European Union Risk Management Plan
SIRTURO (Bedaquiline)

Data lock point for current RMP	30 Jun 2023	Version number	10.2

CHMP Opinion Date = 25 April 2024

QPPV Sign-off Date: 13 May 2024
RMP Version Number: 10.2
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CCI [redacted]

QPPV Name(s):	Dr. Laurence Oster-Gozet, PharmD, PhD
QPPV Signature:	The MAH QPPV has either reviewed and approved this RMP, or approved with an electronic signature appended to this RMP, as applicable.

Details of this RMP Submission	
Version Number	10.2
Rationale for submitting an updated RMP:	To address the CHMP and PRAC joint request for supplementary information (RSI) recieved in procedure EMEA/H/C/002614/II/0056.
Summary of significant changes in this RMP:	Removal of the following from the list of safety concerns: Important identified risks: • Electrocardiogram QT prolonged • Increased transaminases

Other RMP Versions Under Evaluation

RMP Version Number	Submitted on	Procedure Number
Not applicable		

Details of the Currently Approved RMP

Version number of last agreed RMP:	9.1
Approved within procedure	EMEA/H/C/002614/X/0036/G
Date of approval (Competent authority opinion date):	29 January 2021

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PART I: PRODUCT(S) OVERVIEW

Active substance(s) **(International Nonproprietary Name [INN] or common name)**	Bedaquiline (TMC207)
Pharmacotherapeutic group(s) (Anatomical Therapeutic Chemical [ATC] Code)	Antimycobacterials, drugs for treatment of tuberculosis (J04AK05)
Marketing Authorization Holder (MAH)	Janssen-Cilag International, NV
Medicinal products to which the Risk Management Plan (RMP) refers	1
Invented name(s) in the European Economic Area (EEA)	SIRTURO® (further referred to as SIRTURO)
Marketing authorization procedure	Centralized
Brief description of the product	**Chemical class:** diarylquinoline
	Summary of mode of action: Bedaquilinespecifically inhibits mycobacterial adenosine 5'-triphosphate (ATP) synthase, an enzyme that is essential for the generation of energy in *Mycobacterium tuberculosis*. The inhibition of ATP synthase leads to bactericidal effects for both replicating and non-replicating tubercle bacilli.
	Important information about its composition: Not applicable
Reference to the Product Information	Module 1.3.1, Summary of Product Characteristics, Labelling and Package Leaflet
Indication(s) in the EEA	**Current:** SIRTURO is indicated for use as part of an appropriate combination regimen in adult and pediatric patients (5 years to less than 18 years of age and weighing at least 15 kg) with pulmonary tuberculosis (TB) due to *Mycobacterium tuberculosis* resistant to at least rifampicin and isoniazid. Consideration should be given to official guidance on the appropriate use of antibacterial agents.
	Proposed: Not applicable

Dosage in the EEA

Current: The recommended dosage for SIRTURO in adult patients (18 years of age and older) is shown in the table below.

Recommended Dosage of SIRTURO in Adult Patients

Population	Dosing Recommendation	
	Weeks 1 to 2	Weeks 3 to 24[a]
Adults (18 years and older)	400 mg orally once daily	200 mg orally 3 times per week

[a] At least 48 hours between doses

The recommended dosage for SIRTURO in pediatric patients (5 years to less than 18 years of age) is based on body weight and shown in the table below.

Recommended Dosage of SIRTURO in Pediatric Patients (5 years to less than 18 years of age)

Body Weight	Dosing Recommendation	
	Weeks 1 to 2	Weeks 3 to 24[a]
Greater than or equal to 15 kg to less than 20 kg	160 mg orally once daily	80 mg orally 3 times per week
Greater than or equal to 20 kg to less than 30 kg	200 mg orally once daily	100 mg orally 3 times per week
Greater than or equal to 30 kg	400 mg orally once daily	200 mg orally 3 times per week

[a] At least 48 hours between doses

The total duration of treatment with SIRTURO is 24 weeks. When treatment with SIRTURO is considered necessary beyond 24 weeks, treatment may be continued up to 40 weeks in adults, at a dose of 200 mg three times per week.

SIRTURO should be taken orally with food, as administration with food increases oral bioavailability by about 2-fold.

Proposed: Not applicable

Pharmaceutical form(s) and strengths

Current: The 100-mg tablets are uncoated, white to almost white, round, biconvex, 11 mm in diameter, debossed with "T" over "207" on one side and "100" on the other side. Each tablet contains bedaquiline fumarate equivalent to 100 mg of bedaquiline.

The 20-mg tablets are uncoated, white to almost white, oblong (12.0 mm long and 5.7 mm wide), with score line on both sides, debossed with "2" and "0" on one side and plain on the other side. The tablet can be divided into equal doses. Each tablet contains bedaquiline fumarate equivalent to 20 mg of bedaquiline.

Proposed: Not applicable

Is/will the product be subject to additional monitoring in the European Union (EU)?

☐ **Yes** ☑ **No**

PART II: SAFETY SPECIFICATION

Module SI: Epidemiology of the Indication(s) and Target Population(s)

Indication(s)

SIRTURO is indicated for use as part of an appropriate combination regimen in adult and pediatric patients (5 years to less than 18 years of age and weighing at least 15 kg) with pulmonary tuberculosis (TB) due to *Mycobacterium tuberculosis* resistant to at least rifampicin and isoniazid.

Adult Population

Incidence:

According to the World Health Organization (WHO) annual report on Global Tuberculosis Control, there were an estimated 450,000 (range 399,000 to 501,000) new cases of rifampicin-resistant (RR)-TB/multidrug resistant (MDR)-TB globally in 2021. India, the Russian Federation, and Pakistan accounted for nearly 50% of the total RR/MDR-TB cases (WHO 2022c).

The WHO and European Centre for Disease Prevention and Control (ECDC) estimated that there were 73,000 (range 64,000 to 81,000) new RR/MDR-TB cases in the European region in 2021 (WHO 2022c, ECDC 2023).

Prevalence:

MDR-TB has been reported in all regions of the world. The true burden of the disease is likely to be underestimated due to limitations of survey data. The prevalence of MDR-TB is usually presented as the proportion of TB cases exhibiting resistance to anti-TB drugs rifampicin and isoniazid.

Globally in 2021, an estimated 3.6% (95% confidence interval [CI]: 2.7% to 4.4%) of new TB cases and 18% (95% CI: 11% to 26%) of re-treatment TB cases had RR/MDR-TB. Among the 30 high MDR-TB burden countries, the proportion of RR/MDR-TB cases among new cases and previously treated cases of TB reported ranged from 1% (Bangladesh) to 40% (Belarus) and from 4.2% (Kenya) to 76% (Somalia), respectively. The highest proportions of MDR-TB are found in countries in Eastern Europe and Central Asia. In the WHO European region, the estimated proportion of TB cases that have RR/MDR-TB was 26% among new TB cases and 57% among re-treatment TB cases (WHO 2022c). In 2021, RR/MDR-TB was reported for 32.6% of TB patients with drug susceptibility test results in the EU/EEA region (ECDC 2023).

An increasing number of TB cases have been reported that are resistant to rifampicin, any fluoroquinolone, and at least one of the drugs bedaquiline or linezolid, known as extensively drug-resistant tuberculosis (XDR-TB) (according to the WHO 2020 definition, WHO 2022c). XDR-TB has been documented in 182 countries globally. Surveillance data from 182 countries and territories worldwide revealed the average proportion of MDR-TB cases with XDR-TB was

20% (95% CI: 16% to 26%) (WHO 2022c). In the EU/EEA region, XDR-TB was reported for 11.2% of MDR-TB cases tested for second-line drug susceptibility in 2021 (ECDC 2023).

Demographics of the Population Within the Authorized Indication - Age, Sex, Racial and/or Ethnic Origin, and Risk Factors for the Disease:

Age

Across Central and Eastern Europe, the frequency of MDR-TB was much higher in all age groups compared with the rest of the countries and peaked in young adulthood. In other countries, frequency of MDR-TB declined linearly with age-group (WHO 2010). A study conducted at 23 Tuberculosis Network European Trials Group (TBNET) sites in 16 countries in Europe in 2010-2011 reported that the median age of the MDR-TB group was 36 years (Günther 2015).

Sex

Males predominate among TB cases in most countries. However, analysis by the WHO suggested no overall association between MDR-TB and sex of the patient. The aforementioned study conducted at 23 TBNET sites in 16 countries in Europe in 2010-2011 reported that 62.9% of MDR-TB patients were male (Günther 2015).

Ethnicity

In Europe it has been reported that migrants are over-represented among MDR-TB cases in countries with a low incidence of TB. For example, in Germany, migrants comprise 94.0% of MDR-TB cases, but only 58.7% of all TB cases; in the United Kingdom, migrants comprise 90.4% of MDR-TB cases, but only 69.1% of all TB cases; and in France they account for 89.2% of MDR-TB infections, but only 55.6% of all TB cases (Hargreaves 2017).

Risk factors for the disease

The main risk factor for development of resistance among TB cases is incorrect TB treatment, usually associated with intermittent drug use, errors in medical prescription, poor patient adherence, and low quality of TB drugs (Matteelli 2014). In addition, drug-resistant (DR)-TB is increasingly being diagnosed in individuals who have no prior history of TB. This has been interpreted as evidence of direct transmission of DR-TB occurring in communities (Shah 2017). Many other risk factors for drug resistance and for MDR-TB have been identified in studies including previous TB treatment, irregular treatment, female sex, non-permanent residents, urban migration, urban residence, frequent travelers, younger age, lack of sewage in home, alcoholism plus smoking, and lung cavities (Caminero 2010). A systematic review to determine risk factors associated with MDR-TB in Europe found previous TB treatment to be the strongest risk factor. The pooled risk of MDR-TB was 10 times higher in previously treated than never treated patients, with wide heterogeneity among studies. The analysis also found that patients with MDR-TB were more likely to be foreign born, younger than 65 years, male, and human immunodeficiency virus (HIV)-positive (Faustini 2006).

Main Existing Treatment Options:

The standard short-course WHO treatment regimen for drug-susceptible tuberculosis (DS-TB) consists of a 2-month intensive phase during which 4 drugs (isoniazid, rifampicin, pyrazinamide, and ethambutol) are administered, with a continuation phase for 4 months of 2 drugs (usually isoniazid and rifampicin) to which the mycobacterium has been demonstrated to be sensitive (WHO 2017). Drug resistance can develop as a result of improper use of antibiotics in treatment of patients with TB.

MDR-TB is considered curable but cannot be adequately treated with the standard short-course therapy used to treat DS-TB (Chan 2002, Douglas 1999). Prior to the approval of bedaquiline, the drugs available to treat TB had not changed in over 40 years. Until 2016, MDR-TB treatment could last up to 2 years (typically 18 to 24 months) (WHO 2016).

In 2018, the WHO issued a recommendation with a new hierarchy of medicines into 3 groups. In the new recommendation, bedaquiline, the newer generation fluoroquinolones, and linezolid are included in the group A drugs to be prioritized for use in longer regimens for the treatment of MDR-TB. A regimen with at least 4 effective TB medicines, including bedaquiline, during the intensive phase was recommended for patients with RR/MDR-TB (WHO 2018). In addition, the WHO updated its guidelines on the use of short-course regimens in late 2019 to recommend a phasing out of injectable agents, and replacing of the injectable component of the 9- to 12-month short-course regimen with bedaquiline. These various recommendations are now reflected in the current WHO consolidated guidelines issued in 2022, and as a result bedaquiline is a key component of both short-course and longer treatment regimens for MDR-TB in adults and children (WHO 2022a, WHO 2022c). Based on the WHO guidelines of 2022, a 6-month treatment regimen composed of bedaquiline, pretomanid, linezolid, and moxifloxacin is recommended, rather than 9-month or longer (18-month) regimens in RR/MDR-TB patients. Moxifloxacin can be omitted in cases of confirmed fluoroquinolone resistance. The all-oral 9-month or longer regimens are recommended alternatives in patients with RR/MDR-TB (WHO 2022a, WHO 2022b).

Natural History of the Indicated Condition in the Untreated Population, Including Mortality and Morbidity:

The emergence of drug resistance in TB is a major concern. The global distribution of MDR-TB is particularly heterogeneous. *M. tuberculosis* develops drug resistance through genetic mutations which are then amplified by selective pressures due to misuse of anti-TB drugs (Prasad 2014). When the prevalence of DR-TB is high enough, direct transmission of DR strains can then become the predominant mechanism of propagating MDR-TB in any given area (Shah 2017). Until early 2016, MDR-TB patients required a treatment duration of 2 years on average with the substantially more toxic and less potent second-line anti-TB drugs. Cure rates were lower and mortality higher than for DS-TB, particularly if patients are coinfected with HIV. According to the latest WHO data, 59% of RR/MDR-TB patients and 51% of RR/MDR-TB patients who were also resistant to fluoroquinolones were successfully treated (WHO 2022c).

Mortality and case-fatality estimates are uncertain partly due to incomplete coverage of global drug resistance surveillance and the lack of direct measurements of MDR-TB deaths. An estimated 191,000 (range 119,000 to 264,000) deaths caused by RR/MDR-TB occurred in 2021, including those with HIV infection (WHO 2022c). According to treatment outcomes reported by the WHO for the 2019 cohort, 12% of RR/MDR-TB patients died. Based on the Wells 2010 publication, overall mortality still exceeded 10% for patients that made it into good treatment programs, with a range of 8% to 21% (Wells 2010). Two independently conducted meta-analyses from 2009, each including approximately 30 studies in MDR-TB, found death as a reported outcome in 11% of treated patients (Johnston 2009, Orenstein 2009). Another meta-analysis reflecting data from 9,153 treated patients reported a mortality rate of 15.2% (95% CI: 14.5% to 16.0%). Patients who died were significantly older, more likely to be HIV-coinfected, with more extensive disease, and/or had prior therapy (Ahuja 2012).

Important Comorbidities:

Important comorbidities in patients with MDR-TB include HIV/Acquired Immunodeficiency Syndrome (AIDS), diabetes mellitus, and depression.

Pediatric Population

Incidence:

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).

In an analysis published in 2014, it was estimated that 31,948 (95% CI 25,594 to 38,663) children developed MDR-TB globally in 2010 (Jenkins 2014). The estimated number [range] of incident MDR-TB cases in children was largest for the WHO Southeast Asia region (10,000 [4,993 to 15,568]) followed by the Western Pacific region (8,349 [5,639 to 11,610]), the European region (5,645 [4,206 to 7,463]), the African region (4,736 [2,829 to 6,848]), the Eastern Mediterranean region (2,417 [339 to 5,087]), and the Americas (606 [374 to 854]) (Jenkins 2014).

A more recent analysis estimated that 58,000 children developed isoniazid-monoresistant TB, 7,600 RR-TB, 25,000 MDR-TB, and 1,200 XDR-TB[1] in 2014. Incidences varied substantially between regions. Globally, it was estimated that a median 6.9% (interquartile range [IQR] 6.6 to 7.1) of incident TB disease in children was isoniazid-monoresistant, 0.9% (IQR 0.8 to 1.0) was RR-TB, and 2.9% (IQR 2.7 to 3.1) was MDR-TB. Of the children with MDR-TB, a median 4.7% (IQR 4.3 to 5.1) was XDR-TB (Dodd 2016).

[1] Data based on the old WHO definition of XDR-TB from 2013, ie, TB resistant to isoniazid and rifampicin, and in addition to at least one fluoroquinolone and at least one second-line injectable medication. This definition was used to present data from all clinical trials discussed in this RMP.

The estimates of incident TB in children in 2014, by drug-resistance type and WHO region are presented below.

	Isoniazid-monoresistant	Rifampicin-monoresistant	Multidrug-resistant	Extensively drug-resistant
WHO region				
African	16,800 (10,800-25,700)	2,890 (1,860-4,460)	8,230 (5,190-12,800)	245 (151-396)
Americas	1,170 (743-1,810)	113 (69-191)	525 (330-816)	51 (31-86)
Eastern Mediterranean	6,640 (4,280-10,100)	1,290 (811-2,040)	3,340 (2,120-5,160)	185 (110-311)
European	1,610 (1,030-2,510)	179 (113-280)	2,120 (1,320-3,310)	168 (105-265)
Southeast Asia	21,200 (13,700-33,000)	1,820 (1,180-2,840)	6,370 (4,100-9,910)	199 (134-322)
Western Pacific	9,760 (6,320-14,700)	1,080 (705-1,690)	3,540 (2,320-5,400)	244 (159-376)
Global	**58,300 (38,300-87,800)**	**7,630 (5,010-11,500)**	**24,800 (16,100-37,400)**	**1,160 (757-1,770)**

Adapted from Dodd 2016.

Prevalence:

In the aforementioned analysis by Dodd et al, it was estimated that of the 67 million children infected with TB globally, nearly 5 million had isoniazid-monoresistant infections, 600,000 had RR-TB, 2 million had MDR-TB, and 100,000 had XDR-TB (Dodd 2016).

The estimates of the numbers of children infected with TB in 2014, by drug-resistance type and WHO region are presented below.

	Isoniazid-monoresistant	Rifampicin-monoresistant	Multidrug-resistant	Extensively drug-resistant
WHO region				
African	1,040,000 (707,000-1,360,000)	180,000 (137,000-233,000)	489,000 (373,000-640,000)	15,800 (11,200-22,100)
Americas	97,600 (73,300-130,000)	9,560 (6,760-14,200)	44,500 (33,000-60,900)	4,480 (3,030-6,720)
Eastern Mediterranean	583,000 (437,000-775,000)	106,000 (75,330-152,000)	288,000 (212,000-390,000)	15,400 (10,500-22,800)
European	166,000 (123,000-227,000)	17,800 (13,200-24,200)	219,000 (160,000-304,000)	17,300 (12,500-24,100)
Southeast Asia	1,950,000 (1,470,000-2,570,000)	162,000 (122,000-215,000)	586,000 (442,000-769,000)	18,300 (12,900-26,100)
Western Pacific	901,000 (696,000-1,170,000)	103,000 (79,100-135,000)	344,000 (264,000-445,000)	24,700 (18,600-32,300)
Global	**4,810,000 (3,750,000-6,160,000)**	**594,000 (463,000-763,000)**	**2,000,000 (1,560,000-2,580,000)**	**101,000 (78,100-131,000)**

Adapted from Dodd 2016.

Demographics of the Population Within the Authorized Indication – Age, Sex, Racial and/or Ethnic Origin, and Risk Factors for the Disease:

Age

In an analysis of WHO surveillance data, it was found that proportions of MDR-TB in children are similar to those in adults in many countries. In addition, the risk of MDR-TB is similar between children younger than 5 years of age and children 5 to 14 years of age (Zignol 2013).

Globally, an estimated 29,500 children under 5 years of age developed isoniazid-monoresistant TB, 3,920 RR-TB, 12,700 MDR-TB, and 596 XDR-TB in 2014 (Dodd 2016).

Sex

Globally in 2021, there were an estimated 224,878 and 218,864 incident cases of TB in males and females, respectively, under 15 years of age. The male-to-female ratio for children was close to 1 in all WHO regions (WHO 2022c). Estimates of MDR-TB incidence by sex are not available.

Risk factors for the disease

MDR-TB in children, especially in those less than 5 years of age, is an infectious disease usually transmitted through household contacts with MDR-TB. Older children and adolescents may develop cavitary, adult-type TB, which is associated with higher bacillary loads and therefore more natural DR mutations. Mismanagement of TB treatment in these children may lead to the development of drug resistance in their mycobacterial isolates (Schaaf 2012).

Main Existing Treatment Options:

The principles of MDR/XDR-TB treatment regimens in children are similar to those of adults and the same second-line drugs are generally used. Children with culture-confirmed MDR-TB should be treated according to the drug susceptibility testing (DST) result of their own isolate; while children with presumptive MDR-TB, based on contact with a known adult MDR-TB source case, should be treated according to the DST result of the source case's isolate. A regimen should contain at least 4 drugs to which DST shows susceptibility and/or to which the patient or source case is naïve (Schaaf 2012).

The WHO-recommended treatment regimens for children are similar to those for adults. Bedaquiline may be included in the RR/MDR-TB treatment regimens for children 6 to 17 years of age. In children with RR/MDR-TB under 6 years of age, an all-oral 9-12 month or longer regimen containing bedaquiline may be used (WHO 2022a, WHO 2022b).

As mentioned earlier, bedaquiline is now listed as a key component of both short-course and longer treatment regimens for MDR-TB in adults and children (WHO 2022c).

Natural History of the Indicated Condition in the Untreated Population, Including Mortality and Morbidity:

In children with MDR-TB, the resistance is typically a result of transmitted resistance. Because the disease is normally paucibacillary, acquired resistance is less likely (Seddon 2016). The diagnosis and the choice of the appropriate treatment of MDR-TB in children is challenging as it can be difficult to bacteriologically confirm the diagnosis in children who frequently have paucibacillary disease and because of difficulties in collecting respiratory samples in younger children (Schaaf 2016). Few children globally are diagnosed and appropriately treated for MDR-TB. Only approximately 1,000 children have been reported to receive MDR-TB treatment at any time in the past (Harausz 2018). As minimal literature is available on mortality for children with MDR-TB, a recent literature review of mortality in children with TB estimated that 22% (95% CI: 18% to 26%) of children with TB died in the pretreatment era (Jenkins 2017). Given the high number of children with MDR-TB who are untreated, mortality is likely to be significant.

Based on limited data on treatment outcomes in children, it appears that those who are identified, diagnosed, and treated with appropriate therapy have good outcomes. In a systematic review of 8 studies reporting the treatment of MDR-TB in children (n=315), the pooled estimate for treatment success was 82%. Across all studies, 5.9% died, 6.2% defaulted, and 39.1% had an adverse event (AE). The most common drug-related AEs were nausea and vomiting. Other serious adverse events (SAEs) were hearing loss, psychiatric effects, and hypothyroidism (Ettehad 2012). Another meta-analysis of data from 975 children from 18 countries reported 78% of patients treated for MDR-TB had treatment success, 9% died, 2% failed treatment, and 11% were lost to follow-up (Harausz 2018).

A study in South Africa examining predictors of childhood MDR-TB treatment outcomes identified associations between death and malnutrition, extrapulmonary TB, and HIV (Seddon 2012). Another study in Peru reported that children faced significantly higher risk of death or treatment failure if they had severe disease or were underweight (Chiang 2016). These findings are consistent with the Harausz et al meta-analysis where investigators also found that malnutrition and not being treated for HIV during TB treatment significantly increased the risk of poor outcomes (Harausz 2018).

Important Comorbidities:

Important comorbidities in pediatric patients with MDR-TB include HIV/AIDS and malnutrition.

PART II: SAFETY SPECIFICATION

Module SII: Nonclinical Part of the Safety Specification

The safety margins were recalculated using Week 2 data from the STREAM Stage 2 trial.

Key Safety Findings	Relevance to Human Usage
Toxicity	
Single & repeat-dose toxicity	
Bedaquiline, given as single dose, was well tolerated up to 200 mg/kg in mice, up to 600 mg/kg in rats, and up to 300 mg/kg in dogs. Repeated-dose toxicity studies were performed up to 3 months in mice, up to 6 months in rats and up to 9 months in dogs. The plasma bedaquiline exposure (area under the plasma concentration versus time curve [AUC]) in rats and dogs was lower and similar, respectively, to that observed in humans. Bedaquiline was associated with effects in target organs which included monocytic phagocytic system, skeletal muscle, liver, stomach, pancreas, and heart muscle.	The nonclinical data do not indicate a safety concern for humans.
Reproductive and developmental toxicity	
No effects on mating and fertility were seen in male and female rats given bedaquiline at doses up to 6 and 24 mg/kg/day, respectively. Reproduction studies in rats and rabbits revealed no evidence of harm to the fetus. No potential for teratogenicity was identified. In rats and rabbits, no relevant effects on developmental toxicity parameters were observed at exposures respectively similar to and lower than the clinical exposures. No adverse effects were observed in a pre- and postnatal development study in the rat. Concentrations of bedaquiline in rat breast milk were 6- to 12-fold higher than the maximum concentration observed in maternal plasma. Body weight decreases in pups were noted in high dose groups during the lactation period.	The nonclinical data do not indicate a safety concern for reproductive health in humans. In rats, bedaquiline was observed at higher concentrations in breast milk compared with maternal plasma. This may be relevant to human use.

Key Safety Findings	Relevance to Human Usage
Juvenile toxicity	
Bedaquiline was well tolerated in juvenile rats treated from Day 24 to Day 60 of age without any effects up to the no observed adverse effect level (NOAEL) of 15 mg/kg/day (mean AUC_{0-24h} bedaquiline/ *N*-monodesmethyl metabolite [M2] 13.1/10.5 µg.h/mL in males and 35.6/16.3 µg.h/mL in females). The exposure in these juvenile rats was similar to that in adult rats given an equivalent dose of bedaquiline. Bedaquiline-related effects at a higher dose than the NOAEL were similar to those seen in adult rats.	Nonclinical data suggest that the safety profile of bedaquiline in children and adolescents is expected to be similar to the safety profile in adults.
Carcinogenicity and Genotoxicity	
In a rat carcinogenicity study, bedaquiline, at the high doses of 20 mg/kg/day in males and 10 mg/kg/day in females, did not induce any treatment-related increases in tumor incidences. Compared with the clinical exposures, exposures (AUC) in male and female rats were respectively lower and similar for bedaquiline and were 2-fold higher for M2. Genotoxicity tests, in vitro and in vivo, have shown bedaquiline to be free of genotoxic potential.	The nonclinical data do not indicate a safety concern for humans.

Key Safety Findings	Relevance to Human Usage
Safety pharmacology	
Cardiovascular system	
Electrocardiogram QT prolonged	
In vitro data indicated that bedaquiline and M2 have the potential to inhibit the human ether-à-go-go-related gene (hERG) channel. In vivo electrocardiogram (ECG) evaluations were part of repeat-dose toxicity studies in dogs up to 9 months of duration. QT prolongations were absent in all of these studies, with the exception of the 2-/6-month study. In this study, bedaquiline-fumarate was administered daily by the oral route, via gavage at 10 or 40 or 20 mg/kg, or twice weekly at 140 mg/kg. A low daily dose of 10 mg/kg/day or an intermittent dose of 140 mg/kg twice weekly for 6 months did not show any effect on the QT interval corrected for heart rate (QTc) interval or heart rate. Increased QTc intervals were noted in dogs administered 40 mg/kg/day after 2 months. After lowering the dose to 20 mg/kg/day, the QTc intervals were no longer prolonged. At the end of the 6-month dosage period, there was no evidence of altered ECG parameters suggesting no arrhythmias. No QT/QTc interval prolongations were observed after 9-month administration of bedaquiline in dogs at doses up to 18 mg/kg/day. At the NOAEL of this finding, the exposures were approximately 4- or 8-fold higher than the clinical exposures for bedaquiline and M2, respectively.	Data from nonclinical studies of bedaquiline indicate a potential risk for ECG QT prolongation. Electrocardiogram QT prolonged has been removed as an important identified risk as it is adequately reflected in the SmPC in Section 4.4 Special Warnings and Precautions for Use and Section 4.8 Undesirable Effects.
Myocardial injury	
Cardiac muscle degeneration/necrosis was only seen in dogs (after administration of bedaquiline for 6 months at high dose [40 mg/kg/day]). These lesions consisted of minimal multifocal lymphohistiocytic infiltrates with degeneration of cardiomyocytes and/or minimal to slight endocardial fibrosis. The changes were associated with elevated levels of total creatine kinase and cardiac troponin I. No myocardial changes were observed after 9-month administration in dogs at doses up to 18 mg/kg/day despite elevated levels of cardiac troponin I at the high dose of 18 mg/kg/day only. In dogs, at the NOAEL of this finding, the exposures were approximately 4- or 8-fold higher than the clinical exposures for bedaquiline and M2, respectively.	Data from nonclinical studies of bedaquiline indicate a potential risk for myocardial injury. Myocardial injury is no longer an important potential risk because there was no evidence of clinically significant cardiac muscle damage related to bedaquiline in the Phase 2b and 3 trials.

Key Safety Findings	Relevance to Human Usage
Effects on fundic glands Degeneration or atrophy of the stomach was observed in mice and dogs. The lesions were located in the fundus, were multifocal to diffuse, and affected both parietal and chief cells. The inflammatory infiltrate with macrophages/fibrohistiocytosis in the subepithelial tissue is indicative of phospholipidosis. There were no relevant changes in serum gastrin levels in dogs. Once established, these lesions stabilized and did not further progress. Partial recovery was observed after 3 months of treatment cessation. In dogs, at the NOAEL of this finding, the exposures were lower or approximately 2-fold higher than the clinical exposures for bedaquiline and M2, respectively.	The significance of these nonclinical findings in humans is unknown. It is also unknown how these patients could be identified clinically.
Phospholipidosis Changes in the monocytic phagocytic system were seen in the skeletal muscle, pancreas, stomach, and liver of mice, rats, and dogs. Recovery from phospholipidosis was ongoing after treatment cessation. In rats, at the lowest observed adverse effect level of this finding, the exposures were lower than and similar to the clinical exposures for bedaquiline and M2, respectively. In dogs, at the NOAEL of this finding, the exposures were lower than and similar to the clinical exposures for bedaquiline and M2, respectively.	The relevance of the finding of phospholipidosis to humans is unknown. Most of the observed changes in animals occurred after prolonged daily dosing and subsequent increases in plasma and tissue concentrations of the drug, as a consequence of its long-terminal half-life. After treatment cessation, all indications of toxicity exhibited at least partial recovery to good recovery (See SmPC Section 5.3 Preclinical safety data). There is currently no validated biomarker for clinical monitoring of phospholipidosis (Chatman 2009).
Myopathy Degenerative/necrotic lesions were noted in mice, rats, and dogs. These changes were accompanied by increases in aspartate aminotransferase (AST), total creatine kinase, and myoglobin. This change only occurred after prolonged (at least 3-months duration) or high-dose administration and was usually reversible after treatment cessation or a decrease in dose. In rats, at the NOAEL of these findings, the exposures were lower than and similar to clinical exposures for bedaquiline and M2, respectively. In dogs, at the NOAEL of this finding, the exposures were approximately 4- and 8-fold higher than the clinical exposures for bedaquiline and M2, respectively.	Data from nonclinical studies of bedaquiline indicate a potential risk for myopathy. Myopathy is no longer an important potential risk based on cumulative clinical data from the Phase 2b and 3 trials.

Key Safety Findings	Relevance to Human Usage
Pancreatitis	
Minimal to marked changes in the pancreas were observed in dogs and consisted of focal to multifocal chronic pancreatitis. Microvacuolation of acinar cells sometimes associated with minimal single acinar cell necrosis was observed in mice. Changes were associated with increases in amylase and lipase in mice, whereas there were no relevant changes in amylase, lipase, or trypsin-like immunoreactivity in dogs. Partial recovery was observed in dogs after 3 months of treatment cessation. In dogs, at the NOAEL of this finding, the exposures were lower and 2-fold higher than the clinical exposure for bedaquiline and M2, respectively.	Data from nonclinical studies of bedaquiline indicate a potential risk for pancreatitis. Pancreatitis is no longer an important potential risk based on cumulative clinical data from the Phase 2b and 3 trials.
Hepatotoxicity	
Liver histopathological changes were seen in mice (single cell necrosis), rats (centrilobular hypertrophy/vacuolation), and dogs (decreased glycogen-like hepatocellular content, hepatocellular hypertrophy). These changes were associated with relevant increases in liver biomarkers (alanine aminotransferase [ALT], AST, alkaline phosphatase [ALP], and/or gamma-glutamyltransferase [GGT]). The observed liver histopathological changes did not include evidence of cholestasis and no elevation of bilirubin was seen. In rats, at the NOAEL of these findings, the exposures were lower than and similar to clinical exposures for bedaquiline and M2, respectively. In dogs, at the NOAEL, the exposures were approximately 4- or 8-fold higher than the clinical exposure for bedaquiline and M2, respectively.	Data from nonclinical studies of bedaquiline indicate a potential risk for hepatotoxicity. Increased transaminases has been removed as an important identified risk as it is adequately reflected in the SmPC in Section 4.4 Special Warnings and Precautions for Use and Section 4.8 Undesirable Effects. Severe hepatotoxicity is no longer an important potential risk based on cumulative clinical data from the Phase 2b and 3 trials.
Mechanisms for drug interactions	
Drug-drug interactions with potent inhibitors of drug-metabolizing enzymes and transporters	
In vitro testing suggests that cytochrome P450 (CYP)3A4 is the major CYP involved in bedaquiline and M2 metabolism.	Because *N*-demethylation of bedaquiline to M2 followed by subsequent metabolism of M2 is the major bedaquiline metabolic pathway both in vitro and in vivo, and because CYP3A4 was shown to be the major CYP involved in vitro both for bedaquiline and M2 metabolism, CYP3A4 is expected to be the major CYP involved in bedaquiline metabolism in humans. Coadministration of bedaquiline with moderate or strong CYP3A4 inducers decreases bedaquiline plasma concentrations

Key Safety Findings	Relevance to Human Usage
	and may reduce the therapeutic effect. Therefore, coadministration of bedaquiline with moderate or strong CYP3A4 inducers used systemically should be avoided. Coadministration of bedaquiline with CYP3A4 inhibitors does not have a clinically relevant effect on bedaquiline exposure.
	Available information does not suggest any clinically relevant effects regarding transporters. Use in patients using potent inhibitors of drug-metabolizing enzymes is no longer missing information based on cumulative clinical data from the Phase 2b and 3 trials.

Summary of Nonclinical Safety Concerns

Important identified risks	None
Important potential risks	None
Missing information	None

PART II: SAFETY SPECIFICATION

Module SIII: Clinical Trial Exposure

SIII.1. Brief Overview of Development

The clinical development of bedaquiline started in 2005 and includes an extensive program of Phase 1 studies that provided a description of the pharmacokinetic (PK) characteristics of bedaquiline and its drug-drug interaction potential, short-term safety and tolerability profile, as well as recommendations for the administration and dosage.

A short-term Phase 2a proof-of-principle trial TMC207-C202 (C202), was conducted to provide clinical confirmation in participants with DS-TB of the in vitro findings and mouse data of antibacterial activity of bedaquiline. This trial is not included in the all clinical trials population in this RMP due to differences in trial design (active-controlled) and population (participants with DS-TB) compared with the 2 Phase 2b trials TMC207-C208 (C208) and TMC207-C209 (C209).

The conditional marketing authorization of SIRTURO 100-mg tablets, granted on 05 March 2014, is based on the data from the 2 completed Phase 2b trials in adult participants (Trial C208 and Trial C209) with the recommended dose and tablet formulation.

The following clinical trials are included in this EU-RMP for SIRTURO (bedaquiline, formerly referred to as Tibotec Medicinal Compound 207 [TMC207]) for characterization of exposure and safety:

Two Phase 2b trials, C208 and C209, in adult participants:

- Trial C208 was a randomized, double-blind, placebo-controlled, Phase 2b trial designed to evaluate the antibacterial activity, safety, and tolerability of bedaquiline in participants with newly diagnosed sputum smear-positive pulmonary infection with MDR-TB. Participants randomized to the active treatment arm received bedaquiline 400 mg once daily for 2 weeks, followed by 200 mg 3 times a week for 6 weeks (Stage 1 participants) or 22 weeks (Stage 2 participants) in combination with a standard 5-drug, first- and second-line anti-TB regimen.
- Trial C209 was an open-label, Phase 2b trial designed to evaluate the safety, tolerability, and efficacy of bedaquiline as part of an individualized MDR-TB treatment regimen in participants with sputum smear-positive pulmonary MDR-TB. Both newly diagnosed and treatment experienced participants were allowed to enroll. Participants received bedaquiline 400 mg once daily for 2 weeks, followed by 200 mg 3 times a week for 22 weeks.

One Phase 3 trial, STREAM Stage 2 [TMC207TBC3007], in participants 15 years of age and older:

- STREAM Stage 2 was a randomized, open-label, parallel-group, active-controlled Phase 3 trial designed to evaluate an investigational bedaquiline-containing, all-oral 40-week regimen (Regimen C) in participants with RR/MDR-TB. Participants were randomized to

1 of the following regimens: Regimen A, long-course WHO regimen with a recommended 20-month treatment duration; Regimen B (control), injectable-containing 40-week regimen; Regimen C, bedaquiline-containing, all-oral 40-week regimen; or Regimen D, bedaquiline- and injectable-containing 28-week regimen. This trial was sponsored by Vital Strategies, Inc., an affiliate of International Union Against Tuberculosis and Lung Disease (The Union) and conducted under an agreement with Janssen Research and Development, LLC. Due to the following reasons, data from the Phase 3 trial and the earlier Phase 2b trials were not pooled: a 10-year difference in the periods the trials were conducted, a different length for the bedaquiline treatment period and that of the anti-TB drugs in the background regimen (BR), differences in extent of TB resistance in the populations enrolled (ie, inclusion of RR-TB patients only in the STREAM Stage 2 trial), different microbiological methods to evaluate efficacy, different concomitant medications used in the study regimen (both TB medications as part of the BR and other medications such as antiretrovirals), and differences in data collection and presentation. Therefore, exposure and safety data from the STREAM Stage 2 trial are presented separately from the corresponding Phase 2b data in this RMP.

One Phase 2 trial, TMC207-C211 (C211), in adolescents ≥12 to <18 years (Cohort 1) and in children ≥5 to <12 years (Cohort 2):

- Trial C211 is an ongoing, open-label, Phase 2 trial designed to evaluate the PK, safety, tolerability, and antimycobacterial activity of bedaquiline in combination with a BR of MDR-TB medications in children and adolescents 0 months to <18 years of age who have confirmed or probable pulmonary MDR-TB. The data presented in this EU-RMP are from the Week 24 primary analyses of Cohort 1 (≥12 to <18 years) and Cohort 2 (≥5 to <12 years).

SIII.2. Clinical Trial Exposure

Exposure in Randomized Phase 2b Clinical Trials

The randomized Phase 2b clinical trials population includes 1 trial in adults, C208 (N=102).

Exposure to bedaquiline in the randomized Phase 2b clinical trials population is summarized in Tables SIII.1 through SIII.3 for all participants by duration, by age group and sex, and by ethnic or racial origin. Exposure by dose is not presented, as the bedaquiline treatment regimen is standardized such that participants receive a 400-mg once daily dose during the first 2 weeks of treatment and from Week 3 onwards bedaquiline 200 mg 3 times per week.

Table SIII.1: Exposure BY DURATION (by Indication)
(Randomized Phase 2b Clinical Trials Population)

Duration of Exposure (at least)[a]	Persons, n (%)	Person-years
INDICATION: MDR-TB	(N=102)	
Cumulative up to Week 2	101 (99)	
up to Week 4	96 (94.1)	
up to Week 8	94 (92.2)	
up to Week 12[b]	69 (67.6)	
up to Week 16	65 (63.7)	
up to Week 20	65 (63.7)	
up to Week 24	62 (60.8)	
Total	102 (100)	37.2

[a] During Trial C208 bedaquiline 400 mg once daily was given during the first 2 weeks of treatment and from Week 3 onwards bedaquiline 200 mg was given 3 times in a week.
[b] Trial C208 consists of 2 Stages. In Stage 1 of the trial, bedaquiline was administered for 8 weeks, while in Stage 2 the duration of bedaquiline treatment was 24 weeks. This explains the marked drop in exposure after Week 8.

Table SIII.2: Exposure BY AGE GROUP AND SEX (by Indication)
(Randomized Phase 2b Clinical Trials Population)

	Men		Women	
Age Group	Persons, n (%)	Person-years	Persons, n (%)	Person-years
INDICATION: MDR-TB	(N=70)		(N=32)	
18 – 44 years	47 (47)	17	25 (24.5)	9.5
45 – 64 years	23 (22.6)	8.4	7 (6.9)	2.3
≥65 years	0	0	0	0
Total	70 (68.6)	25.4	32 (31.4)	11.8

Table SIII.3: Exposure BY ETHNIC or RACIAL ORIGIN (by Indication)
(Randomized Phase 2b Clinical Trials Population)

Race	Persons, n (%)	Person-years
INDICATION: MDR-TB	(N=102)	
Black	42 (41.2)	13.5
Caucasian	8 (7.8)	3.5
Asian	9 (8.8)	4.4
Other[a]	43 (42.2)	15.8
Total	102 (100)	37.2

[a] "Other" includes 25 South African participants and 18 South American participants.

Exposure in Randomized Phase 3 Clinical Trials

The randomized Phase 3 clinical trials population includes 1 trial in adults, STREAM Stage 2 (N=354, randomized to receive bedaquiline as part of the allocated treatment regimens C+D).

Exposure to bedaquiline in the randomized Phase 3 clinical trials population is summarized in Tables SIII.4 through SIII.6 for all participants by duration, by age group and sex, and by ethnic or racial origin. Exposure by dose is not presented, as the bedaquiline treatment regimen is standardized such that participants receive a 400-mg once daily dose during the first 2 weeks of treatment and from Week 3 onwards, bedaquiline 200 mg 3 times per week.

In this trial, participants who were originally randomized to a non-bedaquiline containing regimen could receive bedaquiline as part of a salvage regimen if clinically indicated. The exposure in person-time for these 32 participants is included in Table SIII.4, separately from the prespecified allocated bedaquiline-containing regimens C+D.

Table SIII.4: Exposure BY DURATION

(Randomized Phase 3 Clinical Trials Population)

	Persons n (%)	Person-years
Regimen C + D: Safety analysis set, N	354	
Cumulative exposure up to		
Week 2	349 (98.6%)	
Week 4	346 (97.7%)	
Week 8	343 (96.9%)	
Week 12	338 (95.5%)	
Week 16	337 (95.2%)	
Week 20	331 (93.5%)	
Week 24	325 (91.8%)	
Week 28[a]	324 (91.5%)	
Week 32	200 (56.5%)	
Week 36	192 (54.2%)	
Week 40[b]	187 (52.8%)	
Week 44	10 (2.8%)	
Week 48	6 (1.7%)	
Week 52	6 (1.7%)	
Week 56	6 (1.7%)	
Week 60	6 (1.7%)	
Week 64	6 (1.7%)	
Week 68	6 (1.7%)	
Week 72	6 (1.7%)	
Week 76	6 (1.7%)	
>Week 76	6 (1.7%)	
Total	354 (100.0%)	234.8
Total exposure in salvage participants	32 (100.0%)	25.7

[a] Regimen D: A 28-week regimen consisting of bedaquiline, levofloxacin, clofazimine, and pyrazinamide supplemented by kanamycin (injectable) and isoniazid dose higher than dose used in Regimens B and C for the first 8 weeks (intensive phase).
[b] Regimen C: A 40-week all-oral regimen of bedaquiline, levofloxacin, clofazimine, ethambutol, and pyrazinamide, supplemented by high-dose isoniazid and prothionamide in the first 16 weeks (intensive phase).
Note: Per study design, participants with MDR-TB, including those with evidence of resistance to at least rifampicin but susceptibility to isoniazid, were included.
Note: A maximum of 14 days of extra treatment (irrespective of reason) was acceptable before classified as treatment extension. In addition, the intensive phase of treatment could have been extended for delayed sputum smear conversion (maximum 8-week extension permitted).
Note: N = 32 participants who were originally randomized to a non-bedaquiline-containing regimen were exposed to bedaquiline as part of an allowed salvage regimen. They are included in a separate presentation of total exposure only.

Note: Duration of exposure to bedaquiline regardless of interruptions = (stop date [latest] – start date [earliest]) + 1 (converted to weeks). If ongoing at the end of the study, stop date imputed with last scheduled visit (contact) date.
Note: Person-years derived as the sum of individual duration (days)/365.25.

Table SIII.5: Exposure BY AGE GROUP AND SEX
(Randomized Phase 3 Clinical Trials Population)

	Men		Women	
	Persons n (%)	Person-years	Persons n (%)	Person-years
Regimen C + D: Safety analysis set, N	216		138	
Age group (years)				
<18 years[a]	1 (0.3%)	0.8	1 (0.3%)	0.8
>=18 to <25 years	30 (8.5%)	18.5	37 (10.5%)	22.4
>=25 to <45 years	123 (34.7%)	85.9	91 (25.7%)	59.6
>=45 to <65 years	59 (16.7%)	39.3	9 (2.5%)	5.8
>=65 years	3 (0.8%)	1.9	0	0
Total	216 (61.0%)	146.3	138 (39.0%)	88.6

Note: Per study design, participants with MDR-TB, including those with evidence of resistance to at least rifampicin but susceptibility to isoniazid, were included.
Note: Duration of exposure to bedaquiline regardless of interruptions = (stop date [latest] – start date [earliest]) + 1 (converted to weeks). If ongoing at the end of the study, stop date imputed with last scheduled visit (contact) date.
Note: Person-years derived as the sum of individual duration (days)/365.25.
[a] Age (years): Per inclusion criterion, participants 15 years of age or older were eligible for study participation in STREAM Stage 2 if otherwise valid. As such, 2 participants <18 years of age were enrolled and randomized in Regimen C.

Table SIII.6: Exposure BY ETHNIC or RACIAL ORIGIN
(Randomized Phase 3 Clinical Trials Population)

	Persons n (%)	Person-years
Regimen C + D: Safety analysis set, N	354	
Race		
Asian	169 (47.7%)	105.7
Black	132 (37.3%)	92.3
White	53 (15.0%)	36.8
Total	354 (100.0%)	234.8

Note: Per study design, participants with MDR-TB, including those with evidence of resistance to at least rifampicin but susceptibility to isoniazid, were included.
Note: Duration of exposure to bedaquiline regardless of interruptions = (stop date [latest] – start date [earliest]) + 1 (converted to weeks). If ongoing at the end of the study, stop date imputed with last scheduled visit (contact) date.
Note: Person-years derived as the sum of individual duration (days)/365.25.

Exposure in All Phase 2b Clinical Trials Including Open Extensions

Adult Population

The all Phase 2b clinical trials adult population includes 2 Phase 2b trials: the randomized, blinded trial previously described (Trial C208 [Stage 1 and 2]), and the open-label trial (Trial C209). Together, the all Phase 2b clinical trials adult population comprises 335 participants, including 102 bedaquiline-treated participants from Trial C208 plus 233 bedaquiline-treated participants from Trial C209.

Exposure to bedaquiline in the all Phase 2b clinical trials adult population is summarized in Tables SIII.7 through SIII.10 for all participants by duration, by age group and sex, by ethnic or racial origin, by baseline renal status, and by HIV serostatus at baseline. Exposure by dose is not presented as the bedaquiline treatment regimen is standardized such that participants receive a 400-mg once daily dose during the first 2 weeks of treatment and from Week 3 onwards bedaquiline 200 mg 3 times per week. Exposure by baseline hepatic function is not presented as participants with abnormal hepatic function were excluded from the trials.

Table SIII.7: Exposure BY DURATION (by Indication)
(All Phase 2b Clinical Trials Population Including Open Extensions/Adult Population)

Duration of Exposure (at least)[a]	Persons, n (%)	Person-years
INDICATION: MDR-TB	(N=335)	
Cumulative up to Week 2	331 (98.8)	
up to Week 4	323 (96.4)	
up to Week 8	317 (94.6)	
up to Week 12[b]	291 (86.9)	
up to Week 16	281 (83.9)	
up to Week 20	277 (82.7)	
up to Week 24	269 (80.3)	
Total	335 (100)	143.7

[a] During Trial C208 bedaquiline 400 mg once daily was given during the first 2 weeks of treatment and from Week 3 onwards bedaquiline 200 mg was given 3 times in a week.
[b] Trial C208 consists of 2 Stages, Stage 1 of the trial runs up to and including Week 8, while the duration of Stage 2 of the trial is 24 weeks. This explains the marked drop in exposure after Week 8.

Table SIII.8: Exposure BY AGE GROUP AND SEX (by Indication)
(All Phase 2b Clinical Trials Population Including Open Extensions/Adult Population)

	Men		Women	
Age Group	Persons, n (%)	Person-years	Persons, n (%)	Person-years
INDICATION: MDR-TB	(N=220)		(N=115)	
18 – 44 years	155 (46.3)	66.4	96 (28.7)	42.5
45 – 64 years	63 (18.8)	26.5	19 (5.7)	7.3
≥65 years	2 (0.6)	1.0	0	0
Total	220 (65.7)	93.9	115 (34.3)	49.8

Table SIII.9: Exposure BY ETHNIC or RACIAL ORIGIN (by Indication)
(All Phase 2b Clinical Trials Population Including Open Extensions/Adult Population)

Race	Persons, n (%)	Person-years
INDICATION: MDR-TB	(N=335)	
Black	117 (34.9)	46.6
Asian	99 (29.6)	46.9
Caucasian	68 (20.3)	30.6
Other[a]	51 (15.2)	19.7
Total	335 (100)	143.7

[a] "Other" includes 25 South African participants and 26 South American participants.

Table SIII.10: Exposure BY SPECIAL POPULATIONS (by Indication)
(All Phase 2b Clinical Trials Population Including Open Extensions/Adult Population)

Population	Persons, n (%)	Person-years
INDICATION: MDR-TB	(N=335)	
Renal impairment		
Normal (CrCl ≥80 mL/min)	298 (86.3)	124.5
Mild (CrCl >50 to <80 mL/min)	42 (12.5)	17.2
Moderate (CrCl >30 to ≤50 mL/min)	4 (1.2)	1.9
Severe (CrCl ≤30 mL/min)	0	0
Coinfection with HIV [a]		
HIV-coinfected	22 (6.6)	8.6
HIV-negative	306 (91.3)	131.9
Unknown	7 (2.1)	3.2

CrCl = creatinine clearance
[a] Coinfection status at baseline.

Pediatric Population

The all clinical trials pediatric population includes Cohort 1 (≥12 to <18 years) and Cohort 2 (≥5 to <12 years) of Trial C211.

Exposure to bedaquiline in the all clinical trials pediatric population for Cohort 1 is summarized in Tables SIII.11 through SIII.13 for all participants by duration, by sex, and by ethnic or racial origin. Exposure by dose is not presented as the bedaquiline treatment regimen is standardized such that participants in Cohort 1 receive a 400-mg once daily dose during the first 2 weeks of treatment and from Week 3 onwards bedaquiline 200 mg 3 times per week.

Table SIII.11: Exposure BY DURATION (by Indication)
(All Clinical Trials Population Including Open Extensions/Pediatric Population/Cohort 1)

	Persons, n (%)	Person-years
INDICATION: MDR-TB	(N=15)	
Cumulative up to Week 2	15 (100)	
up to Week 4	15 (100)	
up to Week 8	15 (100)	
up to Week 12	15 (100)	
up to Week 16	15 (100)	
up to Week 20	15 (100)	
up to Week 24	14 (93.3)	
Total	15 (100)	6.8

Table SIII.12: Exposure BY SEX (by Indication)
(All Clinical Trials Population Including Open Extensions/Pediatric Population/Cohort 1)

	Persons, n (%)	Person-years
INDICATION: MDR-TB	(N=15)	
Female	12 (80.0)	5.5
Male	3 (20.0)	1.3
Total	15 (100)	6.8

Table SIII.13: Exposure BY ETHNIC or RACIAL ORIGIN (by Indication)
(All Clinical Trials Population Including Open Extensions/Pediatric Population/Cohort 1)

	Persons n (%)	Person-years
INDICATION: MDR-TB	(N=15)	
Asian	2 (13.3)	0.9
Black	8 (53.3)	3.6
Caucasian	5 (33.3)	2.3
Total	15 (100)	6.8

Exposure to bedaquiline in the all clinical trials pediatric population for Cohort 2 is summarized in Tables SIII.14 through SIII.16 for all participants by duration, by sex, and by ethnic or racial origin. Exposure by dose is not presented as the bedaquiline treatment regimen is standardized such that participants in Cohort 2 receive a 200-mg once daily dose during the first 2 weeks of treatment and from Week 3 onwards bedaquiline 100 mg 3 times per week.

Table SIII.14: Exposure BY DURATION (by Indication)
(All Clinical Trials Population Including Open Extensions/Pediatric Population/Cohort 2)

	Persons, n (%)	Person-years
INDICATION: MDR-TB	(N=15)	
Cumulative up to Week 2	14 (93.3)	
up to Week 4	14 (93.3)	
up to Week 8	14 (93.3)	
up to Week 12	10 (66.7)	
up to Week 16	10 (66.7)	
up to Week 20	10 (66.7)	
up to Week 24	10 (66.7)	
Total	15 (100)	5.35

Table SIII.15: Exposure BY SEX (by Indication)
(All Clinical Trials Population Including Open Extensions/Pediatric Population/Cohort 2)

	Persons, n (%)	Person-years
INDICATION: MDR-TB	(N=15)	
Female	9 (60)	2.60
Male	6 (40)	2.76
Total	15 (100)	5.35

Table SIII.16: Exposure BY ETHNIC or RACIAL ORIGIN (by Indication)
(All Clinical Trials Population Including Open Extensions/Pediatric Population/Cohort 2)

	Persons, n (%)	Person-years
INDICATION: MDR-TB	(N=15)	
Asian	1 (6.7)	0.18
Black	9 (60)	3.32
Caucasian	5 (33.3)	1.86
Total	15 (100)	5.35

PART II: SAFETY SPECIFICATION

Module SIV: Populations Not Studied in Clinical Trials

SIV.1. Exclusion Criteria in Pivotal Clinical Studies Within the Development Program

Important Exclusion Criteria in Pivotal Clinical Trials Across the Development Program

Criterion 1	**Pediatric participants (<18 years old)**
Reason for being an exclusion criterion	Pediatric participants were excluded from the pivotal trials of the initial bedaquiline clinical development program. The initial indication was sought only for adults with MDR-TB. Experience in adults was required before the safety and efficacy of SIRTURO could be established in pediatric patients. The safety, tolerability, and PK of bedaquiline have subsequently been established in children 5 years to <18 years of age and weighing at least 15 kg. The safety, efficacy, and PK of bedaquiline in children <5 years of age or weighing less than 15 kg have not yet been established. Trial C211 in children and adolescents 0 months to <18 years of age is currently ongoing. In the Phase 3 STREAM Stage 2 trial, participants 15 years of age or older were included.
Included as missing information	No
Rationale (if not included as missing information)	Use of SIRTURO in pediatric patients <5 years of age or weighing less than 15 kg is not within the approved indication.

Important Exclusion Criteria in Pivotal Clinical Trials Across the Development Program

Criterion 2	**Women who were pregnant or breastfeeding**
Reason for being an exclusion criterion	At the time of the initial pivotal trials, per International Council for Harmonisation (ICH) guidelines pregnant women were excluded from bedaquiline clinical trials. Breastfeeding women are usually excluded from clinical trials.
Included as missing information	No
Rationale (if not included as missing information)	As a precautionary measure, the use of SIRTURO during pregnancy should be avoided unless the benefit of therapy is considered to outweigh the risks (SmPC Section 4.6). Women who are treated with SIRTURO should not breastfeed (SmPC Section 4.6).
Criterion 3	**Participants having a significant cardiac arrhythmia defined as an arrhythmia requiring medication.** **Participants with the following QT/QTc interval characteristics at screening:** - **a marked prolongation of QT/QTc interval, eg, repeated demonstration of QT interval corrected for heart rate according to Fridericia (QTcF) interval >450 ms;** - **a history of additional risk factors for Torsade de pointes, eg, heart failure, hypokalemia, family history of long QT syndrome;** - **the use of concomitant medications that prolong the QT/QTc interval listed as disallowed medication in the trial protocol.** - **pathological Q-waves (defined as >40 ms duration or depth >0.4-0.5 mV);** - **evidence of ventricular pre-excitation;** - **ECG evidence of complete or incomplete left bundle branch block or right bundle branch block;** - **evidence of second or third degree heart block;** - **intraventricular conduction delay with QRS duration >120 ms; or** - **bradycardia as defined by sinus rate <50 beats per minute.**
Reason for being an exclusion criterion	Data from nonclinical studies of bedaquiline indicated a potential risk for QT prolongation.
Included as missing information	No

Important Exclusion Criteria in Pivotal Clinical Trials Across the Development Program

Rationale (if not included as missing information)	SIRTURO may prolong the QT interval. This risk has been well-characterized. The SmPC Section 4.4 'Special Warnings and Precautions for Use' contains guidance on monitoring QT interval and electrolytes prior to and during treatment with SIRTURO. ECG QT prolonged is included in Section 4.8 'Undesirable Effects'.
Criterion 4	**Participants with complicated or severe extra-pulmonary manifestations of TB or neurological manifestations of TB.**
Reason for being an exclusion criterion	Patients with complicated or severe extra-pulmonary manifestations of TB or neurological manifestations of TB were outside the target population.
Included as missing information	No
Rationale (if not included as missing information)	Use of SIRTURO in patients with complicated or severe extra-pulmonary manifestations of TB or neurological manifestations of TB is not within the approved indication.
Criterion 5	**Participants with DS-TB**
Reason for being an exclusion criterion	Patients with DS-TB were outside the target population.
Included as missing information	No
Rationale (if not included as missing information)	Use of SIRTURO in patients with DS-TB is not within the approved indication.
Criterion 6	**HIV-infected participants in the Phase 2 trials:** **- who had AIDS-defining illnesses other than TB, or showed severe symptoms of HIV infection** **- having a CD4+ count <300 cells/µL or** **- having received antiretroviral therapy and/or oral or intravenous antifungal medication within the last 90 days** **Also participants, who, in the opinion of the investigator, might need to start antiretroviral treatment during the 24-week treatment period of Trial C208 Stage 2, were not eligible for the trial.** **HIV-infected participants in the Phase 3 STREAM Stage 2 trial having a CD4+ count <50 cells/µL or receiving disallowed antiretroviral treatment.**

Important Exclusion Criteria in Pivotal Clinical Trials Across the Development Program	
Reason for being an exclusion criterion	Inclusion of severely immunocompromised participants could confound the safety and efficacy assessments. During the proof of concept Trial C208, antiretrovirals were disallowed; antiretrovirals were subsequently allowed in the open-label Trial C209 although no participants received concomitant antiretroviral treatment with bedaquiline treatment. During the Phase 3 STREAM Stage 2 trial, selected antiretroviral treatment was allowed.
Included as missing information	No
Rationale (if not included as missing information)	Bedaquiline exposure in patients coinfected with HIV is similar to that in patients not coinfected with HIV. Based on clinical data, coadministration of SIRTURO and CYP3A4 inhibitors (eg, lopinavir/ritonavir) does not have a clinically relevant effect on bedaquiline exposure. Therefore, the coadministration of SIRTURO and CYP3A4 inhibitors is allowed, and no dose adjustment is needed.
Criterion 7	**Participants with the following toxicities at screening in the Phase 2 trials as defined by the enhanced Division of Microbiology and Infectious Diseases (DMID) adult toxicity table (C208: May 2001, C209: November 2007):** - **creatinine grade 2 or greater (>1.5 times the upper limit of normal [ULN]);** - **trypsin like immunoreactivity ≥1.5 times ULN (only to be taken into account prior to implementation of Protocol Amendment III);** - **AST grade 2 or greater (>2.5 times ULN);** - **ALT grade 2 or greater (>2.5 times ULN);** - **ALP grade 2 or greater (>2.5 times ULN); or** - **total bilirubin grade 2 or greater (>1.6 times ULN).** **Participants with the following toxicities at screening in the Phase 3 STREAM Stage 2 trial:** - **AST >3 times ULN or** - **ALT >3 times ULN**
Reason for being an exclusion criterion	Inclusion of participants meeting these criteria could confound the safety and efficacy evaluations of the trial.
Included as missing information	No
Rationale (if not included as missing information)	The risk of increased transaminases has been well-characterized, and is included in Section 4.8 ‘Undesirable Effects’of the SmPC. Section 4.4 ‘Special Warnings and Precautions for Use’ of the SmPC provides sufficient information to mitigate this risk.

SIV.2. Limitations to Detect Adverse Reactions in Clinical Trial Development Programs

The clinical development program is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

SIV.3. Limitations in Respect to Populations Typically Under-represented in Clinical Trial Development Program(s)

Table SIV.2: Exposure of Special Populations Included or Not in Clinical Trial Development Programs

Type of Special Population	Exposure
Pediatric population	The all clinical trials pediatric population included 15 adolescents ≥12 to <18 years (exposure of 6.8 total person-years) and 15 children ≥5 to <12 years (exposure of 5.35 total person-years). STREAM Stage 2 Regimen C included 2 participants ≥15 to <18 years of age (exposure of 0.8 person-years for each participant).
Elderly	Of the 335 participants included in the all Phase 2b clinical trials adult population, 2 (0.6%) participants were 65 years of age or older (exposure of 1.0 person-years). Of the 354 participants included in the randomized Phase 3 clinical trials population, 3 (0.8%) participants were 65 years of age or older (exposure of 1.9 person-years).
Pregnant women	Not enrolled in the pivotal trials of the clinical development program. A total of 13 pregnancies were reported in the completed Phase 2b trials in adult participants (Trial C208 Stage 2 or Trial C209). In addition, the partners of 3 male participants in the bedaquiline treatment group from Trial C208 Stage 2 reported pregnancy during the trial. A total of 15 pregnancies in participants and 7 pregnancies in partners of participants were reported in the allocated bedaquiline-containing Regimens C and D of the STREAM Stage 2 trial.
Breast-feeding women	Not included in the pivotal trials of the clinical development program.
Population with relevant different ethnic or racial origin	Of the 335 participants in the all Phase 2b clinical trials adult population, 117 (34.9%) participants were black (exposure of 46.6 person-years), 99 (29.6%) participants were Asian (exposure of 46.9 person-years), 68 (20.3%) participants were Caucasian (exposure of 30.6 person-years), and 51 (15.2%) participants were of another race (exposure of 19.7 person-years). Of the 354 participants in the randomized Phase 3 clinical trials population, 169 (47.7%) participants were Asian (exposure of 105.7 person-years), 132 (37.3%) participants were black (exposure of 92.3 person-years), and 53 (15.0%) participants were white (exposure of 36.8 person-years).

Type of Special Population	Exposure
	Of the 15 participants in the all clinical trials pediatric population for Cohort 1 (≥12 to <18 years), 8 (53.3%) participants were black (exposure of 3.6 person-years), 5 (33.3%) participants were Caucasian (exposure of 2.3 person-years), and 2 (13.3%) participants were Asian (exposure of 0.9 person-years). Of the 15 participants in the all clinical trials pediatric population for Cohort 2 (≥5 to <12 years), 9 (60.0%) participants were black (exposure of 3.32 person-years), 5 (33.3%) participants were Caucasian (exposure of 1.86 person-years), and 1 (6.7%) participant was Asian (exposure of 0.18 person-years).
Subpopulations carrying relevant genetic polymorphisms	Not included in the clinical development program.
HIV-coinfected patients	Of the 335 participants in the all Phase 2b clinical trials adult population, there were 22 (6.6%) HIV-coinfected participants (exposure of 8.6 person-years). Of the 354 participants in the allocated bedaquiline-containing Regimens C and D of the STREAM Stage 2 trial, 60 (16.9%) were HIV-coinfected participants.
Patients with relevant comorbidities:	
• Patients with hepatic impairment	• A total of 8 adult participants with moderate hepatic impairment (Child-Pugh B) received a single dose of bedaquiline 400 mg in a Phase 1 clinical trial (C112).
• Patients with renal impairment	• Of the 335 participants in the all Phase 2b clinical trials adult population, there were 42 participants with mild renal impairment (creatinine clearance [CrCl] >50 to <80 mL/min) at baseline exposed to bedaquiline for 17.2 person-years and 4 participants with moderate renal impairment (CrCl >30 to ≤50 mL/min) at baseline exposed to bedaquiline for 1.9 person-years.
• Patients with cardiovascular impairment	• Not included in the clinical development program.
• Immunocompromised patients	• Not included in the clinical development program. See the above category of 'HIV-coinfected patients' for exposure data in this population.
• Patients with a disease severity different from inclusion criteria in clinical trials	• Not included in the clinical development program.

Summary of Missing Information Due to Limitations of the Clinical Trial Program

None

PART II: SAFETY SPECIFICATION

Module SV: Postauthorization Experience

SV.1. Postauthorization Exposure

SV.1.1. Method used to Calculate Exposure

Product exposure is estimated at the time of distribution, not at the time of usage. There is a delay between the time a medication is distributed until it is used by a patient.

Patient exposure was estimated by calculation from MAH distribution data. Exposure is based upon finished product. In order to do this, estimates were made as to how much medication equals 1 treatment course. The recommended dosage of bedaquiline for MDR-TB is 4 tablets of 100-mg tablet once daily for the first 2 weeks; from Week 3 to 24, 2 tablets of 100-mg tablet 3 times per week with at least 48 hours between doses, taken with food. The total duration of treatment is 24 weeks. Therefore, for 100-mg tablets, 18.8 g are assumed to equal 1 treatment course. Additionally, for 20-mg tablets, 9.4 g are assumed to equal 1 pediatric treatment course. It is important to note that a patient may receive more than 1 treatment course dosage due to the potential prolonged treatment duration.

SV.1.2. Exposure

Based on a distribution of 13,822,984 g of finished product distributed worldwide (from launch to 28 February 2023), the estimated cumulative non-study postauthorization exposure to bedaquiline is 740,965 completed treatment courses, of which 119,214 completed treatment courses occurred in the European Union (including Iceland, Liechtenstein, and Norway).

Market research sources for non-study postauthorization exposure data are limited for breakdowns such as: age, sex and country and are therefore not provided.

PART II: SAFETY SPECIFICATION

Module SVI: Additional EU Requirements for the Safety Specification

Potential for Misuse for Illegal Purposes

Bedaquiline is a diarylquinoline, which is a class of anti-TB drug. The potential for illegal use is unlikely given that the target of bedaquiline is a mycobacterium. The AE profile for bedaquiline (eg, absence of significant central nervous system effects) does not suggest a risk for abuse.

PART II: SAFETY SPECIFICATION

Module SVII: Identified and Potential Risks

SVII.1. Identification of Safety Concerns in the Initial RMP Submission

Not applicable

SVII.1.1. Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Not applicable

SVII.1.2. Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Not applicable

SVII.2. New Safety Concerns and Reclassification with a Submission of an Updated RMP

The following important potential risks, missing information and important identified risks are removed from the list of safety concerns:

Safety Concern	Justification for Removal
Important Identified Risks	
Electrocardiogram QT prolonged	This risk of electrocardiogram QT prolonged was removed based on PRAC request in procedure EMEA/H/C/002614/II/0056 as it is well-characterized, and the SmPC provides sufficient information to mitigate this risk.
Increased transaminases	The risk of increased transaminases was removed based on PRAC request in procedure EMEA/H/C/002614/II/0056 as it is well-characterized, and the SmPC provides sufficient information to mitigate this risk.
Important Potential Risks	
Severe hepatotoxicity	Severe hepatotoxicity was considered an important potential risk for bedaquiline based on nonclinical findings. In the Phase 2 pivotal trials and the confirmatory STREAM Stage 2 trial, all participants received bedaquiline as part of combination therapy with other known hepatotoxic drugs. No increased risk of severe hepatotoxicity was observed with bedaquiline-containing regimens compared with the comparator regimens. No safety signal for severe hepatotoxicity has been identified in the postmarketing setting. Increased transaminases is listed as an adverse reaction in the SIRTURO SmPC. However, cumulative data do not support a causal association between bedaquiline exposure and the development of severe hepatotoxicity. Severe hepatotoxicity will continue to be monitored through routine pharmacovigilance activities.

Safety Concern	Justification for Removal
Pancreatitis	Pancreatitis was considered an important potential risk for bedaquiline based on nonclinical findings. No cases of pancreatitis were reported during the investigational treatment phase of the bedaquiline Phase 2b trials. In the STREAM Stage 2 trial, AEs coding to preferred terms in the Acute pancreatitis Standardized MedDRA Query (SMQ) were reported for fewer participants in the bedaquiline-containing regimens than in the other regimens. No safety signal for pancreatitis has been identified in the postmarketing setting. Cumulative data do not support a causal association between bedaquiline exposure and pancreatitis. Pancreatitis will continue to be monitored through routine pharmacovigilance activities.
Myopathy	Myopathy was considered an important potential risk for bedaquiline based on nonclinical findings. Myalgia is listed as an adverse reaction in the SIRTURO SmPC. However, no association between bedaquiline use and muscle damage in humans has been identified. No cases of myopathy were reported during the bedaquiline clinical development program, and no safety signal for myopathy has been identified in the postmarketing setting. Cumulative data do not support a causal association between bedaquiline exposure and myopathy. Myopathy will continue to be monitored through routine pharmacovigilance activities.
Myocardial injury	Myocardial injury was considered an important potential risk for bedaquiline based on nonclinical findings. In Trial C208, the frequencies with which laboratory abnormalities related to myocardial injury occurred in participants with MDR-TB were similar to those in participants treated with bedaquiline and in participants who received placebo. In the STREAM Stage 2 trial, no increased risk of myocardial injury was observed with bedaquiline-containing regimens compared to the comparator regimens. No safety signal related to myocardial injury has been identified in the postmarketing setting. Cumulative data do not support a causal association between bedaquiline exposure and myocardial injury. Myocardial injury will continue to be monitored through routine pharmacovigilance activities.

Safety Concern	Justification for Removal
Missing Information	
Long-term effects of bedaquiline treatment on mortality	Long-term effects of bedaquiline treatment on mortality was considered missing information based on findings from Trial C208 Stage 2, in which a higher incidence of death was observed in the bedaquiline treatment group (10/79 [12.7%]) compared to the placebo group (3/81 [3.7%]), the latter having an unexpectedly low mortality rate based on global reported mortality rates for MDR-TB. All but one of the deaths in the bedaquiline-treated participants occurred after bedaquiline was discontinued; no causal relationship to bedaquiline was identified for any of the deaths. Due to the small sample size at the time of approval, the long-term effects of bedaquline treatment on mortality was considered missing information. However, subsequent data have not confirmed an increased risk of death associated with bedaquiline treatment. A recent review of available mortality data from patients treated with bedaquiline-containing regimens, which included data from the multi-country MDR-TB registry (Study TMC207TBC4002) and the published literature, did not identify an increased risk of mortality associated with bedaquiline treatment. In addition, data from the randomized controlled STREAM Stage 2 trial also showed a similar mortality in bedaquiline- and non-bedaquiline-containing regimens. The totality of data accumulated since bedaquiline approval does not indicate an increased risk of mortality with bedaquiline use, including after treatment discontinuation. Long-term effects of bedaquiline treatment on mortality is no longer considered missing information.
Use in patients using potent inhibitors of drug-metabolizing enzymes	Since the approval of bedaquiline in 2012, extensive research on the potential impact of CYP3A4 inhibitors on bedaquiline exposure has been conducted. In Trial C209, long-term coadministration of bedaquiline and clofazimine (a moderate-to-strong CYP3A4 inhibitor) as part of a combination therapy for up to 24 weeks in MDR-TB patients did not affect bedaquiline exposure. In the STREAM Stage 2 trial, long-term coadministration of bedaquiline as part of a combination therapy and lopinavir/ritonavir (a strong CYP3A4 inhibitor) in RR/MDR-TB participants coinfected with HIV resulted in a 20% increase in bedaquiline exposure at Week 24 (95% CI: -10%, 60%). This finding is supported by modeling and simulation. These findings support that coadministration of bedaquiline and CYP3A4 inhibitors does not have a clinically relevant effect on bedaquiline exposure, and no dose adjustment is needed. This is reflected in Section 4.5 of the SmPC. Use in patients using potent inhibitors of drug-metabolizing enzymes is no longer considered missing information.

Safety Concern	Justification for Removal
Prolonged treatment duration	Data on bedaquiline treatment beyond 24 weeks was limited at the time of bedaquiline approval. The STREAM Stage 2 trial demonstrated that administration of bedaquiline for 40 weeks was generally safe and well tolerated and comparable to non-bedaquiline-containing regimens of 40 weeks' duration or longer. No new risks were identified for either the 28-week or the 40-week bedaquiline-containing regimen in the STREAM Stage 2 trial. Prolonged treatment duration is no longer considered missing information.

SVII.3. Details of Important Identified Risks, Important Potential Risks, and Missing Information

Not applicable.

SVII.3.1. Presentation of Important Identified Risks and Important Potential Risks

Not applicable.

SVII.3.2. Presentation of the Missing Information

Not applicable.

PART II: SAFETY SPECIFICATION

Module SVIII: Summary of the Safety Concerns

Table SVIII.1: Summary of Safety Concerns

Important Identified Risks	None
Important Potential Risks	None
Missing Information	None

PART III: PHARMACOVIGILANCE PLAN (Including Postauthorization Safety Studies)

III.1. Routine Pharmacovigilance Activities Beyond Adverse Reaction Reporting and Signal Detection

Specific Follow-up Questionnaires for Safety Concerns	
Safety Concern	Purpose/Description
Not applicable	

Other Forms of Routine Pharmacovigilance Activities		
Activity	Objective/Description	Milestones
Not applicable		

III.2. Additional Pharmacovigilance Activities

Not applicable

III.3. Summary Table of Additional Pharmacovigilance Activities

Table Part III.1: Ongoing and Planned Additional Pharmacovigilance Activities

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				
Not applicable				
Category 3 - Required additional pharmacovigilance activities				
Not applicable				

PART IV: PLANS FOR POSTAUTHORIZATION EFFICACY STUDIES

Table Part IV.1: Planned and Ongoing Postauthorization Efficacy Studies That Are Conditions of the Marketing Authorization or That Are Specific Obligations

Study Status	Summary of Objectives	Efficacy Uncertainties Addressed	Milestones	Due Dates
Efficacy Studies which are conditions of the marketing authorizations				
Not applicable				
Efficacy studies which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
Not applicable				

PART V: RISK MINIMIZATION MEASURES (Including Evaluation of the Effectiveness of Risk Minimization Activities)

Risk Minimization Plan

V.1. Routine Risk Minimization Measures

Not applicable.

V.2. Additional Risk Minimization Measures

Not applicable.

V.2.1. Removal of Additional Risk Minimization Activities

Activity	Safety Concern(s) Addressed/Rationale for the Removal of Additional Risk Minimization Activity
Not applicable	

V.3. Summary of Risk Minimization Measures and Pharmacovigilance Activities

Not applicable.

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of Risk Management Plan for SIRTURO (Bedaquiline)

This is a summary of the risk management plan (RMP) for SIRTURO. The RMP details important risks of SIRTURO, how these risks can be minimized, and how more information will be obtained about SIRTURO's risks and uncertainties (missing information).

SIRTURO's summary of product characteristics (SmPC) and its Package Leaflet (PL) give essential information to healthcare professionals and patients on how SIRTURO should be used.

This summary of the RMP for SIRTURO should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of SIRTURO's RMP.

I. The Medicine and What it is Used For

SIRTURO is authorized for use as part of an appropriate combination regimen in adult and pediatric patients (5 years to less than 18 years of age and weighing at least 15 kg) with pulmonary tuberculosis (TB) due to *Mycobacterium tuberculosis* resistant to at least rifampicin and isoniazid (see SmPC for the full indication). It contains bedaquiline as the active substance and it is given as oral tablets (20 mg or 100 mg of bedaquiline).

Further information about the evaluation of SIRTURO’s benefits can be found in SIRTURO’s EPAR, including in its plain-language summary, available on the European Medicines Agency (EMA) website, under the medicine’s webpage:

https://www.ema.europa.eu/en/medicines/human/EPAR/sirturo

II. Risks Associated with the Medicine and Activities to Minimize or Further Characterize the Risks

Important risks of SIRTURO, together with measures to minimize such risks and the proposed studies for learning more about SIRTURO's risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the PL and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine’s packaging;
- The authorized pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine’s legal status — the way a medicine is supplied to the patient (eg, with or without prescription) can help to minimize its risks.

Together, these measures constitute routine risk minimization measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed, including Periodic Safety Update Report assessment, so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

II.A. List of Important Risks and Missing Information

Important risks of SIRTURO are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of SIRTURO. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the medicine).

List of Important Risks and Missing Information	
Important identified risks	None
Important potential risks	None
Missing information	None

II.B. Summary of Important Risks

There are no important identified risks, important potential risks, or missing information for SIRTURO.

II.C. Postauthorization Development Plan

II.C.1. Studies Which are Conditions of the Marketing Authorization

There are no studies which are conditions of the marketing authorization or specific obligations of SIRTURO.

II.C.2. Other Studies in Postauthorization Development Plan

Not applicable.

PART VII: ANNEXES

Table of Contents

Annex 4: Specific Adverse Drug Reaction Follow-up Forms

Not applicable

Annex 6: Details of Proposed Additional Risk Minimization Activities (if applicable)

Not applicable