EU Risk Management Plan for: Delamanid

RMP version to be assessed as part of this application:

RMP Version number: 5.3

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Date of Final Sign Off: 29 Jan 2025

Rationale for submitting an updated RMP: Modification of the data analysis under additional pharmacovigilance activities in Part III.2 of the Specific Obligation 0002 (SOB0002) according to the recommendations made by PRAC in the Assessment Report of the Annual Renewal #11 (EMEA/H/C/002552/R/0076). SOB0002 is updated to present an analysis with the publicly available data of the endTB Study (Protocol Number NCT02754); in addition, the publicly available data of BEAT-TB Study (Protocol Number NCT04062201) will be discussed and submitted once available. The due date of SOB0002 is Q3 2026. All risks in this RMP remain unchanged.

Summary of significant changes in this RMP:

RMP Part/ Module/ Annex	Summary of Changes
Part 1: Product(s) Overview	None
Part II / Module SI: Epidemiology of the Indication(s) and target population(s)	None
Part II / Module SII - Non-clinical part of the safety specification	None
Part II / Module SIII - Clinical trial exposure	None
Part II / Module SIV - Populations not studied in clinical trials	None
Part II / Module SV - Postauthorisation experience	None
Part II / Module SVI - Additional EU requirements for the safety specification	None
Part II / Module SVII - Identified and potential risks	None
Part II / Module SVIII - Summary of the safety concerns	None
Part III: Pharmacovigilance Plan (including postauthorisation safety studies)	III.2/III.3: Modification of SOB002 as recommended by PRAC in Assessment Report of Annual Renewal #11 (EMEA/H/C/002552/R/0076). The data of the endTB Study will be analysed based on the publicly available data. The BEAT-TB Study is being added; and the publicly available results are to be discussed and submitted once available. The due date of SOB002 is Q3 2026.
Part IV: Plans for postauthorisation efficacy studies	None
Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)	V.3: The description of the additional pharmacovigilance activities for the safety concerns listed in table 5.3-1 were updated to reflect that the analysis of the endTB Study and the discussion of the BEAT-TB Study will be done based on publicly available data.
Part VI: Summary of the risk management plan	Modification of SOB002 as recommended by PRAC in Assessment Report of Annual Renewal #11 (EMEA/H/C/002552/R/0076). The data of the endTB Study will be analysed based on the publicly available data. The BEAT-TB Study is being added; and the publicly available results are to be discussed and submitted once available. The due date of SOB0002 is Q3 2026.
Part VII: Annexes	Annex 2: Modification of SOB002 as recommended by PRAC in Assessment Report of Annual Renewal #11 (EMEA/H/C/002552/R/0076). The data of the endTB Study will be analyzed based on the publicly available data. The BEAT-TB Study is being added; and the publicly available results are to be discussed and submitted once available. The due date of SOB0002 is Q3 2026.

Details of the currently approved RMP:

- Version number: 5.1
- Approved with procedure: EMEA/H/C/002552/R/0070
- Date of approval: 14 Dec 2023

QPPV name: Emiel van Heumen

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorisation holder´s QPPV. The electronic signature is available on file.

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List of In-text Tables

List of Abbreviations, Acronyms, and Definition of Terms

Abbreviation/Acronym	Definition
ACR	Appropriate Combination Regimen
ADR	Adverse Drug Reaction
AE	Adverse Event
AIDS	Acquired Immuno-deficiency Syndrome
APTT	Activated Partial Thromboplastin Time
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area Under the Concentration Time Curve
AV	Atrioventricular
BID	Two times a day
CD	Cell differentiation
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CU	Compassionate Use
CYP	Cytochrome p450
DIC	Disseminated Intravascular Coagulopathy
DST	Drug Susceptibility Testing
DOTS	Directly Observed Therapy Short-Course
EBA	Early Bactericidal Activity
ECG	Electrocardiogram
EEA	European Economic Area
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
EVDAS	EudraVigilance data analysis system
GDG	Guideline Development Group (WHO)
HIV	Human Immunodeficiency Virus
HLT	High Level Term
HPMPC	Hydromellose phthalate
ICH	International Council for Harmonisation
IMP	Investigational Medicinal Product
INN	International Nonproprietary Name
ISS	Investigator sponsored study
MAH	Marketing Authorization Holder
MedDRA	Medical Dictionary for Regulatory Activities
MDR-TB	Multi Drug Resistant Tuberculosis
msec (ms)	Millisecond
MTB	Mycobacterium Tuberculosis
N/A	Not Applicable
NIS	Non-interventional study
OBR	Optimised Background Regimen
OR	Odds ratio
PAES	Post Authorisation Efficacy Study
PASS	Post Authorisation Safety Study
PIP	Paediatric Investigation Plan
PL	Package Leaflet
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	Periodic Safety Update Report
PT	Preferred Term
QD	Once a day

Abbreviation/Acronym	Definition
QPPV	Qualified Person Responsible for Pharmacovigilance in the EU
QTcF	Corrected QT interval - Fridericia's Correction Formula
RBC	Red Blood Cell
RMP	Risk Management Plan
RR-TB	Rifampicin-Resistant Tuberculosis
SAE	Serious adverse event
SCC	Sputum Culture Conversion
SMQ	Standardised MedDRA Queries
SOB	Specific Obligation
SOC	System Organ Class
SmPC	Summary of Product Characteristics
TB	Tuberculosis
TEAEs	Treatment Emergent Adverse Events
TK	Toxicokinetic
TTP	Thrombotic Thrombocytopenic Purpura
WBC	White Blood Cell
WHO	World Health Organization
XDR-TB	Extensively Drug Resistant Tuberculosis

1 PART I: PRODUCT(S) OVERVIEW

Table 1-1 Active Substance Information	
Active substance(s) (INN or common name)	Delamanid, OPC-67683 (hereafter referred to as "Delamanid")
Pharmacotherapeutic group(s) (ATC code):	Antimycobacterial (J04AK06)
Name of marketing authorisation	Otsuka Novel Products GmbH Erika-Mann-Strasse 21 80636 Munich Germany
Medicinal products to which this RMP refers:	1
Invented name of the product in the European Economic Area (EEA)	Deltyba
Marketing authorisation procedure	Centralised
Brief description of the product	Chemical class: Delamanid is a nitrodihydroimidazo-oxazole derivative developed by the Otsuka Pharmaceutical Co., Ltd.
	Summary of mode of action: The pharmacological mode of action of delamanid involves inhibition of the synthesis of the mycobacterial cell wall components, methoxy-mycolic and keto-mycolic acid. The identified metabolites of delamanid do not show anti-mycobacterial activity. Delamanid has been confirmed to have mycobacteria-specific antibacterial activity in vitro and potent anti-TB activity in vivo by oral administration. Delamanid shows potent activity in vitro against pansensitive, drug-resistant and multi-drug-resistant strains of *Mycobacterium tuberculosis* (MTB). Delamanid also has potent in vitro activity against intracellular mycobacteria and both growing and hypoxia-induced dormant strains. Delamanid has no in vitro activity against bacterial species other than mycobacteria. Clinical studies in drug-sensitive TB patients demonstrated robust early bactericidal activity (EBA) of delamanid during the first two weeks of treatment. When co-administered with an optimised background regimen (OBR) for the treatment of multi drug resistant tuberculosis (MDR-TB) patients receiving delamanid-containing regimens experienced an approximately 50% increase in sputum culture conversion (SCC) from growth of MTB to no growth over the first 2 months of treatment compared to those receiving OBR plus placebo. Delamanid does not show cross-resistance with any of the currently used anti-TB drugs except pretomanid. In vitro studies have shown cross-resistance with pretomanid. Bioavailability of delamanid is 2-fold higher when taken with a standard meal compared to ingestion under fasting conditions. Delamanid extensively binds to plasma proteins and has a large volume of distribution. Metabolism of delamanid primarily takes place in plasma by albumin and to a less extent by Cytochrome P450 (CYP) enzymes. Delamanid has an

Table 1-1	**Active Substance Information**
	elimination half-life of about 38 hours. Delamanid and metabolites are excreted in faeces, and not significantly via kidneys.
	Important information about its composition: Each film-coated tablet contains 50 mg delamanid. Excipient with known effect: Each film-coated tablet contains 100 mg lactose (as monohydrate). Other Excipients: Tablet core Hypromellose phthalate (HPMPC) Povidone all-rac-α-Tocopherol Cellulose, microcrystalline Sodium starch glycolate (type A) Carmellose calcium Silica, colloidal hydrated Magnesium stearate Film coating Hypromellose Macrogol 8000 Titanium dioxide Talc Iron oxide yellow (E172)
	Important information about its composition: Each dispersible tablet contains 25 mg delamanid. Other Excipients: -Hypromellose phthalate - Povidone (K-25) - all-rac-α-Tocopherol - Mannitol - Crospovidone - Sucralose - Silica, colloidal hydrated - Cherry micron OT-22685 - Calcium stearate
eCTD link to the proposed product information, as appropriate	See eCTD Module 1 / section 1.3.1/ ema-combined-h-2552-en
Indications	Current: Deltyba is indicated for use as part of an appropriate combination regimen for pulmonary multi-drug resistant tuberculosis (MDR-TB) in adults, adolescents, children, and infants with a body weight of at least (≥) 10 kg when an effective treatment regimen cannot otherwise be composed for reasons of resistance or tolerability. Consideration should be given to official guidance on the appropriate use of antibacterial agents.
	Proposed (if applicable): NA

Table 1-1 Active Substance Information	
Dosage in the EEA	**Posology** Treatment with delamanid should be initiated and monitored by a physician experienced in the management of multidrug-resistant *Mycobacterium tuberculosis*. Delamanid must always be administered as part of an appropriate combination regimen for the treatment of multidrug-resistant tuberculosis. Treatment with an appropriate combination regimen should continue after completion of the 24-week delamanid treatment period according to world health organisation (WHO) guidelines. It is recommended that delamanid is administered by directly observed therapy (DOT). The recommended dose for adults is 100 mg twice daily for 24 weeks Paediatric population Adolescents, children, and infants with a body weight of: • ≥50 kg (film-coated tablets): the recommended dose is 100 mg twice daily for 24 weeks • ≥30 and < 50 kg (film-coated tablets): the recommended dose is 50 mg twice daily for 24 weeks • ≥20 and < 30 kg (dispersible tablets): the recommended dose is 50 mg in the morning (QAM) + 25 mg in the evening (QPM) for 24 weeks • ≥10 and < 20 kg (dispersible tablets): the recommended dose is 25 mg twice daily for 24 weeks Treatment duration: On a case-by-case basis a longer duration of treatment beyond the 24 weeks may be considered for patients treated by Deltyba 50mg film-coated tablets. Elderly patients (>65 years of age) No data are available in the elderly. Renal impairment No dose adjustment is considered necessary in patients with mild or moderate renal impairment. There are no data on the use of delamanid in patients with severe renal impairment and its use is not recommended. Hepatic impairment No dose adjustment is considered necessary in patients with mild hepatic impairment. Delamanid is not recommended in patients with moderate to severe hepatic impairment. Method of administration For oral use. Delamanid should be taken with food
Pharmaceutical Form(s)	Film-coated tablet
	Dispersible tablet

Table 1-1 Active Substance Information	
Pharmaceutical Strength(s)	Film-coated tablet - 50 mg
	Dispersible tablet - 25 mg
Is/will the product subject to additional monitoring in the EU?	Yes

2 PART II: SAFETY SPECIFICATION

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

Indication: Pulmonary MDR-TB

Deltyba is indicated for use as part of an appropriate combination regimen for pulmonary MDR-TB in adults, adolescents, children, and infants with a body weight of at least (≥) 10 kg when an effective treatment regimen cannot otherwise be composed for reasons of resistance or tolerability. Consideration should be given to official guidance on the appropriate use of antibacterial agents.

Brand Names of Concerned Products: Deltyba

Incidence and Prevalence

According to the 2022 WHO Global Tuberculosis Report, in 2021, there were an estimated 10.6 million new (incident) TB cases worldwide (range, 9.9-11.0 million), of which 56.5% were male, 32.5% female; 11% were among children (age <15 years old).[1] People living with human immunodeficiency virus (HIV) made up 6.7% of all TB cases, and the HIV-associated TB is highest in the WHO African Region, with a staggering 86% of TB patients having a positive HIV result. Most TB cases in 2021 occurred in the WHO South-East Asia Region (45%), the WHO African Region (23%) and the WHO Western Pacific Region (18%); smaller proportions of cases occurred in the WHO Eastern Mediterranean Region (8.1%), the WHO Region of the Americas (2.9%) and the WHO European Region (2.2%). The severity of national TB epidemics in terms of the annual number of incident TB cases relative to population size (the incidence rate) varied widely among countries in 2021 (from less than five to more than 500 new and relapse cases per 100 000 population per year). There were under 10 incident cases per 100,000 population in most high-income countries, 150-400 in most of the 30 high TB burden countries, and above 500 in a few countries including the Central African Republic, Gabon, Lesotho, the Philippines and South Africa. The 30 high TB burden countries accounted for 87% of all cases worldwide. Eight countries accounted for more than two thirds of the new cases: India (28%), Indonesia (9.2%), China (7.4%), the Philippines

(7.0%), Pakistan (5.8%), Nigeria (4.4%), Bangladesh (3.6%) and the Democratic Republic of the Congo (2.9%).

Globally, the estimated number of people who developed MDR-TB or RR-TB (MDR/RR-TB) in 2021 was 450,000 incident cases (range 399,000–501,000). In 2021, the estimated proportion of people with TB who had MDR/RR-TB was 3.6% (2.7–4.4%) among new cases and 18% (11–26%) among those previously treated. Three countries share the largest burden of MDR/RR-TB cases: India (26%), the Russian Federation (8.5%), and Pakistan (7.9%).[1]

Globally in 2021, 71% of people (2.4/3.4 million) diagnosed with bacteriologically confirmed pulmonary TB were tested for rifampicin resistance. Among those tested, 141,953 cases of MDR/RR-TB and 25,038 cases of pre-XDR-TB or XDR-TB were detected, giving a combined total of 166,991.[1]

Demographics of the Target Populations

Globally in 2019, male to female ratio was 1.6. The ratio varied by WHO region from 1.1 in the WHO Eastern Mediterranean Region to 2.0 in the European and Western Pacific regions. Among children, the ratio is closer to 1.[2] In 2022 edition of WHO report, there were an estimated 450,000 (range 399,000-501,000) incident cases of MDR/RR-TB in 2021; An estimated 78% of MDR-TB was RR-TB. Geographically, three countries made up 50% of these cases: India (26%), the Russian Federation (8.5%), and Pakistan (7.9%).[1]

Risk Factors for the Disease

The WHO recognizes the importance of several risk factors for the development of TB. In 2017, the WHO created a monitoring framework of 14 indicators associated with increased TB incidence. These include health service indicator (coverage of essential services; current health expenditure per capita; population proportion with large household expenditures on health), prevalence of comorbidities (HIV; smoking; diabetes; alcohol use disorder; undernourishment), and economic indicators (population proportions living below international poverty line, covered by social protection, reliance on clean fuels and technology, or living in slums; Gini index for inequality; gross domestic product). In particular, the strongest medical risk factors that lead to the development of active infection are HIV, diabetes, smoking, alcohol use, and poverty.[1]

A global systematic review and meta-analysis has shown that primary risk factors for MDR-TB relate to TB history and treatment. The strongest factor was the presence of previous TB treatment (Odds ratio (OR) 7.24, 95% CI 4.06-12.89).[3] This was supported

by a systematic review of published reports of risk factors associated with MDR-TB suggests that prior TB treatment is the strongest determinant of MDR-TB in Europe.[4] The other most potent factors also related to this category: non-completion and failure of TB treatment (OR 5.60, 95% CI 3.36-9.32), non-adherence (OR 4.50, 95% CI 1.71-11.82), and presence of previous TB disease (OR 4.42, 95% CI 1.46-13.37). In addition, particular patient characteristics increase the likelihood of MDR TB. These include unemployment (OR 3.00, 95% CI 1.69-5.30) and lack of health insurance coverage (OR 1.99, 95% CI 1.12-3.54). Finally, clinical characteristics are significant risk factors: smear positive (OR 1.72, 95% CI 1.40-2.12), Mantoux test positive (OR 3.38, 95% CI 1.45-7.89), lung cavity (OR 1.92, 95% CI 1.02-3.62), and Beijing strain of TB (OR 5.58, 95% CI 1.66-18.76).[3]

Childhood TB disease is very different from adult TB disease. These differences include time from exposure to disease onset, epidemiologic differences in contagiousness, pathophysiology, bacillary load, and clinical and radiographic manifestations.[5] Most cases of childhood TB have a short period between exposure to a contagious individual and manifestation of symptoms. Differences in the pathophysiology and clinical presentation of TB in children make diagnosis more challenging in children than in adults and definitions of latent infection and active disease are not as clear.[6] Children are also at a much higher risk of progression to active disease than adults.[7] This risk is greatest for infants and children under 2 years of age.[7,8] Overall, the risk of disease is highest in infants and individuals in their late teens; the lowest risk in children is between ages 5 and 10 years, the so-called “safe” school years.[8,9]

Overall, the lifetime risk of progression from infection to active disease is 5% to 20% for immunocompetent older children and 40% to 50% for children in the first 2 years of life.[8] Adolescents have a slightly higher risk of disease progression than adults.[10,11] The age-specific risk of developing TB following MTB infection is shown in Table 2.1-1.[8]

Table 2.1-1 SI-1: Age-specific Risks for Developing Tuberculosis after Primary Infection

Age at Primary Infection	Disease Status	Proportion (%) in Immunocompetent Children
<2 years	No Disease	50-70
	Pulmonary Disease	10-30
	Tuberculosis Meningitis or Miliary Disease	2-10

Table 2.1-1 SI-1: Age-specific Risks for Developing Tuberculosis after Primary Infection		
Age at Primary Infection	**Disease Status**	**Proportion (%) in Immunocompetent Children**
2 to 10 years	No Disease	95-98
	Pulmonary Disease	2-5
	Tuberculosis Meningitis or Miliary Disease	<0.5
>10 years	No Disease	80-90
	Pulmonary Disease	10-20
	Tuberculosis Meningitis or Miliary Disease	<0.5

The extent or severity of the disease in patients older than 14 years is usually defined by the presence of cavities or bilateral disease on chest radiography or smear positivity. In children under 15 years, severe disease includes the presence of cavities, bilateral disease on chest radiography, and disseminated forms the most formidable of which tuberculosis meningitis.[12] Those at greatest risk of severe disease and poor outcome are children under 3 years, children living with HIV, or severely malnourished children. These groups pose the greatest challenge for clinical diagnosis.[13]

Young children acquire MDR-TB mainly through transmission from close contact with an infectious adult or adolescent with MDR-TB. Treatment initiation is often based on bacteriological confirmation and drug susceptibility testing, but this is challenging and of low yield, especially in young children. Treatment can be started without bacteriological confirmation in children in whom MDR-TB is strongly suspected.[5]

Main Treatment Options

WHO guidelines on treatment of drug resistant tuberculosis (2019 update) are generally followed to treat MDR-TB patients. WHO recommends that all patients with TB - children or adults - diagnosed with strains shown to be resistant to rifampicin be placed on an MDR-TB treatment regimen. Conventional MDR-TB regimens for adults and children include the use of at least 4 effective anti-TB medicines. In addition, elective partial resection (lobectomy or wedge resection) may be used alongside a recommended MDR-TB treatment regimen.[14]

Table 2.1-2 shows the antitubercular agents by group. In MDR/RR-TB patients on longer regimens, all three Group A agents and at least one Group B agent must be included to ensure that treatment starts with at least four TB agents likely to be effective, and that at least three agents are included for the rest of treatment after bedaquiline is stopped. If only one or two Group A agents are used, both Group B agents are to be included. If the

regimen cannot be composed with agents from Groups A and B alone, Group C agents are added to complete it (conditional recommendation, very low certainty in the estimates of effect). The 2018 individual patient data of longer regimens was mostly composed of adult patients, with only 181 of the 13,104 (1.4%) cases being below 15 years of age. Notwithstanding, WHO recommendations on longer MDR-TB regimens apply to children as well as adults. Most medicines used in longer regimens have been a part of MDR-TB regimens for many years, in similar combinations for both adults and children. The WHO Guideline Development Group (GDG) recommended the use of bedaquiline in children down to 6 years of age and delamanid down to 3 years of age. Children usually tolerate second-line treatment well and treatment outcomes are generally favourable, but treatment can be challenging, with frequent permanent hearing loss due to side-effects of injectable medicines. Children should benefit from shorter, safer, effective, and tolerable (injectable-free) regimens for MDR-TB. In children, the use of amikacin or streptomycin should be resorted to only when other options are not possible, when testing confirms susceptibility and the possibility to monitor for ototoxicity and nephrotoxicity is present. Shortening the total treatment duration to less than 18 months may be considered in the case of children without severe disease.[2]

Table 2.1-2 SI-2: Antitubercular Agents by Group

Groups & steps	Medicine	
Group A: Include all three medicines	levofloxacin OR moxifloxacin	Lfx Mfx
	bedaquiline	Bdq
	linezolid	Lzd
Group B: Add one or both medicines	clofazimine	Cfz
	cycloserine OR terizidone	Cs Trd
Group C: Add to complete the regimen and when medicines from Groups A and B cannot be used (Medicines in Group C are ranked by decreasing order of usual preference for use subject to other considerations)	ethambutol	E
	delamanid	Dlm
	pyrazinamide	Z
	imipenem-cilastatin OR meropenem	Ipm-Cln Mpm
	amikacin (OR streptomycin)	Am (S)
	ethionamide OR prothionamide	Eto Pto
	p-aminosalicylic acid	PAS

Mortality, Morbidity, and Natural History

TB remains the 2nd leading cause of death from a single infectious agent after COVID-19 and the 13th leading cause of death worldwide. As the cause of TB deaths among HIV-positive people is classified as HIV, death estimates are reported separately for

HIV-positive and HIV-negative. An estimated 1.4 million (range, 1.3-1.5 million) deaths occurred in HIV-negative people in 2021, with a further 187,000 (range, 158,000-218,000) deaths from TB in HIV-positive people.[1]

Most of the estimated increase in TB deaths globally was accounted for by four countries: India, Indonesia, Myanmar and the Philippines. The global number of deaths officially classified as caused by TB in 2021 (1.4 million) was more than double the number caused by HIV/AIDs (0.65 million), and TB mortality has been much more severely impacted by the COVID-19 pandemic than HIV/AIDs.[1]

Globally, 54% of HIV-negative were adult male, 32% were adult female, and 14% were children. Among HIV-positive cases, 51% cases were adult men, 38% were women, and 11% were children. Of note, given children make 11% of total global cases, deaths among children are disproportionate and suggestive of poor access to diagnosis and treatment.[1]

Most of these deaths could have been prevented with early diagnosis and appropriate treatment, as demonstrated in 2017 when, among those whose TB was detected, reported and treated, the global success rate was 85%. In high-income countries with universal healthcare, the proportion of deaths from TB can be as less than 5%. Between 2000 and 2018, TB treatment along prevented an estimated 48 million deaths among HIV-negative people and, when added to ART, an addition 9.8 million among HIV-positive people.[14]

Though younger children are more vulnerable to severe forms of TB disease, there is a dearth of age-disaggregated estimates of paediatric tuberculosis mortality. Furthermore, Official estimates of under-5 child mortality do not include tuberculosis. However, a global estimate was recently estimated in a mathematical modelling study. The authors estimated that 239,000 (uncertainty interval [UI] 194,000-298,000) children under 15 died from TB worldwide in 2015 and 80% (191,000, UI 132,000-257,000) were under 5. The majority of these deaths (70%; 182,000, UI 140,000-239,000) were in the WHO Southeast Asia and Africa Regions. The proportion among children with HIV infections was 17% (39,000, UI 23,000-73,000). A staggering 96% (230,000, UI 185,000-289,000) of these paediatric TB deaths were in children not receiving TB treatment.[15]

Important Comorbidities

Several important comorbidities in TB patients have been identified in published literature. HIV is by far the one of the most important comorbidities identified in TB patients. It has been estimated that the risk of TB reactivation is 20-fold in those infected with HIV. Similarly, TB has been shown to worsen progression of HIV

immunosuppression. There is increasing evidence of the pathophysiology behind this relationship. The dramatic decreased production of interferon gamma and $CD4^+$ T-lymphocytes during an HIV infection leads to reactivation or reinfection by *M. tuberculosis*. Likewise, M. tuberculosis targets alveolar macrophages, up-regulating HIV replication in these cells.[16] The combined effect of this synergy poses a therapeutic challenge for co-infected patients.

With HIV co-infection among MDR-TB patients, the picture for treatment and outcomes worsens dramatically. A meta-analysis of 23 studies showed that overall mortality was 33.5% (95% CI 24.5-42.6%). Adult mortality varied from 1.8% to 87.8% (pooled proportion 38%, 95% CI 28-48.1%). Children had less mortality, varying between 3.2 and 19% (pooled proportion 11.5%, 95% CI 5.9-17.1%). Still, these mortality rates are four times higher than reported in HIV-negative adult populations and double that in HIV-negative children. Treatment success also differed between adults and children. Overall pooled proportion of success was 56.9% (95% CI 46.2-67.6%). Adults ranged 12.2-98.2% (pooled proportion 49.9%, 95% CI 38.5-61.2%); in children success overall was noteworthy at 83.4% (95% CI 74.8-92%). Furthermore, there were low rates of relapse in both adults (1.2%, 95% CI 0.4-2%) and children (0.7%, 95% CI 0-2.4%) as well as failing treatment (adults 4.9%, 95% CI 3.2-6.4%; children 1.8%, 95% CI 0-4.2%). This is consistent with previous reports that support better success rates with access and adherence to ART and MDR TB treatment.[17]

Diabetes is a significant risk factor for TB activation. A recent meta-analysis showed that the increased odds of having active TB, ranging from 1.55 (95% CI 1.39-1.72) in retrospective studies to 3.59 (95% CI 2.25-5.73) in prospective studies. The association was potentiated by microbiological ascertainment for TB (OR 3.03, 95% CI 2.31-3.98), blood testing for diabetes (OR 3.10, 95% CI 2.02-4.74) and uncontrolled diabetes (OR 3.30, 95% CI 2.10-5.14). These factors suggest a causal relationship between TB activation and diabetes.[18]

Depression is frequently associated with chronic physical illnesses and has been linked with a range of adverse clinical outcomes.[19] In many parts of the world, TB is a debilitating, stigmatised communicable disease requiring complex and aggressive treatment.[19] Studies have revealed a bidirectional relationship between depression and TB. Depression is independently associated with increased morbidity, mortality, drug resistance, risk of TB reactivation, and community TB transmission. The depression-TB syndemic follows a biopsychosocial mechanism, including factors like inflammatory cascade, HPA axis dysregulation and psychosocial factors like perceived stigma and

treatment non-adherence; ergo, proper treatment requires an integrative approach for early diagnosis and management of depression in TB.[20]

Studies also report high prevalence rates of psychiatric comorbidity among patients with drug-resistant TB, in particular, and the prevalence of depression significantly correlates with severity and duration of the disease.[21] Although the causal relationships between mental disorders and TB are complex, severe mental disorders are associated with a high risk of TB acquisition and transmission, and also with poorer adherence to anti-TB treatment.[21] In a study conducted in Nigeria, which has the second highest TB disease burden in Africa and ranks fifth among the 22 highest TB burden countries in the world, the prevalence of depression among TB patients (n=88) visiting a DOTS centre was 45.5% as compared with 13.4% of non-TB infected controls (n=81).[22] Elderly patients and those with extensive disease of long duration were significantly more likely to be depressed as compared with other TB patients.[22]

Other comorbidities such as alcoholism, smoking and intravenous drug abuse can also increase the risk of progression from latent TB to active TB.[21]

Monitoring and describing adverse effects of multidrug anti-TB therapy in children is challenging; young children often cannot articulate pain, nausea, vertigo, peripheral neuropathy, anxiety, or confusion. Rashes are common (frequently resulting from various aetiologies) and testing hearing, and vision is more difficult than in adults. In addition to life-threatening and unpleasant effects, TB may cause alterations in growth and neurocognitive development. Children treated for MDR-TB are usually on multiple medications and determining the drug responsible for an adverse effect can be difficult.[23]

2.2 Module SII: Nonclinical Part of the Safety Specification

Table 2.2-1 SII-1: Summary of Key Safety Findings from Nonclinical Studies and Relevance to Human Usage

Key safety findings (from nonclinical studies)	Relevance to human usage
Repeat dose toxicity **Decreased body weight and food consumption** A series of 2-week repeated-dose oral toxicity studies in dogs revealed decreased body weight and food consumption. A 13-week repeated-dose oral toxicity study in dogs revealed decreased body weight and food consumption at 30 mg/kg and higher. Suppressed body weight gain was observed in the males and females of the 30 mg/kg group in a 39-week repeated-dose oral toxicity study in dogs. In repeated-dose oral toxicity studies in rabbits, decreases in body weight and food consumption were observed.	Nutritional status is reduced in patients with TB. Malnutrition can lead to secondary immunodeficiency and subsequent infections. Malnourished TB patients have delayed recovery and higher mortality rates. Weight loss during TB treatment is an important risk factor for drug-induced hepatotoxicity. Normally the nutritional status of patients improves during anti-TB chemotherapy. Nutritional supplementation is recommended. Additional weight loss and reduced food consumption, if they were an adverse effect of delamanid, would have the potential to impair the therapeutic effect and to put patients at additional risk.

Table 2.2-1 SII-1: Summary of Key Safety Findings from Nonclinical Studies and Relevance to Human Usage

Key safety findings (from nonclinical studies)	Relevance to human usage
	However, this has no relevance to human use at therapeutic dose levels since changes occurred at toxic doses and changes in body weight at toxic doses are expected in animal studies.
Whitish stool A series of 2-week repeated-dose oral toxicity studies in dogs revealed whitish stool at 50 mg/kg and higher. In a safety pharmacology study with rats, where delamanid was orally administered at a dose of 1,000 mg/kg, whitish stools were observed. Whitish stool was considered to be delamanid spray-dried powder not absorbed in the intestine. No hepatotoxicity was observed in dogs or rats.	These findings were not considered to represent a safety concern, and whitish stools appear to be related to unabsorbed delamanid material, i.e. no relevance to human use.
Increased haematopoiesis; decreased RBC count, haemoglobin, and haematocrit; anaemia A 13-week repeated-dose oral toxicity study in dogs revealed increased haematopoiesis of bone marrow and extra medullary haematopoiesis in the spleen, liver, and kidney, as well as decreased red blood cells (RBC), haemoglobin, and haematocrit (also platelets and white blood cells (WBC)), all at 100 mg/kg. In all 3 repeated dose toxicokinetic (TK) studies in rabbits, anaemia was observed at 30 mg/kg and 100 mg/kg. Anaemia occurred secondary to haemorrhage which was caused by marked prolongation of blood coagulation time.	Anaemia is a common haematological abnormality in patients with TB although usually mild. Nutritional deficiency can increase the severity of anaemia. TB associated anaemia usually resolves with anti-TB treatment. Increased haematopoiesis may occur during recovery from anaemia. Anaemia however occurred secondary to haemorrhage which was caused by marked prolongation of blood coagulation time - discussed below.
Effects on blood coagulation: prolongation of prothrombin time (PT) and activated partial thromboplastin time (APTT), decreased platelet count, haemorrhage In dogs, decreased platelets and evidence of haemorrhagic bleeding were observed at repeat dose administration of 100 mg/kg delamanid for 13 weeks. In rabbits, prolongation of PT and APTT and evidence of haemorrhagic bleeding were observed at doses of ≥30 mg/kg; evidence of haemorrhage was observed in pregnant dams at doses of ≥10 mg/kg. Similar findings of haemorrhage and prolongation of PT and APTT were noted in mice and rats at doses of 300 mg/kg. Prolongation of PT and/or APTT were accompanied by decreases in the levels of vitamin K dependent coagulation factors in rabbits. In addition, administration of vitamin K ameliorated the prolongation of PT and ameliorated the decrease in coagulation factors: In repeated-dose TK studies in rabbits, prolongation of PT and APTT were observed. The effects of delamanid on blood coagulation were further investigated by single and 4-day repeated oral dosing in female rabbits. Prolongation of PT and/or APTT was accompanied by decreases in the levels of vitamin K dependent blood coagulation factors. In another similar study, intravenous administration of	Hypocoagulopathy is a known feature of TB and particularly during anti-TB treatments. Prolongation of PT and APTT are signs of impaired plasmatic coagulation. This clotting disorder is known to be associated with vitamin K deficiency. Disseminated Intravascular Coagulopathy (DIC) can also occur in TB patients, sometimes attributed to rifampicin. This condition includes findings of prolonged PT and APTT and thrombocytopenia as well. DIC is a life-threatening condition but can sometimes take a subclinical course. Thrombocytopenia in TB can occur due to bone marrow suppression, DIC, Thrombotic Thrombocytopenic Purpura (TTP), due to immune-mediated platelet destruction, or as a side effect of anti-TB therapy (rifampicin). TTP is a rare condition with thrombocytopenia but also potentially fatal.

Table 2.2-1 SII-1: Summary of Key Safety Findings from Nonclinical Studies and Relevance to Human Usage

Key safety findings (from nonclinical studies)	Relevance to human usage
vitamin K completely inhibited the prolongation of PT and reduced the amount of decrease in the levels of vitamin K-dependent coagulation factors in the single-dose test and produced early recovery of the prolonged PT and of the decreased factors in the 3-day repeated dosing test. The effect of daily administration of delamanid on blood coagulation in mice was observed after 4 weeks of administration, although the extent was slight; this was considered a consequence of decreased activity of vitamin K dependent coagulation factors. In a 24-week study in male mice, effects on coagulation parameters were completely counteracted by vitamin K supplementation. In a 13-week repeated-dose oral toxicity study in dogs, changes observed at 100 mg/kg included decreased platelet count. In a 2-week repeated-dose oral toxicity study in female rabbits, haemorrhage in various tissues was observed in one dead animal in the 30 mg/kg group and in the 100 mg/kg group. In a 2-week repeated-dose oral toxicity study in male rabbits, haemorrhage was observed in various tissues in both, the 30 and 100 mg/kg groups. In a rabbit study for reproductive and developmental toxicity, slight haemorrhagic changes in dams were noted at a dose of 10 mg/kg.	Both the plasmatic and cellular coagulopathy predispose to haemorrhages. DIC and TTP are severe conditions and should be ruled out to be the cause of coagulation and bleeding disorders in patients treated with delamanid. Haemorrhages may be acute conditions depending on the site and severity of bleeding. Any bleeding, even occult bleedings into feces or urine may aggravate existing anaemia. It should be noted, however, that the effects on coagulation were limited to high doses in toxicology studies and based thereon no relevance to human use has been identified.
Effect on QT interval In a 39-week repeat-dose oral toxicity study in male dogs at 3 and 30 mg/kg/day and in females at 30 mg/kg/day, prolonged QT interval and corrected QT interval (QTc) were observed in the sixth week of the dosing period and thereafter.	QT interval prolongation has been confirmed as risk during clinical trials.
Protein binding of delamanid to serum ^{14}C-Delamanid extensively binds to isolated plasma proteins and most extensively (>97%) to mouse, rat, dog, rabbit, and human serum albumin and human lipoprotein. The primary metabolites DM-6704, DM-6705, and DM-6706 extensively (>97.4%) bind to mouse, rat, rabbit, dog, and human serum proteins.	TB is associated with decreased levels of serum albumin because of inflammation and malnutrition. Hypoalbuminemia is known to be a negative prognostic factor in general and also in TB patients. Hypoalbuminemia is also related to drug induced hepatotoxicity. Hypoalbuminemia could affect the biodisposition and metabolism of delamanid in TB patients. Changes in protein binding (affecting the free fraction of the drug and metabolites) may occur with hypoalbuminemia.
Metabolism of delamanid The metabolism of delamanid has been investigated both in vivo and in vitro. Delamanid is primarily metabolized into DM-6705 by albumin and to a less extent by CYP1A1 and CYP3A4. DM-6705 appears to be further metabolized to form DM-6704 and DM-6706.	Hypoalbuminemia has been confirmed to be an important factor in the risk for QT interval prolongation during clinical development.

Table 2.2-1 SII-1: Summary of Key Safety Findings from Nonclinical Studies and Relevance to Human Usage	
Key safety findings (from nonclinical studies)	**Relevance to human usage**
Reproductive and Developmental toxicity In the rats, delamanid was not considered to be teratogenic at up to the maximal dose of 300 mg/kg. In addition, delamanid had no effect on development or reproductive function of offsprings. In the rat study, no maternal or developmental toxicity was noted at the maximal feasible dose of 300 mg/kg. In rabbits, the number of early resorptions were significantly higher in the 10 mg/kg/day than the values in the control group though the total number of resorptions and dead foetuses and the incidence of postimplantation loss were not increased evidently. In addition, the number of early resorptions was within the historical control data. Delamanid was also not considered to be teratogenic in rabbits at up to the maximal dose of 10 mg/kg. In a rabbit study, decreased body weight and food consumption and slight haemorrhagic changes in dams and a slight increase in the incidence of early resorption were noted at a toxic dose of 10 mg/kg. The No-Observed-Adverse- Effect-Level (NOAEL) was estimated to be 5 mg/kg in terms of maternal general toxicity and developmental toxicity and the plasma area under the concentration time curve (AUC) 0-24h at that dose on Day 18 of gestation was 8251 ng×h/mL. In terms of reproductive toxicity (maintenance of pregnancy), the NOAEL was estimated to be 10 mg/kg, and the plasma AUC0-24h at that dose on Day 18 of gestation was 6748 ng×h/mL. Rat embryo-fetal development studies of metabolites (DM- 6705 and DM-6718) were conducted. (R)-DM-6705 showed external anomalies, visceral variations, and skeletal variations at the high dose of 30 mg/kg. The NOAEL for (R) - DM-6702 is considered to be 10 mg/kg for both maternal and fetal toxicities. The AUC0-24h for (R)-DM-6702 at the NOAEL on Day 11 was 12,170 ng×h/mL. Findings reported when dams were treated with (S)-DM-6718 were limited to generalized oedema in 2 foetuses All the findings from the rat embryo-fetal development studies for metabolites (DM- 6705 and DM-6718) occur spontaneously in the rat strain used and were within the historical control data range.	Except for a slight increase in the incidence of early reabsorption in rabbits, no evident developmental toxicity of delamanid was noted in either species. The rat fertility-embryonic development study showed no toxic effect on parent animals, fertility, or early embryonic development. Rat and rabbit embryo-fetal development studies did not suggest teratogenicity of delamanid. However, delamanid has not been studied in pregnant women. Thus, there is inadequate information on the use of delamanid in pregnant women.
Excretion of radioactivity into milk was confirmed in fed lactating rats. The elimination half-life of radioactivity was 13.2 hours in milk and 23.5 hours in blood, confirming that radioactivity was eliminated from milk faster than from blood.	In lactating rats administered radiolabelled delamanid, excretion into milk was confirmed. It is not known whether this medicinal product is excreted in human milk. Because a potential risk to the breastfeeding infant cannot be ruled out when treating with delamanid, delamanid is not recommended during breastfeeding.

Need for Additional Non-Clinical Data

No new non-clinical safety concerns or any need for additional non-clinical safety information have been identified.

Conclusions on Nonclinical Data

Table 2.2-2	**SII-2: Summary of Important Safety Concerns from Nonclinical Studies**
Important identified risks	QT interval prolongation
Important potential risks	None

2.3 Module SIII: Clinical Trial Exposure

As of 27 Apr 2023, 1,498 subjects have received delamanid. Estimates of overall cumulative subject exposure from completed and ongoing studies are provided in the tables below.

Clinical Trial Exposure (Cumulative for all Indications)

Table 2.3-1	**SIII-1: Clinical Trial Exposure to Delamanid (Cumulative for all Indications)**	
Duration of Exposure	**Patients**	**Person-Time (days)**
<1 m	654	4,841
1 to <3 m	185	10,559
3 to <6 m	175	24,322
6 to <12 m	484	96,033
≥12 m	0	0
Total	**1,498**	**135,755**

Clinical Trial Exposure by Age, Group and Gender

Table 2.3-2	**SIII-2: Clinical Trial Exposure to Delamanid by Age Group and Gender**			
Age Group	**Patients**		**Person Time (days)**	
	M	**F**	**M**	**F**
Age 0 to <=2	4	4	745	574
Age >2 to <=11	10	11	1,910	2,092
Age >11 to <=17	4	3	735	490
Age >17 to <=64	1,007	453	89,658	39,430
Age > 64	2	0	121	0
Total	**1,027**	**471**	**93,169**	**42,586**

Clinical Trial Exposure by Dose

Table 2.3-3	**SIII-3: Clinical Trial Exposure to Delamanid by Dose**	
Dose of Exposure (Total Daily Dose (mg))	**Patients**	**Person Time (Days)**
5-20	24	2,078
50	25	2,310
100	167	1,958

Table 2.3-3 SIII-3: Clinical Trial Exposure to Delamanid by Dose		
Dose of Exposure (Total Daily Dose (mg))	**Patients**	**Person Time (Days)**
200	799	93,489
300	181	12,587
400	292	21,606
500	5	971
600	5	756
Total	**1,498**	**135,755**

Clinical Trial Exposure by Ethnic Origin

Table 2.3-4 SIII-4: Clinical Trial Exposure to Delamanid by Ethnic Origin		
Ethnic Origin	**Patients**	**Person Time**
Asian	451	49,548
Black	225	18,016
American Indian or Alaska Native	6	21
Caucasian	505	30,938
Other	311	37,232
Total	**1,498**	**135,755**

2.4 Module SIV: Populations Not Studied in Clinical Trials

2.4.1 SIV.1: Exclusion Criteria in Pivotal Clinical Studies Within the Development Programme

Table 2.4.1-1 SIV.1-1: Exclusion Criteria in Pivotal Clinical Studies			
Exclusion Criterion	**Reason for Exclusion**	**Is it considered to be included as missing information?**	**Rationale**
Patients with a history of allergy to any nitro-imidazoles or nitro-imidazole derivatives at any time	-	No	In the EU SmPC section 4.3 Contraindications this exclusion criterion is covered by the following standard wording: "Hypersensitivity to the active substance or to any of the excipients listed in section 6.1."
Pregnant, breastfeeding, or planning to conceive or father a child within the timeframe	Pregnancy and planning to conceive (or father) a child have been exclusion criteria in the clinical trials with delamanid due to the fact that the potential in	No	Delamanid use during pregnancy and breastfeeding is covered in the current EU SmPC section 4.6. Deltyba is

Table 2.4.1-1 SIV.1-1: Exclusion Criteria in Pivotal Clinical Studies			
Exclusion Criterion	**Reason for Exclusion**	**Is it considered to be included as missing information?**	**Rationale**
described in the informed consent form	utero safety impact of delamanid was unknown. There are very limited data from the use of delamanid in pregnant women. Breast-feeding has been an exclusion criterion in the clinical trials with delamanid due to the fact that no data were available on the safety of delamanid in neonates and/or infants. Breast-feeding has not been reported from clinical trials. Pharmacokinetic data in animals have shown excretion of delamanid and or its metabolites in milk. In lactating rats, the Cmax for delamanid in milk was 4-fold higher than that of the blood. It is not known whether delamanid is excreted in human milk. However, excretion in human milk is expected, to a very low extent, based on animal studies that showed excretion of delamanid in milk. No clinical data are available to estimate potential hazards to infants who might be exposed to delamanid via breast milk.		not recommended in pregnant women or in women of childbearing potential unless they are using a reliable form of contraception and women should not breastfeed during treatment with Deltyba.
Patients with current clinically relevant changes in the screening electrocardiogram (ECG) such as any atrioventricular (AV) block, prolongation of the QRS complex over 120 msec (in both male and female patients), or of Corrected QT interval using Fridericia's formula (QTcF) interval over 450 msec	For patients with concurrent cardiovascular disease and/or cardiac arrhythmia, given the QT prolonging potential of delamanid, patients were excluded both to ensure their safety and avoid confounding of the follow up assessment of these patients within the clinical trial.	No	QT interval prolongation is categorized as Important Identified Risk. QT prolongation and Cardiac risk factors are adequately addressed in the current EU SmPC section 4.4 Special warnings and precautions for use.

Table 2.4.1-1 SIV.1-1: Exclusion Criteria in Pivotal Clinical Studies			
Exclusion Criterion	**Reason for Exclusion**	**Is it considered to be included as missing information?**	**Rationale**
in male patients and 470 msec in female patients.			
Use of amiodarone at any time during the previous 12 months, use of other antiarrhythmics for the previous 30 days, and use of certain other medications, including certain antidepressants, antihistamines, and macrolides, for the previous 14 days	The use of previous and concomitant medications with potential for QT interval prolongation such as amiodarone and other anti-arrhythmic was also excluded in order to avoid confounding the safety assessment of delamanid during the trial. Use of amiodarone at any time during the previous 12 months, use of other antiarrhythmics for the previous 30 days, and use of certain other medications, including certain antidepressants, antihistamines, and macrolides were exclusion criteria in clinical trials with delamanid as a precautionary measure and in order to adequately assess efficacy and safety of delamanid without any bias by those drugs.	No	Cardiac risk factors are included in the current EU SmPC section 4.4 Special warnings and precautions for use.
Patients with evidence of clinically significant metabolic, gastrointestinal, neurological, psychiatric, or endocrine diseases, malignancy, or other abnormalities (other than the indication being studied)	Clinically significant neurological or psychiatric diseases were exclusion criteria in clinical trials with delamanid to avoid confounding the safety assessment of these patients. Otsuka has not prospectively studied patients with concurrent metabolic or endocrine diseases such as poorly controlled diabetes mellitus. Diabetes mellitus is known to be a predisposing factor to contract TB and develop active TB via impaired host immunity to TB due to hyperglycaemia. Clinically significant gastrointestinal diseases were exclusion criteria in clinical trials with delamanid. Chronic malabsorption syndromes such as coeliac disease and states of malnutrition	No	Psychiatric and gastrointestinal disorders were previously categorized as important identified risks. Delamanid will probably also be used in combination regimens for patients with concurrent malignancies. However, concurrent malignant disease in patients treated with delamanid does not constitute a relevant safety concern.

Table 2.4.1-1 SIV.1-1: Exclusion Criteria in Pivotal Clinical Studies			
Exclusion Criterion	**Reason for Exclusion**	**Is it considered to be included as missing information?**	**Rationale**
	are associated with an increased risk of TB. Malignancy was an exclusion criterion in clinical trials with delamanid. TB rates are higher in patients (adults and children) with cancer (haematologic conditions and solid tumours). This increased TB rate is most likely due to immunosuppressive effects, either of the malignancy itself or of (radio-) chemotherapy. Anti-TB chemotherapy is indicated in cancer patients infected with mycobacteria[24,25]		
Karnofsky score <50% (<60% while not hospitalized for 242-07-208)	Severe conditions or high-grade diseases and low performance status (Karnofsky Score) with the potential to jeopardize subjects/patients were excluded from clinical trials.	No	Delamanid is indicated for use as part of an appropriate combination regimen for pulmonary MDR-TB in adult patients when an effective treatment regimen cannot otherwise be composed for reasons of resistance or tolerability (EU SmPC). It is highly likely that many of patients treated with Delamanid have low Karnofsky Score. Although it is often used to decide if a patient could be included in a clinical trial, in real-life setting it is not often reported.

Table 2.4.1-1 SIV.1-1: Exclusion Criteria in Pivotal Clinical Studies			
Exclusion Criterion	**Reason for Exclusion**	**Is it considered to be included as missing information?**	**Rationale**
Patients with serum albumin levels <2.8 g/dL[a]	In a clinical study, the presence of hypoalbuminaemia was associated with an increased risk of prolongation of the QTc interval in delamanid treated patients.	No	In the EU SmPC section 4.3 Contraindications this exclusion criterion is covered by the following wording: "Serum albumin < 2.8 g/dl" will remain as a contraindication in the EU SmPC Section 4.3
Patients taking medicinal products that are strong inducers of CYP3A4 (e.g., carbamazepine).[a]	Clinical drug-drug interactions studies in healthy subjects indicated a reduced exposure to delamanid, of up to 45% following 15 days of concomitant administration of the strong inducer CYP3A4 (Rifampicin 300 mg daily) with delamanid (200 mg daily).	No	In the EU SmPC section 4.3 Contraindications this exclusion criterion is covered by the following wording: "Taking medicinal products that are strong inducers of CYP3A4"

2.4.2 SIV.2: Limitations to Detect Adverse Reactions in Clinical Trial Development Programmes

The clinical development programme 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.

2.4.3 SIV.3: Limitations in Respect to Populations Typically Under-represented in Clinical Trial Development Programmes

The following populations have not been studied or studied only to a limited extent:

[a] Please note that this is a contraindication mentioned in the EU SmPC, Section 4.3 and NOT an Exclusion Criteria in Pivotal Clinical Studies. As per the old RMP Template (used until version 2.11) this information was included in the Section 2.4.2: `Effect of Exclusion Criteria in the Clinical Trial Development Program', under the Table 2.4.1-1: `Exclusion Criteria Which will Remain as Contraindications'. However, due to a change in template (used for version 3.1 onwards) the information is included in Section 2.4.1: `Exclusion Criteria in Pivotal Clinical Studies', which is the most relevant Section within the new Template.

Drug use in paediatric patients (0 to 17 years (inclusive) of age):

Limited clinical data are available on drug use in paediatric patients less than 18 years of age.

In consultation with relevant Health Authorities, Otsuka initiated clinical studies in relevant paediatric populations to support the use of delamanid in children with MDR-TB in an approved Paediatric Investigation Plan (PIP).

Trial 242-12-232 investigated the pharmacokinetics (PK) and the safety and tolerability of delamanid administered with food for 10 days to paediatric subjects ages birth to 17 years, inclusive, who were also on therapy with an optimized background regimen (OBR) selected as recommended in World Health Organization guidelines and according to the investigator's best judgment. Delamanid demonstrated an acceptable safety profile in the paediatric population studied during this 10-day trial and no new safety concerns were identified.

Trial 242-12-233 was a 6-month extension to Trial 242-12-232. As described in Section 2.7.3.1. The trial has been completed and data analysed. Safety findings were in line with the adult population, and the indication was extended to include paediatric patients with a body weight of at least (≥) 10 kg.

Considering small size of the paediatric patient cohort in 232 and 233 clinical trial (37 patients), paediatric population (ages 0 to 17 years (inclusive) of age) is still considered underrepresented in clinical trials.

Drug use in elderly patients (i.e., ≥65 years of age):

Clinical data are not available in the elderly population. Previous trials were not designed to investigate delamanid in the elderly. The number of subjects ≥ 65 years of age (n = 1 for healthy subjects, none for patients with uncomplicated TB and MDR TB) was therefore insufficient to detect any differences in safety and tolerability between age groups. The safety and efficacy of delamanid in elderly patients has not been established in clinical trials. However, based on pharmacokinetics results, the present data give no indication for dose adjustment in elderly patients.

Drug use in patients with HIV: For patients with HIV infection and cell differentiation (CD4) cell count <500/mm^3, no clinical data are available. This condition was an exclusion criterion in the late phase clinical trial with delamanid for MDR TB. Drug-interactions with antiretroviral drugs have since been studied in Phase 1 trials.

Use in patients with severe renal impairment:

For patients with concurrent renal disease, very limited clinical data are available. Renal impairment defined as serum creatinine levels ≥265 µmol/L (i.e., 3.00 mg/dL) was an exclusion criterion in clinical trials.

Less than 5% of an oral dose of delamanid is recovered from urine. Mild renal impairment (50 mL/min <CrCLN < 80 mL/min) does not appear to affect delamanid exposure. Therefore, no dose adjustment is needed for patients with mild or moderate renal impairment. However, this is not yet known for patients with severe renal impairment.

Use in patients with severe hepatic impairment:

No dose adjustment is considered necessary for patients with mild hepatic impairment. Delamanid is not recommended in patients with moderate to severe hepatic impairment.

Use during pregnancy:

There are very limited data from the use of delamanid in pregnant women as pregnancy and planning to conceive (or father) a child has been exclusion criteria in the clinical trials with delamanid. In prior clinical trials there were treatment-emergent pregnancies that did not suggest any teratogenic risks. The current EU SmPC advises that Deltyba is not recommended in pregnant women or in women of childbearing potential unless they are using a reliable form of contraception.

Use during breast feeding:

It is not known whether delamanid is excreted in human milk. However, excretion in human milk is expected, to a very low extent, based on animal studies that showed excretion of delamanid in milk. No clinical data are available to estimate potential hazards to infants who might be exposed to delamanid via breast milk. In the EU SmPC breastfeeding while taking delamanid is not recommended.

Table 2.4.3-1 SIV.3-1: Exposure of Special Populations Included or not in Clinical Trial Development Programmes

Type of Special Population	Exposure
Pregnant women	Not included in the clinical development programme
Breastfeeding women	Not included in the clinical development programme
Patients with relevant comorbidities: • Patients with hepatic impairment • Patients with renal impairment	Not included in the clinical development programme

Table 2.4.3-1 SIV.3-1: Exposure of Special Populations Included or not in Clinical Trial Development Programmes	
Type of Special Population	**Exposure**
• Patients with cardiovascular impairment • Immunocompromised patients • Patients with a disease severity different from inclusion criteria in clinical trials	
Population with relevant different ethnic origin	Not included in the clinical development programme
Subpopulations carrying relevant genetic polymorphisms	Not included in the clinical development programme

2.5 Module SV: Post-authorisation Experience

2.5.1 SV.1: Post-authorisation Exposure

Delamanid is currently available on the market in the form of a 50 mg film-coated tablet and a 25 mg dispersible tablet.

2.5.1.1 SV.1.1: Method Used to Calculate Exposure

2.5.1.1.1 Delamanid 50 mg (Film Coated Tablets)

Estimates of patient exposure are based on the availability of monthly sales (product marketed by Otsuka, by Otsuka business partners or distributed via the Global Drug Facility (GDF) and Médecins Sans Frontières (MSF)) and “free goods” distribution (via the Compassionate Use program [CU]). Due to the limitations of this approach (e.g., the actual use of the product by the end-user cannot be confirmed), it is not possible to reliably estimate the number of patients treated with marketed delamanid. Due to a need to collect data from various sources, the cumulative estimates have been calculated based on data cut-off date 31 Mar 2023.

The following assumptions were used to arrive at an estimation of the number of patients treated with delamanid during the period referenced above:

- The Average Defined Dose (ADD) for delamanid is 200 mg daily.
- Each patient received the ADD of 200 mg daily.
- Each patient received this dose for a 24-week duration.
- Each patient received a total dose of CCI mg.

Although up to the DLP of this RMP, paediatric patients with weight with at least 30 kg in the EU/European Economic Area (EEA) were also eligible to receive delamanid 50 mg film-coated tablets, the number of potentially treated paediatric patients in this weight

category is unknown, however, the assumption is that this number is small. Therefore, the estimation is based on the above formula which includes adult patients only.

Based on these sales data, an estimated CCI mg (total cumulative volume) was distributed. Considering the available sales data and the assumptions as described above, the cumulative number of patients exposed to commercial Delamanid 50 mg is estimated to be: CCI

Number of patients exposed is calculated by volume sold [taken from sales data] divided by total dose received per patient:

- CCI mg volume sold ÷ CCI mg total dose per patient = CCI patients exposed

Number of patient days is calculated by number of patients exposed multiplied by duration:

- CCI patients exposed × 168 days duration = CCI patient days

Number of patient-years is determined by dividing patient days by 365:

- CCI patient days ÷ 365 = CCI patient years

2.5.1.1.2 Delamanid 25 mg (Dispersible Tablets)

Extension of the indication to children with weight ≥10 kg and the line extension to 25 mg dispersible tablet was approved on 16 Sep 2021, however, the formulation has not yet been launched in the EU but distributed via the GDF. Due to a need to collect data from various sources, the cumulative estimates have been calculated based on data cut-off date 31 Mar 2023.

The following assumptions were used to arrive at an estimation of the number of patients treated with delamanid 25 mg dispersible tablets.

- The ADD for delamanid is 62.5 mg.
- Each patient received the ADD of 62.5 mg.
- Each patient received this dose for 24 weeks duration.
- Each patient received a total dose of CCI mg.

Based on these sales data, an estimated CCI mg (total cumulative volume) was distributed via the GDF. Considering the available sales data and the assumptions as

described above, the cumulative number of patients exposed to commercial Delamanid 25 mg is estimated to be: CCI .

Number of patients exposed is calculated by volume sold [taken from sales data] divided by total dose received per patient:

- CCI mg volume distributed ÷ CCI mg total dose per patient = CCI patients exposed

Number of patient days is calculated by number of patients exposed multiplied by duration:

- CCI patients exposed × 168 duration = CCI patient days

Number of patient-years is determined by dividing patient days by 365:

- CCI patient days ÷ 365 = CCI patient years

2.5.1.2 SV.1.2: Exposure

2.5.1.2.1 Delamanid 50 mg (Film-coated tablets)

The estimated cumulative number of patients treated with marketed delamanid 50 mg film-coated tablets worldwide as of 31 Mar 2023 was approximately CCI

A summary of the worldwide distribution of delamanid cumulatively until 31 Mar 2023 is presented in Table 2.5.1.2.1-1 below.

Table 2.5.1.2.1-1 SV.1.2-1: Patient Exposure Units Distributed and Patients Exposed/Estimated Patient Years for Delamanid 50 mg Film-coated Tablets (Through 31 Mar 2023)

Country	Total Number of Units Distributed	Number of Patients	Patient-Years of Treatment
	Cumulative to 31 Mar 2023	Cumulative to 31 Mar 2023	Cumulative to 31 Mar 2023
CCI			

Table 2.5.1.2.1-1	SV.1.2-1: Patient Exposure Units Distributed and Patients Exposed/Estimated Patient Years for Delamanid 50 mg Film-coated Tablets (Through 31 Mar 2023)		
Country	Total Number of Units Distributed	Number of Patients	Patient-Years of Treatment
	Cumulative to 31 Mar 2023	Cumulative to 31 Mar 2023	Cumulative to 31 Mar 2023
CCI			

Table 2.5.1.2.1-1	**SV.1.2-1: Patient Exposure Units Distributed and Patients Exposed/Estimated Patient Years for Delamanid 50 mg Film-coated Tablets (Through 31 Mar 2023)**		
Country	**Total Number of Units Distributed**	**Number of Patients**	**Patient-Years of Treatment**
	Cumulative to 31 Mar 2023	**Cumulative to 31 Mar 2023**	**Cumulative to 31 Mar 2023**
CCI			

Table 2.5.1.2.1-1 SV.1.2-1: Patient Exposure Units Distributed and Patients Exposed/Estimated Patient Years for Delamanid 50 mg Film-coated Tablets (Through 31 Mar 2023)			
Country	Total Number of Units Distributed	Number of Patients	Patient-Years of Treatment
	Cumulative to 31 Mar 2023	Cumulative to 31 Mar 2023	Cumulative to 31 Mar 2023
CCI [redacted]			

2.5.1.2.2 Exposure for Investigator-sponsored Studies and Access Programmes

The number of patients/subjects presented below reflect the quantity of distributed IMP/product. The actual number of exposed patients/subjects is only listed for completed investigator sponsored studies (ISS) where the final study report or publication is available. In these cases, the exposed number of patients of 50 mg film-coated tablets are included in the calculation of the overall exposure (see Section 2.5.1.2.1).

The distributed quantities with the exposure from completed ISS as of 31 Mar 2023 are presented in Table 2.5.1.2.2-1.

Table 2.5.1.2.2-1 S.V.1.2-2: Cumulative Patient Exposure Based on Postmarketing Distribution of IMP for Investigator-sponsored Studies and Access Programmes

Study IDs / Study Status	ISS/Access Programme Title	Sponsor	Delamanid Units Shipped to 31 Mar 2023		Number Of Exposed Participants as Per Final Study Report or Publication	Countries
			Formulation	Quantity		
NCT02619994 MDR-END Otsuka ID: 242-402-00002 **Completed**	Delamanid, Linezolid, Levofloxacin, and Pyrazinamide for the Treatment of Patients with Fluoroquinolone-sensitive MDR-TB: A Phase 2, Multicenter, Randomized, Open-label, Clinical Trial	Seoul National University Hospital	50 mg film-coated tablet	CCI	79 Patients[a]	Republic of Korea
NCT02583048 A5343 12005 (DAIDS-ES Registry) Otsuka ID: 242-201-00003 **Completed**	A Trial of the Safety, Tolerability, and Pharmacokinetics of Bedaquiline and Delamanid, Alone and in Combination, among Participants Taking Multidrug Treatment for Drug-Resistant Pulmonary Tuberculosis	National Institute of Allergy and Infectious Diseases (NIAID)	50 mg film-coated tablet		54 Patients[b]	Peru, South Africa
DCAP Otsuka ID: 242-302-00006 **Completed**	Delamanid Clinical Access Programme (DCAP)	National Department of Health, South Africa	50 mg film-coated tablet		412 Patients[c]	South Africa
Otsuka ID: 242-302-00018	Relative Bioavailability of Delamanid 25mg,	Stellenbosch University	50 mg film-coated tablet		26 Patients[d]	South Africa

Table 2.5.1.2.2-1 S.V.1.2-2: Cumulative Patient Exposure Based on Postmarketing Distribution of IMP for Investigator-sponsored Studies and Access Programmes

Study IDs / Study Status	ISS/Access Programme Title	Sponsor	Delamanid Units Shipped to 31 Mar 2023		Number Of Exposed Participants as Per Final Study Report or Publication	Countries
			Formulation	Quantity		
Protocol number: TASK006-DLM-BE **Completed**	50mg and 100mg, Administered to Healthy Adults under Fed Conditions Dispersed in Water Compared to Tablet Form			CCI		
NCT03141060 IMPAACT 2005 20721 (DAIDS-ES Registry Number) Otsuka ID: 242-201-00009 **Ongoing**	A Phase I/II Open-Label, Single-Arm Study to Evaluate the Pharmacokinetics, Safety, and Tolerability of Delamanid in Combination With Optimized Multidrug Background Regimen (OBR) for Multidrug-Resistant Tuberculosis (MDR-TB) in Human Immunodeficiency Virus (HIV)-Infected and HIV-Uninfected Children With MDR-TB	NIAID	50 mg film-coated tablet		NA (status ongoing)	Botswana, India, South Africa, Tanzania
			25 mg dispersible tablet		NA (status ongoing)	
			5 mg dispersible tablet		NA (status ongoing)	

Table 2.5.1.2.2-1 S.V.1.2-2: Cumulative Patient Exposure Based on Postmarketing Distribution of IMP for Investigator-sponsored Studies and Access Programmes

Study IDs / Study Status	ISS/Access Programme Title	Sponsor	Delamanid Units Shipped to 31 Mar 2023		Number Of Exposed Participants as Per Final Study Report or Publication	Countries
			Formulation	Quantity		
NCT03568383 A5300B/I2003B/ PHOENIx Otsuka ID: 242-201-00004 **Ongoing**	Protecting Households On Exposure to Newly Diagnosed Index Multidrug-Resistant Tuberculosis Patients (PHOENIx MDR-TB)	NIAID	50 mg film-coated tablet	CCI	NA (status ongoing)	Botswana, Brazil, Haiti, India, Kenya, Peru, Philippines, South Africa, Thailand, Uganda, Zimbabwe, Vietnam
			25 mg dispersible tablet		NA (status ongoing)	
			5 mg dispersible tablet		NA (status ongoing)	
A5356 Otsuka ID: 242-201-00007 **Ongoing**	A Phase 2a, Prospective, Randomized, Multicenter Trial to Evaluate the Safety, Tolerability, and Initial Efficacy of Linezolid (LZD) Dosing Strategies Combined with Delamanid and Optimized Background Therapy (OBT) for the Treatment of Multidrug Resistant Tuberculosis (MDRTB)	NIAID	50 mg film-coated tablet		NA (status ongoing)	Peru, South Africa
NCT03959566 PanACEA Sudocu	PanACEA Sutezolid Dose-finding and	Ludwig-Maximilians	50 mg film-coated tablet		NA (status ongoing)	South Africa, Tanzania

Table 2.5.1.2.2-1 S.V.1.2-2: Cumulative Patient Exposure Based on Postmarketing Distribution of IMP for Investigator-sponsored Studies and Access Programmes

Study IDs / Study Status	ISS/Access Programme Title	Sponsor	Delamanid Units Shipped to 31 Mar 2023		Number Of Exposed Participants as Per Final Study Report or Publication	Countries
			Formulation	Quantity		
Otsuka ID: 242-302-00013 **Ongoing**	Combination Evaluation	University (LMU)		CCI		
Otsuka ID: 242-302-00016 **Ongoing**	STEM-TB (Strengthening Evidence on Optimal MDR-Tuberculosis Treatment Regimens through Improved Epidemiologic Methods) (protocol title revised)	Partners in Health (PIH)	50 mg film-coated tablet		NA (status ongoing)	Kazakhstan, Peru
NCT04550832 DECODE Otsuka ID: 242-302-00019 **Ongoing**	Delpazolid dose-finding and Combination Development (DECODE)	LegoChem Biosciences, Inc	50 mg film-coated tablet		NA (status ongoing)	South Africa, Tanzania
NCT03828201 DRAMATIC Otsuka ID: 242-302-00020 **Ongoing**	Duration Randomized Anti-MDR-TB And Tailored Intervention Clinical (DRAMATIC) Efficacy and Tolerability of Bedaquiline, Delamanid, Levofloxacin, Linezolid, and	Boston University	50 mg film-coated tablet		NA (status ongoing)	Philippines, Vietnam

Table 2.5.1.2.2-1 S.V.1.2-2: Cumulative Patient Exposure Based on Postmarketing Distribution of IMP for Investigator-sponsored Studies and Access Programmes

Study IDs / Study Status	ISS/Access Programme Title	Sponsor	Delamanid Units Shipped to 31 Mar 2023		Number Of Exposed Participants as Per Final Study Report or Publication	Countries
			Formulation	Quantity		
	Clofazimine to Treat MDR-TB			CCI		
50 mg film-coated tablets	**Not applicable**				**571**	**Not applicable**
25 mg dispersible tablets					**0**	
5 mg dispersible tablets					**0**	
Grand Total					**571**	

a Mok J, et al. 9 months of delamanid, linezolid, levofloxacin, and pyrazinamide versus conventional therapy for treatment of fluoroquinolone-sensitive multidrug-resistant tuberculosis (MDR-END): a multicentre, randomised, open-label phase 2/3 non-inferiority trial in South Korea. *Lancet.* 2022;400(10362):1522-1530.

b Dooley K, et al. QT effects of bedaquiline, delamanid, or both in patients with rifampicin-resistant tuberculosis: a phase 2, open-label, randomised, controlled trial. *Lancet Infect Dis* 2021; 21: 975–83

c Dlamini-Miti JN, et al. South African Delamanid Clinical Access Program (DCAP) for the treatment of Rifampicin-Resistant tuberculosis. Poster presented at: *52nd World Conference on Lung Health*; 19-22 Oct 2021

d Zou Y, et al. Relative bioavailability of delamanid 50 mg tablets dispersed in water in healthy adult volunteers. *Br J Clin Pharmacol*. Published online 2023. doi:10.1111/bcp.15672

2.5.1.2.3 Delamanid 25 mg (Dispersible Tablets)

The estimated cumulative number of patients treated with marketed delamanid 25 mg film-coated tablets worldwide as of 31 Mar 2023 was approximately CCI .

A summary of the worldwide distribution of delamanid cumulatively until 31 Mar 2023 is presented in Table 2.5.1.2.3-1 below.

Table 2.5.1.2.3-1 SV.1.2-3: Patient Exposure Units Distributed and Patients Exposed/Estimated Patient Years for Delamanid 25 mg Dispersible Tablets (Through 31 Mar 2023)

Country	Total Number of Units Distributed	Number of Patients	Patient-Years of Treatment
	Cumulative to 31 Mar 2023	Cumulative to 31 Mar 2023	Cumulative to 31 Mar 2023
CCI			

Table 2.5.1.2.3-1 SV.1.2-3: Patient Exposure Units Distributed and Patients Exposed/Estimated Patient Years for Delamanid 25 mg Dispersible Tablets (Through 31 Mar 2023)			
Country	Total Number of Units Distributed	Number of Patients	Patient-Years of Treatment
	Cumulative to 31 Mar 2023	Cumulative to 31 Mar 2023	Cumulative to 31 Mar 2023
CCI			
Total	CCI		

The 25 mg dispersible tablet has also been distributed as an IMP to treat paediatric patients within the CU program 242-302-00014. The data on the cumulative exposure to delamanid 25 mg dispersible tablets (distributed as an IMP) for CU purposes as of 31 Mar 2023 are presented in Table 2.5.1.2.3-2 (please note, this data is not included in Section 2.5.1.2.2 Exposure for Investigator-sponsored Studies and Access Programmes). Since the actual number of patients exposed to the distributed IMP was known for this source, no estimation or calculation was done, but actual data are presented in the table. Any inconsistencies between the distributed number of units and exposed patients across the countries (e.g. less patients exposed in one country compared to the other country with the similar number of units of the distributed IMP) can be due to the product delivered but administration to patient not yet started during the reporting period, or due to the extended use of the product in some patients (this option is possible as per the CU project protocol).

Table 2.5.1.2.3-2 Exposure to Delamanid 25 mg Dispersible Tablets (IMP) for Compassionate Use		
Country	Number of Units Distributed	Actual Number of Patients Per CU Protocol
	Cumulative to 31Mar2023	Cumulative to 31Mar2023*
CCI		
Total	CCI	

*Patient exposure includes resupply for the extended use in some patients.

2.6 Module SVI: Additional EU Requirements for the Safety Specification

Potential for Misuses for Illegal Purposes

Delamanid has no potential as an illicit drug. However, this issue needs a certain level of awareness due to the fact that the prevalence of addiction to drugs, alcohol, and tobacco is higher among TB patients [redacted] or substances can therefore not be totally excluded.

A cumulative search of the PTs of intentional product misuse and substance abuse in Otsuka's pharmacovigilance database did not reveal any cases of misuse or abuse for delamanid.

PPD

2.7 Module SVII: Identified and Potential Risks

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

The summary of identified safety concerns in the HA approved initial RMP of delamanid (Version #2.2; Procedure 002552; Approval date: 28 April 2014) is presented in Table 2.7.1-1.

Table 2.7.1-1 SVII.1-1: Summary of Safety Concerns in the Initial RMP Submission

Important Identified Risks	QT interval prolongation Paraesthesia Tremor Anxiety
Important Potential Risks	Tinnitus Blurred vision Hypokalaemia Depression Insomnia Blood Cortisol Increased Drug Resistance Drug use during pregnancy Drug use during breastfeeding Nausea Vomiting Liver Disorders
Missing Information	Drug use in Paediatric Population Drug use in elderly patients Drug use in patients with HIV Drug use in patients with severe renal impairment Drug use in patients with severe hepatic impairment Drug-drug interactions

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

There have been no new safety concerns added to the RMP since the initial RMP submission.

No new safety concerns have been added, removed or reclassified in this RMP version 5.3. All risks remain the same as in RMP 5.1.

Historical Risk Reclassifications have been as follows:

In RMP version 3.5 drug resistance was removed as a safety concern and the title of the missing information of Extended use was corrected.

The risk “Drug resistance” had been previously classified as an important identified risk; nevertheless, according to the Assessment Report of the procedure EMEA/H/C/002552/II/0040, the EMA considered bacterial resistance development as an efficacy concern, and not a safety concern. However, as efficacy risk, it remains as an important topic for the benefit-risk balance to be thoroughly discussed in the PSURs.

In addition to that, Extended Use (use of delamanid longer than 24 weeks), earlier classified as missing information, was updated to reflect the exact duration of treatment as per label. As per the EU SmPC, the use of delamanid is recommended for 24 weeks. Therefore, in Summary of Ongoing Safety Concerns, the title of this Missing Information was updated from Extended use (≥24 weeks) to Extended Use (>24 weeks) to replace symbol (≥) with symbol > and thus refer to Extended Use >24 weeks (169 days or more).

After the completion of the trial 242-12-233 Clinical Study Report, submitted during the procedure EMEA/H/C/002552/X/46G, “Missing Information: Drug use in paediatric patients” was amended to “Drug use in paediatric patients with a body weight <10 kg”. Based on evidence for the population 0 to 17 years of age, the indication for delamanid was extended to include paediatric population with a body weight of at least (≥) 10 kg.

In RMP version 4.1, the following reclassifications were made:

- All previous important identified risks but QT prolongation were removed from the list of safety concerns
- All previous important potential risks but Liver disorders, Drug use during pregnancy and Drug use during breastfeeding were removed from the list of safety concerns
- All missing information were removed from the list of safety concerns.

A full justification for further removal of safety concerns was provided within the Type II Variation to Update the List of Adverse Drug Reactions in the Deltyba EU Product Information (Procedure EMEA/H/C/002552/II/0053).Historical changes to the delamanid safety concerns completed during RMP 4.1 are summarized in Table 2.7.2-1.

Table 2.7.2-1 SVII.2-1: Reclassified Safety Concerns

Paraesthesia, Hypoaesthesia and Tremor	
Type of Risk	Important Identified Risk
Change	Paraesthesia: No risk; removed from the List of Safety Concerns Hypoaesthesia and Tremor: Non-important risks; reclassified and removed from the List of Safety Concerns
Reason for Change	Paraesthesia: Available data today does not support a causal association between delamanid and reported adverse events of paraesthesia. Paraesthesia is not considered a delamanid risk. Hypoaesthesia and Tremor: Available data today supports a non-important risk for delamanid. These adverse reactions do not require additional pharmacovigilance activities and can be managed adequately through routine risk minimisation measures.

Table 2.7.2-1 SVII.2-1: Reclassified Safety Concerns	
Psychiatric disorders: Anxiety, Depression, and Insomnia	
Type of Risk	Important Identified Risk
Change	Non-important risks; reclassified and removed from the List of Safety Concerns
Reason for Change	Anxiety, Depression, and Insomnia: Available data today supports a non-important risk for delamanid. These adverse reactions do not require additional pharmacovigilance activities and can be managed adequately through routine risk minimisation measures.
Gastrointestinal disorders: Nausea, Vomiting and Gastritis	
Type of Risk	Important Identified Risk
Change	Non-important risks; reclassified and removed from the List of Safety Concerns
Reason for Change	Nausea, Vomiting and Gastritis: Available data today supports a non-important risk for delamanid. These adverse reactions do not require additional pharmacovigilance activities and can be managed adequately through routine risk minimisation measures.
Tinnitus	
Type of Risk	Important Potential Risk
Change	No risk; reclassified and removed from the List of Safety Concerns
Reason for Change	Available data today does not support a causal association between delamanid and reported adverse events of tinnitus. Tinnitus is not considered a delamanid risk.
Blurred vision	
Type of Risk	Important Potential Risk
Change	No risk; reclassified and removed from the List of Safety Concerns
Reason for Change	Available data today does not support a causal association between delamanid and reported adverse events of blurred vision. Blurred vision is not considered a delamanid risk.
Hypokalaemia	
Type of Risk	Important Potential Risk
Change	No risk; reclassified and removed from the List of Safety Concerns
Reason for Change	Available data today does not support a causal association between delamanid and reported adverse events of hypokalaemia. Hypokalaemia is not considered a delamanid risk.
Blood cortisol level increase	
Type of Risk	Important Potential Risk
Change	Non-important risk; reclassified and removed from the List of Safety Concerns
Reason for Change	Available data today supports a non-important risk for delamanid. These adverse reactions do not require additional pharmacovigilance activities and can be managed adequately through routine risk minimisation measures.
Drug use in elderly patients	
Type of Risk	Missing Information
Change	Reclassified and removed from the List of Safety Concerns
Reason for Change	Available data today identified no safety concern specific to drug use in elderly patients. Safety profile in elderly patients treated with delamanid is overall consistent with the safety profile in adult patients treated with delamanid.
Drug use in patients with HIV	
Type of Risk	Missing Information
Change	Reclassified and removed from the List of Safety Concerns

Table 2.7.2-1 SVII.2-1: Reclassified Safety Concerns	
Reason for Change	Available data today identified no safety concern specific to drug use in patients with HIV. Safety profile in patients with HIV treated with delamanid is overall consistent with the safety profile in adult patients treated with delamanid.
Drug-drug interactions	
Type of Risk	Missing Information
Change	Reclassified and removed from the List of Safety Concerns
Reason for Change	Available data today with respect to drug-drug interactions identified no new safety concern in addition to the important identifed risk of QT interval prolongation. Evidence from all sources, including published literature, supports safe delamanid use in combination with other anti-TB and antiretroviral medications.
Extended use (> 24 weeks)	
Type of Risk	Missing Information
Change	Reclassified and removed from the List of Safety Concerns
Reason for Change	Available data today identified no safety concern as result of delamanid extended use (>24 weeks). Safety profile in patients treated with delamanid longer than 24 weeks is overall consistent with the safety profile in patients treated with delamanid for 24 weeks only.
Drug use in paediatric patients (body weight <10 kg)	
Type of Risk	Missing Information
Change	Reclassified and removed from the List of Safety Concerns
Reason for Change	There is currently no reasonable expectation that the existing pharmacovigilance activities could further characterise the safety profile of delamanid with respect to the missing information of Drug use in paediatric patients (body weight <10 kg).
Drug use in patients with severe renal impairment	
Type of Risk	Missing Information
Change	Reclassified and removed from the List of Safety Concerns
Reason for Change	There is currently no reasonable expectation that the existing pharmacovigilance activities could further characterise the safety profile of delamanid with respect to the missing information of drug use in patients with severe renal impairment.
Drug use in patients with severe hepatic impairment	
Type of Risk	Missing Information
Change	Reclassified and removed from the List of Safety Concerns
Reason for Change	There is currently no reasonable expectation that the existing pharmacovigilance activities could further characterise the safety profile of delamanid with respect to the missing information of drug use in patients with severe hepatic impairment.

The updates of safety concerns in the Risk Management Plan v.4.1 for delamanid were the result of a comprehensive cumulative assessment of safety data from all sources. The assessment included, but was not limited to data on seriousness, severity, outcomes, discontinuation rates, evidence on de- and re-challenge, drug class effects/labels/risks, published literature and data from international public safety databases (EVDAS and Vigibase).

Risk assessment was performed for all delamanid adverse drug reactions (ADRs) for which evidence supported the causal relationship with delamanid. Based on this assessment, QT interval prolongation had been confirmed as an important identified risk. Other important identified risks presented in the previous RMP v.3.5 for which evidence supported an ADR (hypoaesthesia, tremor, anxiety, depression, insomnia, nausea, vomiting, gastritis, and cortisol increased) were re-assessed and classified as non-important risks, which can be adequately managed through routine risk minimisation measures and do not require additional PV activities. Consequently, the remaining identified important risks from RMP v.3.5 were removed in RMP v.4.1.

Those important identified and important potential risks included in the RMP v.3.5 for which evidence did not support a respective ADR were also re-assessed to ensure that a potential risk was not overlooked. As a result of the re-assessment, liver disorder was kept as an important potential risk, although evidence had not supported related ADRs. Tinnitus, blurred vision, paraesthesia, and hypokalaemia were removed from the delamanid safety concerns in RMP v.4.1 since, in addition to no confirmed ADRs, the risk assessment did not indicate an important potential or important identified risk. Drug use during pregnancy and breastfeeding were retained as important potential risks with the outcome of this procedure due to the scarcity of available evidence.

With respect to the missing information, as presented in the RMP v.3.5, apart from the conclusions from the updated list of ADRs and conducted risk assessments, further changes in RMP v.4.1 took into consideration the cumulative assessment of missing information provided in Section 16.4 of the PSUR #12 (DLP 27 Apr 2021) along with public literature on missing information presented regularly in Section 11 of the PSURs. As a result, drug use in elderly patients, drug use in patients with HIV, drug-drug interactions, and extended use (>24 weeks) were removed from the list of safety concerns in RMP v.4.1. Evidence from all sources, including literature, did not support a different safety profile or different risks in elderly patients or in patients with HIV. Regarding the use of delamanid in combination with other anti-TB drugs, anti-retroviral drugs, or other medications, the assessment of data from all available sources does not indicate the existence of any other safety concern as it relates to drug-drug interactions, besides the known risk of QT interval prolongation. This has been supported with several published articles on concomitant use of delamanid with bedaquiline or other anti-TB medications. These articles, along with the most recent scientific literature, had been regularly presented in Section 11 of the delamanid PSURs. The effects of extended delamanid use beyond 24 weeks have been carefully monitored and updated assessments presented in PSURs considering primarily delamanid's potential for covalent binding. Cumulatively, no safety concern could be attributed to the extended use of delamanid. Lastly, since

there was no reasonable expectation that the existing pharmacovigilance activities could further characterise the safety profile of delamanid with respect to missing information, drug use in paediatric patients (body weight <10 kg), drug use in patients with severe renal and severe hepatic impairment were removed from the list of safety concerns in RMP v.4.1.

RMP version 5.0 was updated as a result of the finalization of the Type II Variation procedure related to the EU PASS (EMEA/H/C/002552/II/0061). Based on the completed study and available results, the EU PASS was no longer considered as an additional PV activity. Since evaluation of effectiveness of educational materials for healthcare professionals and patients in the completed EU PASS was in line with the assessments in Delamanid PSURs, the educational materials were deemed to be redundant. In response, the CHMP agreed with the withdrawal of aRMMs for delamanid. In addition, the Important Potential Risks of Drug use during pregnancy and Drug use during breastfeeding were removed as safety concerns since the results of the EU PASS were in line with the known safety profile of Delamanid and additional PV activities and additional risk minimisation measures are no longer required. In addition, the product information is not advising on specific clinical actions to be taken to minimise the risks of Drug use during Pregnancy and Drug use during Breastfeeding.

RMP version 5.1 was updated only to reflect an update on the date the SOB 0002 (results of EndTB study) will be submitted.

2.7.3 SVII.3: Details of Important Identified risks, Important potential risks and Missing Information

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

2.7.3.1.1 SVII.3.1.1: Details of Important Identified Risk: QT Interval Prolongation

Table 2.7.3.1.1-1 SVII.3.1.1-1: Details of Important Identified Risk: QT Interval Prolongation

MedDRA Terms	Clinical trials: Electrocardiogram QT prolonged. Post-market data: Torsade de pointes/QT prolongation (SMQ) - Broad; Torsade de pointes/QT prolongation (SMQ) - Narrow
Potential Mechanisms	QTc prolongation is very closely correlated with delamanid and its major metabolite DM-6705. Plasma albumin and CYP3A4 regulate the formation and metabolism of DM-6705 respectively.
Evidence Sources and Strength of Evidence	QT prolongation has been observed in patients treated with delamanid. This prolongation increases slowly over time in the first 6-10 weeks of treatment and remains stable thereafter. QTc prolongation is very closely correlated with the major delamanid metabolite DM-6705. Plasma albumin and CYP3A4 regulate the formation and metabolism of DM-6705 respectively.

Table 2.7.3.1.1-1	**SVII.3.1.1-1: Details of Important Identified Risk: QT Interval Prolongation**
	In the placebo-controlled trial 242-07-204, in MDR-TB patients receiving 100 mg delamanid twice daily, the mean placebo corrected increases in QTcF from baseline were 7.6 ms at 1 month and 12.1 ms at 2 months. Three percent (3%) of patients experienced an increase of 60 ms or greater at some point during Trial 242-07-204, and 1 patient exhibited a QTcF interval > 500 ms. In Trial 242-09-213, the maximum mean placebo corrected value for QTcF reached 5.9 msec. In Trial 242-12-232, a paediatric clinical study with 37 patients aged 0 to 17 years performed to determine the pharmacokinetics and to evaluate the safety and tolerability of delamanid (treatment duration 10 days), there were no clinically meaningful differences in the mean changes from baseline for the various ECG parameters across the age groups. The mean change from baseline for QTcF reached 4.4 ms at Day 10. Trial 242-12-233 (treatment duration of 6 months) was an open label extension of Trial 242-12-232 and was completed and analysed for patients aged 0 to 17 years. In Trial 242-12-233, the changes in ECG findings were within acceptable limits and QT interval effect was consistent with what was observed in adults. No subjects experienced new onset changes > 480 msec in QTcF, new onset changes > 450 msec in QTcF were experienced by 5/36 (13.8%) subjects, and changes of QTcF ≥ 30 and ≤ 60 msec were experienced by 22/36 (61.1%) subjects. For all cases, the QTc prolongation were not reported as AEs. However, the small sample size of 37 patients between 0 to 17 years of age has to be considered, as well as the lack of a control group for comparison of relative QT effect.
Characterisation of the Risk	**<u>Frequency</u>** Clinical trials (with 95% CI): Available data from completed clinical trials: **242-09-213** In an analysis for a completed clinical study to evaluate the efficacy and safety of delamanid administered orally as 100 mg BID for 2 months followed by 200 mg QD for 4 months in combination with OBR versus placebo with OBR for 6 months (Study 242-09-213), QT interval prolongation was lower than that observed in previous trials. TEAE of ECG QT prolonged was reported for 18/341 (5.3%) patients in the delamanid plus OBR group vs. 5/170 (2.9%) patients in the placebo + OBR group. The maximal mean change in the corrected QT interval using Fridericia's formula (QTcF) (9.2 milliseconds) in the delamanid plus OBR group occurred at weeks 7 and 8, when the regimen switched from 100 mg BID to 200 mg QD. The mean change from baseline for the placebo plus OBR group at Weeks 7 and 8 was 4.7 and 3.9 milliseconds respectively. Thus, an estimate of the placebo-corrected change in QTcF is 4.4 and 5.3 milliseconds at Week 7 and 8, respectively. • The greatest difference in QTcF between treatment arms (placebo corrected change or "delta-delta") over the period of IMP exposure was 5.9 msec (at Week 5). • No cases of Torsades de Pointes were reported **242-07-204** In a clinical study done to evaluate safety, efficacy, and pharmacokinetics of delamanid (Study 242-07-204), frequency of QT interval prolongation was: • 16/161 (9.9%) patients in delamanid 100 mg (twice daily) BID group

Table 2.7.3.1.1-1	**SVII.3.1.1-1: Details of Important Identified Risk: QT Interval Prolongation**
	• 21/160 (13.1%) patients in delamanid 200 mg BID group • 37/321 (11.5%) patients in delamanid overall (95 % CI: 8.2%-15.5%). • The excess of the event QT prolongation over placebo group was 7.8% (95% CI: 3.2%-12.3%) • The mean placebo corrected increases in QTcF from baseline were 7.6 ms at 1 month and 12.1 ms at 2 months. Three percent (3%) of subjects experienced an increase of 60 ms or greater at some point during the trial, and 1 subject exhibited a QTcF interval > 500 ms. No cases of Torsades de Pointes or temporally related events suggestive of proarrhythmias occurred. **242-07-208** In a clinical study done to evaluate safety, tolerability and efficacy of delamanid (**Study 242-07-208**) frequency of QT interval prolongation was: • 4/137 (2.9%) patients in the 100 mg BID group • 2/76 (2.6%) patients in the 200 mg BID group 6/213 (2.8%) patients in delamanid overall (95% CI: 1%-6%) • 6/213 (2.8%) patients in delamanid overall (95% CI: 1%-6%) **242-12-232** A paediatric clinical study done to determine the pharmacokinetics and to evaluate the safety and tolerability of delamanid (**Study 242-12-232**) showed: • No new onset changes > 480 msec in QTcF. • New onset changes > 450 msec in QTcF were experienced by 3 of 37 patients (8.1%) [1 of 7 patients (14.2%) in Group 1 (12-17 years) and 2 of 12 patients (16.6%) in Group 3 (3-5 years)]. • No changes > 60 msec in QTcF. • No cases of Torsades de Pointes were reported. • Two non-serious AEs of QTc prolongation were reported in 2 patients **242-12-233 (continuation of 242-12-232)** A paediatric clinical study done to evaluate the safety, tolerability, pharmacokinetics, and efficacy of delamanid **(Study 242-12-233)** showed: • Five patients (13.9%) [3 of 7 patients (42.9%) in Group 1 (12-17 years), 2 of 6 patients (33.3%) in Group 2 (6-11 years), 0 of 12 and 0 of 11 patients for Groups 3 (3-5 years) and 4 (0-2 years), respectively] with new onset changes > 450 msec in QTcF. • No patient exhibited a QTcF interval > 480 ms. • Two patients (2 of 37 patients, 5.6%) [1 of 7 patients (14.3%) in Group 1 (12-17 years), 1 of 11 patients (9.1%) in Group 4 (0-2 years)] experienced an increase of > 60 ms in QTcF between Days 84 and 126. • No cases of Torsades de Pointes were reported. • No AE of PT QT interval prolonged was reported in this trial. **Healthy volunteers** There were no clinically significant changes in ECG results in any of the completed trials in healthy subjects. The following TEAEs related to ECG abnormalities were reported in completed trials in healthy subjects treated with delamanid (incidence rates reported for delamanid versus placebo): atrial fibrillation, sinus arrest (which turned out as AV block upon retrospective review of the case), and tachycardia (1/422, 0.2% versus 0/96, 0.0% for each). None of these events were serious or resulted in discontinuation of the IMP.

Table 2.7.3.1.1-1	**SVII.3.1.1-1: Details of Important Identified Risk: QT Interval Prolongation**
	Cumulative Post-market data (all sources including spontaneous and other solicited data such as NIS, ISS, CU, registry): The estimated reporting rate as per post-market patient exposure was calculated utilizing a numerator for total number of risk pertinent adverse events assessed causally related by overall conservative causality and a denominator of total post-authorization patients exposed (as presented in Section 2.5.1 SV1 Post-authorisation exposure). For this risk, the reporting ratio was 453/94,981 (0.47%). Of the 376 cases reporting 453 adverse events for the risk concerned, the majority of cases (195) were reported from spontaneous sources, 131 cases were from investigator's sponsored study, 38 cases were reported from non-interventional sources (27 PASS, 11 PMOS) and 12 cases were part of compassionate use project. The reported PTs were Electrocardiogram QT prolonged (415), Syncope (10), Loss of consciousness (9), Cardiac arrest (5), Sudden death (4), Cardiorespiratory arrest (2), Torsade de pointes (2), Ventricular fibrillation (2), Electrocardiogram QT interval abnormal (1), Long QT syndrome (1), Sudden cardiac death (1), and Ventricular tachycardia (1). Study 242-12-402: EU PASS For 9/86 patients related TEAEs of Electrocardiogram QT prolonged were reported. No TEAEs of sudden cardiac death, ventricular extrasystoles or Torsade de pointes were reported. **Cumulative Paediatric Post-marketing data (0 to 17 (inclusive) years of age; all sources including spontaneous and other solicited data such as NIS, ISS, CU, registry):** From the cumulative post-marketing data above, the paediatric population was further analysed. The estimated cumulative reporting rate as per paediatric population (0-17 years) was 14/94,981 (0.01%). Of the cumulative postmarketing cases, 14 were in the paediatric population reporting 17 adverse events (8 cases were reported from spontaneous sources, 3 cases were reported from non-interventional sources and 3 cases were reported as part of compassionate use project). The reported PTs were Electrocardiogram QT prolonged (16) and Loss of consciousness (1). **Cumulative Paediatric Post-marketing data ≥50 kg (all sources including spontaneous and other solicited data such as NIS, ISS, CU, registry):** From the updated cumulative post-marketing data, the population weighing ≥50 kg, was further analysed. The estimated cumulative reporting period for this risk is 3/94,981 (0.003%). Of the 3 post-marketing cases (reporting 3 related AEs), where weight was ≥50 kg, 1 was reported from a spontaneous source, 1 from NIS and 1 from compassionate use. The reported PT was Electrocardiogram QT prolonged (3). **Cumulative Paediatric Post-marketing data ≥30 kg and <50 kg (all sources including spontaneous and other solicited data such as NIS, ISS, CU, registry):** From the updated cumulative post-marketing data, the population weighing ≥30 kg and <50 kg, was further analysed. The estimated cumulative reporting period for this risk is 8/94,981 (0.01%). Of the 6 post-marketing cases (reporting 8 related AEs) where weight was ≥30 kg and <50 kg, 4 cases were reported from

Table 2.7.3.1.1-1	SVII.3.1.1-1: Details of Important Identified Risk: QT Interval Prolongation
	spontaneous source and 2 cases were reported from compassionate use program. The reported PT was Electrocardiogram QT prolonged (8). **Cumulative Paediatric Post-marketing data for children with weight ≥ 20 to < 30 kg (all sources including spontaneous and other solicited data such as NIS, ISS, CU, registry):** From the updated cumulative post-marketing data, the population weighing ≥20 kg to <30 kg was further analysed. The estimated cumulative reporting period for this risk is 2/94,981 (0.002%). This 1 post-marketing case (reporting 2 related AEs) was reported from a spontaneous source for a paediatric patient weighing ≥20 kg to <30 kg. The reported PTs were Loss of consciousness (1) and Electrocardiogram QT prolonged (1). **Cumulative Paediatric Post-marketing data for children with weight ≥ 10 to < 20 kg (all sources including spontaneous and other solicited data such as NIS, ISS, CU, registry):** No data available **Cumulative Paediatric Post-marketing data <10 kg (all sources including spontaneous and other solicited data such as NIS, ISS, CU, registry):** No data available A review of the paediatric cases did not provide enough evidence to support any increased frequency pertaining to this risk for delamanid in the paediatric population. **Seriousness/outcomes** **Clinical trials:** A clinical study done to evaluate the efficacy and safety of delamanid (**Study 242-09-213**) showed: • 6 patients experienced an SAE of QT prolongation in the delamanid plus OBR group (6/341 (1.8%)) • 5 of the SAEs resolved, 1 was considered not related to delamanid and not recovered since the patient later died due to acute respiratory failure secondary to TB progression. A clinical study done to evaluate safety, efficacy and pharmacokinetics of delamanid **(Study 242-07-204**) showed: • 16/321 (5.0%) of the SAEs in delamanid overall. Two patients had Corrected QT interval using Fridericia's formula (QTcF) interval >500 msec. • 12/16 (75.0%) of the SAEs in delamanid overall resolved/recovered. A clinical study done to evaluate safety, tolerability and efficacy of delamanid **(Study 242-07-208)** showed: • 2/213 (0.9%) of the SAEs, one in each dose group (100 mg BID and 200 mg BID). • 2/2 (100%) of the SAEs were resolved/recovered. A clinical study done to evaluate safety, efficacy (sputum culture conversion, in vitro resistance), pharmacokinetics (**Study 242-08-210**) showed:

Table 2.7.3.1.1-1	**SVII.3.1.1-1: Details of Important Identified Risk: QT Interval Prolongation**
	• 1/10 (10%) patient in the 300 mg BID group experienced the SAE. The patient recovered from the SAE. A paediatric clinical study done to determine the pharmacokinetics and to evaluate the safety and tolerability of delamanid **(Study 242-12-232)** showed**:** • No SAEs of QT prolongation. Trial 242-12-233 is an open label extension of Trial 242-12-232 and is completed and analysed for the age groups 0 to 17 years. This study showed for age groups 1, 2, 3 and 4 (0-17 years)**:** • No SAEs of QT prolongation. **Healthy volunteers**: There were no clinically significant changes in ECG results in any of the completed trials in healthy patients. **Cumulative Post-market data (all sources including spontaneous and other solicited data such as NIS, ISS, CU, registry):** There were 376 cases reported cumulatively with 453 adverse events for this risk. Out of those 453 related AEs, 328 AEs were serious, and 125 events were non-serious. There were 14 AEs which reported a fatal outcome including: cardiac arrest (4), sudden death (4), electrocardiogram QT prolonged (2), cardio-respiratory arrest (1), sudden cardiac death (1), Torsade de pointes (1) and ventricular fibrillation (1). The majority of these adverse events were related to the patient's past medical history and concomitant medications. Other reported event outcomes were recovered (193), recovering (109), not recovered (27), otherwise event outcomes were not reported or unknown (110). Study 242-12-402: EU PASS: There were 9 adverse events in 9 patients which were all reported as non-serious. Apart from 1 AE of Electrocardiogram QT prolonged all AEs were reported as recovered or recovering. No fatal outcomes were reported. **Cumulative Paediatric Post-market data (0 to 17 years (inclusive) of age (all sources including spontaneous and other solicited data such as NIS, ISS, CU, registry):** There were 14 cases reported with 17 adverse events. Out of those 17 events, 8 events were reported as serious, and 9 events were non-serious. There were no events with fatal outcome. Other reported event outcomes were recovered (11), recovering (2), not recovered (1) and for the remaining 3 AEs the outcome was not reported or unknown. **Cumulative Paediatric Post-marketing data ≥50 kg (all sources including spontaneous and other solicited data such as NIS, ISS, CU, registry):** There were 3 cases reporting 3 AEs. This event (electrocardiogram QT prolonged) 2 were reported as non-serious and 1 was reported as serious. The reported event outcomes for these events were recovered (2) and recovering (1). **Cumulative Paediatric Post-marketing data ≥30 kg and <50 kg (all sources including spontaneous and other solicited data such as NIS, ISS, CU, registry):** There were 6 cases reporting 8 AEs. Out of those 8 AEs, 4 AEs were serious and 4 were non-serious. There were no events with fatal outcome. Other reported event outcomes were recovered (6), recovering (1) and not recovered (1).

Table 2.7.3.1.1-1	**SVII.3.1.1-1: Details of Important Identified Risk: QT Interval Prolongation**
	Cumulative Paediatric Post-marketing data for children with weight ≥ 20 to < 30 kg (all sources including spontaneous and other solicited data such as NIS, ISS, CU, registry): There was 1 case reporting 2 AEs. Both AEs were assessed as non-serious. The reported outcome for these 2 AEs was unknown. **Cumulative Paediatric Post-marketing data for children with weight ≥ 10 to < 20 kg (all sources including spontaneous and other solicited data such as NIS, ISS, CU, registry):** No data available **Cumulative Paediatric Post-marketing data for children with weight <10 kg (all sources including spontaneous and other solicited data such as NIS, ISS, CU, registry):** No data available A review of the paediatric cases did not provide enough evidence to support any increased seriousness/outcomes pertaining to this risk for delamanid in the paediatric population. **Severity and nature of risk** **Clinical trials:** A clinical study done to evaluate the efficacy and safety of delamanid (**Study 242-09-213**) showed: • In 13/341 (3.8%), 4/341 (1.2%) and 1/341 (0.3%) of the patients in the DLM+OBR group, TEAEs were mild, moderate, and severe, respectively. A clinical study done to evaluate safety, efficacy, and pharmacokinetics of delamanid **(Study 242-07-204)** showed**:** In 35/321 (10.9%), 2/321 (0.6%) and 0/321 (0.0%) of the patients in the overall delamanid plus OBR group, AEs were mild, moderate, and severe, respectively. A clinical study done to evaluate safety, tolerability, and efficacy of delamanid **(Study 242-07-208)** showed**:** • In 5/213 (2.3%), 1/213 (0.5%) and 0/213 (0.0%) of the patients in the overall delamanid plus OBR group, AEs were mild, moderate, and severe, respectively. A clinical study done to evaluate safety, efficacy (sputum culture conversion, in vitro resistance), pharmacokinetics (Study 242-08-210) showed: • The one SAE was mild. A clinical study done to evaluate safety, efficacy, and pharmacokinetics of delamanid (Study 242-06-101) showed: 3/3 SAEs were mild in severity. A paediatric clinical study done to determine the pharmacokinetics and to evaluate the safety and tolerability of delamanid **(Study 242-12-232)** showed**:** • In 2/37 (5.4%) with QT prolonged, both non-serious AEs occurred in age Group 3 (3-5 years) and were mild.

Table 2.7.3.1.1-1	**SVII.3.1.1-1: Details of Important Identified Risk: QT Interval Prolongation**
	Trial 242-12-233 is an open label extension of Trial 242-12-232 and is completed and analysed for the age groups 0 to 17 years. This study showed for age Groups 1, 2, 3 and 4 (0-17 years): • No patients with AE of QT prolonged. **Cumulative Post-market data (all sources including spontaneous and other solicited data such as NIS, ISS, CU, registry):** Overall, there has been no change in the frequency and severity of this risk. Gender distributions in these patients included 165 females and 194 males while gender was unknown for 17 patients. Ages ranged from 9 to 86 years with the median age of 47.5 years old. Considering the nature of the AEs reported pertaining to this risk it is noted that in none of the reported delamanid was used as the sole QTc prolonging agent in the treatment regimen. In the majority of the cases, potential contributing/causative factors like medical history of coronary artery disease, hypertension, arrhythmia, arteriosclerosis, diabetes mellitus and/or hospitalization for concurrent respiratory infection/failure, concomitant medication (bedaquiline, clofazimine, linezolid, moxifloxacin etc.) and pre-existing electrolyte disturbances have been reported. Most of the cases reported 2-3 or more potentially QTc prolonging medications (bedaquiline, clofazimine and moxifloxacin etc.) being used in parallel with delamanid. There were 160 AEs reported (in 144 cases) where delamanid therapy was either suspended/interrupted or was permanently withdrawn. Out of these 160 AEs, 66 had a positive dechallenge where the patient started recovering/resolving after stopping delamanid therapy (temporarily or permanently). Moreover, there were 2 AEs (2 cases) reported where the events reappeared on re-introducing delamanid therapy. One of these patients had a medical history of electrocardiogram QT prolonged, drug resistance, HIV infection, hypokalaemia, hypothyroidism, hypomagnesemia, hypocalcaemia etc. and concomitant medications tenofovir, emtricitabine, efavirenz and nevirapine. The second patient had a medical history of HIV infection, deafness, hepatitis B and blood albumin decreased. The concomitant medications included tenofovir disoproxil fumarate, emtricitabine and efavirenz <u>Study 242-12-402: EU PASS:</u> There were 6 mild and 3 moderate adverse events. The patients' age ranged from 30 - 72 years in 4 male and 5 female patients. All patients were administered with at least a fluoroquinolone concomitantly, while most of them additionally received one to two other anti-TB drugs with a potential QT prolonging effect (clofazimine, bedaquiline). Medical history and concurrent conditions included dyspepsia, cardiovascular diseases (hypertension, arrhythmia, coronary artery disease, angina pectoris), alcohol abuse, drug dependence and psychiatric disorders (anxiety, depression). **Cumulative Paediatric Post-market data (0 to 17 years (inclusive) of age; all sources including spontaneous and other solicited data such as NIS, ISS, CU, registry**): Overall, there has been no change in the frequency and severity of this risk in the paediatric patients administered with delamanid therapy. There were 14 patients who reported the AE of QT prolongation or loss of consciousness including 10 females and 4 male patients. Median age was 13 years. In all cases, 2-3 potentially QTc prolonging medications (e.g. bedaquiline, clofazimine and moxifloxacin) were used in parallel with delamanid.

Table 2.7.3.1.1-1	**SVII.3.1.1-1: Details of Important Identified Risk: QT Interval Prolongation**
	Additionally, many cases reported potential contributing/causative factors like medical history and pre-existing electrolyte disturbances. **Cumulative Paediatric Post-marketing data ≥50 kg (all sources including spontaneous and other solicited data such as NIS, ISS, CU, registry):** There were three patients weighing ≥50 kg reporting electrocardiogram QT prolonged. Two patients, one male and one female, were PPD years old and one female patient was PPD years old. The severity of the AEs was mild (2) and moderate (1). Two of the three patients were also taking other potentially QTc prolonging medication (e.g. bedaquiline, clofazimine and pyramide) in parallel to delamanid. **Cumulative Paediatric Post-marketing data ≥30 kg and <50 kg (all sources including spontaneous and other solicited data such as NIS, ISS, CU, registry):** Overall, there has been no change in the frequency and severity of this risk in the paediatric patients administered with delamanid therapy. There were 6 patients who experienced the AE of electrocardiogram QT prolonged including 1 male and 5 female patients. Ages ranged from 9 to 17 years. The median age was 13 years. **Cumulative Paediatric Post-marketing data for children with weight ≥ 20 to < 30 kg (all sources including spontaneous and other solicited data such as NIS, ISS, CU, registry):** There was 1 patient who weighed ≥20 kg and < 30 kg and reported the AEs of loss of consciousness and electrocardiogram QT prolonged. This was a PPD-year-old female patient who was taking potentially QTc prolonging medications (clofazimine and moxifloxacin) in parallel with delamanid. **Cumulative Paediatric Post-marketing data for children with weight ≥ 10 to < 20 kg (all sources including spontaneous and other solicited data such as NIS, ISS, CU, registry):** No data available **Cumulative Paediatric Post-marketing data <10 kg (all sources including spontaneous and other solicited data such as NIS, ISS, CU, registry):** No data available A review of the paediatric cases did not provide enough evidence to support any increased severity and nature of risk pertaining to this risk for delamanid in the paediatric population.
Risk Groups or risk factors	• Prolonged QTc interval, e.g., congenital long QT syndrome • Female sex; advanced age • Heart disease (bradycardia, cardiac arrhythmias congestive heart failure) • Hypokalaemia, hypomagnesaemia, hypocalcaemia • Combinations of drugs (QT prolonging drugs) • Severe hepatic impairment • Hypoalbuminaemia • Alcohol abuse • Advanced HIV infection

Table 2.7.3.1.1-1	**SVII.3.1.1-1: Details of Important Identified Risk: QT Interval Prolongation**
Preventability	• QT interval prolonging medications should be generally used with caution in combination, as this increases the risk of QT prolongation and associated complications • Not using the drug in patients with a QT interval > 500 ms • Not using the drug in patients with blood albumin values under 2.8 mg/dL. • Prevention of complications related to prolongation of the QT interval: o Administration only after ECG evaluation o Frequency and duration of ECG monitoring depending on the individual patient's condition (see risk factors) o Regular monitoring of serum albumin and electrolyte levels (with supplementation if needed)
Impact on the Risk-benefit Balance of the Product	QT prolongation has been shown to lead to unexpected post-marketing reports of sudden cardiac death and an increased propensity to develop a ventricular tachyarrhythmia (e.g., Torsades de Pointes). Although a direct link between QT interval prolongation and arrhythmogenesis is still unclear, QT prolongation is considered a significant risk factor.[29] Based on the clinical trial programme for delamanid, patients receiving 100 mg twice daily (aged 12 years and older), children (aged 6-11) receiving 50 mg twice daily, children (aged 3-5) receiving 25 mg twice daily, and newborns and infants (aged birth - 2) receiving 5-10 mg twice daily based on body weight, the AE of QT prolongation was not accompanied by clinical symptoms and the event resolved if managed appropriately. The impact of QT prolongation on the individual patient during delamanid therapy is currently assessed as manageable if monitored and addressed according to SmPC and educational materials.
Public Health Impact	Absolute risk cannot be calculated since the size of the target population (patients with MDR-TB in need for delamanid) is unknown. Consequently, actual number of individuals affected, or overall outcome at population level cannot be assessed. Costs for cardiac disorders in general pose a huge burden on public health systems and result in major economic loss resulting from the individual's inability to work. However, the potential impact of QT prolongation on public health resulting from delamanid use is manageable considering the data from clinical trials and post-marketing setting, including published literature, all confirming that with the implementation of the recommendations from SmPC on the ECG, albumin and electrolytes monitoring, the risk can be well controlled.

2.7.3.1.2 SVII.3.1.2: Details of Important Potential Risk: Liver Disorders

Table 2.7.3.1.2-1	**SVII.3.1.2-1: Details of Important Potential Risk: Liver Disorders**
MedDRA Terms	Clinical trial data: SOC Hepatobiliary disorders/SMQ Post-marketing: • Cholestasis and jaundice of hepatic origin (SMQ-Narrow) • Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions (SMQ - Narrow) • Hepatitis, non-infectious (SMQ - Narrow) • Liver related investigations, signs and symptoms (SMQ - Broad) • Liver related investigations, signs and symptoms (SMQ - Narrow)
Potential Mechanisms	The current evidence arising from pre-clinical studies, clinical trials or literature review has not clarified potential mechanism for liver disorders.

Table 2.7.3.1.2-1	**SVII.3.1.2-1: Details of Important Potential Risk: Liver Disorders**
Evidence Sources and Strength of Evidence	Liver disorders are well known complications of TB, and several drugs used as part of the MDR-TB treatment regimens have well-established hepatic side effects. The overall frequency of adverse events related to or indicating liver disorders in the clinical studies with delamanid was very low, with no indication of difference from placebo or of any dose response relationship. Furthermore, there has been no non-clinical evidence for a hepatotoxic effect, nor have there been any signal in laboratory indicators of liver cell injury or cholestatic disease. In cases with adverse events involving hepatic function in which a causal relation with delamanid cannot fully be ruled out, there were other factors, including the underlying disease and concomitant medication, which may have played a causative role in the events. The clinical and non-clinical data do not provide any evidence that would support the plausibility of delamanid as culprit for the findings. In Trial 242-09-213, TEAEs referring to hepatobiliary disorders were similar across treatment groups. The lab values pertaining to liver function tests retrieved during this trial also did not show any significant differences across treatment groups. The frequency of liver disorders in the Phase 1, open-label, multidose, paediatric trial (Study 242-12-232) of 37 patients aged 0-17 years was low with a single occurrence in 1 patient (1/37, 2.7%) in Group 4 (ages 0 to 2 years). Trial 242-12-233 is an open label extension of Trial 242-12-232 and is completed across all age groups (0-17 years). Occurrences included 1 event each of activated partial thromboplastin time prolonged, alanine aminotransferase increased, coagulation time prolonged, hepatic enzyme increased; and 3 events each of liver function test increased and prothrombin time prolonged.
Characterisation of the Risk	**Frequency** Clinical trials (with 95% CI) Available data from completed clinical trials: **Study 242-09-213** The SOC hepatobiliary disorders revealed similar frequencies of TEAEs across the delamanid plus OBR and placebo plus OBR treatment groups; comparing hepatitis toxic, hepatotoxicity, and drug induced liver injury between delamanid plus OBR and placebo plus OBR group, those made up 2.1 vs 0.6%, 6.5 vs 7.1% and 0.3 vs 2.1%, respectively - so comparing total frequencies per treatment arm percentages these are similar across treatment groups; comparing pooled TEAE frequencies on transaminases increased (including AST increased, ALT increased, hepatic enzyme increased, hepatic function abnormal, transaminases increased, hypertransaminasaemia, liver disorder, Gamma-glutamyltransferase increased) frequencies would be 6.8% in delamanid plus OBR vs 12.5% in placebo plus OBR. **242-07-204** A clinical study done to evaluate safety, efficacy and pharmacokinetics of delamanid **(Study 242-07-204)** showed: • 7 (4.3%) patients in the delamanid 100 mg BID group

Table 2.7.3.1.2-1	SVII.3.1.2-1: Details of Important Potential Risk: Liver Disorders
	• 10 (6.3%) patients in the delamanid 200 mg BID group • 17 (5.3%) patients in delamanid overall (95% CI: 3.1% - 8.3%). • The excess of the event over placebo group was -2.8% (95% CI: -7.7% - +2.1%) **242-07-208** A clinical study done to evaluate safety, tolerability, and efficacy of delamanid **(Study 242-07-208)** showed**:** • 20 (15%) patients in the 100 mg BID group • 4 (5.3%) patients in the 200 mg BID group • 24 (11%) patients in delamanid overall (95% CI: 7.4% - 16.3%) **242-12-232** A paediatric clinical study done to determine the pharmacokinetics and to evaluate the safety and tolerability of delamanid **(Study 242-12-232)** showed**:** **Prothrombin Time Prolonged** • 1/37 (2.7%) **242-12-233** Trial 242-12-233 is an open label extension of Trial 242-12-232 and is completed and analysed for the age groups 0 to 17. This study showed for age groups 1, 2, 3, and 4 (0-17 years)**:** **Activated Partial Thromboplastin Time Prolonged** • 1/37 (2.7%) **Alanine Aminotransferase Increased** • 1/37 (2.7%) **Coagulation Time Prolonged** • 1/37 (2.7%) **Hepatic Enzyme Increased** • 1/37 (2.7%) **Liver Function Test Increased** • 3/37 (8.1%) **Prothrombin Time Prolonged** • 3/37 (8.1%) **Healthy volunteers:** • 17 (4.9%) patients in the delamanid only group experienced the AE versus 8 (8.3%) in the placebo group. **Cumulative Post-market data (all sources including spontaneous and other solicited data such as NIS, ISS, CU, registry):** The estimated reporting rate as per post-market patient exposure was calculated utilizing a numerator for total number of risk pertinent adverse events assessed causally related by overall conservative causality and a denominator of total post-authorization patients exposed (as presented in Section 2.5.1 SV1 Post-authorization exposure). Postauthorisation exposure for this risk, the reporting ratio was 387/94,981 (0.41 %) in 260 cases. Of the 260 cases reporting 387 related AEs for the risk concerned, the majority of cases were reported from spontaneous sources (172) and 10 cases from spontaneous literature sources, followed by 41 cases from ISS, 28 cases from non-interventional sources and 9 cases were reported from compassionate use or market research programs.

Table 2.7.3.1.2-1	**SVII.3.1.2-1: Details of Important Potential Risk: Liver Disorders**
	The most frequently reported adverse events (reported 10 or more times) were Alanine aminotransferase increased (63), Aspartate aminotransferase increased (80), Blood alkaline phosphatase increased (10), Blood bilirubin increased (15), Drug-induced liver injury (19), Gamma-glutamyl transferase increased (16), Hepatic enzyme increased (27), Hepatic function abnormal (11), Hepatitis (22), Hepatotoxicity (28) and Hypoalbuminaemia (20). 242-12-402: EU PASS: For 2/86 patients related TEAEs were reported. The PTs were hepatic cytolysis and hepatitis acute. **Cumulative Paediatric Post-marketing date (0 to 17 (inclusive) years of age; all sources including spontaneous and other solicited data such as NIS, ISS, CU, registry):** From the cumulative post-marketing data above, the paediatric population was further analysed. The estimated cumulative reporting rate as per paediatric population, age 8 months to 17 years, post-market exposure for this risk is 33/94,981 (0.03%) in 22 cases. Of the 22 post-marketing paediatric cases (reporting 33 related adverse events associated with liver disorders), 14 cases were reported from spontaneous sources, 5 cases from ISS and 3 cases were reported from the compassionate use or market research programs. The most frequently reported PTs (≥2) were Alanine aminotransferase increased (7), Aspartate aminotransferase increased (4), Hypoalbuminaemia (3) and 2 of each: Ascites, Drug-induced liver injury, Hepatitis, Hepatic cytolysis and Hepatic enzyme increased. For 4 cases either age and weight or weight was not reported. These cases will not be discussed further below for the weight groups but are included in the overall case count of 22 cases/33 AEs: • In 1 case with 1 AE of Alanine aminotransferase increased (non-serious, mild, related, recovered) in an PPD patient, the age and weight were not reported. The patient received 100 mg delamanid bid. • A PPD patient with 2 non-serious AEs of Alanine aminotransferase increased and Aspartate aminotransferase increased, both not related and unknown outcome received 200 mg delamanid reportedly once daily. • A PPD patient with 2 SAEs of Cholestasis and Hepatic cytolysis, both not related, and outcome recovered/resolved, confounded by underlying Hepatitis B and Starvation received 100 mg delamanid with an unknown dose frequency. • An PPD infant with 1 mild (grade 1) and non-serious AE of Alanine aminotransferase increase received delamanid (unknown dosage and duration). AE reported around 55 days after starting delamanid and outcome of the event was resolved. The company assessed the event as not related to delamanid as event resolved without any change in delamanid therapy. Patient was hospitalized at the time of LFTs increase due to Bronchiolitis. **Cumulative Paediatric Post-marketing data ≥ 50 kg (all sources including spontaneous and other solicited data such as NIS, ISS, CU, registry):** There were no cases reported for the peadiatric population weighing ≥ 50 kg.

Table 2.7.3.1.2-1	SVII.3.1.2-1: Details of Important Potential Risk: Liver Disorders
	Cumulative Paediatric Post-marketing data ≥ 30 kg and < 50 kg (all sources including spontaneous and other solicited data such as NIS, ISS, CU, registry): From the cumulative post-marketing data, the paediatric population with body weight of ≥30 kg - <50 kg was further analysed. The estimated cumulative reporting rate as per paediatric population, with a reported weight ≥30 kg - <50 kg, post-market exposure for this risk is 6/94,981 (0.006%). There were 5 cases reporting 6 adverse events in the paediatric population weighing ≥30 kg - <50 kg. Of the 5 post-marketing paediatric cases (reporting 6 adverse events), 2 cases were reported from spontaneous sources, 2 cases were part of compassionate use projects and 1 case from ISS. The most frequently reported PT (≥2) was Hypoalbuminaemia (2). **Cumulative Paediatric Post-marketing data for children with weight ≥20 to <30 kg (all sources including spontaneous and other solicited data such as NIS, ISS, CU, registry):** From the cumulative post-marketing data, the paediatric population with body weight of ≥20 kg and < 30 kg were further analysed. The estimated cumulative reporting rate as per paediatric population, with a reported weight ≥20 kg and < 30 kg, post-market exposure for this risk is 8/94,981 (0.008%). There were 5 cases reporting 8 adverse events in the paediatric population weighing ≥20 kg and < 30 kg. Of the 5 post-marketing paediatric cases (reporting 8 adverse events), 5 cases were reported from spontaneous sources and 1 case from a market research program. The most frequently reported PTs (≥2) were Aspartate aminotransferase increased (2) and Alanine aminotransferase increased (2). **Cumulative Paediatric Post-marketing data for children with weight ≥ 10 to < 20 kg (all sources including spontaneous and other solicited data such as NIS, ISS, CU, registry):** From the cumulative post-marketing data, the paediatric population with body weight of ≥10 kg and < 20 kg were further analysed. The estimated cumulative reporting rate as per paediatric population, with a reported weight ≥10 kg and <20 kg, post-market exposure for this risk is 11/94,981 (0.01%). There were 6 cases reporting 11 adverse events in the paediatric population weighing ≥10 kg and < 20 kg. Of the 6 post-marketing paediatric cases (reporting 11 adverse events), 5 cases were reported from spontaneous sources and 1 from ISS. The most frequently reported PTs (≥2) were hepatic enzyme increased (2) and Hepatitis (2). **Cumulative Paediatric Post-marketing data <10 kg (all sources including spontaneous and other solicited data such as NIS, ISS, CU, registry):** From the cumulative post-marketing data, the paediatric population with body weight of < 10 kg was further analysed. The estimated cumulative reporting rate as per paediatric population, with a reported weight <10 kg, post-market exposure for this risk is 2/82,153 (0.002%). There were 2 cases reported from ISS 242-201-00004 with 1 AE each in the paediatric population weighing < 10 kg. An AE of Transaminases increased was reported in an 8-month-old female with a weight of 7.9 kg.

Table 2.7.3.1.2-1	**SVII.3.1.2-1: Details of Important Potential Risk: Liver Disorders**
	A SAE of Hepatic enzyme increased was reported in an 8-month-old male with a weight of 9.6 kg **Seriousness/outcomes** Clinical trials: A clinical study done to evaluate safety and efficacy of delamanid **(Study 242-09-213)** showed**:** • 0/341 (0.0%) of the SAEs in delamanid group A clinical study done to evaluate safety, efficacy, and pharmacokinetics of delamanid **(Study 242-07-204)** showed**:** • 3/321 (0.9%) SAEs in delamanid overall. 3/3 (100%) of the SAEs recovered/resolved. A clinical study done to evaluate safety, tolerability, and efficacy of delamanid **(Study 242-07-208)** showed**:** • 5/213 (2.3%) SAEs in delamanid overall. 5/5 (100%) of the SAEs recovered/resolved. A paediatric clinical study done to determine the pharmacokinetics and to evaluate the safety and tolerability of delamanid **(Study 242-12-232)** showed**:** • No SAEs of liver disorders Trial 242-12-233 is an open label extension of Trial 242-12-232 and is completed and analysed for the age groups 0 to 17. This study showed for age Groups 1, 2, 3, and 4 (0-17 years)**:** • No SAEs of liver disorders. **Healthy volunteers:** • 0/347 (0.0%) SAEs in the delamanid group **Cumulative Post-market data (all sources including spontaneous and other solicited data such as NIS, ISS, CU, registry):** There were 260 cases reported cumulatively by the DLP with 387 AEs assessed as causally related to this risk. Out of those 387 events, 162 events were serious, and 225 events were non-serious. Five (5) adverse events in 5 cases reported a fatal outcome: Drug-induced liver injury (1), Gamma-glutamyl transferase increased (1), Hepatitis toxic (1), Hyperbilirubinaemia (1) and Spontaneous bacterial peritonitis (1). Other reported AE outcomes were “recovered”, recovering or recovered w. sequelae (n=181) “, and “not recovered” (n=38), or otherwise not reported or unknown (163). 242-12-402: EU PASS: Both TEAEs (PTs hepatic cytolysis and hepatitis acute) were reported as serious and recovered. **Cumulative Paediatric Post-market data (0 to 17 years (inclusive) of age; all sources including spontaneous and other solicited data such as NIS, ISS, CU, registry):** There were 22 paediatric cases reported cumulatively by the DLP with 33 AEs. Out of those 33 AEs, 20 AEs were serious including (≥2 AEs):

Table 2.7.3.1.2-1	SVII.3.1.2-1: Details of Important Potential Risk: Liver Disorders
	Alanine aminotransferase increased (2), Drug-induced liver injury (2), Hepatic cytolysis (2), Hepatitis (2), Hypoalbuminaemia (2), and Hepatic enzyme increased (3). There were no (0) fatal adverse events reported. Other reported event outcomes were “recovered” or “recovering/resolving” (18), not recovered/not resolved (1) and not reported/unknown for rest of the AEs (14). **Cumulative Paediatric Post-marketing data ≥ 50 kg (all sources including spontaneous and other solicited data such as NIS, ISS, CU, registry):** Not applicable **Cumulative Paediatric Post-marketing data ≥ 30 kg and < 50 kg (all sources including spontaneous and other solicited data such as NIS, ISS, CU, registry):** There were 5 cases reporting 6 adverse events in the paediatric population weighing ≥ 30 kg - < 50 kg. Out of those 6 AEs events, 5 AEs were serious: Hypoalbuminaemia (n=2), Alanine aminotransferase increased (1), Ascites (1) and Hepatotoxicity (n=1). There were no (0) fatal adverse events reported. Other reported event outcomes were “recovered” (3) and not reported/unknown (3). **Cumulative Paediatric Post-marketing data for children with weight ≥ 20 to < 30 kg (all sources including spontaneous and other solicited data such as NIS, ISS, CU, registry):** There were 5 cases reporting 8 adverse events in the paediatric population weighing ≥20 kg and < 30 kg. Out of those 8 AEs events, 3 AEs were serious: Blood alkaline phosphatase increased (1), Drug-induced liver injury (1) and Hepatosplenomegaly (1). There were no (0) fatal adverse events reported. Other reported event outcomes were “recovered” (3) and not reported/unknown (5). **Cumulative Paediatric Post-marketing data for children with weight ≥ 10 to < 20 kg (all sources including spontaneous and other solicited data such as NIS, ISS, CU, registry):** There were 6 cases reporting 11 adverse events in the paediatric population weighing ≥10 kg and < 20 kg. Out of those 11 AEs events, 8 AEs were serious: Acute hepatic failure (1), Alanine aminotransferase increased (1), Drug-induced liver injury (1), Hepatic cytolysis (1), Hepatic enzyme increased (2) and Hepatitis (2). There were no (0) fatal adverse events reported. Other reported event outcomes were “recovered” or “resolving” (7), not recovered/not resolved (1) and not reported/unknown (3). **Cumulative Paediatric Post-marketing data <10 kg (all sources including spontaneous and other solicited data such as NIS, ISS, CU, registry):** There were 2 cases reporting 1 AE each in the paediatric population weighing < 10 kg. The SAE of Transaminases increased in an 8-month-old infant was reported as resolved.

Table 2.7.3.1.2-1	SVII.3.1.2-1: Details of Important Potential Risk: Liver Disorders
	The SAE of Hepatic enzyme increased in an 8-month-old infant was reported as resolved. **Severity and nature of risk** **Clinical trials:** A clinical study done to evaluate safety and efficacy of delamanid **(Study 242-09-213)** showed the following severities with respect to PTs subsumed under the SMQ as mentioned below (figures for mild, moderate, severe respectively)**:** • Chronic hepatitis 0/341 (0.0%), 1/341 (0.3%), 0/341 (0.0%) • Drug-induced liver injury 0/341 (0.0%), 1/341 (0.3%), 0/341 (0.0%) • Hepatic steatosis 1/341 (0.3%), 0/341 (0.0%), 0/341 (0.0%) • Hepatitis 0/341 (0.0%), 0/341 (0.0%), 1/341 (0.3%) • Hepatitis acute 0/341 (0.0%), 0/341 (0.0%), 1/341 (0.30%) • Hepatitis toxic 2/341 (0.6%), 3/341 (0.9%), 2/341 (0.6%) • Hepatomegaly 1/341 (0.3%), 1/341 (0.3%), 0/341 (0.0%) • Hepatotoxicity 4/341 (1.2%), 14/341 (4.1%), 4/341 (1.2%) • Hyperbilirubinaemia 4/341 (1.2%), 1/341 (0.3%), 0/341 (0.0%) • Hypertransaminasaemia 1/341 (0.3%), 2/341 (0.6%), 0/341 (0.0%) • Jaundice 0/341 (0.0%), 0/341 (0.0%), 1/341 (0.3%) • Liver disorder 1/341 (0.3%), 0/341 (0.0%), 0/341 (0.0%) • Alanine aminotransferase increased 1/341 (0.3%), 1/341 (0.3%), 0/341 (0.0%) • Aspartate aminotransferase increased 4/341 (1.2%), 0/341 (0.0%), 1/341 (0.3%) • Blood bilirubin increased 0/341 (0.0%), 1/341 (0.3%), 0/341 (0.0%) • Gamma-glutamyltransferase increased 1/341 (0.3%), 1/341 (0.3%), 0/341 (0.0%) • Hepatic enzyme increased 2/341 (0.6%), 0/341 (0.0%), 0/341 (0.0%) • Prothrombin level decreased 0/341 (0.0%), 1/341 (0.3%), 0/341 (0.0%) • Transaminases increased 8/341 (2.3%), 0/341 (0.0%), 0/341 (0.0%) • Hypoalbuminaemia 1/341 (0.3%), 1/341 (0.3%), 0/341 (0.0%) A clinical study done to evaluate safety, efficacy, and pharmacokinetics of delamanid **(Study 242-07-204)** showed**:** • 13 (76.5%) of the AEs were mild in severity. • 3 (17.6%) of the AEs were moderate in severity. • 1 (5.9%) of the AEs was severe in severity. A clinical study done to evaluate safety, tolerability, and efficacy of delamanid **(Study 242-07-208)** showed: • 17 (70.8%) of the AEs were mild in severity. • 6 (25.0%) of the AEs were moderate in severity. • 1 (4.2%) of the AEs were severe in severity. A paediatric clinical study done to determine the pharmacokinetics and to evaluate the safety and tolerability of delamanid **(Study 242-12-232)**

Table 2.7.3.1.2-1	SVII.3.1.2-1: Details of Important Potential Risk: Liver Disorders
	showed the following severities with respect to PTs subsumed under the SMQ as mentioned below**:** **Prothrombin Time Prolonged** • 1 (2.7%) of the AEs was mild. Trial 242-12-233 is an open label extension of Trial 242-12-232 and is completed and analysed across all age groups (0-17 years). This study showed the following severities with respect to PTs subsumed under the SMQ as mentioned below for age Groups 1, 2, 3, and 4 (0-17 years)**:** **Activated Partial Thromboplastin Time Prolonged** • 1 (2.7%) of the AEs was mild. **Alanine Aminotransferase Increased** • 1 (2.7%) of the AEs was mild **Hepatic Enzyme Increased** • 1 (2.7%) of the AEs was mild **Coagulation Time Prolonged** • 1 (2.7%) of the AEs was mild **Liver Function Test Increased** • 3 (8.1%) of the AEs were mild **Prothrombin Time Prolonged** • 3 (8.1%) of the AEs were mild **Healthy volunteers:** • 17 (100%) of the AEs were mild in severity. **Cumulative Post-market data (all sources including spontaneous and other solicited data such as NIS, ISS, CU, registry):** Overall, there has been no change in the severity of this risk. Gender distributions in these patients included 112 females and 143 males while gender was unknown for 5 patients. Ages ranged from 8 months to 83 years with the median age of 38 years. For 11 cases the age was not reported. The vast majority of adult patients received 100 mg delamanid BID or reportedly 200 mg daily. The main co-suspect medications administered were anti-TB drugs including bedaquiline, amoxicillin-clavunate, linezolid, clofazimine, cycloserine, terizidone, pyrazinamide, para-aminosalicylic acid, isoniazid, kanamycin, moxifloxacin and levofloxacin. There were many additional confounding factors for the reported AEs including further co-suspect medications (e. g. antiretroviral [ARV], NSAID) and medical history of HIV infection, alcohol abuse, hepatitis A, B or C, DILI, liver disorder respectively injury, malnutrition and Drug Rash with Eosinophilia and Systemic Symptoms (DRESS). 242-12-402: EU PASS: The adverse event of hepatic cytolysis in a PPD-year-old female was reported as severe. Co-administration of pyrazinamide, moxifloxacin and clofazimine was considered a confounding factor. The AE of acute hepatitis in a PPD-year-old male was reported as mild. Underlying chronic hepatitis C and the use of concomitant anti-TB drugs with hepatotoxic potential were considered as confounding factors.

Table 2.7.3.1.2-1	SVII.3.1.2-1: Details of Important Potential Risk: Liver Disorders
	Cumulative Paediatric Post-marketing date (0 to 17 years (inclusive) of age; all sources including spontaneous and other solicited data such as NIS, ISS, CU, registry): Of the 22 cases, there were 15 females and 7 male patients. Ages ranged from 8 months to 17 years of age (for 1 case age was not reported). The primary co-suspect medications administered in the paediatric population included bedaquiline, amoxicillin-clavulanic acid, linezolid, ethionamide cycloserine, terizidone, moxifloxacin, pyrazinamide, kanamycin and PAS. There were many additional confounding factors for the reported AEs including further co-suspect medications (e. g. ARV) and medical history of HIV infection, liver injury, hepatitis A or B, malnutrition and DRESS. **Cumulative Paediatric Post-marketing data ≥ 50 kg (all sources including spontaneous and other solicited data such as NIS, ISS, CU, registry):** Not Applicable **Cumulative Paediatric Post-marketing data ≥ 30 kg and < 50 kg (all sources including spontaneous and other solicited data such as NIS, ISS, CU, registry):** There were 5 cases in 5 female patients in the paediatric population weighing ≥ 30 kg - < 50 kg. All patients received a daily dose of 200 mg delamanid. **Cumulative Paediatric Post-marketing data for children with weight ≥20 to < 30 kg (all sources including spontaneous and other solicited data such as NIS, ISS, CU, registry):** There were 5 cases in 4 female and 1 male patients in the paediatric population weighing ≥20 kg and < 30 kg. 1 patient received 50 mg daily and 4 patients received 100 mg daily **Cumulative Paediatric Post-marketing data for children with weight ≥10 to < 20 kg (all sources including spontaneous and other solicited data such as NIS, ISS, CU, registry):** There were 6 cases in 2 male and 4 female patients in the paediatric population weighing ≥10 kg and < 20 kg. One patient received 25 mg QD, one patient received 25 mg BID, 2 patients received 50 mg BID, one patient received 200 mg QD and for one patient an unknown dose BID was reported. **Cumulative Paediatric Post-marketing data <10 kg (all sources including spontaneous and other solicited data such as NIS, ISS, CU, registry):** There was 1 female and 1 male case in the paediatric population weighing < 10 kg. The female patient received 25 mg respectively 30 mg delamanid daily and the AE of transaminases increased was reported to be grade 2 (moderate). Soon after delamanid was withdrawn, a helminthic infection was identified, and the baby was put on therapy with mebendazole after which AST grade 1 was reported. Liver is frequently the primary organ to be involved in human helminthic infestation.

Table 2.7.3.1.2-1	**SVII.3.1.2-1: Details of Important Potential Risk: Liver Disorders**
	The male patient received 30 mg QD, and the AE hepatic enzyme increased was reported to be grade 3 (severe). The baby had a recent history of bronchiolitis before starting delamanid therapy and was admitted to hospital for the same.
Risk Groups or risk factors	Despite a multi-drug regimen resulting in drug-induced liver injury, advanced age, hypoalbuminaemia and alcohol consumption, along with advanced disease state, have been shown to be independent risk factors for liver disorders (specifically drug induced liver disease) in pulmonary tuberculosis patients[30]
Preventability	Currently available data do not provide clear evidence on delamanid's role in liver disorders. Considering the risk groups and risk factors, most of all concomitant medications, monitoring for signs and symptoms of liver injury would enable earlier detection and intervention/drug discontinuation to prevent serious or irreversible outcomes like liver failure.
Impact on the Risk-benefit Balance of the Product	Patients with chronic liver disorders suffer from debilitating fatigue, pruritus, loss of esteem, depression, and complications of cirrhosis.[31,32] These disorders can lead to the reduction of health-related quality of life as reflected in the disturbances of cognitive, behavioural, physical and social aspects of well-being and therefore lead to physical and psychological problems.[33] However, considering the deadly disease treated the benefit of delamanid treatment outweighs this potential risk.
Public Health Impact	Delamanid is always administered in combination with other anti-TB drugs, where one or more of them have liver toxicity as a known adverse drug reaction. Absolute risk cannot be calculated since the size of the target population (patients with MDR-TB in need for delamanid) is unknown. Consequently, actual number of individuals affected, or overall outcome at population level cannot be assessed.

2.7.3.2 SVII.3.2: Presentation of the Missing Information

None.

2.8 Module SVIII: Summary of the Safety Concerns

Table 2.8-1	**SVIII-1: Summary of Ongoing Safety Concerns**
Important Identified Risks	QT interval prolongation
Important Potential Risks	Liver disorders
Missing Information	None

3 PART III: PHARMACOVIGILANCE PLAN (Including Post-authorisation Safety Studies)

3.1 III.1: Routine Pharmacovigilance Activities

The MAH maintains systems and standard practices for Routine Pharmacovigilance activities to collect reports of suspected adverse reactions (including spontaneous reports, reports from clinical studies, reports of pregnancy/lactation exposures, overdoses and medication errors); prepare reports for regulatory authorities (e.g., individual case safety reports, PSURs, etc.), and maintain continuous monitoring of the safety profile of approved products (including signal detection, issue evaluation, updating of labelling, and liaison with regulatory authorities). The MAH maintains a Pharmacovigilance System Master File which contains details of these systems and standard practices.

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None

3.2 III.2: Additional Pharmacovigilance Activities

endTB (Evaluating Newly approved Drugs for multidrug-resistant TB)

Protocol Number: NCT02754765 (Clinicaltrials.gov)

Summary

Study Status: The study is completed, enrolment was completed in October 2021 with the overall inclusion of 754 patients.

Rationale: The endTB study aims to identify multiple new, effective regimens by comparing five experimental regimens containing one or two new drugs in patients with fluoroquinolone-susceptible MDR-TB.

Population: Adults and adolescents (>15 years old) with pulmonary TB with M. tuberculosis resistant to RIF and without resistance to fluoroquinolones.

Design: The endTB is a randomized, controlled, open-label, multi-country Phase III study evaluating the efficacy of new combination regimens for treatment of MDR-TB. The study will enroll in parallel across 5 experimental groups and one standard-of-care control group. Study participation in all groups will be 104 weeks post randomization. In the experimental arms, treatment will be for 39 weeks, and post-treatment follow up for an additional 65 weeks. In the control arm, treatment will be delivered according to local practice (and WHO guidelines); duration may vary and will be approximately 86 weeks for the conventional regimen and 39-52 weeks for the standardized shorter regimen.

The 5 experimental arms in the study are as follows:

- Bedaquiline + Linezolid + Fluoroquinolone (moxifloxacin) + Pyrazinamide
- Bedaquiline + Clofazimine + Linezolid + Fluoroquinolone (Levofloxacin) + Pyrazinamide
- Bedaquiline + Delamanid + Linezolid + Fluoroquinolone (Levofloxacin) + Pyrazinamide
- Delamanid + Clofazimine + Linezolid + Fluoroquinolone (Levofloxacin) + Pyrazinamide
- Delamanid + Clofazimine + Fluoroquinolone (moxifloxacin) + Pyrazinamide

Control arm:

- Composed according to local practice and WHO guidelines. Conventional or shorter standardized treatment regimens may be used, in compliance with WHO recommendations.

Summary of Objectives:

The primary objective is to assess whether the efficacy of experimental regimens at 73 weeks is non-inferior to that of the control.

Additional objectives:

To compare the efficacy of experimental regimens at 39 and 104 weeks to that of the control; to compare the frequency of and time to early treatment response (culture conversion) in experimental regimens to that of the control. To compare, at 73 and 104 weeks, the proportion of patients who experienced failure or relapse or died or experienced grade 3 or higher AEs or SAEs in the experimental arms to that in the control arm. To compare, at 73 weeks, the proportion of patients who experience grade 3 or higher QTc prolongation in experimental regimens to that in the control arm.

Milestones:

Final Analysis Report based on publicly available data

Due Date:

Q3 2026

BEAT-TB (Building Evidence for Advancing New Treatment for Rifampicin Resistant Tuberculosis (RR-TB) Comparing a Short Course of Treatment (Containing Bedaquiline, Delamanid and Linezolid) With the Current South African Standard of Care)

Protocol Number: NCT04062201 (Clinicaltrials.gov)

Summary

Study Status: The study was completed on 15 Apr 2024 with a total of 402 participants.

Rationale: To compare the efficacy and safety of a Study Strategy consisting of 6 months of bedaquiline (BDQ), delamanid (DLM), and linezolid (LNZ), with levofloxacin (LVX) and clofazimine (CFZ) compared to the current South African Standard of Care (Control Strategy) for 9 months for the treatment of rifampicin resistant (RR-TB) Tuberculosis.

Population: Children from 6 years of age and adults diagnosed with RR-TB with or without resistance to isoniazid (INH) and/or fluoroquinolones, including breastfeeding and/or pregnant women.

Design: BEAT-TB is a phase 3, open label, multi-centre, randomized controlled study. The interventions are:

- Experimental arm: Bedaquiline + Linezolid + Delamanid + Clofazimine + Levofloxacin
- Control arm: Bedaquiline + Isoniazid + Ethambutol + Pyrazinamide + Linezolid + Clofazimine + Levofloxacin

Summary of Objectives:

The primary objective of the study is to evaluate the efficacy and safety of the Study Strategy, specifically to demonstrate that the intervention or Study Strategy has non-inferior efficacy to the Control Strategy.

- Efficacy: The proportion of participants with a successful outcome at the end of treatment (from week 24 to 76); and the proportion of participants with a successful outcome at the end of follow up at 76 weeks post treatment initiation
- Safety: The proportion of participants who experience grade 3 or greater adverse events during treatment and up to 30 days following the end of treatment

Milestones:

Discussion of results based on publicly available data

Due Date:

Q3 2026

3.3 III.3: Summary Table of Additional Pharmacovigilance Activities

Table 3.3-1 III.3-1: 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 authorisation (key to benefit risk) There are no outstanding imposed mandatory additional pharmacovigilance activities considered key to the Benefit Risk of the product.				
Category 2- Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
endTB NCT02754765	In order to further investigate the use of delamanid in different combination treatment regimens as per approved indication as well as safety, the MAH will submit the results of the endTB (Evaluating Newly approved Drugs for multidrug-resistant TB) study, a randomized, controlled Phase III study in adults and adolescents with multi-drug-resistant tuberculosis conducted by Médecins Sans Frontières, including a critical discussion of the publicly available data with a focus on the evaluation of delamanid i.e. including as possible an analysis based on the agreed statistical analysis plan and with an additional discussion when deviating from it.	The following Safety objectives will be evaluated from EndTB based on the publicly available data: 1) To compare, at 104 weeks, the proportion of patients who died of any cause in the experimental arms to that in the control arm 2) To compare, at 73 and 104 weeks, the proportion of patients who experience AEs of Grade 3 or higher AEs or SAEs of any grade in the experimental arms to that in the control arm 3) To compare, at 73 weeks, the proportion of patients who experience QTc prolongation Grade 3 or higher in the experimental regimens to that in the control arm	Final Analysis Report	Q3 2026
BEAT-TB NCT04062201	The publicly available results from the BEAT-TB Study conducted by Wits Health Consortium will be submitted and discussed.	The following Safety objective will be discussed from BEAT-TB based on the publicly available data: 1) The proportion of participants who experience grade 3 or	Discussion of results	Q3 2026

Table 3.3-1	**III.3-1: Ongoing and Planned Additional Pharmacovigilance Activities**			
Study Status	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
		greater adverse events during treatment and up to 30 days following the end of treatment. This includes participants who experienced adverse events grade 3 or higher of QT interval prolongation and liver disorders.		
Category 3- Required additional pharmacovigilance activities There are no required additional pharmacovigilance activities.				

4 PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

There are no PAES planned or ongoing for delamanid.

5 PART V: RISK MINIMISATION MEASURES (including evaluation of the effectiveness of risk minimisation activities)

5.1 V.1: Routine Risk Minimisation Measures

Table 5.1-1	**V.1-1: Description of Routine Risk Minimisation Measures by Safety Concern**
Safety Concern	**Routine Risk Minimisation Activities**
Important Identified Risks	
QT Interval Prolongation	**Routine risk communication:** SmPC Sections 4.3, 4.4, 4.5, 4.8 PL Section 2 and 4 **Routine risk minimisation activities recommending specific clinical measures to address the risk:** Recommendation for ECG before initiation of treatment and monthly during the full course of treatment with delamanid is included in SmPC Section 4.4. It is further recommended that treatment not be initiated in patients with specific cardiac risk factors unless the possible benefit of delamanid is considered to outweigh the potential risks. Legal Status: Prescription only medicine.

Table 5.1-1	**V.1-1: Description of Routine Risk Minimisation Measures by Safety Concern**
Safety Concern	**Routine Risk Minimisation Activities**
Important Potential Risks	
Liver Disorders	**Routine risk communication:** SmPC Section 4.8 PL Section 4 Legal Status: Prescription only medicine.
Missing Information	None

5.2 V.2: Additional Risk Minimisation Measures

Additional Risk Minimisation Measures were removed within the procedure EMEA/H/C/ EMEA/H/C/002552/II/0061 based on the data provided in EU PASS (242-12-402) Final Study Report and a justification in the Clinical Overview.

5.3 V.3: Summary of Risk Minimisation Measures

Table 5.3-1	**V.3-1: Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern**	
Safety Concern	**Risk Minimisation Measures**	**Pharmacovigilance Activities**
Important Identified Risks		
QT Interval Prolongation	*Routine risk minimisation measures:* SmPC Sections 4.3, 4.4, 4.5, 4.8 PIL Section 2 and 4 Recommendation for ECG before initiation of treatment and monthly during the full course of treatment with delamanid is included in SmPC Section 4.4. It is further recommended that treatment not be initiated in patients with specific cardiac risk factors unless the possible benefit of delamanid is considered to outweigh the potential risks. Prescription only medicine. *Additional risk minimisation measures:* None	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:* None. *Additional pharmacovigilance activities:* As per the SOB002, based on the analysis of the publicly available data, the endTB Study (NCT02754765) will provide additional information on delamanid's safety profile when administered in different combination of treatment regimens. The study will assess the proportion of patients in the experimental arms with either QTc interval prolongation of Grade 3 or higher at 73 weeks to that in the control arm as a secondary endpoint. In addition, publicly available results from the BEAT-TB (NCT04062201) Study conducted by Wits Health Consortium will be discussed, including QT interval prolongation grade 3 or higher.

Table 5.3-1	**V.3-1: Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern**	
Safety Concern	**Risk Minimisation Measures**	**Pharmacovigilance Activities**
Important Potential Risks		
Liver Disorders	*Routine risk minimisation measures:* SmPC Section 4.8 PL Section 4 Prescription only medicine. *Additional risk minimisation measures:* None.	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:* None. *Additional pharmacovigilance activities:* As per SOB002, based on the analysis of the publicly available data, the endTB Study (NCT02754765) will provide additional information on delamanid's safety profile when administered in different combination of treatment regimens. The study will assess the proportion of patients with AEs of Grade 3 or higher AEs or SAEs of any grade in the experimental arms to that in the control arm as a secondary endpoint, including hepatotoxicity. In addition, publicly available results from the BEAT-TB (NCT04062201) Study conducted by Wits Health Consortium will be discussed, including hepatotoxicity grade 3 or higher.
Missing Information	None	None

6 PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

6.1 Summary of the Risk Management Plan for Deltyba

This is a summary of the risk management plan (RMP) for Deltyba. The RMP details important risks of Deltyba, how these risks can be minimised.

Deltyba's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Deltyba should be used.

This summary of the RMP for Deltyba 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 Deltyba's RMP.

6.1.1 I: The Medicine and What it is Used for

Deltyba is indicated for use as part of an appropriate combination regimen for pulmonary multi-drug resistant tuberculosis (MDR-TB) in adults, adolescents, children, and infants with a body weight of at least (≥) 10 kg when an effective treatment regimen cannot otherwise be composed for reasons of resistance or tolerability (see SmPC for more details). It contains delamanid as the active substance and it is given orally.

Further information about the evaluation of Deltyba's benefits can be found in Deltyba's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage:

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

6.1.2 II: Risks Associated with the Medicine and Activities to Minimise or Further Characterise the Risks

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

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

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals.
- Important advice on the medicine's packaging.
- The authorised 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 (e.g., with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, (including PSUR assessment) so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

6.1.2.1 II.A: A List of Important Risks and Missing Information

Important risks of Deltyba are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. 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 Deltyba. 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.

Table 6.1.2.1-1 II.A-1: List of Important Risks and Missing Information

Important Identified Risks	QT interval prolongation
Important Potential Risks	Liver disorders
Missing Information	None

6.1.2.2 II.B: Summary of Important Risks

Table 6.1.2.2-1	**II.B-1: Important Identified Risk: QT Interval Prolongation**
Evidence for linking the risk to the medicine	QT prolongation has been observed in patients treated with delamanid. This prolongation increases slowly over time in the first 6-10 weeks of treatment and remains stable thereafter. QTc prolongation is very closely correlated with the major delamanid metabolite DM-6705. Plasma albumin and CYP3A4 regulate the formation and metabolism of DM-6705 respectively. In the placebo-controlled trial 242-07-204, in MDR-TB patients receiving 100 mg delamanid twice daily, the mean placebo corrected increases in QTcF from baseline were 7.6 ms at 1 month and 12.1 ms at 2 months. Three percent (3%) of patients experienced an increase of 60 ms or greater at some point during Trial 242-07-204, and 1 patient exhibited a QTcF interval >500 ms. In Trial 242-09-213, the maximum mean placebo corrected value for QTcF reached 5.9 msec. In Trial 242-12-232, a paediatric clinical study with 37 patients aged 0-17 years performed to determine the pharmacokinetics and to evaluate the safety and tolerability of delamanid (treatment duration 10 days), there were no clinically meaningful differences in the mean changes from baseline for the various ECG parameters across the age groups. The mean change from baseline for QTcF reached 4.4 ms at Day 10. Trial 242-12-233 (treatment duration of 6 months) is an open label extension of Trial 242-12-232 and is completed and analysed across all age groups (0-17 years). In Trial 242-12-233, the ECG assessment did not show clinically significant effects of delamanid on QT intervals. No subjects experienced new onset changes > 480 msec in QTcF and new onset changes > 450 msec in QTcF were experienced by 5/36 (13.8%) subjects. However, the small sample size of 37 patients between 0 to 17 years of age has to be considered, as well as the lack of a control group for comparison of relative QT effect.
Risk factors and risk groups	• Prolonged QTc interval, e. g. congenital long QT syndrome • Female sex; advanced age • Heart disease (bradycardia, cardiac arrhythmias congestive heart failure) • Hypokalaemia, hypomagnesaemia, hypocalcaemia • Combinations of drugs (QT prolonging drugs) • Severe hepatic impairment • Hypoalbuminaemia • Alcohol abuse • Advanced HIV infection

Table 6.1.2.2-1	**II.B-1: Important Identified Risk: QT Interval Prolongation**
Risk minimisation measures	**Routine risk minimisation measures:** SmPC Sections 4.3, 4.4, 4.5, 4.8 PIL Section 2 Recommendation for ECG before initiation of treatment and monthly during the full course of treatment with delamanid is included in SmPC Section 4.4. It is further recommended that treatment not be initiated in patients with specific cardiac risk factors unless the possible benefit of delamanid is considered to outweigh the potential risks. Prescription only medicine. **Additional risk minimisation measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities**: Based on publicly available data, the endTB study (NCT02754765) will provide additional information on delamanid's safety profile when administered in different combination of treatment regimens. The study will assess the proportion of patients in the experimental arms with either QTc interval prolongation of Grade 3 or higher at 73 weeks to that in the control arm as a secondary endpoint. In addition, publicly available results from the BEAT-TB study (NCT04062201) conducted by Wits Health Consortium will be discussed. See section II.C of this summary for an overview of the post-authorisation development plan.

Table 6.1.2.2-2	**II.B-2: Important Potential Risk: Liver Disorders**
Evidence for linking the risk to the medicine	Liver disorders are well known complications of TB, and several drugs used as part of the MDR-TB treatment regimens have well-established hepatic side effects. The overall frequency of adverse events related to or indicating liver disorders in the clinical studies with delamanid was very low, with no indication of difference from placebo or of any dose response relationship. Furthermore, there has been no non-clinical evidence for a hepatotoxic effect, nor have there been any signal in laboratory indicators of liver cell injury or cholestatic disease. In cases with adverse events involving hepatic function in which a causal relation with delamanid cannot fully be ruled out, there were other factors, including the underlying disease and concomitant medication, which may have played a causative role in the events. The clinical and non-clinical data do not provide any evidence that would support the plausibility of delamanid as culprit for the findings. In Trial 242-09-213, TEAEs referring to hepatobiliary disorders were similar across treatment groups. The lab values pertaining to liver function tests retrieved during this trial also did not show any significant differences across treatment groups.

Table 6.1.2.2-2 II.B-2: Important Potential Risk: Liver Disorders	
	The frequency of liver disorders in the Phase 1, open-label, multidose, paediatric trial (Study 242-12-232) of 37 patients aged 0-17 years was low with a single occurrence in 1 patient (1/37, 2.7%) in Group 4 (ages 0 to 2 years). Trial 242-12-233 is an open label extension of Trial 242-12-232 and is completed across all age groups (0-17 years). Occurrences included 1 event each of activated partial thromboplastin time prolonged, alanine aminotransferase increased, hepatic enzyme increased; and 3 events each of liver function test increased and prothrombin time prolonged.
Risk factors and risk groups	Despite a multi-drug regimen resulting in drug-induced liver injury, advanced age, hypoalbuminaemia and alcohol consumption, along with advanced disease state, have been shown to be independent risk factors for liver disorders (specifically drug induced liver disease) in pulmonary tuberculosis patients.
Risk minimisation measures	**Routine risk minimisation measures:** SmPC Section 4.8 PL Section 4 Prescription only medicine **Additional risk minimisation measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** Based on publicly available data, the endTB study (NCT02754765) will provide additional information on delamanid's safety profile when administered in different combination of treatment regimens. The study will assess the proportion of patients with AEs of Grade 3 or higher AEs or SAEs of any grade in the experimental arms to that in the control arm as a secondary endpoint, including hepatotoxicity. In addition, publicly available results from the BEAT-TB study (NCT04062201) conducted by Wits Health Consortium will be discussed. See section II.C of this summary for an overview of the post-authorisation development plan.

6.1.2.3 II.C: Post-authorisation Development Plan

II.C.1 Studies which are Conditions of the Marketing Authorisation

endTB - Evaluating Newly approved Drugs for multidrug-resistant TB and BEAT-TB - Building Evidence for Advancing New Treatment for Rifampicin Resistant Tuberculosis (RR-TB) Comparing a Short Course of Treatment (Containing Bedaquiline, Delamanid and Linezolid) With the Current South African Standard of Care

Description: In order to further investigate the use of delamanid in different combination treatment regimens as per approved indication as well as safety, the MAH should submit the results of the endTB (Evaluating Newly approved Drugs for multidrug-resistant TB) study, a randomized, controlled Phase III study in adults and adolescents with multi-drug-

resistant tuberculosis conducted by Médecins Sans Frontières, including a critical discussion of the publicly available data with a focus on the evaluation of delamanid i.e. including as possible an analysis based on the agreed statistical analysis plan and with an additional discussion when deviating from it. In addition, publicly available results from the BEAT-TB study conducted by Wits Health Consortium will be submitted and discussed.

Due Date: Q3 2026

II.C.2 Other Studies in Post-authorisation Development Plan

There are no studies required for delamanid.

7 PART VII: ANNEXES

7.4 Annex 4: Specific Adverse Drug Reaction Follow-up Forms

Not applicable.

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

Not applicable