28 January 2021
EMA/CHMP/598014/2020
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

SIRTURO

International non-proprietary name: bedaquiline

Procedure No. EMEA/H/C/002614/X/0036/G

Note

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

Administrative information

Name of the medicinal product:	Sirturo
MAH:	Janssen-Cilag International NV Turnhoutseweg 30 2340 Beerse BELGIUM
Active substance:	BEDAQUILINE FUMARATE
International Non-proprietary Name/Common Name:	bedaquiline
Pharmaco-therapeutic group (ATC Code):	drugs for treatment of tuberculosis, other drugs for treatment of tuberculosis (J04AK05)
Therapeutic indication:	Sirturo is indicated for use as part of an appropriate combination regimen for pulmonary multidrug-resistant tuberculosis (MDR-TB) in adult and paediatric patients (5 years to less than 18 years of age and weighing at least 15 kg) when an effective treatment regimen cannot otherwise be composed for reasons of resistance or tolerability (see sections 4.2, 4.4 and 5.1). Consideration should be given to official guidance on the appropriate use of antibacterial agents.
Pharmaceutical form:	Tablet
Strengths:	20 mg and 100 mg
Route of administration:	Oral use
Packaging:	blister (alu/alu) and bottle (HDPE)
Package sizes:	20 mg: 60 tablets 100 mg: 24 tablets and 188 tablets

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List of abbreviations

AE	adverse event
AFB	acid-fast bacilli
ALT	alanine aminotransferase
AM	amikacin
AST	aspartate aminotransferase
AUCxh	area under the plasma concentration-time curve from the time of dose administration up to x hours post-dose
BMI	body mass index
BR	background regimen
CFZ	clofazimine
CI	confidence interval
CM	capreomycin
CXR	chest X-ray
DS	drug susceptible
DST	drug susceptibility testing
EMB	ethambutol
HIV	human immunodeficiency virus
IGRA	Interferon Gamma Release Assay
INH	isoniazid
ITT	intent-to-treat
KM	kanamycin
LFX	levofloxacin
M=F	Missing=Failure
MDR(-TB)	multidrug-resistant (tuberculosis)
MDR-TBH&R	multidrug-resistant tuberculosis excluding pre-XDR and XDR (ie, resistant only to INH and RMP)
MGIT	Mycobacteria Growth Indicator Tube
MIC	minimal inhibitory concentration
mITT	modified intent-to-treat
MXF	moxifloxacin
NTP	National Tuberculosis Program
PK	pharmacokinetic(s)
POP-PK	population pharmacokinetic
pre-XDR(-TB)	+pre-extensively drug resistant (tuberculosis)
PTO	protionamide
PZA	pyrazinamide
qd	once daily
QTcF	QT interval corrected for heart rate using Fridericia's method
RMP	rifampin (rifampicin)
RR-TB	rifampicin-monoresistant tuberculosis
SCE	Summary of Clinical Efficacy
SMQ	Standardized Medical Dictionary for Regulatory Activities Queries
TB	tuberculosis
Tiw	three times per week
TST	Tuberculosis Skin Testing
ULN	upper limit of normal
WHO	World Health Organization

1. Background information on the procedure

1.1. Submission of the dossier

Janssen-Cilag International NV submitted on 22 November 2019 a group of variations consisting of an extension of the marketing authorisation and the following variation:

Variation(s) requested		Type
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

Extension application to add a new strength (20 mg tablets), grouped with a type II variation (C.I.6.a) to extend the existing indication to include treatment of paediatric patients aged from 5 years to less than 18 years of age and weighing more than 15 kg, based on the results of the Week 24 analysis of Cohort 2 (paediatric subjects aged ≥5 to <12 years) of Study TMC207-C211. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, and 5.2 of the SmPC are proposed to be updated and the Package Leaflet is updated accordingly. Furthermore, the PI is brought in line with the latest QRD template version 10.1. The RMP (version 4.4) is updated in accordance.

The legal basis for this application refers to:

Article 7.2 of Commission Regulation (EC) No 1234/2008 – Group of variations

Sirturo was designated as an orphan medicinal product EU/3/05/314 on 26/08/2005 in the following condition: Treatment of tuberculosis

The new 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/0403/2018 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0403/2018 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

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

Protocol assistance

The MAH did not seek Protocol assistance at the CHMP.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Filip Josephson Co-Rapporteur: n/a

The application was received by the EMA on	22 November 2019
The procedure started on	2 January 2020
The Rapporteur's first Assessment Report was circulated to all CHMP members on	23 March 2020
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	31 March 2020
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	17 April 2020
The CHMP agreed on the consolidated List of Questions to be sent to the MAH during the meeting on	30 April 2020
The MAH submitted the responses to the CHMP consolidated List of Questions on	16 July 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	25 August 2020
The CHMP agreed on a List of Outstanding Issues in writing and/or in an oral explanation to be sent to the MAH on	17 September 2020
The MAH submitted the responses to the CHMP List of Outstanding Issues on	09 October 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	28 October 2020
The CHMP agreed on a 2nd List of Outstanding Issues in writing and/or in an oral explanation to be sent to the MAH on	12 November 2020
The CHMP adopted a report on similarity of Sirturo with Granupas, Deltyba and Pretomanid FGK (see Appendix 1)	12 November 2020
The MAH submitted the responses to the 2nd CHMP List of Outstanding Issues on	17 November 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to the 2nd List of Outstanding Issues to all CHMP members on	25 November 2020

The CHMP agreed on a 3rd List of Outstanding Issues in writing to be sent to the MAH on	10 December 2020
The MAH submitted the responses to the 3rd CHMP List of Outstanding Issues on	18 December 2020
PKWP provided responses to questions raised by the CHMP on The CHMP considered the views of the PKWP as presented in the written responses.	12 January 2021
The Rapporteurs circulated the Joint Assessment Report on the responses to the 3rd List of Outstanding Issues to all CHMP members on	15 January 2021
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Sirturo on	28 January 2021

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Tuberculosis (TB) is a transmissible disease caused by M. tuberculosis that commonly affects the lungs but can also spread to other organs. In 2017, there were an estimated 10.0 million prevalent TB cases (range: 9.0-11.1 million) and approximately 1.6 million people (range: 1.5-1.7 million) died.

Multidrug-resistant TB (MDR-TB) is TB that does not respond to at least isoniazid and rifampicin, which are the two most powerful anti-TB drugs. The two main reasons why multidrug resistance continues to emerge and spread are mismanagement of TB treatment and person-to-person transmission.

2.1.2. Epidemiology

According to WHO, the anti-TB drug resistance surveillance data in 2017 show that 4.1% of new and 19% of previously treated TB cases in the world are estimated to have rifampicin- or multidrug-resistant tuberculosis (MDR/RR-TB). In 2016, an estimated 600 000 new cases of MDR/RR-TB emerged globally. MDR/RR-TB caused 240 000 deaths in 2016. Most cases and deaths occurred in Asia.

Routine surveillance data on MDR-TB among children are not available globally. Based on several mathematical models, approximately 3% of children with TB are estimated to have MDR-TB. Global estimates of the burden of MDR-TB in children range from 25,000 to 32,000 incident cases annually (Jenkins 2014, Dodd 2016).

2.1.3. Clinical presentation, diagnosis

When a person develops active TB disease, the symptoms (such as cough, fever, night sweats, or weight loss) may be mild for many months. This can lead to delays in seeking care, and results in transmission of the bacteria to others. People with active TB can infect 5–15 other people through close contact over the course of a year. Without proper treatment, 45% of HIV-negative people with TB on average and nearly all HIV-positive people with TB will die. Common symptoms of active lung TB are cough with sputum and blood at times, chest pains, weakness, weight loss, fever and night sweats.

Many countries still rely on a long-used method called sputum smear microscopy to diagnose TB. Trained laboratory technicians look at sputum samples under a microscope to see if TB bacteria are present. Microscopy detects only half the number of TB cases and cannot detect drug-resistance.

Diagnosing MDR-TB can be both complex and expensive. Since 2010 WHO recommends the use of the rapid test Xpert MTB/RIF, which is a nucleic acid test. The test can simultaneously detect TB and resistance to rifampicin and diagnosis can be made within 2 hours from sputum sample. Since 2016, four new diagnostic tests were recommended by WHO to use at peripheral health centres where Xpert MTB/RIF cannot be used. The four tests include one test for identify TB and three additional tests to detect resistance to first- and second-line TB drugs.

Childhood TB disease is also often accompanied by or confused with important co-morbid conditions that may be reported as the primary illness or primary cause (e.g., acute bacterial pneumonia, HIV-related disease such as Pneumocystis carinii pneumonia, lymphoid interstitial pneumonia, or wasting, malnutrition, bacterial or viral meningitis).

Confirmation of TB in children is particularly difficult mainly because bacteriologic confirmation is often not achieved, especially in younger children. Case detection in young children is poor due to the paucibacillary nature of the disease in children (less than 10% of pulmonary TB in young children is acid-fast bacilli [AFB] smear-positive), and because they cannot expectorate sputum on demand. Also, considering that MDR-TB is mainly a bacteriological diagnosis through culture and drug susceptibility testing, a complete diagnosis of MDR-TB in children is often unavailable. As a result, a high proportion of childhood TB cases are diagnosed based on clinical criteria without microbiological confirmation. This absence of microbiological confirmation restricts both the ability to directly measure the incidence of TB in children and to routinely assess the risk of MDR-TB among these cases. Exposure to a source case with MDR-TB is a common diagnostic tool for detection of TB in children and adolescents.

2.1.4. Management

The WHO recommends an MDR-TB treatment regimen consisting of an intensive phase of 4 to 6 months with kanamycin, moxifloxacin, prothionamide, clofazimine, pyrazinamide, high-dose isoniazid, and ethambutol, followed by a 5-month continuation phase with moxifloxacin, clofazimine, pyrazinamide, and ethambutol. This regimen is recommended for all patients (children and adults, excluding pregnant women) with pulmonary MDR-TB/RR TB who did not previously receive second-line TB drugs and in whom resistance to fluoroquinolones and second-line injectables has been excluded or is considered highly unlikely (i.e., uncomplicated MDR-TB) (WHO 2016a). In 2013, the WHO expert group concluded that bedaquiline may be added to a WHO-recommended regimen in adults with pulmonary MDR-TB when an effective regimen containing 4 second-line drugs in addition to pyrazinamide cannot be designed (e.g., due to intolerance or resistance to second-line drugs); or when there is documented evidence of resistance to any fluoroquinolone in addition to multidrug resistance. The WHO Expert Committee on Selection and Use of Essential Medicines recommended inclusion of 5 TB medications, including bedaquiline, in the WHO Model List of Essential Medicines in 2015.

The principles of MDR/XDR-TB treatment regimens used in children are similar to those of adults and the same second-line drugs are generally used. A regimen should contain at least 4 drugs to which drug susceptibility testing shows susceptibility and/or to which the patient or source case is naïve (Schaaf 2012). Since the commonly used first- and second-line anti-TB drugs to treat DS-TB and MDR-TB were developed in adult patients, dose recommendations for use in children are often found to be inadequate.

About the product

Bedaquiline is a diarylquinoline and an anti-mycobacterial agent that is being developed as part of a combination therapy for pulmonary TB due to MDR M. tuberculosis. Bedaquiline inhibits specifically mycobacterial adenosine 5'- triphosphate (ATP) synthase, an enzyme that is essential for the generation of energy in mycobacteria. The inhibition of ATP synthase leads to bactericidal effects for both replicating and non-replicating (dormant) tubercle bacilli.

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 adults and 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".

Type of Application and aspects on development

The applicant is submitting the following grouping according to article 7.2 (b) of the variation regulation (cases for grouping variations listed in Annex III to Commission Regulation (EC) No 1234/2008):

- New strength 20 mg (tablets) developed as an age appropriate formulation Extension of a marketing authorisation under Annex I to Commission Regulation (EC) No 1234/2008.

- Broadening of the currently approved indication for bedaquiline in adults and adolescent patients as part of a combination therapy of pulmonary tuberculosis (TB) due to multidrug-resistant (MDR) M. tuberculosis, to include the paediatric patient population aged ≥5 to <12 years: Type II variation.

For this purpose, the MAH has conducted a single-armed study including 15 paediatric subjects (age 5-10 years weighing 16-36 kg), of which 10 completed the treatment phase. A new tablet (20 mg) was used to administer half the adult dose (200 mg QD for 14 days, followed by 100 mg TIW for 22 weeks). The purpose of this study was to extrapolate efficacy and safety from adults to paediatric patients, where the aim was to match the plasma exposure of bedaquiline in paediatric patients to the 60% – 140% range for the adult geometric mean AUC0-168h at steady-state for a dose of 100 mg three times per week.

The applicant has consulted PDCO regarding sample size. EMA accepted in 19 December 2018 a modification of an agreed paediatric investigation plan for bedaquiline (fumarate), (Sirturo), (EMEA-000912-PIP01-10-M04) in accordance with Regulation (EC) No 1901/2006 of the European Parliament and of the Council.

No new non-clinical data have been submitted in this application, which is considered acceptable.

2.2. Quality aspects

2.2.1. Introduction

The current application concerns a line extension for Sirturo to add a new strength of 20 mg tablets developed as an age appropriate formulation.

The finished product is presented as tablets containing 20 mg of bedaquiline, in the form of fumarate salt, as the active substance.

Other ingredients are microcrystalline cellulose, crospovidone, colloidal anhydrous silica, hypromellose, polysorbate 20, and sodium stearyl fumarate.

The product is available in high density polyethylene (HDPE) bottles fitted with child-resistant polypropylene (PP) closure, as described in section 6.5 of the SmPC.

2.2.2. Active Substance

There were no changes made to this section as the same active substance (bedaquiline) is used to produce the new strength of 20 mg tablets as the currently approved strength of 100 mg tablets. The synthesis and quality of the active substance was assessed in conjunction with the application for the already approved 100 mg tablets and was found acceptable.

General Information

The chemical name of bedaquiline (INN) is (1R,2S)-1-(6-bromo-2-methoxy-3-quinolinyl)-4-(dimethylamino)-2-(1-naphtalenyl)-1-phenyl-2-butanol compound with fumaric acid (1:1), corresponding to the molecular formula $C_{32}H_{31}BrN_2O_2 \cdot C_4H_4O_4$. It has a relative molecular mass of 671.58 (555.50 + 116.07) g/mol and the following structure:

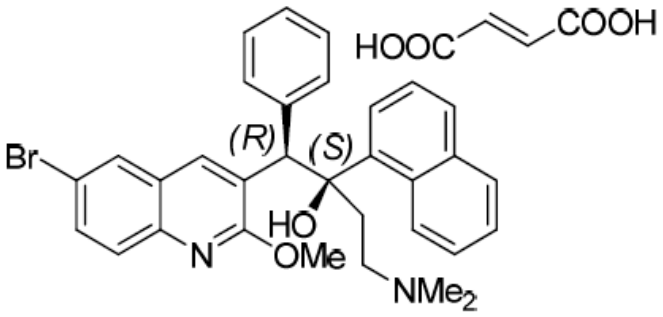


Figure 1: Active substance structure

Bedaquiline fumarate is a white to almost white powder. It contains two asymmetric carbon atoms, C-1 (R), C-2 (S) and exhibits ability to rotate the orientation of linearly polarized light (optical rotation). The substance is non-hygroscopic. It is practically insoluble in aqueous media over a wide pH range and very slightly soluble in 0.01 N HCl. The substance is soluble in a variety of organic solvents. Due to the low solubility Log KD (log P) could not be determined experimentally.

In Biopharmaceutics Classification System (BCS) bedaquiline is classified as a Class 2 compound (expressing low solubility and high permeability).

Bedaquiline exhibits polymorphism. The active substance manufacturing process is designed to consistently yield the same polymorphic form. This form was observed in all active substance batches manufactured to date using the intended commercial synthetic process.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

The finished product is supplied as an immediate release, white to almost white, oblong tablet for oral administration with a break-mark on both sides and debossed with "2" and "0" on one side. The tablet has dimensions of nominally 12.0 x 5.7 mm and may be split along the break-mark into 2 halves to facilitate dosing, if required. The tablet formulation contains 24.18 mg of bedaquiline active substance in the form of its fumaric acid salt equivalent to 20.00 mg bedaquiline free-base (eq. 20 mg tablet). All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC.

Pharmaceutical development

The bedaquiline 20 mg tablet formulation uses the same active substance that is used in the approved bedaquiline 100 mg tablet. The active substance manufacturing process and the associated specifications have been approved, and the active substance used to manufacture the bedaquiline 20 mg tablet is manufactured in compliance with these specifications.

To obtain an oral tablet suitable for the paediatric population, the excipients present in the approved bedaquiline 100-mg tablet were optimized.

Age appropriate formulations were developed using standard pharmaceutical excipients and standard manufacturing process. Consideration was given to functionality of each excipient and beneficial effect it will have on the finished product performance.

All excipients used in the finished product formulation are well characterized and widely used in pharmaceutical preparations. The excipients used in the proposed commercial formulation have detailed monographs in relevant pharmacopoeias (Ph. Eur., USP/NF). There are no non-compendial or novel excipients used in the finished product formulation.

The ability of the excipients to perform their function within a certain concentration range and throughout shelf life of the proposed commercial formulation was demonstrated through a formulation robustness study, which has been adequately described.

The quality target product profile (QTPP) was developed taking into account relevant paediatric guidelines, including ICH E11 (2000) and subsequent addendum, ICH E11 (R1) from 2017, to assure efficacy by ensuring accurate dosing, and enhanced patient compliance. The QTPP for the new age appropriate formulation was defined as an immediate release oral scored tablet, containing bedaquiline fumarate active substance, equivalent to 20 mg bedaquiline free base. The finished product was required to have a sufficiently low level of impurities and microbial burden.

The development of the QC dissolution method for the new strength was sufficiently discussed and is considered acceptable.

A dissolution specification was proposed considering the overview of dissolution profiles of various batches including clinical batches, development batches and registration batches. Upon request, the MAH has also

evaluated the proposed dissolution specification based on the results for the clinical batches as per the reflection paper EMA/CHMP/QWP/336031/2017.

The specification is based on clinical batches and is adequately justified.

Additionally, the administration of crushed tablets with food (soft foods (e.g., yoghurt, apple sauce, mashed bananas or porridge)) was also taken into consideration during the formulation development. During the procedure, the SmPC and package leaflet were revised to reflect and clarify the different methods of administration.

Excipient compatibility and manufacturing process knowledge from the approved bedaquiline 100 mg tablet was used as a reference point for developing the age appropriate formulation.

Optimization of the excipients and manufacturing process led to the identification of 2 oral dosage forms that would be suitable for the paediatric population:

The relative bioavailability of a 100 mg dose of the bedaquiline 20 mg tablet (G003) used in the clinical studies, and the bedaquiline 20 mg/g granules was compared to the approved bedaquiline 100 mg tablet in a relative bioavailability trial (TMC207TBC1002). In conclusion, the age appropriate formulations (i.e. the two versions of the 20 mg tablet (G003 and the 20 mg/g granules) were found to have bioavailability comparable to that of the bedaquiline 100 mg tablet.

Based on the bioavailability results, manufacturability, stability, and convenience and accuracy of dosing, the 20 mg tablet (G003) was selected for further adaptation and evolved to G008 which is the intended for commercialisation.

The G003 bedaquiline 20 mg tablet was unscored and was further adapted to obtain a 20 mg scored tablet, which would allow increased dosing flexibility (i.e., 10 mg dose increments).

The resulting bedaquiline 20 mg tablet (G008) with break-mark, is proposed as the commercial formulation. This later version of the 20 mg tablet (G008) was also successfully bridged with the approved 100 mg strength through bioavailability Study TMC207TBC1004 (refer to Clinical aspects below).

The primary packaging is HDPE bottle with a child-resistant closure as stated in the SmPC. The material complies with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

Sirturo is formulated as an uncoated immediate release tablet.

The finished product process is considered to be a standard manufacturing process using granulation, followed by blending and compression. No intermediates are isolated during the process. A flowchart and an adequate description of the manufacturing process have been provided.

The manufacturing process was adequately described. The Applicant has developed a science-based criticality analysis approach to determine the critical controls for the finished product manufacturing process. Critical steps have been identified and properly evaluated at the commercial scale. The in-process controls are adequate for this pharmaceutical form.

It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner.

Formal validation will be performed post-approval on the first three consecutive commercial batches, prior to launching the product. An acceptable validation plan has been provided. Since the process has been extensively evaluated and the critical process parameters for the process have been identified and characterised at full scale it was considered sufficient to provide a validation plan and perform the validation post-approval.

Product specification

The finished product is controlled by testing attributes relevant for this dosage form. The finished product specification includes tests for appearance, identity of the active (HPLC), assay (HPLC), degradation products (HPLC), uniformity of dosage units, dissolution and microbial purity.

The proposed specifications were justified based on the batch and stability results and are adequate for assuring the product quality and therefore were accepted.

The proposed degradation product specifications (chromatographic purity) are fully consistent with the ICH Q3B Guideline on Impurities in New Drug Products. All the batches analysed to date comply with the proposed specifications at release and during stability testing. The specifications for specified and unspecified degradation products, and for total degradation products are considered appropriate and adequately justified.

The requested risk assessment on the presence of nitrosamines as a potential impurity of bedaquiline fumarate has been performed. Relevant parts of the manufacturing of the active substance and the final finished product have been considered. The Applicant concluded that no nitrosamine risk is identified for bedaquiline fumarate active substance, bedaquiline 20 mg tablets, which included assessing the potential for the excipients to contain nitrosamine impurities and for nitrosamine impurities to be formed during the manufacturing process. An assessment of the proposed commercial container closure system, HDPE bottles, also showed no nitrosamine risk. This is considered acceptable.

The potential presence of elemental impurities in the finished product has been assessed on a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. The information on the control of elemental impurities is satisfactory.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Full method validation data was provided for the non-compendial (in-house) analytical methods.

Satisfactory information regarding the reference standards used has been presented.

All finished product batches meet the proposed commercial specifications. The batch analysis results confirm the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data from 3 commercial scale batches of finished product stored for up to 18 months under long term conditions (25 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. These are representative to those proposed for marketing and were packed in the proposed commercial primary packaging. The test methods used for stability testing are the same as the proposed commercial test methods.

The currently available stability data indicate that the bedaquiline 20 mg tablet is chemically and physically stable under light ICH conditions, for at least 12 months at 5 ºC, at least 18 months at 25 ºC /60% RH and

30 ºC /75% RH, for at least 6 months at 40 ºC/75% RH, and for at least 3 months at 50 ºC upon storage in the proposed commercial packaging systems.

Based on available stability data, and in accordance with ICH Q1E, the shelf-life of 30 months and the storage precautions (`store in the original container and keep the container tightly closed in order to protect from light and moisture´) as stated in the SmPC (section 6.3) are acceptable.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the finished product has been presented in a satisfactory manner. The reproducibility of the manufacturing process has been suitably demonstrated.

The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

From a Quality point of view this line extension application to add a new age appropriate strength (20 mg tablets) is acceptable.

2.2.6. Recommendations for future quality development

N/A

2.2.7. Pharmacology

No new non-clinical pharmacology studies have been submitted in this application, which is considered acceptable by the CHMP.

2.2.8. Pharmacokinetics

No new non-clinical pharmacokinetics studies have been submitted in this application, which is acceptable.

2.2.9. Toxicology

No new non-clinical toxicology studies have been submitted in this application, this is acceptable by the CHMP.

In the initial authorisation application (EMEA/H/C/2614) a juvenile toxicity study in the rat following oral administration of bedaquiline (TMC207-NC119, GLP) was submitted and reviewed. A brief summary of the findings from the juvenile toxicity study is presented herein since the present application includes the paediatric patient population aged ≥5 to ≤12 years.

Juvenile SD rats were administered TMC207-fumarate (bedaquiline) daily from Day 24 to Day 60 of age, which corresponds to the period from early childhood (2-5 years) and into puberty, at dose levels of 0 (vehicle), 5, 15 or 45 mg/kg/day. TMC207-fumarate (bedaquiline) was given orally by gavage in 20% w/v HP-β-CD in a volume of 5 mL/kg (12 rats/sex/group). During the 8-week recovery period, animals were assessed for effects on sexual maturation, neuro-behavioural responses, mating performance and fertility (20 additional animals/sex/group).

At the high dose, bedaquiline-related effects were similar to those in adult rats including TMC207-related changes in the muscular tissue (diffuse inflammation and/or degeneration in skeletal muscle, oesophagus and tongue), liver (hypertrophy) and kidneys (corticomedullary mineralization). Changes were no longer present after approximately 8 weeks of recovery, with exception of the corticomedullary mineralization in the kidneys, which was still ongoing. There were no new target organs of toxicity, compared to findings in adult rats. NOAEL exposure levels at the end of the treatment period are approximately 0.7-fold the human exposure to unchanged bedaquiline and 1.8-fold the human exposure to M2 (human data from trial TMC207-C208, end of stage I).

2.2.10. Ecotoxicity/environmental risk assessment

A full ERA is submitted, including Phase I and Phase II, tier A and B. This report is assessed after the submission of the initial MAA in 2012. The substance bedaquiline is classified as a PBT substance.

Table 1

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		

This ERA report differs from the initial report only in the prevalence data used to calculate the Fpen, and consequently only these data are assessed.

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 Applicant, 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 $PEC_{surfacewater}$ of 0.00084 µg/L.; i.e. > 0.01 threshold

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 adults and all paediatric patients (0 to 18 years of age).

Using this $PEC_{surfacewater}$ to calculate risk quotients (ratio $PEC_{surfacewater}$r/$PNEC_{water}$ 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 has been included in the Package Leaflet:

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

2.2.11. Discussion on non-clinical aspects

No new non-clinical studies have been submitted in this application, which is acceptable to the CHMP.

Toxicology

The present application is intended to broaden the currently approved indication for bedaquiline to include the paediatric patient population aged ≥5 to ≤12 years. A juvenile toxicity study in the rat following oral administration of bedaquiline (TMC207-NC119, GLP) was previously submitted and assessed in the initial MAA for bedaquiline. In this juvenile toxicity study, there were no major differences in target organ toxicity between juvenile and adult rats and no additional toxicity was identified in the juvenile rat. There were some observations of males with small flaccid testes/small epididymides although considered unlikely to be treatment related.

Environmental risk assessment (ERA)

In a recent type II variation procedure for Sirturo (bedaquiline) concerning an extension of indication to include patients 12 years of age and older (Procedure No. EMEA/H/C/002614/II/0033/G), the applicant recalculated the market penetration factor (Fpen) using prevalence data for both the pediatric and the adult populations and the ERA was updated accordingly. Using the prevalence data for both the adult and the complete pediatric populations (0 to 18 years of age) a refined Fpen of 0.00042% was calculated and a $PEC_{surfacewater}$ of 0.00084 µg/L was generated, which in turn results in a calculated risk ratio $PEC_{surfacewater}/PNEC_{water}$ below 1.

2.2.12. Conclusion on the non-clinical aspects

The non-clinical studies are sufficient to support the extended indication and new strength. There are no major objections for approving the current application for bedaquiline from a non-clinical perspective.

2.3. Clinical aspects

2.3.1. Introduction

This application is intended to broaden the currently approved indication for bedaquiline to include the paediatric patient population aged ≥5 to ≤12 years based on the week 24 analysis of Cohort 2 of study TMC207-C211 (including subjects aged ≥5 to ≤12 years with confirmed or probably pulmonary MDR-TB), to provide dosing recommendations for paediatric patients weighing ≥15 kg, and too seek registration of the 20 mg bedaquiline scored tablet formulation (G008) as an age-appropriate formulation.

This application contains data from two relative bioavailability studies, study TMC207TBC1002 and TMC207TBC1004 as well as data from Cohort 2 of the paediatric study TMC207-C211 (week 24 data) as seen in Table 2 and Table 3 below.

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.

Table 2- Tabular overview of clinical studies TMC207TBC1002 and TMC207-C211

Study (Phase, Status)	Treatment	Number of Subjects	Primary Objectives	Source Reference and Study Synopsis Location
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[b] - BDQ 100-mg single dose as 5 grams of oral granules containing 20-mg/g oral granulate[c]	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.	Mod5.3.1.2/TMC207TBC1002-CSR Mod5.3.1.2/TMC207TBC1002-synopsis
Pediatric Subjects With Confirmed or Probable Multidrug-resistant Tuberculosis				
TMC207-C211 (Phase 2, ongoing)	**Cohort 1[d]** (≥12 to <18 years) - BDQ[e] 400 mg qd for first 14 days - BDQ[e] 200 mg tiw (intakes at least 2 days apart) for following 22 weeks (ie, the adult dose regimen)	Enrolled N=15		
	Cohort 2 (≥5 to <12 years) - BDQ[e] 200 mg qd for first 14 days - BDQ[e] 100 mg tiw (intakes at least 2 days apart) for following 22 weeks	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.	Mod5.3.3.2/TMC207-C211-W24-Cohort 2-CSR Mod5.3.3.2/TMC207-C211-W24-Cohort 2-synopsis
	Cohort 3[d] (≥2 to <5 years) - BDQ[e] 8 mg/kg qd for first 14 days[f] - BDQ[e] 4 mg/kg tiw (intakes at least 2 days apart) for following 22 weeks[f]	Planned N=15		
	Cohort 4[d] (0 months to <2 years) Dose TBD based data from the previous cohorts[e]	Planned N=15		

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

[a] Bedaquiline oral tablet formulation was used, containing 100 mg bedaquiline per tablet (ie, the registered adult tablet, formulation F001), taken with food in Study TMC207-C211 and both with and without food in Study TMC207TBC1002.

[b] The age-appropriate oral formulation G003 was used (unscored 20-mg tablet), with and without food (to be swallowed with water as a whole tablet, dispersed in water or crushed and mixed with yoghurt).

[c] The age-appropriate oral formulation G0004 was used (20 mg/g oral granules), with and without food (to be dispersed in water or sprinkled on and mixed with yoghurt).

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

[e] An age-appropriate oral formulation is/will be used in Cohorts 2, 3, and 4 (scored 20-mg tablet, formulation G008), containing 20 mg bedaquiline per tablet, taken with food (to be swallowed with water as a whole or split tablet, dispersed in water, or crushed and mixed with yoghurt).

[f] Planned dose per protocol amendment 6.

Table 3 - Tabular overview of clinical study TMC207TBC1004

Study ID EudraCT Number First Patient First Visit (FPFV) / Completion date (Day Month Year) Study Status	Country(ies): Number of Centers	Phase Study Description/Design, Study Population Primary Objective(s)	Total Number of Subjects	Study Drug(s): Formulation (Route of Administration) Dose Regimen Duration of Treatment	Number of Subjects Treated by Treatment Group (Treatment Sequence)	Type of Study Report Issue Date CTD Location of Report
Study Type						
Module 5.3.1.2 Comparative Bioavailability and Bioequivalence Studies						
TMC207TBC1004 2018-004306-26 FPFC: 16 September 2019 / Completion date: 09 January 2020 Completed	Belgium: 1 center	Phase 1 Single-center, open-label, randomized, 3-way crossover study in healthy adult subjects Assess the relative oral bioavailability of a single 100-mg dose of bedaquiline administered as different test tablet formulations compared to the reference commercial tablet formulation SIRTURO® (F001) under fasted conditions, and then to assess the effect of a standardized breakfast on oral bioavailability of the different test tablet formulations	Enrolled: N=36	Treatment A: 100 mg bedaquiline administered as 1x100-mg oral reference tablet (F001) fasted Treatment B: 100 mg bedaquiline administered as 1x100-mg oral test tablet 1 (JNJ-16175328-AEP-G010) fasted Treatment C: 100 mg bedaquiline administered as 1x100-mg oral test tablet 2 (JNJ-16175328-AEP-G011) fasted Treatment D: 100 mg bedaquiline administered as 1x100-mg oral test tablet 3 (JNJ-16175328-AEP-G012) fasted Treatment E: 100 mg bedaquiline administered as 1x100-mg oral test tablet 1 (JNJ-16175328-AEP-G010) fed Treatment F: 100 mg bedaquiline administered as 1x100-mg oral test tablet 2 (JNJ-16175328-AEP-G011) fed Treatment G: 100 mg bedaquiline administered as 1x100-mg oral test tablet 3 (JNJ-16175328-AEP-G012) fed Single dose in 3 subsequent periods, with a washout period of at least 28 between the periods	n=6 (A-B-E) n=6 (A-C-F) n=6 (A-D-G) n=6 (B-A-E) n=6 (C-A-F) n=6 (D-A-G)	Full Study Report 01 July 2020 Mod5.3.1.2/TMC207TBC1004-CSR

CSR = clinical study report; FPFC = first patient first consent; n = number of subjects

2.3.2. Pharmacokinetics

- ***Bioanalytical method***

Study TMC207-C211 Cohort 2 was analysed according to the method validation and is found acceptable as well as the within study analysis for study TMC207-C211 Cohort 2.

The relative bioavailability study TMC207TBC1004 was analysed according to the method validation report and is found acceptable as well as the within study analysis for study TMC207TBC1004.

Some minor issues were identified in assessment of the bioanalysis report for study TMC202TBC1002. However this study was considered of limited value for this application and these issues were not further pursued.

Relative bioavailability study - TMC207TBC1002

This was an open-label, randomised, 3-way crossover study in three panels of healthy, adult subjects (12 subjects in each panel), to assess the relative bioavailability of 100 mg bedaquiline after single-dose administration of two age appropriate 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).

In this study, the 20mg unscored tablet (G003) was selected as the most appropriate age appropriate formulation, which was then further developed to a 20 mg scored tablet (G008) used in study TMC207-C211 from Cohort 2 and onwards. The result for G004 is therefore not presented.

Bioequivalence was demonstrated for $AUC_{0\text{-}72h}$ and C_{max} between bedaquiline 100mg commercial tablet and G003 when administrated with a standardized breakfast and standardized regular-fat yoghurt but was not demonstrated when administrated under fasting condition.

***Relative bioavailability study* - TMC207TBC1004**

In this study the relative bioavailability was tested for three different 100-mg tablet test formulations (treatment B, C and D) versus the already approved 100 mg tablet formulation F001 (treatment A). Treatment B, further referred to as G010, has the same composition both qualitatively and quantitatively as well as similar dissolution profiles in the PBDT test as 5x formulation of G008 (applied formulation). Therefore, this study is assessed as relevant for the G008 formulation as well.

This was an open-label, randomized, 3-panel, 3-way crossover study in 36 healthy adult volunteers to assess the relative bioavailability of a single 100-mg dose of bedaquiline administered as 3 different 100-mg test tablet formulations, including G010, compared to a single dose of F001 under fasted conditions. The study also assessed the effect of a standardized breakfast on the oral bioavailability of the 3 different test tablet formulations, including G010 (Treatment E). The standardized breakfast consisted of 4 slices of bread, 2 slices of ham or cheese, butter, jelly, and 1 glass of water or 1 cup of milk (8oz). This meal contained approximately 533 kcal (189 from fat, 268 from carbohydrates, and 76 from protein). Blood samples were collected over 672 hours (28 days) after drug administration in each period. A wash-out period of at least 28 days was performed between each treatment. The result from the study is given in the tables below:

Table 4

Table 4: Summary of the Statistical Analysis of the Pharmacokinetic Parameters of Bedaquiline After Single Oral Administration of Bedaquiline at 100 mg as Reference Tablet F001 and as G010 in Fasted Conditions - Formulation Effect; Pharmacokinetics Data Statistical Analysis Set (Study TMC207TBC1004)

PK Parameter	Geometric LSMeans			Geometric LSMeans Ratio (%)			
	Treatment	N	Geometric LSM	Comparison	PE	90%CI	Intra-subject CV (%)
C_{max} (ng/mL)	A	35	389				33.8
	B	11	350	B vs A	89.95	70.88; 114.15	
AUC_{72h} (ng.h/mL)	A	35	6,774				23.8
	B	11	6,230	B vs A	91.97	77.60; 109.00	
AUC_{last} (ng.h/mL)	A	35	11,963				19.2
	B	11	11,315	B vs A	94.58	82.42; 108.53	

LSM: Least square means, PE: Point estimate (Geometric LS mean ratio), CI: Confidence interval, CV: Coefficient of variation
Treatment A: 100 mg Bedaquiline Oral Reference Tablet, F001, Fasted
Treatment B: 100 mg Bedaquiline Oral G010, Fasted

Table 5

Table 5: Summary of the Statistical Analysis of the Pharmacokinetic Parameters of Bedaquiline After Single Oral Administration of Bedaquiline at 100 mg as G010 in Fasted and Fed Conditions - Food Effect; Pharmacokinetics Data Statistical Analysis Set (Study TMC207TBC1004)

		Geometric LSMeans		Geometric LSMeans Ratio (%)			
PK Parameter	Treatment	n	Geometric LSM	Comparison	PE	90%CI	Intra-subject CV (%)
C_{max} (ng/mL)	B	12	324				29.8
	E	12	1,101	E vs B	339.87	277.87; 415.70	
AUC_{72h} (ng.h/mL)	B	12	5,712				19.2
	E	12	12,663	E vs B	221.70	194.31; 252.96	
AUC_{last} (ng.h/mL)	B	12	10,183				16.4
	E	12	24,008	E vs B	235.77	210.69; 263.85	

LSM: Least square means, PE: Point estimate (Geometric LS mean ratio), CI: Confidence interval, CV: Coefficient of variation
Treatment B: 100 mg Bedaquiline Oral G010, Fasted
Treatment E: 100 mg Bedaquiline Oral G010, Fed

Pharmacokinetic Analysis of Bedaquiline (TMC207) and M2 for Paediatric Subjects Recruited in Study TMC207-C211

Study TMC207-C211 Cohort 2

The paediatric study is an open-label, multi-centre, single-arm, ongoing Phase 2 study in children and adolescents 0 months to <18 years of age (in 4 different age cohorts). The primary objectives are to evaluate the safety and tolerability of bedaquiline over a 24-week treatment period in each age cohort and the pharmacokinetics (PK) of bedaquiline to provide guidance on dose selection for each of the age cohorts evaluated in this study. Rich sampling was conducted during week 2 and 12. At week 24 a trough sample was collected.

Cohort 2 received half the adult dose (200 mg daily the first 2 weeks, followed by 100 mg three times weekly) as the age appropriate formulation G008. Cohort 2 consisted of 15 children aged ≥5 to 10 years, 60% were female. The children weighed 14-36 kg (median 23 kg). Two subjects discontinued bedaquiline treatment prior to week 2, and five subjects did not have bedaquiline intake at week 12 and week 24,. In addition, one subject had the week 12 rich PK samples collected on a day without bedaquiline administration. In total, three subjects discontinued due to AEs

Methods

The pharmacokinetic analysis was conducted using model-based analysis. A previously developed population PK model developed across 9 adult clinical studies in both healthy subjects and subjects with MDR-TB (presented in the MAA EMEA/H/C/2614) was adapted to account for body weight-related changes in children (5 to <12 years) by allometric scaling of clearance and volume parameters based on total body weight was included, with fixed allometric exponents to 0.75 and 1 for the respective parameters. The adult exposure was simulated using the final adult model from the initial MAA, without allometric exponents.

For each paediatric subject, the maximum a posteriori (MAP) estimates of individual PK parameters were determined and appended to the dataset. Concentrations were simulated for each interested dummy time points using the MAP PK parameter estimates. Area under the plasma concentration-time curve from time of administration to 168 hours (total of 3 doses) (AUC168h) at Weeks 12 and 24 were determined using NCA analysis of the simulated concentrations. The exposure metrics were then tabulated and graphically compared to the simulated adult AUC168h at Weeks 12 and 24 for a dose of 200 mg three times per week. Additionally, the mean AUC168h at Weeks 12 and 24 was compared to the 60% – 140% range for the adult

geometric mean AUC168h (86200 ng.hr/mL – 201000 ng.h/mL) at steady-state for a dose of 200 mg three times per week.

Model performance

A prediction corrected visual predictive check (pcVPC) plot (Figure 2) and goodness-of-fit plots (Figure 3) including data from both cohort 2 (children 5-10 years) at week 2, 12 and 24 is displayed below.

Figure 2. Prediction-corrected Visual Predictive Check for Bedaquiline in Cohort 2 at Week 2 (Top), Week 12 (Middle), and Week 24 (Bottom) (Study TMC207-C211)

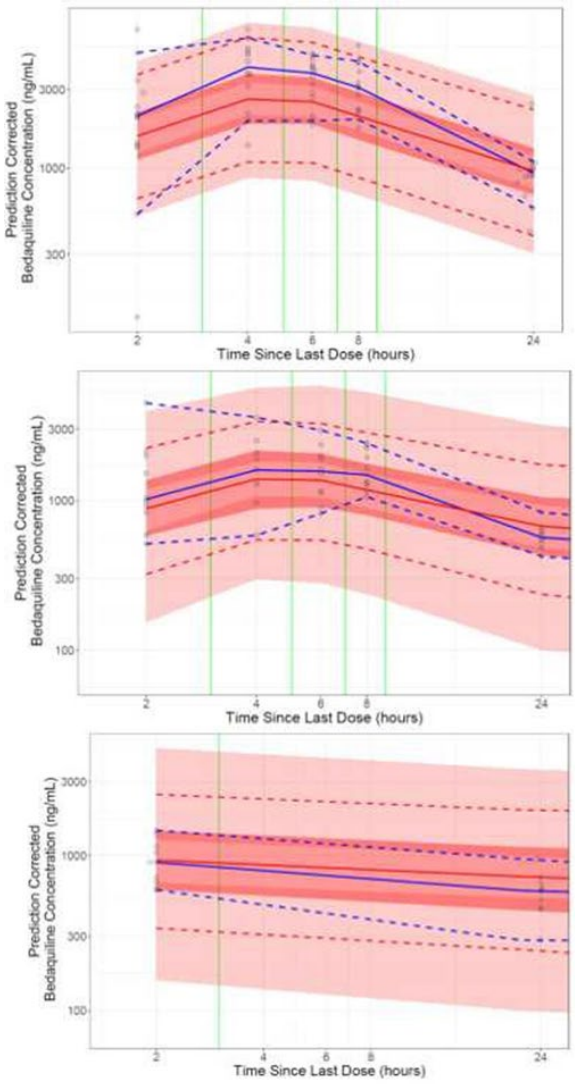
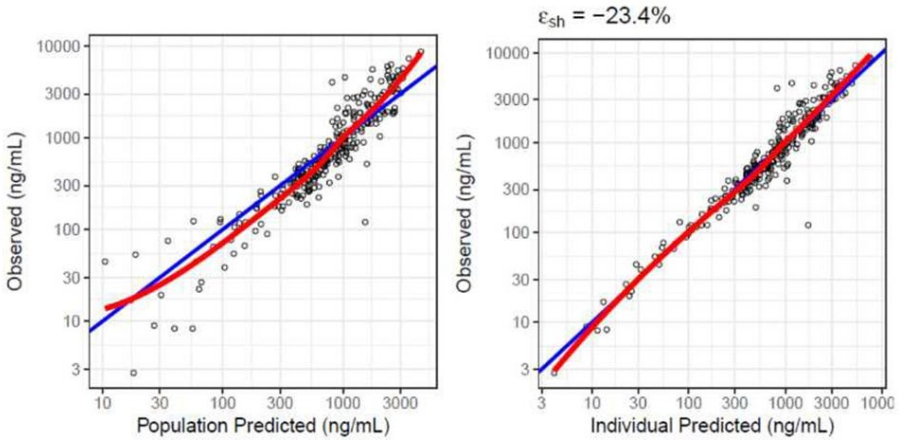


Figure 3. Goodness-of-Fit Plots for the Bedaquiline Model With the Transit Absorption Model Applied on the Cohort 2 Data (Study TMC207-C211, Cohort 2)

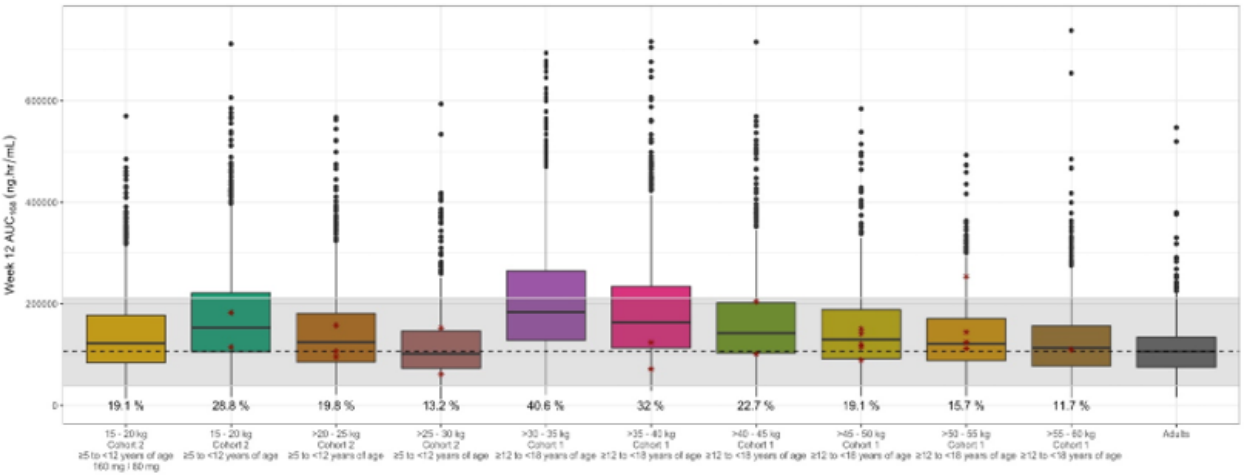


Simulated bedaquiline exposure

The predicted and simulated AUC168h by week and weight group for cohort 2, and the observed and simulated AUC168h by week, weight and dose group comparing cohort 2 to adults were presented for the initial suggested posology (200 mg qd/100 mg tiw). Figure 4 and Figure 5 show cohort simulations for cohort 2 with 160/80 mg dosing as alternative posology for 15 < 20 kg weight.

Figure 4: Boxplots Presenting the Percentage of Simulated Subjects That Fall Outside the Adult 5th and 95th Exposure Percentile per Weight Group for Cohort 1 and Cohort 2 at Week 12

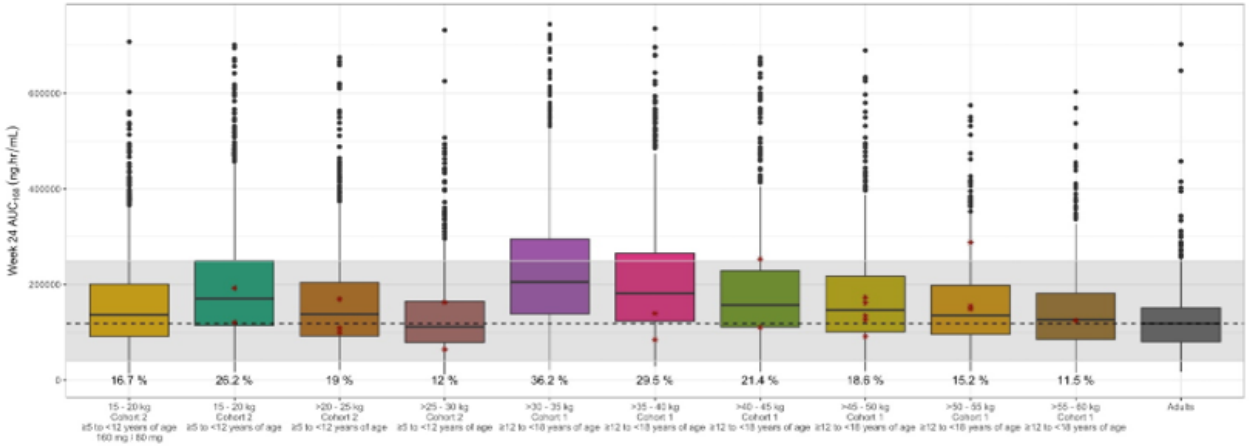
Figure 11: Boxplots Presenting the Percentage of Simulated Subjects That Fall Outside the Adult 5th and 95th Exposure Percentile per Weight Group for Cohort 1 and Cohort 2 at Week 12



Note: red stars=observed AUC_{168h} in Cohort 1 and 2, thick solid black lines=median of the simulated data per weight group, hinges (top and bottom of the boxes)=25th and 75th percentiles of the simulated data (ie, IQR), top and bottom whiskers extents to the largest and smallest values that are within 1.5*IQR of the hinges respectively, values of simulated data outside the whiskers are represented with dots, shaded grey area=90% PI (5th –95th percentile) of simulated AUC_{168h} in adults, dashed black lines=median of simulated AUC_{168h} in adults. The percentage of subjects outside the adults 90% PI range is depicted below each weight band. The left boxplot for the 15 to <20 kg weight band is presenting the simulation for a 160 mg qd/80 mg tiw regimen. The remaining boxplots present simulations based on the doses studied.
Abbreviations: AUC_{168h}=area under the plasma concentration-time curve from time of administration to 168 hours post dose; IQR=interquartile range; PI=prediction interval.

Figure 5: Boxplots Presenting the Percentage of Simulated Subjects That Fall Outside the Adult 5th and 95th Exposure Percentile per Weight Group for Cohort 1 and Cohort 2 at Week 24

Figure 12: Boxplots Presenting the Percentage of Simulated Subjects That Fall Outside the Adult 5th and 95th Exposure Percentile per Weight Group for Cohort 1 and Cohort 2 at Week 24



Note: red stars=observed AUC_{168h} in Cohort 1 and 2, thick solid black lines=median of the simulated data per weight group, hinges (top and bottom of the boxes)=25th and 75th percentiles of the simulated data (ie, IQR), top and bottom whiskers extents to the largest and smallest values that are within 1.5*IQR of the hinges respectively, values of simulated data outside the whiskers are represented with dots, shaded grey area=90% PI (5th –95th percentile) of simulated AUC_{168h} in adults, dashed black lines=median of simulated AUC_{168h} in adults. The percentage of subjects outside the adults 90% PI range is depicted below each weight band. The left boxplot for the 15 to <20 kg weight band is presenting the simulation for a 160 mg qd/80 mg tiw regimen. The remaining boxplots present simulations based on the doses studied.
Abbreviations: AUC_{168h}=area under the plasma concentration-time curve from time of administration to 168 hours post dose; IQR=interquartile range; PI=prediction interval.

Based on simulation above, new 160 mg qd for 2 weeks followed by 80 mg tiw for 22 weeks as the regimen for children aged 5 to <12 years weighing 15 to <20 kg is proposed. For children weighing 20 to <30 kg, the it was proposed to maintain the originally dosing regimen of 200 mg qd/100 mg tiw (Table 6)

Table 6

Table 3: Recommended Dosing Regimens for SIRTURO as Currently Proposed in the SmPC

	Weeks 1 to 2	Weeks 3 to 24
Adults	400 mg qd	200 mg tiw
Pediatric patients 5 to 18 years old		
Weighing ≥30 kg	400 mg qd	200 mg tiw
Weighing ≥20 to <30 kg	200 mg qd	100 mg tiw
Weighing ≥15 to <20 kg	160 mg qd	80 mg tiw

qd=once daily; SmPC=Summary of Product Characteristics; tiw=three times a week

Note: A = Week 12, B = Week 24, red stars = observed AUC_{168h} in Cohort 2, dots = simulated AUC_{168h}, solid black lines = median simulated AUC_{168h}, brown dashed lines = 5th and 95th percentile of simulated AUC_{168h}, shaded grey area = 90% PI (5th – 95th percentile) of simulated AUC_{168h} in adults, dashed black lines = median of simulated AUC_{168h} in adults. Abbreviations: AUC_{168h}=area under the plasma concentration-time curve from time of administration to 168 hours post dose.

Exposure derived using non-compartmental approach

The exposure of bedaquiline and its active metabolite M2 are presented in Table 7. A population model based analysis of M2 was not conducted. In Table 8 and Table 9 a summary of the bedaquiline and M2 exposure during maintenance treatment is presented and compared with the exposure in adolescent and adults. The Cmin in paediatric subjects is higher at week 24 compared to adults.

Table 7. Noncompartmental pharmacokinetics of bedaquiline and M2 in cohort 2

Noncompartmental Pharmacokinetics of Bedaquiline and M2 in Cohort 2 (Study TMC207-C211 | Primary Analysis, DB Cutoff 10JAN2019) (Age Cohort: Cohort 2 [≥5 to <12 Years of Age])

	Day 14[a]	Week 12	Week 24
Bedaquiline			
N	13[b,c]	10[d]	10[d]
AUC_{24h} (ng.h/mL)	60,800±27,400	32,200±16,300	-[e]
C_{min} (ng/mL)	1,000±644	461±173	626±274
C_{max} (ng/mL)	4,560±1,920	2,430±1,670	-[e]
t_{max} (h)	4 (2;8)	4 (2;8)	-[e]
M2			
N	13[b]	10[d]	10[d]
AUC_{24h} (ng.h/mL)	10,600±3,250	5,400±2,110	-[e]
C_{min} (ng/mL)	339±142	175±71.4	190±61.3
C_{max} (ng/mL)	535±180	282±84	-[e]
t_{max} (h)	6 (0;8)	8 (0;24)	-[e]

Note: Expressed as mean ± standard deviation, except for t_{max} where median and range are provided.

[a] As Week 2 rich PK data were collected following the final loading dose (ie, Day 14 of the loading phase) in some subjects, and the first maintenance dose in other subjects, NCA results were stratified by dose within the cohort.

[b] Two subjects discontinued bedaquiline prior to Week 2 rich PK sampling: one subject due to an AE hepatotoxicity and 1 subject due to having a DS-TB infection.

[c] One subject ceased treatment and restarted with an additional loading dose regimen. As such there are competing Week 2 results available for this subject, with exposure metrics following the first loading dose regimen presented in this table.

[d] Five subjects did not have bedaquiline intake at Week 12 or Week 24 and were excluded from the analysis: 3 subjects discontinued bedaquiline due to an AE of hepatotoxicity, 1 subject due to having a DS-TB infection, and 1 subject due to having an infection with nontuberculous mycobacteria.

[e] At Week 24 only a trough sample (C_{min}) was drawn. For calculation of bedaquiline exposure (AUC) at Week 24, population pharmacokinetics were used.

Table 8. Across-study summary of PK of bedaquiline in plasma after multiple-dose administration of bedaquiline (maintenance dose) in subjects with MDR-TB (Studies TMC207-C211 [Cohorts 1 and 2, current submission] and TMC207-C208 [Original submission])

	Mean±SD; t_{max}: Median (Range)					
	200 mg tiw				100 mg tiw	
Parameter	**TMC207-C208 (Stage 1)[a] Week 8 Adults**	**TMC207-C211 (Cohort 1)[a] Week 12 Adolescents (12 to <18 Years)**	**TMC207-C208 (Stage 2)[a] Week 24 Adults**	**TMC207-C211 (Cohort 1)[a] Week 24 Adolescents (12 to <18 Years)**	**TMC207-C211 (Cohort 2)[b] Week 12 Children (5 to <12 Years)**	**TMC207-C211 (Cohort 2)[b] Week 24 Children (5 to <12 Years)**
n	18	15	19	12	10	10
t_{max}, h	5.03 (2.75-8.33)	4 (2-8)	5.05 (3.07-6.77)	-	4 (2-8)	-
C_{min}, ng/mL	620.2±466.3	544±263	355.2±169.5	774±420	461±173	626±274
C_{max}, ng/mL	1,659±722	1,800±736	1,267±435	-	2,430±1,670	-
AUC_{24h}, ng.h/mL	-	26,300±10,300	-	-	32,200±16,300	-
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 postdose; BR=background regimen; C_{max}=maximum plasma concentration; C_{min}=minimum plasma concentration; MDR-TB= multidrug-resistant tuberculosis; n=maximum number of subjects with data; PK=pharmacokinetics; 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.

[a] Bedaquiline was administered as the 100-mg commercial tablet (F001).

[b] Bedaquiline was administered as the proposed age-appropriate 20-mg scored tablet (G008).

Source: Mod5.3.3.2/TMC207-C211-W24-Cohort2-CSR/SuppDoc_PKreport/Tab9, Tab10, Tab13, and Tab15; Mod5.3.5.1/TMC207-C208-Stage 1-Final-CSR/Tab26; Mod5.3.5.1/TMC207-C208-Stage 2-Final-CSR/Tab25

Table 9. Across-study summary of PK of M2 in plasma after multiple-dose administration of bedaquiline (maintenance dose) in subjects with MDR-TB (Studies TMC207-C211 [Cohorts 1 and 2, current submission] and TMC207-C208 [Original submission])

	Mean±SD; t_{max}: Median (Range)					
	200 mg tiw				100 mg tiw	
Parameter	TMC207-C208 (Stage 1) [a] Week 8 Adults	TMC207-C211 (Cohort 1) [a] Week 12 Adolescents (12 to <18 Years)	TMC207-C208 (Stage 2) [a] Week 24 Adults	TMC207-C211 (Cohort 1) [a] Week 24 Adolescents (12 to <18 Years)	TMC207-C211 (Cohort 2) [b] Week 12 Children (5 to <12 Years)	TMC207-C211 (Cohort 2) [b] Week 24 Children (5 to <12 Years)
n	18	15	19	12	10	10
t_{max}, h	6.99 (0-48.0)	24 (0-24)	12.1 (5.0-48.1)	-	8 (0-24)	-
C_{min}, ng/mL	217.4±119.3	188±62	120.3±56.98	256±137	175±71.4	190±61.3
C_{max}, ng/mL	300.7±143.2	297±133	178±70.7	-	282±84	-
AUC_{24h}, ng.h/mL	-	5,620±1,580	-	-	5,400±2,110	-
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 postdose; BR=background regimen; C_{max}=maximum plasma concentration; C_{min}=minimum plasma concentration; M2=*N*-monodesmethyl bedaquiline; MDR-TB= multidrug-resistant tuberculosis; n=maximum number of subjects with data; PK=pharmacokinetics; 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.
[a] Bedaquiline was administered as the 100-mg commercial tablet (F001).
[b] Bedaquiline was administered as the proposed age-appropriate 20-mg scored tablet (G008).
Source: Mod5.3.3.2/TMC207-C211-W24-Cohort2-CSR/SuppDoc_PKreport/Tab11, Tab12, Tab17, and Tab18; Mod5.3.5.1/TMC207-C208-Stage 1-Final-CSR/Tab28; Mod5.3.5.1/TMC207-C208-Stage 2-Final-CSR/Tab26

2.3.3. Discussion on clinical pharmacology

The MAH has conducted a study in children aged 5 to 10 years administered a loading dose of 200 mg QD for 14 days followed by a maintenance dose of 100 mg TIW, as formulation G008. The adult population PK model was used to estimate the individual PK parameters in children and to simulate paediatric exposure, however this was built using data where adults were given the adult tablet formulation. Children in cohort 2 have been given G008 and therefore a posology in children 15-30 kg with this formulation could be approved.

For cohort 2, the pcVPCs and goodness-of-fit plots indicate that the model underpredicts the median at week 2 (does not capture Cmax). The predictions based on the pcVPCs for week 12 and 24 indicate that the model better captures the median for the remaining subjects at later timepoints. As the median exposure is adequately predicted at week 12 and 24, the model is considered sufficient to be used for simulation of exposure at week 12 and 24 that can be used for comparison to exposures in adults, however, the reason for the slightly higher than expected exposure during the first weeks of treatment compared to adults, which the model does not capture is unknown.

The aim with this type of paediatric application is that based on exposure data and simulations, to extrapolate efficacy and safety from a large adult population where a benefit risk is established at a certain exposure.

Since paediatric subjects weighing 15-20 kg presented significantly higher exposure using half the adult dose, the MAH was asked to evaluate the possibilities for mimicking the exposure seen in adults, which would be possible by using the new paediatric formulation of 20 mg dispersible tablets. The MAH has provided the requested boxplots and tables to evaluate a more optimal exposure of bedaquiline in different weight bands, which suggest that a dose of 160 mg gd for two weeks followed by 80 mg tiw up to week 24 for 15-20 kg, will mimic the exposure in adults in a suitable way.

The adjusted dose regimen in paediatric subjects weighing 15-20 kg proposed by the MAH is endorsed. The average bedaquiline Cmax is higher in children >5 to 11 years compared to adolescent. As the sampling is sparse, non-compartmental calculation of AUC of the bedaquiline and M2 exposure is not optimal. A model-based prediction of exposure would have improved the reliability of the exposure values. Based on the presented average values of C_{min} at week 24, it is concluded that the exposure of M2 is higher in adolescent

and children (age ≥5 to <18 years) compared to adults. This is expected, as the exposure of bedaquiline, on average is higher in this population compared to adults.

Two relative bioavailability studies were submitted in this application. In study TMC207TBC1002 an earlier formulation (G003) was used instead of the applied formulation (G008) that was used in Cohort 2 of study TMC207-C211.

In study TMC207TBC1004 a 100 mg tablet formulation (G010) is used as test product instead of the applied formulation (G008). The compositions of 5 x 20 mg tablets (G008) and 1 x 100 mg tablet (G010) are identical (qualitatively and quantitatively). Both formulations have a disintegration time of ca 3 minutes. This means that after 3 minutes a suspension with identical composition will be present in the stomach for both formulations, i.e. 1 tablet of G010 and 5 tablets of G008.

In vivo dissolution of a lipophilic drug substance will be enhanced since the presence of bile salts, fatty acids, cholesterol and proteins in the gastrointestinal fluids improves the solubility in vivo. This was reflected in the results from the Physiology Based Dissolution Testing (PBDT).

Based on the above, the two formulations 5 x 20 mg G008 and 1 x 100 mg G010 as is considered comparable and the relative bioavailability study TMC207TBC1004 is thus relevant for the G008 formulation as well.

In study TMC207TBC1004 bioequivalence was shown for AUClast but not for C_{max} under fasting condition. The confidence interval for Cmax was outside the acceptance criteria of 80.00-125.00 but the point estimate was well within and only 10% lower compared to F001. However, for this type of application strict bioequivalence is not a requirement as it is for generic applications. In this case a clinical justification can be accepted, that the deviation does not affect efficacy or safety.

Study TMC207TBC1004 was however performed under fasting condition. Since the applied product always should be taken with food, it would had been preferred that the relative bioavailability study also had been performed together with food. However, since the food effect has been studied for G010 as part of the study where the food effect (3.4-fold increase in C_{max} and 2.2-2.4-fold increase in AUC) seems largely similar with the food effect reported for F001 (for which Cmax and AUClast increased 2.6- and 1.9- fold respectively when taken together with a non-high fat breakfast) it is assessed as less critical that the relative bioavailability study was performed under fasting condition. Based on this it is not considered likely that there will be a relevant difference in exposure between G010 and F001 when taken with food or between one tablet of G010 and five tablets of G008 taken with food, based on the similarity of one tablet of G010 and five tablets of G008, see above.
In addition, the previously performed study with formulation G003 versus F001 was performed in the fed state, and although this study was not sufficient to conclude on interchangeability since G003 and G008 had different composition, this study also adds support that there is no indication of a formulation dependent food effect.

In study TMC207TBC1004, a whole tablet was administered, while the 20 mg tablet may also be dispersed in water. However, based on the previous study with the G003 formulation (which was dispersed in water), it is not considered likely that dispersion of the G008 formulation would significantly affect exposure.

In conclusion, a significant difference in total exposure between the applied five 20 mg tablets and the already approved 100mg tablet formulation given in fed condition is not likely, considering that there is no indication of a formulation dependent food effect and that BE was demonstrated in the fasted state for

AUClast in study TMC207TBC1004. A slight difference in Cmax cannot be excluded, however, a limited difference in this parameter is not expected to result in clinical issues since AUC is the most important parameter for safety.

Thus, five 20 mg tablets are considered interchangeable with one 100 mg tablet in the SmPC.

Additional expert consultation

PKWP has also been consulted to advise on the interchangeability between 100 mg (F001) tablet and five 20 mg (G008) tablets.

According to the Sirturo SmPC, bedaquiline should be taken with food, as administration with food increases oral bioavailability by about 2 fold compared to administration under fasted conditions. Therefore, a comparative bioavailability study under fed conditions is considered the best bridge to demonstrate bioequivalence of two bedaquiline formulations. Hence, for generic applications which rely only on a comparative bioavailability study to bridge to the benefit/risk of the innovator product, a comparative bioavailability study under fed conditions is considered necessary (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **). However, when more clinical data are available such as for this extension of indication for Sirturo, these additional data can be taken into consideration for bridging bioequivalence between the marketed 100 mg tablet (F001) with five 20 mg (G008) tablets.

These additional data provided to the PKWP are:

- A comparative bioavailability study TMC207TBC1004 comparing a 100 mg tablet G010 with a 100 mg tablet F001 (market formulation) under fasted conditions.
- The compositions of 5 x 20 mg tablets (G008) and 1 x 100 mg tablet (G010) are identical (qualitatively and quantitatively). Both formulations have a disintegration time of ca 3 minutes.
- Dissolution data in physiologically based solutions (PBDT).

TMC207TBC1004 was performed for formulation-screening. In study TMC207TBC1004, a 100 mg tablet formulation (G010) is used as test product instead of the applied formulation (G008). Comparative bioavailability between 100 mg tablet formulation (G010) and 100 mg tablet formulation (F001) was conducted under fasted conditions. In addition, food effect of formulation G010 was investigated.

In study TMC207TBC1004 bioequivalence between 100 mg tablet formulation (G010) and 100 mg tablet formulation (F001) was shown for AUClast. The confidence interval for Cmax was outside the acceptance criteria of 80.00-125.00 but the point estimate was well within and only 10% lower compared to F001.

The PKWP acknowledges that study TMC207TBC1004 was a comparative bioavailability study during the clinical development and therefore a limited amount of subjects was included and the study was not powered to demonstrate bioequivalence within the conventional acceptance criteria 80-125%. It is agreed with the Rapporteur that the results of study TMC207TBC1004 support comparable bioavailability between 100 mg tablet formulation (G010) and 100 mg tablet formulation (F001) under fasted conditions.

Further, these results can be extrapolated to the 20 mg tablet G008 because of qualitatively identical and quantitatively proportional composition, same manufacturing method and similarity of the dissolution profiles (pH 1.2, 4.5 and 6.8 buffers and the QC method).

The across study comparison between the food effect for both formulations suggests a qualitatively similar food effect for G010 and F001 formulation and is supportive for a formulation independent food effect. In this respect the demonstration of bioequivalence between another formulation G003 (with different composition) and the F001 under fed condition is considered also relevant because it further strengthens a formulation independent food effect. This further reduces the uncertainty in the exchangeability between one 100 mg (F001) tablet with five 20 mg (G008) tablets and strengthened the relevance of demonstration of equivalence in study TMC207TBC1004.

The results of the Physiology Based Dissolution Testing showed a rapid dissolution of 5 x 20 mg tablets (G008) and 1 x 100 mg tablets G010 and F001. This is reassuring in respect of the reported 'low' solubility of the bedaquiline and that there is no effect of formulation on the dissolution. However, without an IVIVC dissolution tests cannot substitute in vivo bioavailability.

In conclusion, the PKWP considers comparative bioavailability study under fed conditions as the best bridge to demonstrate bioequivalence of two bedaquiline formulations, however, a totality of evidence approach is considered acceptable for applications when more clinical data are available as is the case for Sirturo. The findings of study TMC207TBC1004 conducted in fasted state are relevant for the decision whether one 100 mg (F001) tablet is interchangeable with five 20 mg (G008) tablets, because the results obtained with the 100 mg tablet G010 can be extrapolated to the 20 mg tablet G008 and there is no indication for a formulation dependent food effect. There remains some uncertainty as this concerns an indirect comparison and equivalence within 80-125% boundaries under fed conditions cannot be concluded. This uncertainty should be viewed considering the clinical relevance/therapeutic window of the product.

2.3.4. Conclusions on clinical pharmacology

The applicant has presented the exposure with formulation G008 (20 mg dispersible tablet) in children 5-11 years, stratified on weight cohorts. It is concluded that children who weigh less have a higher exposure of bedaquiline compared to adults with the proposed posology. The simulations with the proposed posology show that the average exposure is higher in the weight group 15-20 kg compared to adults. Since the new 20 mg tablet can be administered dispersed in water or mixed with food, it would be manageable to also treat children weighing 15-20 kg with a suitable dose. A re-evaluation of the dose bands was therefore suggested. The applicant has provided a re-evaluation and the new dosing in children 15-20 kg is 160 mg qd / 80 mg tiw. The exposure is still slightly higher than in adults but closer to adult exposure than 200 mg qg / 100 mg tiw. This update is supported.

It is agreed with the applicant that five 20 mg tablets are interchangeable with one 100 mg tablet in the SmPC.

2.4. Clinical efficacy

2.4.1. Main study

This application concerns the results from **cohort 2 in the study TMC207-C211**, which is a clinical phase 2, still ongoing, multicentre, single arm, open-label study including four different cohorts which are based on age group. The primary objective was to evaluate the PK, safety and tolerability of BDQ over a 24-week

treatment period in each age cohort and to provide guidance on dose selection for each of the age cohorts, the study is not designed to determine efficacy. Cohort 1 (≥12-<18 years) has already been evaluated in the procedure EMEA/H/C/002614/II/0033/G. Cohort 2 includes 15 paediatric subjects ≥5-<12 years of age with confirmed or probable multidrug-resistant tuberculosis (MDR-TB) infection, which were enrolled and treated with bedaquiline in combination with an individualized background regimen (BR).

The study was executed in the Philippines, Russia and South Africa.

Methods

The included paediatric subjects had confirmed of probable pulmonary MDR-TB and 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 paediatric TB practice and guidelines (Guidelines for Clinical and Operational Management of Drug-Resistant Tuberculosis. Paris, France: International Union Against Tuberculosis and Lung Disease 2013; World Health Organization: Guidance for national tuberculosis programmes on the management of tuberculosis in children 2014; Consensus Statement on Research Definitions for Drug-Resistant Tuberculosis in Children. J Pediatric Infect Dis Soc. 2013). Confirmed or probable disease was defined at screening and the categorization was revised postbaseline.

The intent-to-treat (ITT) analysis set including all subjects, regardless of their compliance with the protocol, and who had at least 1 intake of bedaquiline, and was used for the PK and safety analyses. The modified ITT (mITT) analysis set, i.e., the ITT population excluding subjects who do not have confirmed or probable MDR-TB, was used for the tuberculosis (TB) treatment outcome analysis.

The final TB treatment outcome can only be assessed in the Week 120 (final) analysis, after completion of all anti-TB treatment. In this application, the evaluation of clinical treatment outcome of bedaquiline for the treatment of pulmonary MDR-TB is based on data up to Week 24 as part of the Week 24 primary analysis for Cohort 2, which was conducted to assess the primary study objectives of PK and safety at this time point. The term "TB treatment outcome at Week 24" is used to describe the available data on TB treatment outcome at this timepoint.

Treatments

Previous anti-TB treatment

Fourteen of 15 (93.3%) subjects had received second-line anti-TB drugs in the 8 weeks prior to baseline and one subject did not use any anti-TB drugs prior to baseline. Per eligibility criteria, subjects had to be starting the initial MDR-TB regimen at baseline or have started an MDR-TB regimen within 8 weeks of baseline. The most frequently used previous anti-TB medications were PZA (in 14 [93.3%] subjects), LFX (in 13 [86.7%] subjects), KM and EMB (both in 11 [73.3%] subjects), and INH and terizidone (TRD) (both in 8 [53.3%] subjects). Others were used in at most 6 of 15 subjects. Previous use of RMP was reported for 1 of 15 (6.7%) subjects, respectively.

BDQ treatment

The paediatric subjects received 200 mg once daily (qd) for 14 days, followed by 100 mg three times per week (tiw) for 22 weeks (i.e. half the adult dosing regimen) using a new 20 mg tablet. This application includes the treatment outcome and resistance results from the Week 24 primary analysis for Cohort 2

(database cut-off 10 January 2019). The BDQ treatment was combined with a background regimen based on (WHO) guidelines for treatment of MDR-TB (Long BR or Short BR, where available), National Tuberculosis Program (NTP) treatment guidelines and current standard of care at the study site.

Background regimen (BR)

The most frequently used anti-TB medications in the baseline BR (i.e., the BR used during the first 14 days of the Bedaquiline Treatment phase) for subjects in the ITT analysis set were LFX (in all 15 [100%] subjects), PZA (in 13 [86.7%] subjects), KM and EMB (both in 11 [73.3%] subjects), and TRD (in 8 [53.3%] subjects).

The number of anti-TB drugs in the baseline BR and throughout the Bedaquiline Treatment phase ranged from 3 to 8 for subjects in the ITT analysis. All subjects started bedaquiline treatment in combination with at least 4 BR drugs, except for one subject that had 3 drugs in the baseline BR. This subject with probable MDR-TBH&R infection started with a baseline BR consisting of KM, LFX, and EMB. Prior to screening, the subject received PZA as part of MDR-TB treatment, but increases in uric acid were observed and PZA was discontinued.

Table 10. Background Regimen at Baseline; ITT (Study TMC207-C211 Cohort 2. Primary Analysis, DB Cut-off 10JAN2019)

	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	2 (13.3%)
Kanamycin	11 (73.3%)
Fluoroquinolones	15 (100.0%)
Levofloxacin	15 (100.0%)
Miscellaneous anti-TB drugs	15 (100.0%)
Capreomycin	2 (13.3%)
Clofazimine	1 (6.7%)
Cycloserine	1 (6.7%)
Ethambutol	11 (73.3%)
Ethionamide	6 (40.0%)
Isoniazid	6 (40.0%)
PAS-C	4 (26.7%)
Protionamide	3 (20.0%)
Pyrazinamide	13 (86.7%)
Terizidone	8 (53.3%)

BR = background regimen; DB = database; ITT = intent-to-treat; N = number of subjects; n = number of subjects with this observation; PAS-C = para-aminosalicylic acid; TB = tuberculosis; TMC207 = bedaquiline.
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].
Source: Mod5.3.3.2/TMC207-C211-W24-Cohort 2-CSR/Tab5

Objectives

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

Outcomes/endpoints

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 4 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.

d) Have the last culture negative for MDR-TB within analysis window and have completed overall prescribed TB treatment at Week 24 for subjects with only one postbaseline sputum sample available but unable to produce sputum up to the Week 24 window.

Resistance assessment

DST was done at baseline (or screening, if baseline was not available) and was only repeated on the last positive sample and in case of relapse/re-infection. In case of relapse/re-infection or acquired resistance to any used drug (including a 4-fold increase in BDQ minimal inhibitory concentrations [MICs]), genotyping was performed on both baseline and postbaseline isolates. No genotyping was done up to the database cut-off date of the Week 24 primary analysis for Cohort 2. DST for BDQ was done by determining the MIC of BDQ in 7H11 agar. Up to the database cut-off date of the Week 24 primary analysis for Cohort 2, one subject had postbaseline susceptibility data available.

Statistical methods

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.

Subgroup analyses were performed by country (Russia, South Africa), baseline cavitation (no cavitation or cavitations <2cm, cavitations ≥2 cm in one lung), baseline extent of resistance, TB-type, pyrazinamidine susceptibility, number of drugs in BR, BMI, baseline albumin abnormality, baseline BDQ MIC, time to positive MGIT signal and baseline AFB score.

Demographic data and baseline disease characteristics

Table 11. Demographic Data; ITT (Study TMC207-C211 Cohort 2. Primary Analysis, DB Cut-off 10JAN2019)

	TMC207/BR
Analysis set: Intent-to-treat, N	15
Country, n (%)	
N	15
Philippines	1 (6.7%)
Russian Federation	5 (33.3%)
South Africa	9 (60.0%)
Sex, n (%)	
N	15
Female	9 (60.0%)
Male	6 (40.0%)
Age (years)	
N	15
Mean (SD)	7.2 (1.42)
Median	7.0
Min; Max	(5; 10)
Race, n (%)	
N	15
Asian	1 (6.7%)
Black	9 (60.0%)
White	5 (33.3%)
Weight (kg)	
N	15
Mean (SD)	23.63 (5.822)
Median	22.60
Min; Max	(13.9; 35.5)
Body mass index (kg/m²)	
N	15
Mean (SD)	15.61 (2.166)
Median	16.20
Min; Max	(11.1; 18.8)

BR = background regimen; DB = database; ITT = intent-to-treat; max = maximum; min = minimum; N = number of subjects; n = number of subjects with this observation; SD = standard deviation; TMC207 = bedaquiline.
The denominator for the percentage calculations is the total number of subjects in the ITT population.
Source: Mod5.3.3.2/TMC207-C211-W24-Cohort 2-CSR/Tab2

Table 12. Baseline Disease Characteristics; ITT (Study TMC207-C211 Cohort 2. Primary Analysis, DB Cut-off 10JAN2019)

	TMC207/BR
Analysis set: Intent-to-treat, N	15
Extent of resistance of *M. tuberculosis* strain, n (%)	
N	15
Confirmed MDR-TB	10 (66.7%)
$MDR\text{-}TB_{H\&R}$	5 (33.3%)
RR-TB	5 (33.3%)
Probable MDR-TB	3 (20.0%)
$MDR\text{-}TB_{H\&R}$	1 (6.7%)
Pre-XDR-TB injectable resistant	2 (13.3%)
DS-TB[a]	1 (6.7%)
Other[b]	1 (6.7%)
Baseline albumin abnormality, n (%)	
N	15
High	2 (13.3%)
Normal	13 (86.7%)
Cavitation, n (%)	
N	15
No cavitations or cavitations < 2 cm	12 (80.0%)
Cavitations >= 2 cm in one lung	3 (20.0%)

BR = background regimen; DB = database; DS-TB = drug-susceptible tuberculosis; ITT = intent-to-treat; $MDR\text{-}TB_{H\&R}$ = multidrug-resistant tuberculosis excluding pre-extensively drug-resistant tuberculosis and extensively drug-resistant tuberculosis; N = number of subjects; n = number of subjects with this observation; pre-XDR-TB = pre-extensively drug-resistant tuberculosis; RR-TB = rifampicin-monoresistant tuberculosis; TMC207 = bedaquiline.

[a] One subject was enrolled in the study as having probable MDR-TB and treated, but was found as having DS-TB per GeneXpert test collected on Day -1 and performed on Day 1 (results became available postbaseline), and thus no longer qualified for the study.

[b] One subject was enrolled in the study as having probable MDR-TB and treated, but was found to have a culture positive for nontuberculous mycobacteria (results became available postbaseline), and thus no longer qualified for the study.

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

Extent of resistance:

DS-TB if sensitive to isoniazid and rifampin, or sensitive only to rifampin;
RR-TB if resistant to rifampin (isoniazid DST is missing or sensitive);
$MDR\text{-}TB_{H\&R}$ if resistant to isoniazid and rifampin;
Pre-XDR-TB if resistant to rifampin and isoniazid and additionally, resistant to at least one fluoroquinolone and sensitive to kanamycin/amikacin and capreomycin OR sensitive to fluoroquinolones and resistant to kanamycin/amikacin and/or capreomycin.

Source: Mod5.3.3.2/TMC207-C211-W24-Cohort 2-CSR/Tab3

One (6.7%) subject was infected with a DS-TB *M. tuberculosis* strain and one (6.7%) subject was infected with nontuberculous mycobacteria (based on GeneXpert and culture data, respectively, that became available postbaseline). These two subjects discontinued bedaquiline treatment and study procedures, and the subject with DS-TB was eventually lost to follow-up and discontinued the study.The majority of subjects (12 of 15 [80.0%] subjects) had no cavitations or cavitations <2 cm. For 2 of 15 (13.3%) subjects, abnormally high albumin was observed at baseline. Note that HIV-positive subjects were excluded from Cohort 2 per protocol.

Previous anti-TB treatment

Fourteen of 15 (93.3%) subjects had received second-line anti-TB drugs in the 8 weeks prior to baseline and one subject did not use any anti-TB drugs prior to baseline. Per eligibility criteria, subjects had to be starting the initial MDR-TB regimen at baseline or have started an MDR-TB regimen within 8 weeks of baseline. The

most frequently used previous anti-TB medications were PZA (in 14 [93.3%] subjects), LFX (in 13 [86.7%] subjects), KM and EMB (both in 11 [73.3%] subjects), and INH and terizidone (TRD) (both in 8 [53.3%] subjects). Others were used in at most 6 of 15 subjects. Previous use of RMP was reported for 1 of 15 (6.7%) subjects, respectively.

Results

Seventeen subjects were screened for Cohort 2, of which 15 were enrolled and treated with BDQ in combination with a BR. Fifteen subjects were included in the ITT and 13 subjects in the mITT analysis set (excluding subjects without confirmed MDR-TB or probable MDR-TB). The youngest child included in this cohort was 5 and the oldest was 10 years old and the weight span was 16-36 kg. Five of 15 (33.3%) subjects in the ITT analysis set discontinued bedaquiline treatment, of whom 3 subjects discontinued due to adverse event (AE) of hepatotoxicity, one subject due to having a drug-susceptible (DS)-TB infection, and one subject due to having an infection with nontuberculous mycobacteria.

Study termination

Five of 15 (33.3%) subjects in the ITT analysis set discontinued BDQ treatment of whom three subjects discontinued due to an AE of hepatotoxicity. The other two subjects discontinued due to not having MDR-TB infection (one with nontuberculous mycobacteria and one with DS-TB infection), one of them was followed for survival and the other was lost to follow up.

Ten of 15 (66.7%) subjects in the ITT analysis set completed intake of BDQ as planned and were ongoing in the study at the time of the database cut-off date.

Table 13. Drug, Study Procedure, and Study Termination; ITT (Study TMC207-C211 Cohort 2. Primary Analysis, DB Cut-off 10JAN2019)

	TMC207/BR
Analysis set: Intent-to-treat, N	15
TMC207 treatment	
Completed	10 (66.7%)
Discontinued	5 (33.3%)
Adverse event	3 (20.0%)
Sponsor decision[a]	1 (6.7%)
Susceptibility to rifampicin[b]	1 (6.7%)
Background regimen	
Ongoing	9 (60.0%)
Completed	4 (26.7%)
Discontinued	2 (13.3%)
Sponsor decision[a]	1 (6.7%)
Susceptibility to rifampicin[b]	1 (6.7%)
Study Procedure[c]	
Ongoing	13 (86.7%)
Discontinued	2 (13.3%)
Sponsor decision[a]	1 (6.7%)
Susceptibility to rifampicin[b]	1 (6.7%)
Study	
Ongoing	14 (93.3%)
Discontinued	1 (6.7%)
Lost to follow-up[b]	1 (6.7%)

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

[a] The subject was infected with nontuberculous mycobacteria.

[b] The subject was infected with DS-TB.

[c] Subjects who discontinued from study drug and study procedures were followed up for survival until 120 weeks postbaseline, unless they withdrew from the study (ie, withdrew consent/assent). Survival follow-up was for confirmation of survival status only (alive/dead) and collection of targeted adverse events (adverse events resulting in death regardless of cause of death and relationship to study treatment).

Duration of treatment

Table 14. Treatment Duration; ITT and mITT (Study TMC207-C211 Cohort 2. Primary Analysis, DB Cut-off 10JAN2019)

	TMC207 / BR	
	TMC207 Treatment Phase	Background Regimen
Analysis set: Intent-to-treat, N	15	15
Treatment duration (weeks)		
N	15	15
Mean (SD)	18.57 (8.209)	54.92 (27.789)
Median	23.86	61.00
Range	(0.9; 24.1)	(1.6; 92.3)
Analysis set: Modified intent-to-treat, N[a]	13	13
Treatment duration (weeks)		
N	13	13
Mean (SD)	20.69 (6.285)	62.55 (20.641)
Median	24.00	70.00
Range	(8.1; 24.1)	(24.3; 92.3)

BR = background regimen; DB = database; DS-TB = drug-susceptible tuberculosis; ITT = intent-to-treat; MDR-TB = multidrug-resistant tuberculosis; mITT = modified intent-to-treat; N = number of subjects; SD = standard deviation; TMC207 = bedaquiline.
For ongoing subjects, duration (weeks) is calculated as: (cutoff date - first intake date + 1) / 7.
[a] Excluding the subjects without confirmed or probable MDR-TB, ie, one subject having a DS-TB infection and one subject having an infection with nontuberculous mycobacteria.
Source: Mod5.3.3.2/TMC207-C211-W24-Cohort 2-CSR/Tab8

Susceptibility

Susceptibility results for BDQ at baseline are available for 2 of 13 subjects in the mITT analysis set; all strains were susceptible to bedaquiline according to the EUCAST breakpoint of S≤0.25 mg/L and R >0.25 mg/L.

Protocol deviations

Table 15. Protocol Deviations; ITT (Study TMC207-C211 Cohort 2. Primary Analysis, DB Cut-off 10JAN2019)

	TMC207/BR	
	ITT	mITT
Analysis set: Intent-to-treat, N	15	13
Major	4 (26.7%)	2 (15.4%)
Entered but did not satisfy criteria[a]	2 (13.3%)	0
Received wrong treatment or incorrect dose	2 (13.3%)	2 (15.4%)
Other	1 (6.7%)	1 (7.7%)

The denominator for the percentage calculations is the total number of subjects in the respective population.
[a] The 2 subjects met the eligibility criteria at screening but post-screening microbiology results (culture and GeneXpert) that became available postbaseline resulted in the protocol deviations.

Treatment compliance

Table 16. Compliance to Bedaquiline; ITT (Study TMC207-C211 Cohort 2. Primary Analysis, DB Cut-off 10JAN2019

	TMC207/BR
	Exposure
Analysis set: Intent-to-treat, N	15
Day 1 up to Day 14 (Loading Phase)	15
100%	14 (93.3%)
]50%,0%[[a]	1 (6.7%)
Day 15 up to Last Visit (Maintenance Phase)	14[a]
[105%,100%[	2 (14.3%)
100%	3 (21.4%)
]100%,95%]	5 (35.7%)
]50%,0%[	4 (28.6%)[b]

The denominator for the percentage calculations is the total number of subjects in each phase.

[a] One subject was discontinued during the Loading Phase due to rifampicin susceptibility, thus did not enter the Maintenance Phase.

[b] One subject was discontinued during the Maintenance Phase due to infection with nontuberculous mycobacteria and 3 subjects due to an AE of hepatotoxicity.

Treatment outcome Week 24

None of the subjects converted and subsequently discontinued study or study procedures before Week 24. Consequently, the results according to the different analysis methods (primary M=F, end-censored M=F, and no overruling) are identical.

After 24 weeks of treatment with bedaquiline in combination with BR, 6 of 13 subjects (46.2%, with a 95% CI of 20.4%; 73.9%) had a favourable treatment outcome. Three (23.1%) subjects did not complete TB treatment since they prematurely discontinued BDQ treatment due to hepatotoxicity.

Table 17. Favourable Treatment Outcome (Week 24 Primary Analysis); mITT (StudyTMC207-C211, cohort 2. Primary Analysis, DB Cut-off 10JAN2019)

	TMC207/BR	
	n (%)	95% CI
Analysis set: Modified intent-to-treat, N	13	
Favorable treatment outcome	6 (46.2%)	(20.4%; 73.9%)
No favorable treatment outcome	7 (53.8%)	
Not completed overall prescribed TB treatment	3 (23.1%)[c]	
Global TB assessment[a] not completely resolved[b]	5 (38.5%)[c]	
Evaluable confirmed TB subject does not meet microbiology criteria	0	

BR = background regimen; CI = confidence interval; DB = database; mITT = modified intent-to-treat; N = number of subjects; n = number of subjects with this observation; TB = tuberculosis; TMC207 = bedaquiline.
95% CI is from Wilson score interval with continuity correction.
[a] The investigator's global TB assessment, performed according to the Consensus Statement,[7] is a clinical assessment of the subject's condition that includes an assessment of signs and symptoms of TB and the assessment of radiological improvement through the standardized criteria of the Consensus Statement.
[b] Ie, had an investigator's global TB assessment of 'partially resolved' or 'not resolved'.
[c] One subject had an investigator's global TB assessment of 'not resolved' in addition to not completing the overall prescribed TB treatment.
Source: Mod5.3.3.2/TMC207-C211-W24-Cohort 2-CSR/Tab27

Radiological improvement as well as resolution of signs and symptoms were assessed as part of the investigator's global TB-assessment. Chest X- ray results were available for 13 subjects at Week 4 and for 12 subjects at Week 24. At Week 4, radiological improvement was observed for 8 subjects. By Week 24, radiological improvement was observed for 12 subjects. Results for resolution of signs and symptoms were available for 13 subjects at Week 4 and for 12 subjects at Week 24. At Week 4, only 1 subject had signs and symptoms 'resolved'. By Week 24, signs and symptoms were 'resolved' for 10 subjects, 'partially resolved' for one subject, and 'not resolved' for one subject.

2.4.2. Discussion on clinical efficacy

This application concerns the results from **cohort 2 in the study TMC207-C211**, which is a clinical phase 2, still ongoing, multicentre, single arm, open-label study including four different cohorts which are based on age group. The primary objective was to evaluate the PK, safety and tolerability of BDQ over a 24-week treatment period in each age cohort and to provide guidance on dose selection for each of the age cohorts, the study is not designed to determine efficacy. Cohort 2 included 15 paediatric subjects ≥5-<12 years of age with confirmed or probable multidrug-resistant tuberculosis (MDR-TB) infection, which were enrolled and treated with bedaquiline in combination with an individualized background regimen (BR). These paediatric subjects received 200 mg once daily (qd) for 14 days, followed by 100 mg three times per week (tiw) for 22 weeks (i.e. half the adult dosing regimen) using a new 20 mg tablet. This application includes the treatment outcome and resistance results from the Week 24 primary analysis for Cohort 2 (database cut-off 10 January 2019).

At Week 24, signs and symptoms were considered resolved for ten of the subjects. However, treatment outcome is not considered possible to assess fully until Week 120, and in this report only data from primary Week 24 analysis is available. This is considered acceptable since it is fully endorsed that efficacy of treatment with BDQ in MDR-TB in paediatric subjects can be extrapolated based on systemic exposure. The

primary objective is therefore to establish a paediatric dose for children at the age of 5-12 years, resulting in an exposure similar to adults.

2.4.3. Conclusions on the clinical efficacy

Since it is fully endorsed that efficacy and safety can be extrapolated based on systemic exposure, the primary objective is to establish a dose in adolescence resulting in an exposure of BDQ similar to adults.

2.5. Clinical safety

This application includes the safety results from the Week 24 primary analysis for Cohort 2 of Study TMC207-C211 (database cut-off date 10 January 2019) in paediatric subjects aged ≥5 to <12 years with confirmed or probable multidrug-resistant tuberculosis (MDR-TB) infection. The paediatric subjects received BDQ in combination with a background regimen (BR) in accordance with the WHO guidelines for treatment of MDR-TB (Long BR or Short BR, where allowed), National Tuberculosis Program treatment guidelines and current standard of care at the study site. The paediatric subjects received BDQ 200 mg once daily (qd) for 14 days, followed by 100 mg three times per week (tiw) for 22 weeks using a new oral tablet formulation (20-mg oral scored tablet, G008), administered with food. All safety analyses were conducted on the ITT analysis set, i.e., all 15 subjects who had at least one intake of BDQ, regardless of their compliance with the protocol.

Patient exposure

At the database cut-off date of this primary analysis, all subjects in the ITT analysis set had completed the Week 24 visit or discontinued earlier. No subjects had completed the study.

Table 18. Number of Subjects at Each Visit; ITT (Study TMC207-C211 Cohort 2. Primary Analysis, DB Cut-off 10JAN2019)

	ITT	mITT
Baseline	15 (100.0%)	13 (100.0%)
Day 1	15 (100.0%)	13 (100.0%)
Week 2	15 (100.0%)	13 (100.0%)
Week 4	14 (93.3%)	13 (100.0%)
Week 6	14 (93.3%)	13 (100.0%)
Week 8	14 (93.3%)	13 (100.0%)
Week 12	13 (86.7%)	13 (100.0%)
Week 16	13 (86.7%)	13 (100.0%)
Week 20	13 (86.7%)	13 (100.0%)
Week 24	13 (86.7%)	13 (100.0%)
Week 28	12 (80.0%)	12 (92.3%)
Week 32	11 (73.3%)	11 (84.6%)
Week 40	11 (73.3%)	11 (84.6%)
Week 48	9 (60.0%)	9 (69.2%)
Week 60	7 (46.7%)	7 (53.8%)
Week 72	3 (20.0%)	3 (23.1%)
Week 84	4 (26.7%)	4 (30.8%)
Week 96	1 (6.7%)	1 (7.7%)

Adverse events

Table 19. Summary of Adverse Events; ITT (Study TMC207-C211 Cohort 2. Primary Analysis, DB Cut-off 10JAN2019)

Summary	TMC207 Treatment Phase	Overall Treatment Phase
Analysis set: Intent-to-treat, N	15	15
Any adverse events	12 (80.0%)	12 (80.0%)
Serious adverse events	1 (6.7%)	2 (13.3%)
AEs of at least grade 3	8 (53.3%)	8 (53.3%)
AEs of grade 4	3 (20.0%)	3 (20.0%)
AEs leading to permanent discontinuation of bedaquiline	3 (20.0%)	3 (20.0%)
AEs leading to permanent discontinuation of BR[a]	4 (26.7%)	4 (26.7%)

[a] This could be one or more drugs included in the BR.

During the treatment with BDQ, 12/15 (80%) of the subjects experienced at least one AE, all illustrated in the table below. Infection and infestations were the SOC with highest incidence of reported AEs (8/15 [53.3%] subjects). The most frequently reported AEs during the BDQ treatment phase were increased blood creatine phosphokinase (CK) and prolonged prothrombin time (both in 5/15 [33.3%] subjects), and hepatotoxicity (3/15 [20.0%] subjects).

Table 20. Adverse Events (Regardless of Severity and Drug Relatedness) by Body System and Preferred Term; ITT (Study TMC207-C211 Cohort 2. Primary Analysis, DB Cut-off 10JAN2019

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 (%)	12 (80.0%)	12 (80.0%)
Ear and labyrinth disorders	2 (13.3%)	2 (13.3%)
Deafness bilateral	1 (6.7%)	1 (6.7%)
Deafness unilateral	1 (6.7%)	1 (6.7%)
Eye disorders	0	1 (6.7%)
Conjunctivitis allergic	0	1 (6.7%)
Gastrointestinal disorders	1 (6.7%)	1 (6.7%)
Vomiting	1 (6.7%)	1 (6.7%)
General disorders and administration site conditions	1 (6.7%)	1 (6.7%)
Pyrexia	1 (6.7%)	1 (6.7%)
Hepatobiliary disorders	3 (20.0%)	3 (20.0%)
Hepatotoxicity	3 (20.0%)	3 (20.0%)
Infections and infestations	8 (53.3%)	8 (53.3%)
Acarodermatitis	0	2 (13.3%)
Adenoiditis	1 (6.7%)	1 (6.7%)
Ear infection	1 (6.7%)	1 (6.7%)
Gastroenteritis	0	1 (6.7%)
Lower respiratory tract infection	0	1 (6.7%)
Nasopharyngitis	1 (6.7%)	1 (6.7%)
Otitis media	2 (13.3%)	2 (13.3%)
Tinea faciei	0	2 (13.3%)
Tinea infection	1 (6.7%)	1 (6.7%)
Upper respiratory tract infection	2 (13.3%)	2 (13.3%)
Urinary tract infection	1 (6.7%)	1 (6.7%)
Varicella	0	1 (6.7%)
Investigations	6 (40.0%)	6 (40.0%)
Alanine aminotransferase increased	1 (6.7%)	2 (13.3%)
Aspartate aminotransferase increased	2 (13.3%)	2 (13.3%)
Blood creatine phosphokinase increased	5 (33.3%)	5 (33.3%)
Blood glucose increased	1 (6.7%)	1 (6.7%)
Blood potassium increased	1 (6.7%)	1 (6.7%)
Prothrombin time prolonged	5 (33.3%)	5 (33.3%)
Musculoskeletal and connective tissue disorders	0	1 (6.7%)
Arthralgia	0	1 (6.7%)
Psychiatric disorders	1 (6.7%)	2 (13.3%)
Abnormal behaviour	1 (6.7%)	2 (13.3%)
Renal and urinary disorders	1 (6.7%)	1 (6.7%)
Haematuria	1 (6.7%)	1 (6.7%)

Respiratory, thoracic and mediastinal disorders	0	1 (6.7%)
Rhinitis allergic	0	1 (6.7%)
Skin and subcutaneous tissue disorders	0	3 (20.0%)
Dry skin	0	2 (13.3%)
Pain of skin	0	1 (6.7%)
Rash vesicular	0	1 (6.7%)

n: number of subjects with 1 or more events.

Severity of AEs

During the treatment phase of BDQ, eight (53.3%) of the subjects experienced at least one grade 3 or 4 adverse event.

- Three subjects (20%) experienced hepatotoxicity grade 3 (two subjects) or 4 (one subject). One of the subjects with grade 3, subsequently developed a hepatotoxicity grade 4 after the treatment phase of BDQ was ended. All three subjects permanently discontinued the treatment with BDQ (see discontinuation due to AEs).

- Four subjects (26.7%) reported with increased creatine phosphokinase grade 3

- Three subjects (20%) reported with prolonged prothrombin time grade 3

- One subject, after the end of BDQ treatment phase, reported two events of increased ALT and AST grade 3.

AEs possible related to BDQ

During the BDQ Treatment phase, three (20.0%) subjects experienced AEs considered at least possibly related to BDQ. Age, weight and exposure of BDQ has not been provided.

- One subject was reported with a grade 1 AE of vomiting on Day 15 of BDQ treatment. The event was considered possibly related to BDQ and not related to the BR. No action was taken towards BDQ. The event resolved the same day.

- One subject was reported with a grade 2 AE of hepatotoxicity on Day 14 of BDQ treatment with concurrent transaminase elevations. The severity of the event evolved to grade 3 (Day 25), grade 4 (Day 84) and back to grade 3 (Day 97). The event was considered possibly related to BDQ and BR for the entire duration. BDQ was permanently discontinued due to this event on Day 57. The event resolved after a total duration of 114 days.

- One subject was reported with a grade 3 AE of hepatotoxicity on Day 56 of BDQ treatment with concurrent transaminase elevations. The event was considered possibly related to BDQ and BR. BDQ was permanently discontinued due to this event on Day 71. On Day 172, after re-introduction of BR drugs, the severity of the event evolved to grade 4. The hepatotoxicity AE was considered not related to BDQ at this time. All BR was interrupted by Day 177. On Day 201, the severity of the AE evolved to grade 3 and the event was considered possibly related to BDQ. The event resolved after a total duration of 166 days.

AEs possible related to TB infection or BR

During the BDQ Treatment phase, 5 of 15 (33.3%) subjects experienced at least one AE considered at least possibly related to the BR.

Table 21. AEs That Were Considered at least Possibly Related to BR by Body System and Preferred Term; ITT (StudyTMC207-C211 Cohort 2. Primary Analysis, DB Cut-off 10JAN2019)

MedDRA System Organ Class Dictionary-derived Term	TMC207 Treatment Phase	Overall Treatment Phase
Analysis set: Intent-to-treat, N	15	15
Any adverse event considered at least possibly related to BR, n (%)	5 (33.3%)	6 (40.0%)
Ear and labyrinth disorders	2 (13.3%)	2 (13.3%)
Deafness bilateral	1 (6.7%)	1 (6.7%)
Deafness unilateral	1 (6.7%)	1 (6.7%)
Hepatobiliary disorders	3 (20.0%)	3 (20.0%)
Hepatotoxicity	3 (20.0%)	3 (20.0%)
Investigations	0	1 (6.7%)
Alanine aminotransferase increased	0	1 (6.7%)
Aspartate aminotransferase increased	0	1 (6.7%)
Prothrombin time prolonged	0	1 (6.7%)
Psychiatric disorders	1 (6.7%)	2 (13.3%)
Abnormal behaviour	1 (6.7%)	2 (13.3%)
Skin and subcutaneous tissue disorders	0	1 (6.7%)
Dry skin	0	1 (6.7%)

n: number of subjects with 1 or more events.

During the BDQ Treatment phase, 2 of 15 (13.3%) subjects experienced at least one AE considered at least possibly related to TB infection (increased blood creatine kinase).

AEs of special interest

The following AEs were defined as AEs of special interest: acute pancreatitis, rhabdomyolysis/myopathy, severe cutaneous adverse reactions, torsade de pointes/QT prolongation, drug-related hepatic disorders. During the BDQ Treatment phase, eight (53.3%) subjects experienced at least one AE of special interest. No additional subjects were at the data lock point reported with AEs of special interest after the end of the BDQ Treatment phase.

Table 22. MQ Events of Interest by Grouped Term; ITT (Study TMC207-C211 Cohort 2. Primary Analysis, DB Cut-off 10JAN2019)

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 (%)	8 (53.3%)	8 (53.3%)
No adverse event of interest, n (%)	7 (46.7%)	7 (46.7%)
Drug-related hepatic disorders - comprehensive search (SMQ)	8 (53.3%)	8 (53.3%)
Drug-related hepatic disorders - severe events only (SMQ)	3 (20.0%)	3 (20.0%)
Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions (SMQ)	3 (20.0%)	3 (20.0%)
Hepatotoxicity	3 (20.0%)	3 (20.0%)
Liver related investigations, signs and symptoms (SMQ)	2 (13.3%)	2 (13.3%)
Alanine aminotransferase increased	1 (6.7%)	2 (13.3%)
Aspartate aminotransferase increased	2 (13.3%)	2 (13.3%)
Liver-related coagulation and bleeding disturbances (SMQ)	5 (33.3%)	5 (33.3%)
Prothrombin time prolonged	5 (33.3%)	5 (33.3%)

n: number of subjects.

Table 23. Adverse Events of Special Interest over Time; ITT (Study TMC207-C211 Cohort 2. Interim Analysis, DB Cut-off 10JAN2019)

SMQ Term, Sub-SMQ Terms and Dictionary-derived Term	Week 1 - 12	Week 13 - 24	Week 25 - 36	Week 37 - 48	Week 49 - 60	Week 61 - 72	Week 73 - 84	Week 85 - 96
Part B: Adverse Events of Special Interest 1) Incidence Phase: Overall Treatment Phase								
Analysis set: Intent-to-treat, N	15	13	13	12	8	8	4	3
Drug related hepatic disorders - comprehensive search (SMQ)	5 (33.3%)	5 (38.5%)	2 (15.4%)	2 (16.7%)	0	0	0	0
Drug related hepatic disorders - severe events only (SMQ)	3 (20.0%)	1 (7.7%)	1 (7.7%)	0	0	0	0	0
Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions (SMQ)	3 (20.0%)	1 (7.7%)	1 (7.7%)	0	0	0	0	0
Hepatotoxicity	3 (20.0%)	1 (7.7%)	1 (7.7%)	0	0	0	0	0
Liver related investigations, signs and symptoms (SMQ)	2 (13.3%)	1 (7.7%)	1 (7.7%)	1 (8.3%)	0	0	0	0
Alanine aminotransferase increased	1 (6.7%)	0	1 (7.7%)	0	0	0	0	0
Aspartate aminotransferase increased	2 (13.3%)	1 (7.7%)	0	1 (8.3%)	0	0	0	0
Liver-related coagulation and bleeding disturbances (SMQ)	2 (13.3%)	3 (23.1%)	0	2 (16.7%)	0	0	0	0
Prothrombin time prolonged	2 (13.3%)	3 (23.1%)	0	2 (16.7%)	0	0	0	0

Only AEs with complete start and end date or for which the end date is imputed per SAP are included in this table.

Prolonged prothrombin time

Five of the 15 subjects had a prolonged prothrombin time laboratory abnormality at screening. None of the 15 subjects had a prolonged prothrombin time laboratory abnormality at baseline. Seven (46.7%) subjects had a graded treatment-emergent prolonged prothrombin time laboratory abnormality (any grade) during the BDQ Treatment phase. Of these subjects, Prolonged prothrombin time was reported as an AE in five (33.3%) subjects, in which no clinical symptoms was observed, and the laboratory abnormality resolved while BDQ treatment was continued. Three of the events were grade 3.

Drug related hepatic disorder

Increased transaminases were reported as AEs in five (33.3%) of the subjects. AEs of hepatotoxicity grade 3 or 4 were reported in three (20.0%) subjects and led to discontinuation of BDQ. The two subjects with increased ALT and AST (one subject) and ALT (one subject) were grade 1 and did not lead to discontinuation of BDQ. In one of the subjects who already had experienced drug related grade 1 hepatic disorder during the treatment phase of BDQ, two grade 3 SAEs related to increased ALT and AST was reported after the treatment phase of BDQ was ended (further info in section "serious AEs").

Serious adverse events and deaths

Serious AEs

Table 24. Serious Adverse Events by Body System and Preferred Term; ITT (StudyTMC207-C211 Cohort 2. Primary Analysis, DB Cut-off 10JAN2019)

MedDRA System Organ Class Dictionary-derived Term	TMC207 Treatment Phase	Overall Treatment Phase
Analysis set: Intent-to-treat, N	15	15
Any serious adverse event, n (%)	1 (6.7%)	2 (13.3%)
Hepatobiliary disorders	1 (6.7%)	1 (6.7%)
Hepatotoxicity	1 (6.7%)	1 (6.7%)
Investigations	0	1 (6.7%)
Alanine aminotransferase increased	0	1 (6.7%)
Aspartate aminotransferase increased	0	1 (6.7%)

DB = database; MedDRA = Medical Dictionary for Regulatory Activities; ITT= intent-to-treat; N = number of subjects; n = number of subjects with 1 or more events; TMC207 = bedaquiline.
Source: Mod5.3.3.2/TMC207-C211-W24-Cohort 2-CSR/Tab16

One subject was reported with a grade 4 SAE hepatotoxicity on Day 14. Further information on this subject, see "discontinuation due to AEs".

One additional subject experienced two grade 3 SAEs related to increased AST after the end of BDQ treatment phase. At baseline, transaminases were within normal limits (ALT was 18 U/L and AST was 39 U/L). During the BDQ Treatment phase, the subject experienced four episodes of increased AST grade 1 and also a grade 1 AE related to prolonged prothrombin time. On Day 231, 64 days after bedaquiline treatment was completed, the subject was reported with a grade 1 AE of increased ALT, AST was within normal limits. On Day 277, (110 days after end of BDQ treatment), transaminase levels worsened to ALT (329 U/L) grade 4 and AST (233 U/L) grade 3. Bilirubin and ALP were within normal limits, no clinical symptoms related to hepatotoxicity were reported. These events were considered not related to BDQ, probably related to BR (at the time of the grade 3 AE, the BR included PAS-C, LFX, PTO, and PZA), and not related to TB infection. Treatment with BR was interrupted. On Day 277, the subject also experienced a grade 3 AE of prolonged prothrombin time that was non-serious, not considered related to BDQ, possible related to BR and not related to TB. The BR was interrupted, and the prolonged prothrombin time was resolved after 5 days. On Day 288, ALT and AST levels had improved to 170 U/L (grade 3) and 96 U/L (grade 2), respectively, and improved further to grade 1 on Day 314. The AEs were still ongoing at the time of database lock. The observed BDQ AUC_{24h} and Cmax at Week 2 was 84,600 ng*h/mL and 5,990ng/mL, respectively. The average AUC_{24h} and Cmax value for Cohort 2 at Week 2 is 60,800 ng*h/mL and 4,560 ng/mL, respectively. The observed BDQ

AUC_{24h} and Cmax at Week 12 was 35,900 ng*h/mL and 2,290 ng/mL, respectively. The average AUC_{24h} and Cmax value for Cohort 2 at Week 12 is 32,200 ng*h/mL and 2,430 ng/mL, respectively. The observed BDQ Cmin at Week 24 (ie, last day of BDQ intake) is 859 ng/mL. The average Cmin value for Cohort 2 at Week 24 is 626 ng/mL.

Deaths

No deaths were reported during the study up to the database cut-off date of the Week 24 primary analysis. None of the subjects who prematurely discontinued the study had up to the database cut-off date died during follow-up for survival.

Laboratory findings

The most frequently observed treatment-emergent graded laboratory abnormalities during the BDQ Treatment phase were prothrombin time prolonged in 7 (46.7%) subjects, ALT increased in 6 (40.0%) subjects, and AST increased in 5 (33.3%) subjects.

Table 25. Treatment-emergent Graded Laboratory Abnormalities (Worst Grade) During the Treatment Phases; ITT (Study TMC207-C211 Cohort 2. Primary Analysis, DB Cut-off 10JAN2019)

	TMC207 Treatment Phase	Overall Treatment Phase
Analysis set: Intent-to-treat, N	15	15
Chemistry		
Alanine Aminotransferase		
N	15	15
Grade 1	3 (20.0%)	3 (20.0%)
Grade 3	2 (13.3%)	0
Grade 4	1 (6.7%)	4 (26.7%)
Amylase, Pancreatic		
N	15	15
Grade 1	2 (13.3%)	2 (13.3%)
Grade 2	1 (6.7%)	2 (13.3%)
Aspartate Aminotransferase		
N	15	15
Grade 1	2 (13.3%)	2 (13.3%)
Grade 3	2 (13.3%)	3 (20.0%)
Grade 4	1 (6.7%)	1 (6.7%)
Creatinine[a]		
N	15	15
Grade 1	6 (40.0%)	6 (40.0%)
Grade 2	2 (13.3%)	3 (20.0%)
Gamma Glutamyl Transferase		
N	15	15
Grade 1	1 (6.7%)	1 (6.7%)
Grade 3	3 (20.0%)	2 (13.3%)
Grade 4	0	1 (6.7%)
Hypercalcemia		
N	15	15
Grade 1	4 (26.7%)	5 (33.3%)
Grade 2	0	1 (6.7%)
Hyperglycemia		
N	15	15
Grade 1	2 (13.3%)	3 (20.0%)
Hyperkalemia		
N	15	15
Grade 1	2 (13.3%)	2 (13.3%)
Hyperuricemia		
N	15	15
Grade 2	2 (13.3%)	4 (26.7%)
Hypoglycemia		
N	15	15
Grade 1	1 (6.7%)	3 (20.0%)
Hypokalemia		
N	15	15
Grade 1	2 (13.3%)	3 (20.0%)
Hypomagnesemia		
N	15	15
Grade 1	1 (6.7%)	1 (6.7%)

Hyponatremia		
N	15	15
Grade 2	1 (6.7%)	1 (6.7%)
Hematology		
Neutrophils and Precursors		
N	15	15
Grade 1	1 (6.7%)	2 (13.3%)
Neutrophils, Segmented		
N	15	15
Grade 1	1 (6.7%)	2 (13.3%)
Prothrombin Time		
N	15	15
Grade 1	2 (13.3%)	3 (20.0%)
Grade 2	1 (6.7%)	1 (6.7%)
Grade 3	4 (26.7%)	6 (40.0%)

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.

a. the toxicity grading for creatine elevations was initially determined using the age-specific ULN, although the DMID toxicity table uses grading for creatinine on the adult ULN.

For an overview of subjects with creatinine values above the age-specific reference range and the associated toxicity grading based on the adult ULN, refer to Table 26.

Table 26. Overview of Subjects with Creatinine Value Above the Age- and Gender-specific Normal Range; ITT (Study TMC207-C211 Cohort 2. Primary Analysis, DB Cut-off 10JAN2019

Subject ID	Phase	Time Point	Day	Creatinine (umol/L)	Normal Range	Grade*
A	Overall Treatment	Week 48	336	80	23 -57	Grade 1
B	TMC207 Treatment	Week 4	33	59	14 -57	Grade 0
C	Screening	Screening	-20	49	14 -48	Grade 0
	TMC207 Treatment	Week 16	115	50	14 -48	Grade 0
	TMC207 Treatment	Week 20	139	52	14 -48	Grade 0

*Based on DMID grading for subjects 2 -12 years old using adult ULN (110 umol/L for male and 101 umol/L for female). Grade 1 is 0.7-1.0 x ULN, Grade 2 is 1.1-1.6 x ULN, Grade 3 is 1.7-2.0 x ULN, Grade 4 is >2.0 x ULN.

Increased creatine phosphokinase (CK)

Creatine kinase is a component of the parameter "Myopathy or Neuromuscular Junction Impairment", which includes both clinical symptoms and CK elevation. Based on the DMID grading scale, CK is considered a non-graded laboratory abnormality since it is not listed as a standalone laboratory parameter. In order to allow grading the laboratory parameters independent from clinical symptoms, CK was further analysed in this report according to the DAIDS toxicity grading scale, which includes grading for creatine kinase as a standalone laboratory parameter.

Seven (46.7%) subjects experienced treatment-emergent abnormally high creatine kinase MB (analysed as non-graded abnormality), however all were ≤5x ULN and none were associated with clinical symptoms or reported as AE.

Five (33.3%) subjects were reported with an AE of blood creatine phosphokinase increase during the treatment with BDQ and are further presented below. Two additional subjects had a treatment emergent CK laboratory abnormality after the end of the BDQ Treatment phase. According to the DAIDS toxicity grading scale, 3 (20.0%) subjects experienced at least one treatment emergent graded CK laboratory abnormality during the BDQ Treatment phase, which was grade 1 for two (13.3%) subjects and grade 2 for one (6.7%) subject. None of the subjects had a CK abnormality ≥10x ULN (corresponding to grade 3 creatine kinase increased according to the DAIDS toxicity grading scale). After the end of the BDQ Treatment phase, no additional subjects were reported with blood CK increased AEs. As described below, exposure data was available in four of the five subjects in which AEs of CK elevation were reported. Two of the four subjects were reported to have a higher AUC_{24h} as well as C_{max} at Week 2 compared to the average observed in the cohort 2, one of the subjects with a exposure of bedaquiline at week 2 was reported with a higher AUC_{24h} and a slightly higher C_{max} at week 12 compared to average. None of the events were considered related to study drug and no action was taken and the events of increased CK resolved.

- One subject experienced a grade 3 AE of blood CK increased on Day 59 of BDQ treatment. CK was 568 U/L (grade 1; normal range: 18-158 U/L) on that day and CK MB was 13.8 µg/L (above ULN; normal range: 0.6-6.3µg/L). The subject had a baseline CK of 519 U/L (grade 1) and CK MB of 19.6 µg/L (above ULN). The event was considered doubtfully related to BDQ and BR, and not related to TB infection. No action was taken towards the study drug. On Day 59, the subject had a QTcF increase from baseline of 30 ms corresponding to an actual value of 407ms. No other ECG abnormalities or concurrent muscle-related AE were reported. The increased event of CK resolved after a duration of 83 days. CK was 278 U/L on that day and CK MB was 9.6 µg/L. During the screening phase, the subject experienced the grade 3 AEs of increased CK and CK MB increased that were both resolved approximately one month before start of the AE during the BDQ treatment phase, after a duration of 15 and 9 days, respectively. The observed bedaquiline AUC_{24h} and C_{max} at Week 2 was 58,520ng*h/mL and 4,730ng/mL, respectively. The average AUC_{24h} and C_{max} value for Cohort2 at Week2 is 60,800ng*h/mL and 4,560 ng/mL, respectively. The observed bedaquiline AUC_{24h} and C_{max} at Week12 was 20,785ng*h/mL and 1,270ng/mL, respectively. The average AUC_{24h} and C_{max} value for Cohort 2 at Week 12 is 32,200 ng*h/mL and 2,430ng/mL, respectively. The observed bedaquiline C_{min} at Week 24 was 570 ng/mL. The average C_{min} value for Cohort 2 at Week 24 was 626 ng/mL.

- One subject experienced a grade 1 AE of increased CK on Day 55 of BDQ treatment. CK was 234 U/L (above ULN but grade 0; normal range: 18-158 U/L) on that day and CK MB was 6.7 µg/L (above ULN; normal range: 0.6-6.3µg/L). The subject had a baseline CK of 237 U/L (above ULN but grade 0) and CK MB of 5.8µg/L (normal). The event was considered not related to BDQ, BR, and TB infection. No action was taken towards the study drug. The event resolved after a duration of 12 days. CK was 79 U/L on that day. CK MB was not available; it was 3.5 µg/L on Day 85. On Day 168 of BDQ intake, the subject experienced a new grade 3 AE of increased CK in blood of 1084 U/L (grade 2) and CK MB was 31.5 µg/L (above ULN; normal range: 0.6-6.3 µg/L). The event was considered not related to BDQ, BR, and TB infection. No action was taken towards the study drug. The event resolved after a duration of 7 days, where CK MB was 2.9 µg/L but no CK laboratory data was available for that day. The subject did not have any ECG abnormalities nor ECG- or muscle-related AEs. The observed bedaquiline AUC_{24h} and C_{max} at Week 2 was 76,330ng*h/mL and 5,760ng/mL, respectively. The average AUC_{24h} and C_{max} value for Cohort 2 at Week2 is 60,800ng*h/mL and 4,560 ng/mL, respectively. The observed bedaquiline AUC_{24h} and C_{max} at Week12 was 39,098ng*h/mL and 2,720ng/mL, respectively. The average AUC_{24h} and C_{max} value for Cohort 2 at Week12 is 32,200 ng*h/mL and 2,430 ng/mL, respectively. The observed bedaquiline C_{min} at Week 24 was 937 ng/mL. The average C_{min} value for Cohort2 at Week 24 is 626ng/mL.

- One subject experienced a grade 1 AE of increased CK in blood on Day 14 of BDQ treatment. CK was 509 U/L (above ULN but grade 0; normal range: 18-354 U/L) on that day and CK MB was 7.3 µg/L (above ULN; normal range: 0.6-6.3µg/L). The subject had a baseline CK of 250 U/L (normal) and CK MB of 4.8µg/L (normal). The event was considered not related to BDQ, BR, and TB infection. No action was taken towards the study drug. The event resolved after a duration of 22 days, where CK was 324 U/L, but no CK MB was not available for that day. On Day 42 of BDQ intake, the subject experienced a new grade 1 AE of increased CK in blood of 396 U/L (above ULN but grade 0). CK MB was not available for that day. The event was considered not related to BDQ, BR, and TB infection. No action was taken towards the study drug. The event resolved after a duration of 15 days where CK was 281 U/L and CK MB was 4.9 µg/L. The subject did not have any ECG abnormalities nor ECG- or muscle-related AEs. The observed bedaquiline AUC_{24h} and C_{max} at Week 2 was 61,739ng*h/mL and 5,470ng/mL, respectively. The average AUC_{24h} and C_{max} value for Cohort 2 at Week2 is 60,800ng*h/mL and 4,560 ng/mL, respectively. The observed bedaquiline AUC_{24h} and C_{max} at Week12 was 38,130ng*h/mL and 2,400ng/mL, respectively. The average AUC_{24h} and C_{max} value for Cohort 2 at Week 12 is 32,200 ng*h/mL and 2,430 ng/mL, respectively. The observed bedaquiline C_{min} at Week 24 was 963 ng/mL. The average C_{min} value for Cohort 2 at Week 24 is 626 ng/mL.

- One subject experienced a grade 1 AE of increased CK in blood at screening phase (Day - 1). CK was 240 U/L (above ULN but grade 0; normal range: 18-147U/L) on that day; creatine kinase MB was not available. On Day 14 of BDQ treatment, the severity had progressed to grade 3 and CK was 847U/L (grade1) and creatine kinase MB was 16.4 µg/L (above ULN; normal range: 0.6-6.3µg/L). On Day 42 of BDQ treatment, the severity of the AE evolved to grade 1, with CK 151 U/L (above ULN but grade 0). The event was not considered related to BDQ, BR, and TB infection. No action was taken towards the study drug. The event resolved after a duration of 56 days with a CK of 120 U/L and CK MB was 3.0 µg/L. On Day 97 of BDQ intake, the subject experienced a new grade 1 AE of increased CK in blood of 178 U/L (above ULN but grade 0), CK MB was not available for that day but was 4.7 µg/L on Day 109. The event was considered not related to BDQ, BR, and TB infection. No action was taken towards the study drug. The event resolved after a duration of 30 days when CK was 132 U/L (normal) but CK MB was not available at any other time point during the event. The subject did not have any ECG abnormalities nor ECG- or muscle-related AEs. The observed bedaquiline AUC_{24h} and C_{max} at Week 2 was 84,610ng*h/mL and 5,990ng/mL, respectively. The average AUC_{24h} and C_{max} value for Cohort 2 at Week2 is 60,800ng*h/mL and 4,560 ng/mL, respectively. The observed bedaquiline AUC_{24h} and C_{max} at Week12 was 35,945ng*h/mL and 2,290ng/mL, respectively. The average AUC_{24h} and C_{max} value for Cohort2 at Week 12 is 32,200 ng*h/mL and 2,430ng/mL, respectively. The observed bedaquiline C_{min} at Week 24 was 859 ng/mL. The average C_{min} value for Cohort2 at Week24 is 626ng/mL.

- One subject experienced a grade 3 AE of increased blood CK on Day 11 of BDQ treatment, with a CK of 1085 U/L (grade 1; normal range: 18-295U/L) and CK MB was 8.1 µg/L (above ULN; normal range: 0.6-6.3µg/L). This subject had a baseline CK of 154 U/L (normal) and creatine kinase MB of 2.7 µg/L. The event was considered not related to BDQ and BR and possibly related to TB infection. No action was taken towards the study drug. On Day 11, the subject had a QTcF increase from baseline of 37 ms corresponding to an actual value of 418 ms. No other ECG abnormalities or concurrent muscle-related AE were reported. The blood CK increased AE was still ongoing at the time of database lock. No other CK laboratory data was available. This subject discontinued bedaquiline treatment on Day11, so no further PK results are available.

Electrocardiogram

There were no clinically relevant changes in mean HR during the BDQ Treatment phase. Mean absolute values in QTcF remained stable during the BDQ Treatment phase. Mean changes from baseline for QTcF at

the 5-hour assessment time points (ie, at the time of Cmax) were comparable to those at pre-treatment time points (i.e., at the time of C_{min}). In addition to BDQ, all subjects had LFX and one subject had CFZ in their BR, which may also cause QT interval prolongation.

No subjects were observed with a QTcF value of more than 500 ms during the BDQ Treatment phase or the Overall Treatment phase, and no significant ECG abnormalities for HR or PR and QRS duration were observed.

Discontinuation due to adverse events

Table 27. Adverse Events Leading to Permanent Discontinuation of TMC207 by Body System and Preferred Term; ITT (Study TMC207-C211 Cohort 2. Interim Analysis, DB Cut-off 10JAN2019)

MedDRA System Organ Class Dictionary-derived Term	TMC207 Treatment Phase	Overall Treatment Phase
Analysis set: Intent-to-treat, N	15	15
Any adverse event leading to permanent discontinuation of TMC207, n (%)	3 (20.0%)	3 (20.0%)
Hepatobiliary disorders	3 (20.0%)	3 (20.0%)
Hepatotoxicity	3 (20.0%)	3 (20.0%)

n: number of subjects with 1 or more events.

- One subject was reported with a grade 4 SAE of hepatotoxicity on Day 14 including ALT and gamma-glutamyl transferase (GGT) were grade 3 increased, and AST was grade 4 increased. At baseline, the subject had increased transaminases (grade 2 ALT and grade 3 AST). Treatment with BDQ and BR (which included KM, LFX, EMB, ethionamide [ETO], PZA and TRD) was interrupted (on Day 17 for BDQ and on Day 24 for BR), and the subject recovered from the SAE after 79 days. No clinical symptoms related to hepatotoxicity were reported, and bilirubin and prothrombin time were within normal limits. After staggered reintroduction of BR drugs (EMB, LFX, ETO, and TRD) between Day 87 and Day 103 and BDQ on Day 110, the subject was reported with a new AE of hepatotoxicity (grade 4) on Day 169. The subject had increased liver enzymes (grade 4 ALT and AST, and grade 3 GGT) but no clinical symptoms related to the hepatotoxicity. The event was considered non-serious, doubtfully related to BDQ, possibly related to BR, and not related to TB infection. BDQ was permanently discontinued due to this AE and BR was interrupted. The AE was resolved after a duration of 34 days. From Day 215, the subject continued in the study on a BR consisting of EMB, isoniazid (INH), LFX, and TRD. The subject had increases in both AST and ALT ≥10x ULN at several time points during the study after BDQ was interrupted or discontinued (maximum value for ALT was 786 U/L, and 638 U/L for AST; both grade 4). The laboratory criteria for Hy's law were not met for this subject. Bilirubin and prothrombin time were within normal limits throughout the study. The observed BDQ AUC_{24h} and Cmax at Week 2 for this subject was 55,800 ng*h/mL and 4,390 ng/mL, respectively. The average AUC_{24h} and Cmax value for Cohort 2 at Week 2 is 60,800 ng*h/mL and 4,560 ng/mL, respectively. At Week 12, there was no BDQ intake due to the interruption on Day 17, the observed BDQ AUC_{24h} and Cmax at Week 12 was 10,700 ng*h/mL and 515 ng/mL, respectively. The average AUC_{24h} and Cmax value for Cohort 2 at Week 12 is 32,200ng*h/mL and 2,430 ng/mL, respectively. There was no PK information available from Week 24 for this subject.

- One subject was reported with a grade 2 AE hepatotoxicity on Day 14. On that day, ALT and AST were grade 2 increased, and GGT was grade 1 increased. The subject had ALT and GGT within normal limits and

grade 1 AST at baseline. The AE of hepatotoxicity was considered possibly related to BDQ and BR (which included KM, LFX, EMB, ETO, INH, PZA and TRD), and not related to TB infection. Upon progression of AE severity to grade 3 on Day 25 (ALT and AST were grade 3, and GGT was grade 1), treatment with BDQ was permanently withdrawn and BR was interrupted. No clinical symptoms related to hepatotoxicity were reported and bilirubin and prothrombin time were within normal limits. On Day 67, the subject was reported with the grade 1 AE varicella. The AE was considered not related to bedaquiline and BR. Aciclovir and calamine were used to treat the varicella. Based on the evolution of liver enzymes, the severity of the AE evolved to grade 4 (Day 84) and grade 3 (Day 97). The subject recovered from the hepatotoxicity after a duration of 114 days. After reintroduction of BR (EMB, KM, and LFX on Day 138; TRD and ETO on Day 144), the subject was reported with a new grade 4 AE of hepatotoxicity on Day 152 (when the subject was no longer on BDQ treatment). The subject had increased liver enzymes (grade 4 ALT, grade 3 AST, and grade 2 GGT) but no clinical symptoms related to the hepatotoxicity. The event was considered non-serious, not related to BDQ, possibly related to BR, and not related to TB infection. Treatment with TRD was interrupted and ETO was discontinued. On Day 162, the severity of the AE evolved to grade 3. The AE was resolved after a duration of 25 days (Day176). From Day 190 onwards, the subject continued in the study on a BR consisting of EMB, LFX, TRD, PAS-C, and CFZ. This subject had increases in ALT ≥10x ULN at several time points during the study (maximum value for ALT was 448 U/L [grade 4] and 310 U/L for AST [grade 3]). The bilirubin and prothrombin time were within normal limits throughout the study. The observed BDQ AUC_{24h} and Cmax at Week 2 was 34,000 ng*h/mL and 1,960ng/mL, respectively. The average AUC_{24h} and Cmax value for Cohort 2 at Week 2 is 60,800 ng*h/mL and 4,560 ng/mL, respectively. At Week 12 (4 December 2017), there was no BDQ intake due to permanent discontinuation of BDQ on 3 November 2017, and the observed BDQ AUC_{24h} and Cmax at Week 12 was 9,920 ng*h/mL and 583 ng/mL, respectively. The average AUC_{24h} and Cmax value for Cohort 2 at Week 12 is 32,200ng*h/mL and 2,430 ng/mL, respectively. At Week 24 (20 February 2018), the observed bedaquiline C_{min} at Week 24 was 226 ng/mL. The average C_{min} value for Cohort 2 at Week 24 is 626 ng/mL.

- One subject was reported with a grade 3 AE hepatotoxicity on Day 56. On that day, ALT, AST and GGT were grade 3 increased. During the screening phase, liver enzymes were increased (maximum grade 3 for ALT, grade 1 for AST, grade 2 for GGT). Liver enzymes were lower at baseline (grade 1 for ALT, AST, and GGT). The event was considered possibly related to BDQ and BR (which included AM, LFX, CFZ, EMB, ETO, INH, and PZA), and not related to TB infection. Treatment with BDQ was permanently discontinued on Day 71 and the BR was interrupted (PZA on Day 56; INH on Day 61; CFZ on Day 71; AM, LFX, EMB, and ETO on Day72). No clinical symptoms related to hepatotoxicity were reported and bilirubin was within normal limits. Prothrombin time was above ULN but grade 0 on Day 56 and therefore not reported as AE. Upon improvement of liver enzymes (to grade 1), BR drugs were (re)introduced in a non-staggered manner on Day 160 and 161. All BR was interrupted again by Day 177 as liver enzymes had worsened on Day 172 (ALT to grade 4, AST to grade 3, and GGT to grade 2). From Day 201, liver enzymes improved again. The AE was resolved after a duration of 166 days. From Day 217 onwards, the subject continued in the study on a BR consisting of EMB, CFZ, LFX, and LZD. The subject had an increase in ALT ≥10x ULN during the study (maximum value for ALT was 362 U/L [grade 4] and 243 U/L for AST [grade 3]). The bilirubin was within normal limits throughout the study. Prothrombin time was within normal limits throughout the study except on Day 56 (above ULN but grade 0) and Day 111 (grade 1).

The observed BDQ AUC_{24h} and Cmax at Week 2 was 33,600 ng*h/mL and 2,220ng/mL, respectively. The average AUC_{24h} and Cmax value for Cohort 2 at Week 2 is 60,800 ng*h/mL and 4,560 ng/mL, respectively. At Week 12 (15 May 2018), there was no BDQ intake due to permanent discontinuation of BDQ on 4 May 2018, the observed BDQ AUC_{24h} and Cmax at Week 12 was 8,470 ng*h/mL and 436 ng/mL, respectively. The

average AUC_{24h} and Cmax value for Cohort 2 at Week 12 is 32,200ng*h/mL and 2,430 ng/mL, respectively. At Week 24 (13 August 2018), the observed BDQ C_{min} at Week 24 was 119 ng/mL. The average C_{min} value for Cohort 2 at Week 24 is 626 ng/mL.

Post-marketing experience

BDQ is not approved for paediatric patients <12 years of age. Janssen Global Safety Database from Janssen Research & Development LLC for the period from the database cut-off date of the Week 24 primary analysis of Cohort 1 (15 June 2018) up to the cut-off date of 14 June 2019 retrieved 15 cases that involved post-marketing (and thus off-label) use of BDQ in patients <18 years, of which 6 of them were <12 years old and briefly described below. These cases have been reported in the PBRERs/PSURs of Sirturo approved for adult subjects.

- one patient, BDQ treatment regimen 200 mg tiw, was reported with hepatitis 5 months after initiation of BDQ.

- one patient, BDQ treatment regimen 300 mg qd (confirmation of dose has been requested by the MAH), was reported with hepatic cytolysis, acute hepatic failure 5 months after initiation of BDQ, CFZ, LZD and DLM.

- one patient, BDQ treatment regimen 100 mg tiw, was reported with severe optic neuritis 8 months after initiation of BDQ, LZD, MFZ and CFZ.

- one patient, BDQ treatment regimen 100 mg tiw, had a history of autism and experienced anger outbursts 4.5 months after initiation of BDQ. The reporter considered the event related to CS and DLM.

- one patient, diagnosed with pulmonary TB with meningeal involvement, BDQ treatment regimen 50 mg tiw, was reported with grade 2 generalized tonic-clonic seizure 18 days after initiation of BDQ, INH, PTO, CS, MFX and PTO. The event was probably related to INH and CS according to the reporter.

- one patient, unknown dose, initiation of treatment with BDQ for drug-resistant *Mycobacterium abscessus* lung infection, and a significant improvement was observed while on therapy.

2.5.1. Discussion on clinical safety

It is considered fully endorsed to extrapolate safety data from adults to paediatric subjects based on systemic exposure, therefore a limited study conducted in paediatric subjects is acceptable. The safety results supporting this application consist of data from the Week 24 primary analysis for Cohort 2 of Study TMC207-C211 (database cut-off date 10 January 2019) paediatric subjects aged ≥5 to <12 years with confirmed or probable multidrug-resistant tuberculosis (MDR-TB) infection. The youngest child included in this cohort was 5 and the oldest was 10 years old and the weight span was 16-36 kg. The paediatric subjects received BDQ in combination with a background regimen (BR) a dose of BDQ of 200 mg once daily (qd) for 14 days, followed by 100 mg three times per week (tiw) for 22 weeks (i.e. half adult dose) using a new oral tablet formulation (20-mg oral scored tablet, G008), administered with food.

During the BDQ Treatment phase, 12 of 15 (80.0%) subjects experienced at least one AE. The SOC with the highest reported incidence of AEs was infections and infestations (8 [53.3%] subjects). The most frequently reported AEs during the BDQ Treatment phase were increased blood creatine phosphokinase grade 3 and prolonged prothrombin time grade 3 (both in 5 [33.3%] subjects), and hepatotoxicity grade 3-4 (3 [20.0%]

subjects). One additional subject was reported with hepatotoxicity as a SAE after the treatment phase of BDQ was ended.

During the treatment phase, one subject discontinued treatment BDQ during the loading phase (due to hepatoxicity) and four subjects discontinued during the maintenance phase. In total, five (33.3%) subjects in the ITT analysis set discontinued BDQ treatment, of whom three subjects discontinued due to adverse event (AE) of hepatotoxicity, one subject due to having a drug-susceptible (DS)-TB infection, and one subject due to having an infection with nontuberculous mycobacteria. No events of death were reported up to the database cut-off date of Week 24.

Due to the small sample size it is not possible to allow any firm conclusions regarding the frequency of observed adverse events. No new safety concerns have been identified in this cohort and it therefore appears that a similar safety profile of BDQ in adults can also be expected in paediatric subjects. BDQ has already in adults been associated with increased levels of liver transaminases as well as QT prolongation, however, in this study four (26.6%) of the subjects weighing 19-22 kg were observed with significantly increased transaminases classified as grade 3-4 hepatotoxicity, and three of them discontinued the treatment with BDQ even though no clinical symptoms were presented. Discontinuation of the treatment with BDQ in subjects diagnosed with MDR-TB might be an efficacy issue since they are not receiving their highly needed treatment. Since the new age appropriate formulation is available that can be dispersed or mixed with food, an additional weight band has been added in section 4.1. of the SmPC for the paediatric subjects weighing 15-20 kg (160 mg gd for two weeks followed by 80 mg tiw up to week 24) in order to mimic the exposure in adults.

2.5.2. Conclusions on the clinical safety

It is fully endorsed to extrapolate safety data from adults to paediatric subjects based on systemic exposure. In this interim-analysis of a single-armed cohort including 15 paediatric subjects treated with half the adult dose of BDQ as in the treatment regimen for adults, no safety issues not already described were reported.

2.6. Risk Management Plan

Safety concerns

Important Identified Risks	Electrocardiogram QT prolonged
	Increased transaminases
Important Potential Risks	Severe hepatotoxicity
	Pancreatitis
	Myopathy
	Myocardial injury
Missing Information	Long-term effects of bedaquiline treatment on mortality
	Use in patients using potent inhibitors of drug-metabolizing enzymes
	Prolonged treatment duration

Pharmacovigilance plan

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
Not applicable				
Category 2 - Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
Confirmatory Phase 3 study STREAM Stage 2 The evaluation of a standard treatment regimen of anti-tuberculosis drugs for patients with MDR-TB Ongoing	To investigate the efficacy and safety, including mortality, of the adapted 'Bangladesh' regimen and of bedaquiline in combination with the BR followed by a treatment-free follow-up.	Important identified risks: Electrocardiogram QT prolonged, Increased transaminases Important potential risks: Severe hepatotoxicity, Pancreatitis, Myopathy, Myocardial injury Missing information: Long-term effects of bedaquiline treatment on mortality, Use in patients using potent inhibitors of drug-metabolizing enzymes, Prolonged treatment duration	Updates on study progress by including information on the number of subjects enrolled/completed:	Annual updates on study progress in the frame of annual renewal submissions
			Interim IDMC recommendation when half of the patients reach W76:	4Q 2020
			Final analysis – Clinical Study Report:	4Q 2023
Category 3 - Required additional pharmacovigilance activities				
Multi-Country MDR-TB Disease Registry (TBC4002) A multi-country prospective multi-drug resistant tuberculosis patient registry to monitor bedaquiline safety, utilization, and emergence of resistance. Ongoing	To investigate the effectiveness, safety, including mortality, and drug resistance of bedaquiline in combination with the BR in MDR-TB patients followed by a treatment-free follow-up.	Important identified risks: Electrocardiogram QT prolonged, Increased transaminases Important potential risks: Severe hepatotoxicity, Pancreatitis, Myopathy, Myocardial injury Missing information: Long-term effects of bedaquiline treatment on mortality, Use in patients using potent inhibitors of drug-metabolizing enzymes, Prolonged treatment duration	Interim reports:	Semiannual
			Final study report:	4Q 2020

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: 4Q 2020.

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
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, 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: 4Q 2020.

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
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: 4Q 2020.

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
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: 4Q 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: 4Q 2020.

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
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: 4Q 2020.
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; • 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: 4Q 2020.

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Use in patients using potent inhibitors of drug-metabolizing enzymes	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 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: 4Q 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: 4Q 2020.

Conclusion

The CHMP and PRAC considered that the risk management plan version 4.4 is acceptable.

2.7. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the MAH fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

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.

2.8. Product information

2.8.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the MAH show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

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 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 2017, there were an estimated 10.0 million prevalent TB cases (range: 9.0-11.1 million) and approximately 1.6 million people (range: 1.5-1.7 million) died. *M. tuberculosis* develops drug resistance through genetic mutations which are then amplified by selective pressures due to misuse of anti-TB drugs.

Routine surveillance data on MDR-TB among children are not available globally. Based on several mathematical models, approximately 3% of children with TB are estimated to have MDR-TB. Global estimates of the burden of MDR-TB in children range from 25,000 to 32,000 incident cases annually.

3.1.2. Available therapies and unmet medical need

Multidrug-resistant tuberculosis (MDR-TB) is a form of TB caused by bacteria that do not respond to isoniazid and rifampicin, which are the most powerful first-line anti-TB drugs. The WHO recommends an MDR-TB treatment regimen consisting of an intensive phase of 4 to 6 months with kanamycin, moxifloxacin, prothionamide, clofazimine, pyrazinamide, high-dose isoniazid, and ethambutol, followed by a 5-month continuation phase with moxifloxacin, clofazimine, pyrazinamide, and ethambutol.

The principles of MDR/XDR-TB treatment regimens used in children are similar to those of adults and the same second-line drugs are generally used. A regimen should contain at least 4 drugs to which drug susceptibility testing shows susceptibility and/or to which the patient or source case is naïve. Since the commonly used first- and second-line anti-TB drugs to treat DS-TB and MDR-TB were developed in adult patients, dose recommendations for use in children are often found to be inadequate.

BDQ has been authorized in adult subjects only since 2014 and was recently approved in adolescence (>12-≤18 years old) for combination regimen for pulmonary multidrug-resistant tuberculosis (MDR-TB) when an effective treatment regimen cannot otherwise be composed for reasons of resistance or tolerability.

3.1.3. Main clinical studies

This application concerns the results from the study TMC207-C211, which is a clinical phase 2, still ongoing, multicentre, single arm, open-label study including four different cohorts which are based on age group. This application concerns Cohort 2. The primary objective was to evaluate the PK, safety and tolerability of BDQ over a 24-week treatment period in each age cohort and to provide guidance on dose selection for each of the age cohorts, the study is not designed to determine efficacy.

Cohort 2 included 15 paediatric subjects ≥5-<12 years of age with confirmed or probable multidrug-resistant tuberculosis (MDR-TB) infection, which were enrolled and treated with BDQ in combination with an individualized background regimen (BR). These paediatric subjects received 200 mg once daily (qd) for 14 days, followed by 100 mg three times per week (tiw) for 22 weeks (i.e. half the adult dosing regimen) using a new 20 mg tablet. This application includes the treatment outcome and resistance results from the Week 24 primary analysis for Cohort 2 (database cut-off 10 January 2019).

3.2. Favourable effects

Efficacy assumptions are based on PK bridging through sufficiently similar exposure in children, as in the adult cohort in which clinical efficacy was demonstrated. The exposure estimates at the proposed posology are presumed to achieve this.

At Week 24, signs and symptoms were considered resolved for ten of the subjects (data available for 12 subjects). Radiological improvement was also observed at that time point in the 12 subjects from which data was available. Conversion into negative culture was observed in 3 of 3 subjects at Week 24.

3.3. Uncertainties and limitations about favourable effects

The assumption of clinical benefit is based on PK bridging assuming similar susceptibility of microorganisms, and drug distribution to relevant anatomical structures.

3.4. Unfavourable effects

Hepatotoxicity grade 3-4 was observed in three subjects (20%) during the treatment phase of BDQ. Clinical symptoms related to hepatotoxicity was not reported but all three subjects discontinued their treatment due to the high increase in liver transaminases. None of the subjects met the criteria of Hy´s law. One additional subject experienced SAE of hepatotoxicity after the treatment phase of BDQ was ended, the subject had a higher exposure of BDQ compared to the other paediatric subjects. All four subjects reported with hepatotoxicity weighted about 20 kg.

Prolonged prothrombin time was reported as an AE in five (33.3%) subjects, in which no clinical symptoms was observed, and the laboratory abnormality resolved while BDQ treatment was continued. Three of the events were grade 3. None of the 15 subjects had a prolonged prothrombin time laboratory abnormality at baseline. None of the subjects discontinued the study due to the reported AE.

AEs with non-graded treatment-emergent increase of creatine kinase (CK) was reported in five (33.3%) of the subjects during the treatment phase of BDQ. Two additional subjects had a treatment emergent CK laboratory abnormality after the end of the BDQ Treatment phase. None of the subjects discontinued the study due to the reported AE.

It should be noted that the aim of this cohort study was to obtain data to evaluate the possibilities for extrapolation to adults, however, all reported AEs in this limited study are already known based on data provided from the adult studies. No new safety issue has been detected.

3.5. Uncertainties and limitations about unfavourable effects

This is a limited study comprising 15 paediatric subjects, and the data provided is interim data from Week 24. The bridging of the safety database based on similar exposure is a core part of the safety demonstration.

All subjects were treated with 3-5 other drugs, some of them with potential to cause hepatotoxicity (such as pyrazinamide). It might therefore be challenging to evaluate whether BDQ only was associated with the observed AEs of hepatotoxicity or if it was a result of treatment with the BR and/or BDQ.

3.6. Effects Table

Table 28. Effects Table for Sirturo, paediatric indication ≥5-12 years.

Effect	Short Description	Treatment		Control	Uncertainties/ Strength of evidence	References
Radiological improvement	Week 24 interim analysis	12/12 (100%)		N/A	- Results only available for 12 subjects. - The final TB treatment outcome can only be assessed in the Week 120 (final) analysis, after completion of all anti-TB treatment. - The primary objective of this study is PK	Study TMC207-C211 Cohort 2
Resolution of signs and symptoms	Week 24 interim analysis	10/12 (80%)		N/A	- Results only available for 12 subjects. - The final TB treatment outcome can only be assessed in the Week 120 (final) analysis, after completion of all anti-TB treatment. - The primary objective of this study is PK	Study TMC207-C211 Cohort 2
Negative culture	Week 24 interim analysis	3/3 (100%)		N/A	Results only available from 3 subjects	Study TMC207-C211 Cohort 2
Hepatotoxicity	Three subjects discontinued treatment due to grade 3 or 4 hepatotoxicity	3/15 (20%)		N/A	Hepatotoxicity is a known AE in adult subjects treated with BDQ. The subjects were also treated with other drugs (BR) that have hepatotoxicity as known AEs	Study TMC207-C211 Cohort 2
prothrombin time prolonged	Normal at baseline. Three of the events were grade 3.	5/15 (33.3%)		N/A	Reported as AE	Study TMC207-C211 Cohort 2
Increased CK	Five during the treatment and two additional subjects after the end of the treatment	5/15 (33.3%)		N/A	Reported as AE	Study TMC207-C211 Cohort 2

Abbreviations: CK=creatine kinase

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Multidrug-resistant tuberculosis (MDR-TB) is a form of TB caused by bacteria that do not respond to isoniazid and rifampicin, which are the most powerful first-line anti-TB drugs. The emergence of MDR-TB is of major

concern to global TB control. The need for new therapeutic options has been critical, and recently authorized and novel antibiotic such as BDQ therefore represents an additional and valuable therapeutic treatment option.

BDQ is authorized for treatment of adults with MDR-TB. Based on the same microbial target and assumptions of similar pathophysiology, it is considered acceptable to extrapolate safety and efficacy data from adults to paediatric subjects based on similar systemic exposure.

The proposed posology allows the bridging of efficacy claims.

The simulations of the proposed posology show that the average exposure is higher in the weight group 15-20 kg compared to adults, and a dose adjustment for this weight band has therefore been added.

Within the dataset supporting this application, now new AEs that might be associated with BDQ has been identified in paediatric subjects and the reported AEs are in line with the ones that are known from studies in adult subjects.

3.7.2. Balance of benefits and risks

The benefits are considered to outweigh risks.

3.8. Conclusions

The overall benefit-risk of Sirturo is positive.

4. Recommendations

Similarity with authorised orphan medicinal products

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

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Sirturo 20 mg tablets is favourable in the following indication:

Sirturo is indicated for use as part of an appropriate combination regimen for pulmonary multidrug resistant tuberculosis (MDR TB) in adult and paediatric patients (5 years to less than 18 years of age and weighing at least 15 kg) when an effective treatment regimen cannot otherwise be composed for reasons of resistance or tolerability (see sections 4.2, 4.4 and 5.1).

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

The CHMP therefore recommends the extension of the marketing authorisation for Sirturo subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription.

Conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

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.

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

Risk Management Plan (RMP)

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

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.

Specific Obligation to complete post-authorisation measures for the conditional marketing authorisation

This being a conditional marketing authorisation and pursuant to Article 14a(4) of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

Description	Due date
The MAH will evaluate additional efficacy and safety data of bedaquiline in different treatment regimen compared to a regimen that does not include bedaquiline (confirmatory Phase III study) following an agreed protocol.	• Annual updates on study progress in the frame of annual renewal submissions • Final analysis - Clinical Study Report 4Q 2023

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0403/2018 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

In addition, CHMP recommends the variation to the terms of the marketing authorisation concerning the following change:

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

Extension application to add a new strength (20 mg tablets), grouped with a type II variation (C.I.6.a) to extend the existing indication to include treatment of paediatric patients aged from 5 years to less than 18 years of age and weighing at least 15 kg, based on the results of the Week 24 analysis of Cohort 2 (paediatric subjects aged ≥5 to <12 years) of Study TMC207-C211. As a consequence of the extended indication, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 and 5.3 of the SmPC have been updated and the Package Leaflet has updated accordingly. Furthermore, the annexes have been brought in line with the latest QRD template version 10.1. The RMP (version 4.4) is updated in accordance.

Attachments

1. Product Information (changes highlighted) as adopted by the CHMP on 28 January 2021.

Appendix

1. CHMP AR on similarity dated 28 January 2021