.29,43 HIV contributes significantly to the paediatric disease burden and child mortality.

The spread of drug-resistant strains of *M. tuberculosis* is increasingly recognized as a major problem for children in countries with significant transmission of drug-resistant disease. Surveillance data on MDR-TB in children are limited. Based on a systematic review of the literature, it is estimated that around 999,792 (95% CI, 937,877-1,055,414) children (under 15 years of age) developed TB in 2010, of whom 31,948 (95% CI, 25,594-38,663) had MDR-TB.

3.1.2. Available therapies and unmet medical need

Bedaquiline is approved for the treatment of multidrug-resistant tuberculosis (MDR-TB) as part of an appropriate combination regimen in adults aged 18 years and older. This application aimed to include adolescents ≥12 to <18 years (and weighing more than 30 kg) within the scope of approved use.

Tuberculosis is a major global health problem. It is well recognized that estimating the incidence of TB in children is difficult and that published estimates vary. As reported in the 2013 Consensus Statement generated from an international panel of opinion leaders on childhood TB, both TB in young children and drug-resistant TB in all children are serious and life-threatening disorders with few treatment options. Affected children are potentially further harmed by the dearth of data to guide use of existing drugs. New agents with improved efficacy and safety profiles, new mechanisms of action that would not be affected by cross-resistance to strains of *M. tuberculosis* already resistant to currently used anti-TB drugs, and formulations of drugs that can be used in all paediatric age groups are needed.

3.2. Favourable effects

After 24 weeks of treatment with bedaquiline in combination with the background regimen, 7 of 15 subjects (46.7%, with a 95% CI of 22.3%; 72.6%) had a favorable treatment outcome. For 7 out of the 8 subjects without a favorable treatment outcome, the reason was `signs and symptoms not completely resolved per investigator's global TB assessment´. CHMP agreed nevertheless that these data are to be considered

descriptive, since it is considered that the efficacy of a product for the treatment of *M. tuberculosis* can be extrapolated from adults to children, provided that the systemic exposure is comparable. Therefore, the primary objective is to establish a dose in adolescence resulting in an exposure of bedaquiline which is comparable to that observed in adults, which has been shown in the case of the study programme presented in this application. CHMP concluded that bedaquiline at the proposed dose can be used for treatment of MDR-TB in adolescents ≥12 to <18 years of age weighing >30 kg, with similar effects as those seen in adults.

3.3. Unfavourable effects

The main safety findings come from the adult studies. The main adverse events identified for bedaquiline are transaminitis and QT-prolongation. No adolescent-specific side effects have been identified.

3.4. Uncertainties and limitations about unfavourable effects

In adolescents weighing 30-40 kg there might be a risk of overexposure, which could theoretically increase the risk for AEs such as hepatotoxicity and prolonged QT-interval. CHMP agreed to add a warning about this in section 4.4. of the Sirturo SmPC, in view of the existing incertitude and of the potential life-threatening adverse events (QT prolongation, hepatotoxicity).

3.5. Benefit-risk assessment and discussion

3.5.1. Importance of favourable and unfavourable effects

Tuberculosis (TB) is a life-threatening disease, and there is an unmet need for new medicines to treat multi-drug resistant TB (MDR-TB). In this context bedaquiline has emerged as an important medicine for the treatment of MDR-TB. The possibility of extrapolating efficacy and safety from adults to adolescents based on similar biology and on a comparable exposure is accepted, and therefore the suitability of the selected dose in adolescent subjects relies on the population PK model. In the provided modelling the adolescent week 12 weight stratified AUC168h exposure shows that a relatively high number of subjects weighing 30-40 kg are projected to have exposures moderately above the adult target exposure (60-140%), however the median is within the adult target exposure. CHMP considered this reassuring for granting the extension of indication in adolescents (12 years and older) weighing more than 30 kg.

3.5.2. Balance of benefits and risks

In this application, efficacy and safety are mainly extrapolated from adults to adolescents. A risk of overexposure compared to what is seen in adults has been defined in subjects weighing 30-40 kg. This could theoretically increase the risk for AEs such as hepatotoxicity and prolonged QT-interval. However, there is no clear exposure-response relation understood for these side effects. CHMP agreed to add a warning about this in section 4.4. of the Sirturo SmPC, in view of the existing incertitude and of the potential life-threatening adverse events. Underexposure is from a clinical point of view considered a more direct and well-defined risk that is moderate overexposure compared to what is seen in adults, as underexposure may result in treatment failure with subsequent emergence of resistance. CHMP agreed that any alternative posology that would be practically feasible in these patients would be associated with a risk of underexposure, which is not considered acceptable in the treatment of MDR-TB. Therefore, it was agreed that the benefit-risk balance for Sirturo is considered positive for the proposed dose in the agreed target population.

3.6. Conclusions

The overall B/R of Sirturo for pulmonary multidrug resistant tuberculosis (MDR TB) in adolescent patients

(12 years to less than 18 years of age and weighing at least 30 kg) when an effective treatment regimen cannot otherwise be composed for reasons of resistance or tolerability is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following group of variations acceptable and therefore recommends the variations to the terms of the Marketing Authorisation, concerning the following changes:

Variations accepted		**Type**	**Annexes affected**
C.I.6.z	C.I.6.z - Change(s) to therapeutic indication(s) - Other variation	Type II	I and IIIB
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I

Grouping of an Extension of Indication to include patients 12 years of age and older and weighing more than 30 kg for SIRTURO and a Type II variation to change an existing recommendation about the management of a bedaquiline overdose in Section 4.9 of the SIRTURO SmPC.

The extension of indication is supported by the Week 24 analysis of Cohort 1 (adolescent subjects aged ≥12 to <18 years) of Study TMC207-C211. Based on these data, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC are also updated. The Package Leaflet is updated in accordance.

An updated version of the RMP was included in the submission.

Conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list)) provided for under Article 107c (7) of Directive 2001/83/EC and published on the European medicines' web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk management plan (RMP)

The marketing authorisation holder shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

In addition, an updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0371/2016 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 Deltyba and Granupas within the meaning of Article 3 of Commission Regulation (EC) No. 847/200. See appendix 1.

5. EPAR changes

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

Scope

Grouping of an Extension of Indication to include patients 12 years of age and older and weighing more than 30 kg for SIRTURO and a Type II variation to change an existing recommendation about the management of a bedaquiline overdose in Section 4.9 of the SIRTURO SmPC.

The extension of indication is supported by the Week 24 analysis of Cohort 1 (adolescent subjects aged ≥12 to <18 years) of Study TMC207-C211. Based on these data, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC are also updated. The Package Leaflet is updated in accordance.

An updated version of the RMP was included in the submission.

Summary

Please refer to the Scientific Discussion (EMEA/H/C/002614/II/0033/G).