RISK MANAGEMENT PLAN
For
Pretomanid
Version 2.1

RMP Version to be Assessed as Part of this Application:

RMP Version Number	2.1
Data Lock Point for this RMP	13-Aug-2023
Date of Final Sign Off	13-Mar-2024
Rationale for Submitting an Updated RMP	RMP amended in line with CHMP/PRAC Rapporteur's updated assessment report procedure EMEA/H/C/005167/II/0019/G dated 29-Feb-2024.
Summary of Significant Changes in this RMP	The following significant changes were made in the current RMP: Part II Module SVII and SVIII, Part V.1 and V.3, Part VI.II.A and II.B: • Removal of "QT prolongation" and "hepatotoxicity" from the list of important safety concerns

Other RMP Versions Under Evaluation:

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Details of the Current RMP:

Version Number	1.0
Approved with Procedure	Centralized procedure: EMA/H/C/005167
Date of Approval (Opinion Date)	31-Jul-2020

Approver	Dr. Eiko Soehlke, MD MPH, EEA QPPV
Signature	RMP has been reviewed and approved by the marketing authorisation applicant's QPPV and that the electronic signature is on file.
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LIST OF ABBREVIATIONS

Abbreviation	Definition
ADR	Adverse Drug Reaction
ATC	Anatomical Therapeutic Chemical Classification System
CHMP	Committee for Medicinal Products for Human Use
CMDh	Coordination Group for Mutual Recognition and Decentralised Procedures – Human
DCP	Decentralised Procedure
DDD	Daily Defined Dose
DHPC	Direct Healthcare Professional Communication
EEA	European Economic Area
EPAR	European Public Assessment Report
EU	European Union
EURD	European Union Reference Date
HCP	Healthcare Professional
ICSR	Individual Case Safety Report
MAA	Marketing Authorization Applicant
MAH	Marketing Authorization Holder
MRP	Mutual Recognition Procedure
PAC	Patient Alert Card
PL	Package Leaflet
PPP	Pregnancy Prevention Programme
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	Periodic Safety Update Report
PTC	Patient Treatment Course
PTD	Patient Treatment Days
PTM	Patient Treatment Months
PTY	Patient Treatment Years
PVA	Pharmacovigilance Agreement
QPPV	Qualified Person for Pharmacovigilance
MedDRA	Medical Dictionary for Regulatory Activities
DLP	Data Lock Point
SmPC	Summary of Product Characteristics
WHO	World Health Organization

PART I: PRODUCT(S) OVERVIEW

Table 1: Part 1.1-Product Overview

Active Substance(s)	Pretomanid
Pharmacotherapeutic Group(s) (ATC Code)	Antimycobacterials, drugs for treatment of tuberculosis, other drugs for treatment of tuberculosis, ATC code: J04AK08
Marketing Authorisation Holder	Mylan IRE Healthcare Limited Unit 35/36 Grange Parade Baldoyle Industrial Estate Dublin 13 Ireland
Medicinal Products to Which this RMP Refers	1
Invented Name(s) in the European Economic Area (EEA)	Dovprela
Marketing Authorisation Procedure	Centralized procedure: EMA/H/C/005167
Brief Description of the Product	Summary of mode of action: Pretomanid is a nitroimidazooxazine antimycobacterial drug with a complex mode of action. Pretomanid kills actively replicating Mycobacterium tuberculosis, by inhibiting mycolic acid biosynthesis thereby blocking cell wall production. Under anaerobic conditions, against non-replicating bacteria, pretomanid acts as a respiratory poison following nitric oxide release. All of these activities require nitro-reduction of pretomanid within the mycobacterial cell by the deazaflavin-dependent nitroreductase, Ddn, which is dependent on the reduced form of the cofactor F420. Reduction of F420 is accomplished by the F420-dependent glucose-6-phosphate dehydrogenase, Fgd1.
Hyperlink to the Product Information:	Link to proposed PI
Indication(s) in the EEA	Current: Dovprela is indicated in combination with bedaquiline and linezolid, in adults, for the treatment of pulmonary extensively drug resistant (XDR), or treatment-intolerant or nonresponsive multidrug-resistant (MDR) tuberculosis (TB).
	Proposed: Dovprela is indicated in combination with bedaquiline and linezolid for the treatment of adults with pulmonary tuberculosis (TB) due to *Mycobacterium tuberculosis* resistant to all of isoniazid, rifampicin, a fluoroquinolone and a second line injectable antibacterial drug and adults with pulmonary TB due to *M. tuberculosis* resistant to both isoniazid and rifampicin, who are treatment-intolerant or nonresponsive to standard therapy.
Dosage in the EEA	Current: The recommended dosage is 200 mg (one tablet) pretomanid once daily, for 26 weeks.

	Pretomanid should be administered only in combination with bedaquiline (400 mg once daily for 2 weeks followed by 200 mg 3 times per week [with at least 48 hours between doses] orally for a total of 26 weeks) and linezolid (1,200 mg daily orally for up to 26 weeks).
	Proposed: The recommended dosage is 200 mg (one tablet) pretomanid once daily, for 26 weeks. Pretomanid should be administered only in combination with bedaquiline (400 mg once daily for 2 weeks followed by 200 mg 3 times per week [with at least 48 hours between doses] orally for a total of 26 weeks) and linezolid (600 mg daily orally for up to 26 weeks).
Pharmaceutical Form(s) and Strengths	Current: Tablets. Each tablet contains 200 mg pretomanid.
Is the Product Subject to Additional Monitoring in the EU?	Yes

PART II: SAFETY SPECIFICATION

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

Dovprela is indicated in combination with bedaquiline and linezolid for the treatment of adults with pulmonary tuberculosis (TB) due to *Mycobacterium tuberculosis* resistant to all of isoniazid, rifampicin, a fluoroquinolone and a second line injectable antibacterial drug and adults with pulmonary TB due to *M. tuberculosis* resistant to both isoniazid and rifampicin, who are treatment-intolerant or nonresponsive to standard therapy.

Tuberculosis (TB) is a communicable disease that is a major cause of ill health and one of the leading causes of death worldwide. TB is caused by the bacillus Mycobacterium tuberculosis.

Drug-resistant TB (DR-TB) continues to be a public health threat, whereby resistance to rifampicin – the most effective first-line drug – is of greatest concern. WHO uses five categories to classify cases of DR-TB:

- Isoniazid-resistant TB (Hr-TB),
- Rifampicin-resistant TB (RR -TB)
- MDR-TB (Multidrug-resistant TB): resistance to rifampicin and isoniazid,
- Pre-XDR-TB (pre-extensively drug-resistant TB): resistance to rifampicin and any fluoroquinolone
- XDR-TB (extensively drug-resistant TB): resistance to rifampicin plus any fluoroquinolone plus at least one of the drugs bedaquiline and linezolid. [1]

Prevalence / Incidence:

Worldwide, 10.6 million incident cases of TB were estimated in 2021, with most affected WHO regions being South-East Asia (45%), Africa (23%) and Western Pacific (18%). 2.2% of cases were reported from the WHO European region, which includes countries of the European Union (EU) and the European Economic Area (EEA) as well as non-EU/EEA countries such as the Russian Federation and Turkey. Of the 10.6 million cases, an estimate of 450.000 incident cases were either Rifampicin (RR)- or multidrug (MDR)-resistant. [2]

In 2021 there was a total of 33, 527 TB case notifications reported in the EU/EEA, amounting to a prevalence of 7.4 cases per 100,000. Of these 21 397 bacteriologically confirmed TB cases notified in 2021, 16 544 (77.3%) had drug susceptibility testing results for at least rifampicin. Of these, 695 (4.2%) had rifampicin resistance/multidrug resistance. In 2021, the proportion of TB cases with rifampicin resistance or with resistance to multiple anti-TB drugs was similar to that in 2020 (rifampicin resistance 4.4% in 2021 and 4.3% in 2020, and resistance to multiple anti-TB drugs 3.8% for both years).

In 2021, 54.4% of RR/MDR-TB cases (404 of 742) had drug-susceptibility testing results for any fluoroquinolone. Among these, 115 (28.5%) met the definition for pre-XDR. The majority (68.7%, 79 of 115) of pre-XDR cases had drug-susceptibility testing results reported for at least one other Group A drug. Of these cases, 43 (54.4%) met the XDR case definition. The proportion increased in 2021 (from 45.1%, 37 in 2020), but the numbers reported remain low overall. [3]

Natural history of the indicated condition in the <untreated> population, including mortality and morbidity:

TB is caused by the bacillus Mycobacterium tuberculosis, which is spread when people who are sick with TB expel bacteria into the air (e.g. by coughing). A person needs to inhale only a few germs to become infected.

About a quarter of the global population is estimated to have been infected with TB, but 90 – 95% of people infected will not go on to develop TB disease and some will clear the infection. If TB disease develops, common symptoms are prolonged cough (sometimes with blood), chest pain, weakness, fatigue, weight loss, fever and night sweats. Symptoms may be mild for many months, so it is easy to spread TB to others without knowing it. The symptoms people get depend on where in the body TB becomes active. TB typically affects the lungs (pulmonary TB), but can affect other sites such as the kidneys, brain, spine and skin as well. [5] Without treatment, the mortality rate from TB is high. Studies of the natural history of TB disease in the absence of treatment with anti-TB drugs (conducted before drug treatments became available) found that about 70% of individuals with sputum smear-positive pulmonary TB died within 10 years of being diagnosed. [2]

Demographics of the population in the proposed indication –age, gender, and risk factors for the disease:
TB can affect anyone, regardless of age and gender. Globally, of the cases of TB (DS- and MDR-/XDR-TB) diagnosed in 2021, 89% were in adults, thereof 56.5% in men and 32.5% in women, and 11% were in children (aged <15 years). [2] In the EU/EEA in 2020, children under 15 years only accounted for 1,218 (3.8%) of 31,551 new and relapse TB cases reported. In adults, men were affected twice as often as women. [4]

Risk factors
There are two ways of acquiring MDR/XDR-TB:

- direct transmission of drug-resistant TB from one person to another
- *de novo* mutation during TB treatment

In 2021, the estimated percentage of MDR/XDR-TB among new pulmonary TB cases, indicative of direct transmission, was 3.6% worldwide [2].
Percentages in 2020 for EU/EEA countries and for the WHO European region were 2.8% and 23.1% respectively [4].
The most important risk factor for MDR/XDR-TB due to *de novo* mutation is a history of prior TB treatment. Further risk factors associated with developing MDR/XDR-TB vary according to setting, and may include being born in a foreign country, aged under 65 years, drug-addiction, HIV positive, homelessness, and imprisonment. [6]

The main existing treatment options:
Dovprela is indicated in combination with bedaquiline and linezolid for the treatment of adults with pulmonary tuberculosis (TB) resistant to isoniazid, rifampicin, a fluoroquinolone and a second line injectable antibacterial drug or adults with pulmonary TB resistant to isoniazid and rifampicin who are treatment-intolerant or nonresponsive to standard therapy.

Treatment for DR-TB is more challenging than for drug-susceptible (DS-TB). MDR-TB, pre-XDR and XDR-TB all take substantially longer to treat than DS-TB and require the use of second-line drugs.

Recently, WHO published the 2022 update of its consolidated guidelines for the treatment for drug-resistant tuberculosis.

WHO´s recommendations, including all-oral shorter and longer regimens for MDR/RR-TB, monitoring of patients on treatment, the timing of ART in MDR/RR-TB patients living with HIV and the use of surgery for patients receiving MDR-TB treatment, are presented in below table[1]:

[1] (a) = new recommendation, (b) = reprinted recommendation

1. The 6-month bedaquiline, pretomanid, linezolid and moxifloxacin (BPaLM) regimen for MDR/RR-TB and pre-XDR-TB (a)	
1.1	WHO suggests the use of the 6-month treatment regimen composed of bedaquiline, pretomanid, linezolid (600 mg) and moxifloxacin (BPaLM) rather than 9-month or longer (18-month) regimens in MDR/RR-TB patients. (Conditional recommendation, very low certainty of evidence)
2. The 9-month all-oral regimen for MDR/RR-TB (a)	
2.1	WHO suggests the use of the 9-month all-oral[2] regimen rather than longer (18-month) regimens in patients with MDR/RR-TB and in whom resistance to fluoroquinolones has been excluded. (Conditional recommendation, very low certainty of evidence)
3. Longer regimens for MDR/RR-TB (b)	
3.1	In multidrug- or rifampicin-resistant tuberculosis (MDR/RR-TB) patients on longer regimens, all three Group A agents and at least one Group B agent should 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 the treatment if 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 of evidence)
3.2	**Kanamycin and capreomycin** are not to be included in the treatment of MDR/RR-TB patients on longer regimens. (Conditional recommendation, very low certainty of evidence)
3.3	**Levofloxacin or moxifloxacin** should be included in the treatment of MDR/RR-TB patients on longer regimens. (Strong recommendation, moderate certainty of evidence)
3.4	**Bedaquiline** should be included in longer multidrug-resistant TB (MDR-TB) regimens for patients aged 18 years or more. (Strong recommendation, moderate certainty of evidence) **Bedaquiline** may also be included in longer MDR-TB regimens for patients aged 6–17 years. (Conditional recommendation, very low certainty of evidence) In children with MDR/RR-TB aged below 6 years, an all-oral treatment regimen containing **bedaquiline** may be used. (Conditional recommendation, very low certainty of evidence)
3.5	**Linezolid** should be included in the treatment of MDR/RR-TB patients on longer regimens. (Strong recommendation, moderate certainty of evidence

[2] 9-month all-oral: this regimen consists of bedaquiline (used for 6 months), in combination with levofloxacin/moxifloxacin, ethionamide, ethambutol, isoniazid (high-dose), pyrazinamide and clofazimine (for 4 months, with the possibility of extending to 6 months if the patient remains sputum smear positive at the end of 4 months), followed by treatment with levofloxacin/moxifloxacin, clofazimine, ethambutol and pyrazinamide (for 5 months). Ethionamide can be replaced by 2 months of linezolid (600 mg daily).

3.6	Clofazimine and cycloserine or terizidone may be included in the treatment of MDR/RR-TB patients on longer regimens. (Conditional recommendation, very low certainty of evidence)
3.7	Ethambutol may be included in the treatment of MDR/RR-TB patients on longer regimens. (Conditional recommendation, very low certainty of evidence)
3.8	Delamanid may be included in the treatment of MDR/RR-TB patients aged 3 years or more on longer regimens. (Conditional recommendation, moderate certainty of evidence) In children with MDR/RR-TB aged below 3 years delamanid may be used as part of longer regimens. (Conditional recommendation, very low certainty of evidence)
3.9	Pyrazinamide may be included in the treatment of MDR/RR-TB patients on longer regimens. (Conditional recommendation, very low certainty of evidence)
3.10	Imipenem–cilastatin or meropenem may be included in the treatment of MDR/RR-TB patients on longer regimens. (Conditional recommendation, very low certainty of evidence)
3.11	Amikacin may be included in the treatment of MDR/RR-TB patients aged 18 years or more on longer regimens when susceptibility has been demonstrated and adequate measures to monitor for adverse reactions can be ensured. If amikacin is not available, streptomycin may replace amikacin under the same conditions. (Conditional recommendation, very low certainty in the estimates of effect)
3.12	Ethionamide or prothionamide may be included in the treatment of MDR/RR-TB patients on longer regimens only if bedaquiline, linezolid, clofazimine or delamanid are not used, or if better options to compose a regimen are not possible. (Conditional recommendation against use, very low certainty of evidence)
3.13	P-aminosalicylic acid may be included in the treatment of MDR/RR-TB patients on longer regimens only if bedaquiline, linezolid, clofazimine or delamanid are not used, or if better options to compose a regimen are not possible. (Conditional recommendation against use, very low certainty of evidence)
3.14	Clavulanic acid should not be included in the treatment of MDR/RR-TB patients on longer regimens. (Strong recommendation against use, low certainty of evidence)
3.15	In MDR/RR-TB patients on longer regimens, a total treatment duration of 18–20 months is suggested for most patients; the duration may be modified according to the patient's response to therapy. (Conditional recommendation, very low certainty of evidence)
3.16	In MDR/RR-TB patients on longer regimens, a treatment duration of 15–17 months after culture conversion is suggested for most patients; the duration may be modified according to the patient's response to therapy. (Conditional recommendation, very low certainty of evidence)
3.17	In MDR/RR-TB patients on longer regimens containing amikacin or streptomycin, an intensive phase of 6–7 months is suggested for most patients; the duration may be modified according to the patient's response to therapy. (Conditional recommendation, very low certainty of evidence)

4. Regimen for rifampicin-susceptible and isoniazid-resistant TB (b)	
4.1	In patients with confirmed rifampicin-susceptible, isoniazid-resistant tuberculosis, treatment with rifampicin, ethambutol, pyrazinamide and levofloxacin is recommended for a duration of 6 months. (Conditional recommendation, very low certainty in the estimates of effect)
4.2	In patients with confirmed rifampicin-susceptible, isoniazid-resistant tuberculosis, it is not recommended to add streptomycin or other injectable agents to the treatment regimen. (Conditional recommendation, very low certainty of evidence)
5. Monitoring patient response to MDR/RR-TB treatment using culture (b)	
5.1	In multidrug- or rifampicin-resistant tuberculosis (MDR/RR-TB) patients on longer regimens, the performance of sputum culture in addition to sputum smear microscopy is recommended to monitor treatment response. It is desirable for sputum culture to be repeated at monthly intervals. (Strong recommendation, moderate certainty in the estimates of test accuracy)
6. Starting antiretroviral therapy in patients on MDR/RR-TB regimens (b)	
6.1	Antiretroviral therapy is recommended for all patients with HIV and drug-resistant tuberculosis requiring second-line antituberculosis drugs, irrespective of CD4 cell count, as early as possible (within the first 8 weeks) following initiation of antituberculosis treatment. (Strong recommendation, very low certainty of evidence)
7. Surgery for patients on MDR/RR-TB treatment (b)	
7.1	In patients with rifampicin-resistant tuberculosis (RR-TB) or multidrug-resistant TB (MDR-TB), elective partial lung resection (lobectomy or wedge resection) may be used alongside a recommended MDR-TB regimen. (Conditional recommendation, very low certainty of evidence)

Important co-morbidities:

Important co-morbidities identified in the treatment of drug-susceptible TB are human immunodeficiency virus (HIV) infection, diabetes mellitus, chronic kidney disease, malnutrition, alcohol misuse, and tobacco use MDR-/XDR-TB treatment programs often report high proportions of these comorbidities, with the prevalence of HIV, diabetes mellitus, and alcohol misuse exceeding 10-20% in several large MDR-/XDR-TB cohort studies [7].

The patients enrolled in Study Nix-TB (phase 3, pivotal study for the proposed indication) were a chronically medically ill group with significant morbidity going into the trial. They were patients with the categories of TB infection historically the most refractory to successful treatment and long-term beneficial outcomes. Most of them had been failing prior therapy and had had their clinical TB infection for a substantial period of time. Prior to enrollment, they had continuous known TB infections for a mean of 22 months, just short of 2 years, with a range of 2 weeks to over 8 years (99 months). Forty-nine percent of the group were HIV co-infected, and during the trial all of these patients took anti-retroviral medication in addition to the trial medications. The mean body mass index (BMI) at screening was 20.4, at the lower end of normal.

Part II: Module SII - Non-clinical Part of the Safety Specification

Key safety findings from non-clinical studies and relevance to human usage:

1. Toxicity

Key Safety findings (from non-clinical studies)	Relevance to human usage
Toxicity	
Single-dose and repeated-dose toxicity	
Nervous system-related effects: In mice given daily oral doses of pretomanid for 4 weeks, central nervous system (CNS)-related clinical signs (spasm, jump-and-tumble, and abnormal spontaneous motor activity) were observed at doses that exceeded the maximum tolerated dose [8]. By contrast, CNS-related findings were not observed following daily administration at up to 250 mg/kg for 13 weeks in female CD-1 mice [9] or four weeks in CByB6F1 mice, which are wild-type litter mates of Tg.*ras*H2 transgenic mice [10] In rats, an Irwin screen in males given single doses revealed that pretomanid caused depressed neural function decreased touch response, body tone and grooming at ≥150 mg/kg. In repeat dose studies in rats, doses of ≥500 mg/kg/day for 2 weeks ([11] and [12]) or ≥100 mg/kg/day for 13 or 26 weeks ([13] and [14]) were associated with clinical signs of hyperactivity, sensitivity, ataxia, and convulsions. CNS related clinical signs were never seen in rats dosed for 26 weeks at ≤30 mg/kg/day, thus this was considered to be the 26-week no observed effect level (NOEL) for CNS effects. After 26 weeks of administration at the NOEL, C_{max} and AUC_{0-24} values were greater in females than in males and were approximately 7.6 µg/mL and 116 h*µg/mL, respectively. These values are approximately twice the predicted exposure in patients at the maximum recommended human dose (MRHD) of 200 mg/day (3.1 µg/mL and 57 h*µg/mL, respectively). In monkeys, CNS-related clinical signs included ataxia and convulsions followed by lateral recumbency and ataxia, or front limb tremors at a dose of 1000 mg/kg/day pretomanid given for two weeks [12]. In longer repeat dose studies in which monkeys were given ≥100 mg/kg/day pretomanid, ataxia and convulsions were rare but observed in 2 studies ([15] and [16]). CNS-related clinical signs were not seen in monkeys dosed for 39 weeks at ≤50 mg/kg/day and as such, this was considered to be the 39-week NOEL for CNS effects. After 39 weeks of administration at the NOEL, mean C_{max} and AUC_{0-24} values were greater in males than in females and were approximately 5.2 µg/mL and 55.4 h*µg/mL, respectively. These values are higher than (C_{max}) or similar to	The incidence of treatment-emergent adverse events (TEAEs) in the standardized MedDRA query (SMQ) for convulsions was low across the clinical development program, ranging from 0% in Study ZeNix (bedaquiline, pretomanid, and linezolid [BPaL]), the MDR-TB pooling group, and the phase 2 pretomanid-alone pooling group to 1.8% (2 subjects) in Study Nix-TB (BPaL). The incidence of convulsion events in the all-pretomanid and HRZE groups of the DS-TB pooling group were 0.3% (2 subjects) and 0.4% (1 subject), respectively. One of the pretomanid-exposed subjects (Study NC-002) had no prior history of seizures. The other pretomanid-exposed subject (Study NC-006), who had a history of heavy alcohol use, continued and completed the study regimen without interruption after the seizure and then had another seizure 28 days after completion of the regimen. In Study Nix-TB, 1 of the 2 subjects with seizure-type events had a prior history of seizure, and the other subject was found to have a CNS tuberculoma. It was concluded that the available clinical data does not raise concern that pretomanid may cause convulsion in the proposed regimen.

Key Safety findings (from non-clinical studies)	Relevance to human usage
(AUC_{0-24}) the predicted exposures in patients at the MRHD of 200 mg/day (3.1 µg/mL and 57 h*µg/mL, respectively).	
Testicular degeneration/atrophy: Testicular toxicity, reflected in seminiferous tubule degeneration, germ cell depletion, and infertility, was seen in mice and rats, but not monkeys, treated with pretomanid. In rats, testicular damage showed some evidence of being reversible, albeit slowly, after short durations of dosing at levels near the threshold for toxicity (30 mg/kg/day); however, testicular damage was irreversible at higher dose levels (≥100 mg/kg/day) ([13]; [17]; [14]). The no adverse effect levels for testicular toxicity in rats in CRL Study QTC00007 and Covance Study 7504-170 were 30 and 10 mg/kg/day, respectively, which corresponded with pretomanid plasma AUC_{0-24h} exposures of 84 and 27.5 µg•hr/mL (human exposure for 200 mg/day dose = 57.4 µg•hr/mL; NC-005 CSR). A 13-week study in sexually mature cynomolgus monkeys showed decreased sperm count and motility and an increased ratio of abnormal to normal sperm at ≥150 mg/kg/day pretomanid [18]. No treatment-related histopathologic findings in the testes were observed, and the findings resolved during the recovery period as food consumption and body weight increased. No testicular findings were identified in sexually mature male monkeys given daily oral doses of pretomanid of up to 1000 mg/kg for 2 weeks followed by a 2-week post-treatment period [12] or up to 100 mg/kg for 39 weeks [16]. At the 39 week no-effect level for testicular effects in SRIM962.12 (100 mg/kg/day), C_{max} averaged 6.8 to 8.8 µg/mL, and AUC0-24 averaged 61 to 112 µg•hr/mL. These values are approximately twice the predicted exposure in patients at the MRHD of 200 mg/day (3.1 µg/mL and 57 µg•hr/mL, respectively).	Due to the nonclinical findings, male reproductive hormones were studied in Studies NC-002, NC-005, and NC-006, which showed no evidence of treatment-associated testicular toxicity. In addition, a search for TEAEs associated with fertility disorders across the 19 studies in the clinical development program identified no events in any male subject and one event in a female subject, which was menstruation irregular. Although the available clinical data does not raise concern that pretomanid may cause testicular toxicity in the proposed regimen, testicular toxicity will continue to be monitored as an important potential risk.
Cataracts: In rats, cataracts developed in a few animals given pretomanid at 300 mg/kg/day for 13 weeks [13] or 100 mg/kg/day for 26 weeks [14]. In the 26-week study, the no-effect level for cataracts was 30 mg/kg/day, which produced C_{max} and AUC_{0-24} values of 7.6 µg/mL and 116 µg•hr/mL, respectively. These values were more than twice the predicted exposure in subjects at the maximum recommended human dose of 200 mg/day (3.1 µg/mL and 57 µg•hr/mL, respectively). In monkeys, cataracts developed in 2 animals given pretomanid at 450 mg/kg for 4 weeks and then 300 mg/kg for 12 more weeks [15]. The cataracts were not present at the end of dosing but arose during a 13-week recovery period. Conversely, in a second more	Due to the earlier nonclinical findings, since July 2009, clinical studies with pretomanid exposure longer than 14 days have included slit-lamp examinations with careful age-related eye disease study 2 (AREDS2) scoring of lens opacities; these studies have shown no association of concern between pretomanid exposure and cataracts in humans. The safety of pretomanid with respect to cataract development was also evaluated

Key Safety findings (from non-clinical studies)	Relevance to human usage
rigorous 13-week study in which monkeys were given daily oral doses of pretomanid at 300 mg/kg for 13 weeks and then maintained for an additional 20-week recovery period [18], frequent eye exams were conducted, but no cataracts developed. Cataracts also did not develop in monkeys given daily oral doses of pretomanid at 100 mg/kg for 39 weeks [16]. Taken together, these studies suggest that the no-effect level for cataracts was 100 mg/kg/day, which produced average C_{max} and AUC_{0-24} values of 10.0 µg/mL and 124 µg•hr/mL, respectively. These values were more than twice the predicted exposure in subjects at the MRHD of 200 mg/day (NC-005). Therefore, nonclinical studies suggested that ophthalmic exam should be included in pretomanid clinical trials.	by searching for TEAEs in the SMQ for lens disorders. Fourteen subjects (12.8%) in Study Nix-TB reported TEAEs in this SMQ, the most frequent being visual acuity reduced (5.5% of subjects). The subject incidence of lens disorder events in the other study/pooling groups ranged from 0% in Study ZeNix and the MDR TB and phase 2 pretomanid alone pooling groups to 5.2% in the HRZE control group of the DS-TB pooling group. No event in this SMQ for any pooling group was considered serious or resulted in discontinuation of the study treatment regimen. It was concluded that the extensive evaluation of lens opacities in the clinical development program did not raise any concern in humans that pretomanid may cause cataracts in the proposed regimen.
<u>Reproductive/developmental toxicity</u>	
In animal reproduction studies, pregnant rats were dosed orally with pretomanid at 10, 30, and 100 mg/kg/day during organogenesis (gestational Days 7 to 17). Rats showed no evidence of adverse developmental outcomes, but maternal toxicity (including reduced body weight gain) was observed at and above 30 mg/kg/day. At this dose, the exposure was approximately 1.8 times the exposure for the MRHD on an AUC basis. Pregnant rabbits were dosed orally with pretomanid during organogenesis (gestational Days 7 to 19) at 10, 30, and 60 mg/kg/day. No evidence of adverse development outcomes was observed when oral doses of pretomanid were administered to dams during organogenesis (gestational Days 7 to 20) at doses up to 60 mg/kg/day (approximately 1.5 times the systemic exposure for the MRHD on an AUC basis. In a pre- and postnatal development study, there were no adverse developmental effects in pups of pregnant rats orally dosed with up to 20 mg/kg/day from gestational Day 6 through lactation. Pups of pregnant females dosed at 60 mg/kg/day (approximately 1.5 times the MRHD on an AUC basis) had lower body weights	There are no studies or available data on pretomanid use in pregnant women. There is no information regarding the presence of pretomanid in human milk, or its effects on milk production or the breastfed infant. Other nitroimidazole derivatives are present in human breast milk. Pretomanid has been detected in rat milk. Because of the potential for adverse reactions in suckling children, a decision should be made whether to discontinue breastfeeding or to discontinue pretomanid, taking into account the benefit of breastfeeding for the child and the benefit of therapy for the women. “Use in pregnancy” is included under missing information in this RMP.

Key Safety findings (from non-clinical studies)	Relevance to human usage
and a slight delay in the age at which the air-drop righting reflex developed. These effects occurred at a maternally toxic dose (based on maternal weight loss, reduced body weight gain, and reduced food consumption). Analysis of maternal and fetal plasma drug levels indicated that pretomanid accumulated to similar levels in the fetuses as in the mothers. Pretomanid was present in milk of lactating female rats administered the drug and was present in the plasma of nursing rats.	
Genotoxicity and Carcinogenicity Pretomanid was negative in all eight genotoxicity studies performed. However, one of the metabolites (M50) that is found in rat, monkey and human plasma was positive in a screening Ames assay. M50 is not a major metabolite in humans and exposure to M50 relative to the parent drug is higher in the rat (24%) and monkey (18%) than in humans (6%). Pretomanid was not teratogenic when administered to pregnant rats or rabbits. A carcinogenicity study in Tg.rasH2 transgenic mice has been completed, and there were no pretomanid-induced early deaths, tumors, non-neoplastic microscopic findings, or gross necropsy findings. Oral administration of pretomanid produced plasma exposure to both PA-824 and its metabolite M50 at all dose levels. A 2-year carcinogenicity study in rats with pretomanid is ongoing.	No concerns raised

2. Safety Pharmacology

Key Safety findings (from non- clinical studies)	Relevance to human usage
Cardiovascular system, including potential effect on the QT interval	
Overall, pretomanid administration at a dose of 50 mg/kg had no effect on either the respiratory or CNS systems and an equivocal effect on the cardiovascular system by prolongation of the QT interval. The results of 3 *in vitro* cardiovascular (human ether-à-go-go-related gene [hERG]) studies of pretomanid demonstrated inhibition of potassium channel current with a half-maximal inhibitory concentration of approximately 17 to 20 µM, suggesting the potential for pretomanid to cause prolongation of	A thorough QT study in humans (DMID-10-0058) showed only a small effect (<5 ms) of single oral doses of 400 mg and 1000 mg pretomanid on QT interval and further data from the clinical development program do not indicate that QT prolongation/Torsade de pointes is a concern in humans at doses of up to 200 mg/day.

Key Safety findings (from non- clinical studies)	Relevance to human usage
the QT interval in human. In subsequent *in vivo* studies, QT prolongation was observed in monkeys given pretomanid at doses of 150 and 450 mg/kg, with an equivocal effect (one of 4 monkeys at 8 hours postdose) at 50 mg/kg. The lowest dose associated with QT prolongation (150 mg/kg) substantially (more than 3-fold) exceeds human exposures at a dose of 200 mg. There was no evidence of an interactive effect on QT prolongation when pretomanid was administered at a dose of 100 mg/kg with bedaquiline (100 mg/kg) to dogs, or at a dose of 50 mg/kg with moxifloxacin (30 or 100 mg/kg) to monkeys. The cardiovascular effects of pretomanid were also evaluated as parts of several repeat-dose toxicity studies. In cynomolgus monkeys given daily oral doses of 50, 150, 450, or 1000 mg/kg pretomanid for 15 days, heart rate decreased and QT interval duration increased at doses ≥450 mg/kg/day [12]. Compared with baseline, mean QTc interval (QT interval divided by the cube root of the RR interval) increased by 9%, 6%, 6%, 16%, and 29% after 2 weeks of administration of vehicle or pretomanid at 0, 50, 150, 450, or 1000 mg/kg/day, respectively. At 450 mg/kg/day (the highest dose evaluated), the increase had resolved by 2 weeks after dosing stopped. At the no-effect level (150 mg/kg), plasma exposure (C_{max}) to pretomanid was more than 3 times as great as in human subjects at 200 mg/day. No ECG changes were observed during treatment in monkeys given pretomanid doses of 50, 150, or 450/300 (450 decreased to 300 on Day 37) mg/kg/day for 3 months [15], or doses of 25, 50, or 100 mg/kg/day for 9 months [16].	QT prolongation is a known adverse reaction of bedaquiline. In the Nix-TB study, a modest QT prolongation of <10 ms was observed (pre-dose change from baseline, QTcF); effect sizes of at least this magnitude have been reported with the use of bedaquiline. Although pretomanid has been shown to cause a mild QT prolongation that is not clinically significant, the combination of pretomanid with bedaquiline in the BPaL regimen may result in a QT prolongation of modest size in patients such as those in Nix-TB. Therefore, QT prolongation is included as an important identified risk for the use of the BPaL regimen.

3. Other toxicity-related information or data incl. relevant mechanistic studies

Not applicable

Part II: Module SIII - Clinical Trial Exposure

To data lock point, the clinical development program for pretomanid conducted by development partner TB Alliance comprised 20 completed clinical studies of pretomanid and various pretomanid-containing combinations. These 20 studies consist of three phase 3 studies; seven phase 2 studies; and 10 phase 1 studies; two of the phase 1 studies were conducted by sponsors other than TB Alliance. Two of the completed phase 3 studies, Nix-TB and ZeNix, evaluated the efficacy, safety and tolerability of bedaquiline, pretomanid, and linezolid (BPaL) in the proposed indication. One completed phase 3 study (NC-006) and three completed phase 2 studies (NC-008, NC-005 and NC-002) evaluated pretomanid containing regimens other than BPaL; these studies also included a randomized, standard-of-care control arm for the DS-TB treatments. The remaining four

phase 2 studies, all completed, evaluated pretomanid or pretomanid containing regimens other than BPaL in subjects with pulmonary DS-TB.

Hereafter, information on clinical trial exposure is presented from all completed clinical trials and separately from those studies conducted with the currently approved BPaL regimen, Nix-TB and ZeNix.

In both studies, patients were treated for 6 months (extendable to 9 months if a patient's culture remained or reverted to positive during treatment). Only 3 subjects were extended to 9 months; the rest were treated for 6 months.

Table 2: SIII.1a- Duration of exposure

Cumulative for All Indications (Person Time): All subjects		
Duration of Exposure	**Patients**	**Person Time**
<1 m	509	19.20
1 to <3 m	445	67.28
3 to <6 m	374	138.14
≥6 m etc.	461	231.28
Total Person Time	1484	303.9

Table considers total duration of therapy, regardless of interruptions or missed doses.
Note that only two patients received more than six months therapy when interruptions and missed doses are excluded.
Person time is represented in person years of exposure.

Table 3: SIII.1b- Duration of exposure

Cumulative for All Indications (Person Time): Study Nix-TB and ZeNix (BPaL regimen)		
Duration of Exposure	**Patients**	**Person Time**
<1 m	1	0.04
1 to <3 m	99	16.96
3 to <6 m	93	45.74
≥6 m etc.	97	49.69
Total Person Time	290	112.43

Table considers total duration of therapy, regardless of interruptions or missed doses.
Note that only two patients received more than six months therapy when interruptions and missed doses are excluded.
Person time is represented in person years of exposure.

Table 4: SIII.2a- Age Group and Gender: All subjects Exposed to Pretomanid

Age Group	**Patients**		**Person Time**	
	M	**F**	**M %**	**F %**
Adolescents (e.g. 12 to 17 Years)	1	1	0.08	0.16
Adults (e.g. 18 to 64 years)	1178	589	98.74	99.4
65-74 Years	10	2	0.83	0.33
75-84 Years	4	0	0.33	0
85 + Years	0	0	0	0
Total	1193	592	100	100

Table considers total duration of therapy, regardless of interruptions or missed doses.
Note that only two patients received more than six months therapy when interruptions and missed doses are excluded.
There are four patients in Study NC-002 that did not report an age and are excluded from this table.

Table 5: SIII.2b- Age Group and Gender: Study Nix-TB and ZeNix (BPaL regimen)

Age Group	Patients		Person Time	
	M	F	M %	F %
Adolescents (e.g. 12 to 17 Years)	1	1	0.55	0.12
Adults (e.g. 18 to 64 years)	178	110	99.44	99.09
65-74 Years	-	-	-	-
75-84 Years	-	-	-	-
85 + Years	-	-	-	-
Total	179	111	100	100

Table considers total duration of therapy, regardless of interruptions or missed doses.
Note that only two patients received more than six months therapy when interruptions and missed doses are excluded.

Table 6: SIII.3- Dose

Not applicable

Table 7: SIII.4a- Ethnic Origin: All subjects Exposed to Pretomanid

Ethnic Origin	Patients		Person Time	
	Male	Female	Male %	Female %
White	260	151	14.5	25.42
Black	730	298	40.8	50.1
Asian	28	14	1.56	2.35
Other	177	131	9.89	22.0
Total	1789	594	100	100

Table considers total duration of therapy, regardless of interruptions or missed doses
Note that only two patients received more than six months therapy when interruptions and missed doses are excluded.

Table 8: SIII.4a- Ethnic Origin: Study Nix-TB and ZeNix (BPaL regimen)

Ethnic Origin	Patients		Person Time	
	Male	Female	Male %	Female %
White	76	40	42.45	30.0
Black	92	57	51.39	51.35
Asian	0	0	0	0
Other	11	14	6.14	12.6
Total	179	111	100	100

Table considers total duration of therapy, regardless of interruptions or missed doses
Note that only two patients received more than six months therapy when interruptions and missed doses are excluded.

Part II: Module SIV - Populations Not Studied in Clinical Trials

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

Important exclusion criteria from Study Nix-TB are discussed below.

Exclusion criteria referring to medical history

1. Any condition in the Investigator's opinion (i.e., an unstable disease such as uncontrolled diabetes or cardiomyopathy, extra-pulmonary TB requiring extended treatment), where participation in the trial would compromise the well-being of Subject or prevent, limit or confound protocol specified assessments.
Reason for exclusion: avoid confounding factors affecting safety and efficacy assessments and patient safety
Is it considered to be included as missing information?: No
Rationale: The decision to treat with pretomanid will be taken by the healthcare professional after consideration of the patient's medical history/present medical condition and the product information.

2. Abuse of alcohol or illegal drugs, that in the opinion of the Investigator would compromise the Subjects' safety or ability to follow through with all protocol-specified visits and evaluations.
Reason for exclusion: avoid confounding factors affecting safety and efficacy assessments
Is it considered to be included as missing information?: No
Rationale: As stated in the SmPC, alcohol should be avoided while on pretomanid, especially in patients with impaired hepatic function. The decision to treat with pretomanid will be taken by the healthcare professional after consideration of the patient's medical history/present medical condition and the product information. This is considered sufficient.

3. In the judgment of the Investigator, the patient is not expected to survive for more than 12 weeks.
Reason for exclusion: avoid confounding factors affecting safety and efficacy assessments
Is it considered to be included as missing information?: No
Rationale: The decision to treat with pretomanid will be taken by the healthcare professional after consideration of the patient's medical history/present medical condition and the product information.

4. Karnofsky score <50 within 30 days prior to entry.
Reason for exclusion: avoid confounding factors affecting safety and efficacy assessments
Is it considered to be included as missing information?: No
Rationale: The decision to treat with pretomanid will be taken by the healthcare professional after consideration of the patient's medical history/present medical condition and the product information.

5. Body Mass index (BMI) <17 kg/m²
Reason for exclusion: avoid confounding factors affecting safety and efficacy assessments
Is it considered to be included as missing information?: No
Rationale The decision to treat with pretomanid will be taken by the healthcare professional after consideration of the patient's medical history/present medical condition and the product information.

6. History of allergy or known hypersensitivity to any of the trial Investigational Medicinal Products or related substances.
Reason for exclusion: subject safety; subjects with known hypersensitivity to pretomanid or any of the excipients are at greater risk of hypersensitivity reactions.
Is it considered to be included as missing information?: No
Rationale: To data lock point, there have been no reports of serious, systemic hypersensitivity in patients receiving BPaL. Pretomanid is contraindicated in patients with hypersensitivity to the active substance or to any of the excipients. This is considered to be sufficient.

7. HIV infected Subjects having a CD4+ count ≤ 50 cells/µL;
For HIV infected Subjects having a CD4+ count >50 cells/µL:

a. Currently treated with or will need to initiate antiretroviral therapy (ART) which is not compatible with the allowed ARTs and is not considered an appropriate candidate for switching to a regimen of antiretroviral agents (ARVs) which is allowed. Examples of allowed treatment include but are not limited to the following. If there are any questions, discuss with the Sponsor Medical Monitor for confirmation of appropriate ARV regimen.

i. Nevirapine based regimen consisting of nevirapine in combination with any NRTIs;

ii. Lopinavir/ritonavir (Aluvia™) based regimen consisting of lopinavir/ritonavir (Aluvia™) in combination with any NRTIs;

iii. The combination of tenofovir/lamivudine/abacavir should be considered in patients with normal renal function to address myelosuppression cross toxicity of zidovudine and linezolid;

iv. An alternate regimen that may be considered if the above are not appropriate is a triple nucleosidase reverse transcriptase inhibitors (NRTI) based regimen consisting of zidovudine, lamivudine and abacavir may be used with caution. Regimens including zidovudine should be used with special caution as zidovudine and linezolid may both cause peripheral nerve toxicity;

v. Raltegravir in combination with nucleoside reverse transcriptase inhibitors (NRTIs).

b. Cannot ensure a 2-week interval between commencing IMP and the start of ART, if not already on ARTs.

Reason for exclusion:
a. bedaquiline drug-drug interactions
b. to avoid immune reconstitution inflammatory syndrome (IRIS)
Is it considered to be included as missing information?: No
Rationale:
a) Recommendations for the concomitant use of antiretroviral medicinal products is provided in Section 4.5 of the product information for bedaquiline [19].
b) This restriction was to avoid IRIS, a condition associated with the initiation of anti-retroviral therapy or switching to a more potent antiretroviral therapy concurrent with starting anti-TB therapy, confounding the safety assessments.

8. Having participated in other clinical studies with dosing of investigational agents within 8 weeks prior to trial start or currently enrolled in an investigational study that includes treatment with medicinal agents. Subjects who are participating in observational studies or who are in a follow up period of a trial that included drug therapy may be considered for inclusion.
Reason for exclusion: to avoid confounding factors affecting safety and efficacy assessments; patient safety
Is it considered to be included as missing information?: No
Rationale: The decision to treat with pretomanid will be taken by the healthcare professional after consideration of the patient's medical history/present medical condition and the product information.

9. Significant cardiac arrhythmia requiring medication.

10. Subjects with the following at Screening:

a. QTcF interval on ECG >500 msec. Subjects with QTcF > 450 must be discussed with the sponsor medical monitor before enrolment.

b. History of additional risk factors for Torsade de Pointes, (e.g., heart failure, hypokalemia, family history of Long QT Syndrome);

c. Clinically significant ventricular arrhythmias;

d. Subjects with other cardiac abnormalities that may place them at risk of arrhythmias must be discussed with the sponsor medical monitor before enrolment. Such abnormalities include: Evidence of ventricular pre-excitation (e.g., Wolff Parkinson White syndrome); Electrocardiographic evidence of complete or clinically significant incomplete left bundle branch block or right bundle branch block; Evidence of second or third degree heart block; Intraventricular conduction delay with QRS duration more than 120 msec.

9-10: Reason for exclusion: Bedaquiline is known to prolong the QT interval [19].
Is it considered to be included as missing information?: No
Rationale: QT prolongation is a known adverse reaction of bedaquiline. In the Nix-TB study, a modest QT prolongation of <10 ms was observed (pre-dose change from baseline, QTcF); effect sizes of at least this magnitude have been reported with the use of bedaquiline. Although pretomanid has been shown to cause a mild QT prolongation that is not clinically significant, the combination of pretomanid with bedaquiline in the BPaL regimen may result in a QT prolongation of modest size in patients such as those in Nix-TB. Therefore, QT prolongation is included as an important identified risk for the use of the BPaL regimen.

11. Females who have a positive pregnancy test at Screening or already known to be pregnant, breast-feeding, or planning to conceive a child during the study or within 6 months of cessation of treatment. Males planning to conceive a child during the study or within 6 months of cessation of treatment.
Reason for exclusion: Pregnant and lactating women are routinely excluded from clinical trials to protect the health of the fetus and avoid confounding factors due to pregnancy. The exclusion of males planning to conceive a child during the study or within 6 months of cessation of treatment is due to preclinical findings in rats and mice (note, however, no testicular toxicity was observed in monkeys).
Is it considered to be included as missing information?: Yes for pregnancy
Rationale: not applicable for pregnancy ("use in pregnancy" is included as missing information). Available pharmacodynamic/toxicological data in animals have shown excretion of pretomanid in milk. A risk to the suckling child cannot be excluded. A decision must be made whether to discontinue breastfeeding or to discontinue pretomanid, taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman.
For testicular toxicity, the non-clinical findings in monkeys and the clinical studies were reassuring (see Module SII). Testicular toxicity is included as an important potential risk in this RMP.

12. A peripheral neuropathy of Grade 3 or 4, according to Division of Microbiology and Infectious Disease (DMID). Or, subjects with a Grade 1 or 2 neuropathy which is likely to progress/worsen over the course of the study, in the opinion of the Investigator.
Reason for exclusion: peripheral neuropathy is a known adverse drug reaction for linezolid [20] and ARVs used for the treatment of HIV infection.
Is it considered to be included as missing information?: No
Rationale: Neuropathic toxicities associated with linezolid were generally reversible or improved with appropriate monitoring and interruption or adjustment of linezolid dosing. Peripheral neuropathy, as well as optic neuropathy, are known adverse effects of long-term use of linezolid [20].

Exclusion criteria referring to specific treatments

13. Concomitant use of Monoamine Oxidase Inhibitors (MAOIs) or prior use within 2 weeks of treatment assignment.
Reason for exclusion: Linezolid is a monoamine oxidase inhibitor and should not be used in patients taking any medicinal product which inhibits monoamine oxidases A or B or within two weeks of taking any such medicinal product [20].
Is it considered to be included as missing information?: No
Rationale: A warning regarding the concomitant use of MAOIs inhibitors is provided in the product information for linezolid [20]. This is considered sufficient.

14. Concomitant use of serotonergic antidepressants or prior use within 3 days of treatment assignment if Investigator foresees potential risks for serotonin syndrome when combined with linezolid.
Reason for exclusion: Linezolid is a monoamine oxidase inhibitor. There is a small but documented risk of serotonin syndrome in patients taking linezolid along with serotonin agonists [21].
Is it considered to be included as missing information?: No
Rationale: To the data lock point, no events suggestive of serotonin syndrome were seen on BPaL in Study Nix-TB. As stated in the study [20], linezolid should not be taken together with serotonergic agents, except where administration of linezolid and concomitant serotonergic agents is essential. In such cases, patients should be closely observed for signs and symptoms of serotonin syndrome such as cognitive dysfunction, hyperpyrexia, hyperreflexia and incoordination. This is considered sufficient.

15. Concomitant use of any drug known to prolong QTc interval (including, but not limited to, amiodarone, bepridil, chloroquine, chlorpromazine, cisapride, cyclobenzaprine, clarithromycin, disopyramide, dofetilide, domperidone, droperidol, erythromycin, fluoroquinolones, halofantrine, haloperidol, ibutilide, levomethadyl, mesoridazine, methadone, pentamidine, pimozide, procainamide, quinidine, sotalol, sparfloxacin, thioridazine).
Reason for exclusion: QT prolongation is a known adverse drug reaction for bedaquiline [19] and moderate QT prolongation was observed in monkeys treated at a pretomanid dose of ≥150 mg/kg.
Is it considered to be included as missing information?: No
Rationale: QT prolongation is a known adverse reaction of bedaquiline. In the Nix-TB study, a modest QT prolongation of <10 ms was observed (pre-dose change from baseline, QTcF); effect sizes of at least this magnitude have been reported with the use of bedaquiline. Although pretomanid has been shown to cause a mild QT prolongation that is not clinically significant, the combination of pretomanid with bedaquiline in the BPaL regimen may result in a QT prolongation of modest size in patients such as those in Nix-TB. Therefore, QT prolongation is included as an important identified risk for the use of the BPaL regimen.

16. Concomitant use of any drug known to induce myelosuppression.
Reason for exclusion: myelosuppression is a known adverse drug reaction for linezolid [20].
Is it considered to be included as missing information?: No
Rationale: Myelosuppression (including anemia, leukopenia, thrombocytopenia, and pancytopenia) has been reported in patients receiving linezolid [20]; the anemia in particular can be life threatening. When linezolid dosing, as part of the BPaL regimen, was reduced, interrupted, or discontinued, the observed hematologic abnormalities were reversible. Complete blood counts should be monitored regularly in patients while receiving linezolid as part of the BPaL regimen, and decreasing or interrupting linezolid dosing should be considered in patients who develop or have worsening myelosuppression.

17. Use of any drugs or substances within 30 days prior to dosing known to be strong inhibitors or inducers of cytochrome P450 enzymes (including but not limited to quinidine, tyramine, ketoconazole, fluconazole, testosterone, quinine, gestodene, metyrapone, phenelzine, doxorubicin, troleandomycin, cyclobenzaprine, erythromycin, cocaine, furafylline, cimetidine, dextromethorphan). Exceptions may be made for subjects that have received 3 days or less of one of these drugs or substances, if there has been a wash-out period before administration of IMP equivalent to at least 5 half-lives of that drug or substance.

Reason for exclusion: Co-administration of pretomanid and medicinal products that strongly induce cytochrome P450 enzymes may decrease pretomanid plasma concentrations and reduce its therapeutic effect. Conversely, strong inhibitors of cytochrome P450 enzymes may increase pretomanid plasma concentrations.

Is it considered to be included as missing information?: No

Rationale: A phase 1, open-label PK study (Study A5306(CL-011)) in healthy volunteers evaluated the drug-drug interactions of pretomanid with efavirenz, ritonavir-boosted lopinavir, and rifampicin. Co-administration of pretomanid with efavirenz or ritonavir-boosted lopinavir resulted in small effects (≤35% on $AUC_{0\text{-}24h}$) on pretomanid PK parameters, so it is acceptable to treat drug resistant-TB patients that also have HIV with these 2 anti-HIV drugs and pretomanid. However, the $AUC_{0\text{-}24h}$ of pretomanid with co-administration of the CYP3A4 inducer rifampicin was reduced by 66% (90% CI 58% - 73%). Thus, the antimycobacterial rifampicin has a substantially larger effect on pretomanid exposure. Rifampicin and other strong CYP3A4 inducers should not be administered with pretomanid.

18. Subjects may have previously been treated for DS/MDR-TB (with specific exceptions for bedaquiline and/or linezolid as noted below) provided that treatment is/was discontinued at least 3 days prior to treatment assignment.

Reason for exclusion: To take part in the study, persons being treated for DS/MDR-TB, with the exception of bedaquiline and/or linezolid (see below), had to discontinue these medicines at least 3 days prior to treatment assignment.

Is it considered to be included as missing information?: No

Rationale: These patients were excluded from Study Nix-TB to avoid confounding the efficacy results and not for safety reasons.

19. Subjects should not receive more than 2 weeks of bedaquiline or linezolid prior to enrolment/first dose of IMP.

Reason for exclusion: To minimize confounding factors in the clinical trial setting.

Is it considered to be included as missing information?: No

Rationale: These patients were excluded from Study Nix-TB to avoid confounding the efficacy results and not for safety reasons.

20. Subjects with the following toxicities at Screening (labs may be repeated) as defined by the enhanced Division of Microbiology and Infectious Disease (DMID) adult toxicity table (November 2007):

- **a. Serum potassium less than the lower limit of normal for the laboratory;**
- **b. Hemoglobin level grade 2 or greater (<8.0 g/dL);**
- **c. Platelets grade 2 or greater (<75,000/mm^3);**
- **d. Absolute neutrophil count (ANC) <1000/mm^3;**
- **e. Aspartate aminotransferase (AST)**
  - **Grade 3 or greater (> 3.0 x upper limit of normal [ULN]) to be excluded;**
  - **Greater than ULN must be discussed with and approved by the sponsor Medical Monitor**

f. Alanine aminotransferase
- **Grade 3 or greater (> 3.0 x ULN) to be excluded**
- **greater than ULN must be discussed with and approved by the sponsor medical monitor;**

g. Total bilirubin:
- **Grade 3 or greater (≥2.0 x ULN), or if ≥1.5 up to 2.0 x ULN when accompanied by an increase in other liver function test (ALT, AST, alkaline phosphatase [Alk Phos], or gamma-glutamyltransferase [GGT]);**
- **1-1.5 x ULN must be discussed with and approved by the sponsor Medical Monitor**

h. Direct bilirubin:
- **Greater than ULN to be excluded**

i. Serum creatinine level greater than 2 times upper limit of normal

j. Albumin <32 g/L

Reason for exclusion: a) patients with low serum potassium were excluded for reasons of cardiac safety, b-d) patients with low hemoglobin, platelet, or ANC were excluded due to the potential for myelosuppression with linezolid [20]. Patients with high liver enzyme values were excluded due to the potential risk of hepatotoxicity.
Is it considered to be included as missing information?: no
Rationale:
a) QT prolongation is included as an important identified risk.
b-d) Myelosuppression has been reported in patients receiving linezolid. It is recommended that patients who receive linezolid should have their blood counts (including hemoglobin levels, platelets, and total and differentiated leucocyte counts) closely monitored [20].
e-h) Hepatotoxicity is included as an important identified risk in this RMP. It is recommended that patients who receive pretomanid have their liver function monitored at the initiation of treatment and regularly thereafter in accordance with the recommendations provided in the SmPC.
i) As stated in the SmPC, the safety and efficacy of pretomanid in populations with renal impairment have not been established. No data are available. Use in patients with renal impairment is not recommended.
j) Decreased albumin levels are associated with many conditions (e.g., inflammatory processes, undernutrition or liver or kidney problems).

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.

To the data lock point, a total of 1153[3] subjects were exposed to any dose of pretomanid. Of these, 109 subjects had been exposed to BPaL regimen in the ongoing, phase 3 Study Nix-TB. Of the 109 subjects who received pretomanid as part of the BPaL in Study Nix-TB, the majority (97/109) were exposed for the full 6 months.
For Study Nix-TB (phase 3, pivotal) the subjects were to receive BPaL for 6 months (extendable to 9 months), with 24 months of follow-up. To database lock, the mean follow-up time (time from last dose of any study drug to last contact) was 301.6 days (range 0 to 758) days, and 15 subjects (13.8%) have completed the entire study (i.e., 24 months of follow up).

[3] Not including exposure in the ongoing, blinded ZeNix study.

This is considered sufficient to detect adverse reactions with a long latency and those caused by prolonged and cumulative exposure.

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

Table 9: SIV- Exposure of special populations included or not in clinical trial development programmes

Type of Special Population	Exposure
Pregnant Women	Pregnant women and women planning pregnancy within 6 months of cessation of treatment were excluded from clinical trials and participants of childbearing potential were to use effective birth control to avoid pregnancy. Eight pregnancies have been reported to data lock point in the pretomanid clinical development program. Six of the subjects were treated with pretomanid and 2 were treated with HRZE. Two of the pretomanid pregnancies and 1 of the HRZE pregnancies resulted in the birth of an infant with no congenital abnormalities. Two pregnancies (1 pretomanid and 1 HRZE) ended in elective abortion. In one pretomanid subject, the pregnancy ended in spontaneous abortion (a serious TEAE), and another pretomanid subject, the pregnancy was ectopic (also a serious TEAE). The outcome of the sixth pretomanid subject's pregnancy is unknown. One pregnancy has been reported in the pretomanid studies that are not part of the development program. The subject had completed pretomanid combination therapy in Study NA_00093014, followed by a course of isoniazid and rifampicin as part of a local TB program. She gave birth to a healthy infant approximately 8 months after her last dose of isoniazid/rifampicin.
Breastfeeding Women	Breastfeeding women were excluded from clinical trials. There were no reports of breastfeeding in the clinical development program.

Patients with Relevant Comorbidities Patients with Hepatic Impairment Patients with Renal Impairment Patients with Cardiovascular Impairment Immunocompromised Patients Patients with a Disease Severity Different from Inclusion Criteria in Clinical Trials	<u>Hepatic impairment</u> Patients with hepatic impairment[4] were not included in the clinical development program. A phase 1 special population study (DMID 13-0053) is ongoing in subjects with mild/moderate/severe hepatic impairment and matched non hepatically impaired subjects (screening in progress). <u>Renal impairment</u> Patients with renal impairment[5] were not included in the clinical development program. A phase 1 special population study (DMID 15-0037) is planned in subjects with mild/moderate/severe renal impairment and matched non-renally impaired subjects. <u>Patients with cardiovascular impairment</u> Patients with significant cardiac arrhythmia (requiring medication) or with risk factors for Torsade de Pointes (e.g. heart failure, hypokalemia, family history of Long QT Syndrome) were excluded from Study Nix-TB. <u>Immunocompromised patients</u> Forty-nine percent (49%) of the patients in Study Nix-TB were HIV co-infected, and during the trial all of these patients took anti-retroviral medication in addition to the trial medications. <u>Patients with a disease severity different from inclusion criteria in clinical trials</u> The clinical development program included subjects with DS-TB as well as subjects with MDR-TB and XDR-TB. Subjects who received BPaL in the ongoing, phase 3 studies, Study Nix-TB and Study ZeNix, had XDR-TB or treatment-intolerant or nonresponsive MDR-TB (or pre-XDR-TB in Study ZeNix) and, thus, were a population with more severe illness (including greater prevalence of human immunodeficiency virus [HIV] coinfection) than other study populations. There were no clinical studies with pretomanid with non-pulmonary TB.

Type of Special Population	Exposure
Population with Relevant Different Ethnic Origin	To data lock point, slightly over half of subjects in the clinical development program (56.9%) were black. White and Asian subjects composed 16.6% and 1.5%, respectively, of the population. Another 25.0% of subjects were classified as having a race of "other" (i.e., race not recorded as white, black, or Asian). In Study Nix-TB, 76.1% of subjects were black. One (0.9%) subject was white and 22.9% of subjects were classified as having a race of "other." Exposure by race is presented in Part II: Module SIII.
Subpopulations Carrying Relevant Genetic Polymorphisms	Not included in the clinical development program.
Other	Not included in the clinical development program.

Part II: Module SV - Post-authorisation Experience

SV.1 Post-authorisation Exposure

SV.1.1 Method Used to Calculate Exposure

The MAH is marketing pretomanid in [redacted] he patient exposure has been estimated based on the available cumulative sales data for pretomanid. This data is gathered worldwide from Viatris Inc. These figures are compiled from data available at the time of writing and may not represent exact patient consumption. They may include packs that are lodged with wholesalers, pharmacists or representatives.

The methodology used for calculating an estimate of patient exposure for pretomanid is:

$$\text{Patient Treatment Course (PTC)} = \frac{\text{Total mg sold}}{\text{Total dose received per course}}$$

[4] Defined as aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) of Grade 3 or greater (>3.0 x upper limit of normal [ULN] (greater than ULN had to be discussed with and approved by the sponsor medical monitor) or total bilirubin of Grade 3 or greater (≥2.0 x ULN) or if ≥1.5 up to 2.0 x ULN when accompanied by an increase in another liver function test (ALT, AST, Alk Phos, or GGT) (1-1.5 x ULN had to be discussed with and approved by the sponsor medical monitor) or direct bilirubin greater than ULN.

[5] Defined as serum creatinine level greater than 2 x ULN or Albumin <32 g/L.

As per the company CCDS, the recommended dosage of pretomanid is 200 mg tablet once daily for 26 weeks. Therefore, 36,400 mg are assumed to equal one treatment course.

SV.1.2 Exposure

The patient exposure has been presented below from the date of initial sale until the data lock point of this report.

Table 10: SV- Cumulative exposure from Non-study post-authorisation exposure by dose and country

Formulation	Country	Strength	Quantity Sold (no. of tablets)	Total Mg Sold	Exposure in PTC
Tablets	EU*	200 mg	1,193,920	238,784,000	6,560
Tablets	Non-EU	200 mg	1,220,180	244,036,000	6,704
Total				482,820,000	13,264

*Based on US-FDA approval to IDA foundation (Netherlands) to support low middle-income countries

Part II: Module SVI - Additional EU Requirements for the Safety Specification

Potential for Misuse for Illegal Purposes

Pretomanid is not considered to have abuse potential in the targeted indication based on its mechanism of action and safety profile. Drug abuse with pretomanid is unlikely, as studies have shown no evidence of psychoactive reinforcing effects from use of the drug.

Part II: Module SVII - Identified and Potential Risks

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

Viatris has RMP version 1.0 for pretomanid procedure number EMA/H/C/005167 approved on 31-Jul-2020, with the following safety concerns:

Table 11: SVII.1- Summary of safety concerns

Important Identified Risks	QT prolongation
Important Potential Risks	Hepatotoxicity Testicular toxicity
Missing Information	Use in pregnancy

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

Not applicable as this is not an initial RMP submission.

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

Not applicable as this is not an initial RMP submission.

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

"QT prolongation" previously classified as important identified risk, and "hepatotoxicity" previously classified as important potential risk are removed from the list of safety concerns in line with CHMP/PRAC Rapporteur's updated assessment report procedure EMEA/H/C/005167/II/0019/G dated 29-Feb-2024. Both risks are considered to have been characterised and appropriately managed by routine pharmacovigilance.

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

For the risk characterization, TEAEs are presented from studies Nix-TB and ZeNix in which all participants received bedaquiline, pretomanid, and linezolid (BPaL), in accordance with the proposed indication.

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

Table 12: SVII.2- Testicular toxicity

Potential Mechanisms	Not known
Evidence Source(s) and Strength of Evidence	Testicular toxicity was observed in rats and mice without exposure margin to the MRHD. Decreased fertility to complete infertility was observed in male rats treated with oral pretomanid. There were no direct effects of pretomanid on reproductive organs in monkeys given oral pretomanid for 3-months and 9-months. Decreased sperm motility, total sperm count and increased abnormal sperm ratio were observed in monkeys, which were considered as effects of substantial decreases in food consumption and body weight at high dose levels. Based upon the preclinical data, rodents are susceptible to pretomanid-induced testicular injury. Serum levels of the male reproductive hormones are biomarkers that are altered in association with this injury. In the preclinical study of primates, no pretomanid-related alterations in testis or male reproductive hormones were observed. Studies of male reproductive hormones showed no evidence of treatment-associated testicular toxicity, and no events of fertility disorders were reported in male patients in the Nix-TB study and ZeNix study.
Characterisation of the Risk	Due to the nonclinical findings, male reproductive hormones were studied in Studies NC 002, NC-005, and NC 006, which showed no evidence of treatment-associated testicular toxicity. Also, no events of testicular toxicity were reported in ZeNix. In addition, a search for TEAEs associated with fertility disorders across the 19 studies in the clinical development program identified no events in any male subject and only one event in a female subject, which was menstruation irregular.
Risk Factors and Risk Groups	Not known
Preventability	Not known

Impact on the Risk-benefit Balance of the Product	Dovprela is indicated in combination with bedaquiline and linezolid for the treatment of adults with pulmonary tuberculosis (TB) resistant to isoniazid, rifampicin, a fluoroquinolone and a second line injectable antibacterial drug or adults with pulmonary TB resistant to isoniazid and rifampin who are treatment-intolerant or nonresponsive to standard therapy. Given the severity of the indication and an absence of findings in humans, the impact of this potential risk is estimated to be low.
Public Health Impact	Testicular toxicity would affect the individual only; no public health impact is expected.

SVII.3.2. Presentation of the Missing Information

Table 13: SVII.3- Use in Pregnancy

Evidence Source	Although animal studies do not indicate direct or indirect harmful effects with respect to embryo-fetal development, there is a limited amount of data and no controlled clinical studies in pregnant women.
Population in Need of Further Characterisation	Pregnant women

Part II: Module SVIII - Summary of the Safety Concerns

Table 14: SVIII- Summary of safety concerns

Important Identified Risks	None
Important Potential Risks	Testicular toxicity
Missing Information	Use in pregnancy

PART III: PHARMACOVILIGANCE PLAN

The Pharmacovigilance System Master File contains details of the system and processes that the MAH/Applicant has in place to identify and/or characterize the risks recognised in the safety specification.

III.1 Routine Pharmacovigilance Activities

Routine pharmacovigilance activities only.

III.2 Additional Pharmacovigilance Activities

As current routine pharmacovigilance activities are sufficient, no additional pharmacovigilance activities are recommended.

III.3 Summary Table of Additional Pharmacovigilance Activities

None

PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

There are no planned or on-going imposed post-authorization efficacy studies.

PART V: RISK MINIMISATION MEASURES

Risk Minimisation Plan

V.1 Routine Risk Minimisation Measures

Table 15: Part V.1- Description of routine risk minimisation measures by safety concern

Safety Concern	Routine Risk Minimisation Activities
Testicular toxicity	Routine risk communication: SmPC sections 4.6, 5.3 Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond the Product Information: Legal status: prescription only
Use in Pregnancy	Routine risk communication: SmPC section 4.6 PL section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond the Product Information: Legal status: prescription only

V.2 Additional Risk Minimisation Measures

Routine risk minimisation activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

V.3 Summary Table of Pharmacovigilance and Risk Minimisation Activities by Safety Concern

Table 16: Part V.3- Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Testicular toxicity	Routine risk communication: SmPC sections 4.6, 5.3 Routine risk minimisation activities recommending specific clinical measures to address the risk:	Additional pharmacovigilance activities: None

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
	None Other routine risk minimisation measures beyond the Product Information: Legal status: prescription only Additional risk minimization measures: None	
Use in Pregnancy	Routine risk minimisation measures: SmPC section 4.6 PL section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond the Product Information: Legal status: prescription only Additional risk minimisation measures: None	Additional pharmacovigilance activities: None

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of Risk Management Plan for Dovprela (pretomanid)

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

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

This summary of the RMP for Dovprela should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all of 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 Dovprela 's RMP.

I. The Medicine and What it is Used For

Dovprela is authorised in combination with bedaquiline and linezolid for the treatment of adults with pulmonary tuberculosis (TB) due to *Mycobacterium tuberculosis* resistant to all of isoniazid, rifampicin, a fluoroquinolone and a second line injectable antibacterial drug and adults with pulmonary TB due to *M. tuberculosis* resistant to both isoniazid and rifampicin, who are treatment-intolerant or nonresponsive to standard therapy (see SmPC for the full indication). It contains pretomanid as the active substance and it is given by mouth.

Further information about the evaluation of Dovprela’s benefits can be found in Dovprela’s EPAR, including in its plain-language summary, available on the EMA website[6].

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

Important risks of Dovprela, together with measures to minimise such risks and the proposed studies for learning more about Dovprela '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.

[6]EMA website under the medicine’s webpage: https://www.ema.europa.eu/en/documents/rmp-summary/pretomanid-fgk-epar-risk-management-plan-summary_en.pdf

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*.

If important information that may affect the safe use of Dovprela is not yet available, it is listed under 'missing information' below.

II.A List of Important Risks and Missing Information

Important risks of Dovprela are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Dovprela. 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 (e.g. on the long-term use of the medicine).

Table 17: Part VI.1- Summary of safety concerns

List of Important Risks and Missing Information	
Important Identified Risks	None
Important Potential Risks	Testicular toxicity
Missing Information	Use in pregnancy

II.B Summary of Important Risks

Table 18: Part VI.2- Testicular toxicity

Evidence for Linking the Risk to the Medicine	Testicular toxicity was observed in rats and mice without exposure margin to the maximum recommended human dose (MRHD). Decreased fertility to complete infertility was observed in male rats treated with oral pretomanid. There were no direct effects of pretomanid on reproductive organs in monkeys given oral pretomanid for 3-months and 9-months. Decreased sperm motility, total sperm count and increased abnormal sperm ratio were observed in monkeys, which were considered as effects of substantial decreases in food consumption and body weight at high dose levels. Based upon the preclinical data, rodents are susceptible to pretomanid-induced testicular injury. Serum levels of the male reproductive hormones are biomarkers that are altered in association with this injury. In the preclinical study of primates, no pretomanid-related alterations in testis or male reproductive hormones were observed. Studies of male reproductive hormones showed no evidence of treatment-associated testicular toxicity and no events of fertility disorders were reported in male patients in the Nix-TB study and ZeNix study.
Risk Factors and Risk Groups	Not known.

Risk Minimisation Measures	Routine risk communication: SmPC sections 4.6, 5.3 Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond the Product Information: Legal status: prescription only Additional risk minimization measures: None
Additional Pharmacovigilance Activities	None

Table 19: Part VI.3- Use in pregnancy

Risk Minimisation Measures	Routine risk minimisation measures: SmPC section 4.6 PL section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond the Product Information: Legal status: prescription only Additional risk minimisation measures: None

II.C Post-Authorisation Development Plan

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

There are no studies which are conditions of the marketing authorisation or specific obligation of Dovprela.

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

There are no studies required for Dovprela.

Annex 4 - Specific Adverse Drug Reaction Follow-up Forms

Not applicable.

Annex 6 - Details of Proposed Additional Risk Minimisation Activities (If Applicable)

Not applicable.

Annex 7 - Other Supporting Data (Including Referenced Material)

[1] "Meeting report of the WHO expert consultation on the definition of extensively drug-resistant tuberculosis. (2021, January 22). Meeting Report of the WHO Expert Consultation on the Definition of Extensively Drug-resistant Tuberculosis. https://www.who.int".

[2] "Global Tuberculosis Report 2022. (2022, October 27). Global Tuberculosis Report 2022.".

[3] "3. European Centre for Disease Prevention and Control. Tuberculosis. In: ECDC. Annual epidemiological report for 2021. Stockholm: ECDC; 2023.".

[4] "Tuberculosis surveillance and monitoring in Europe 2022 –2020 data. (2022, March 24). European Centre for Disease Prevention and Control.".

[5] "World Health Organization. (n.d.). Tuberculosis (TB). World Health Organization. https://www.who.int/news-room/fact-sheets/detail/tuberculosis".

[6] "Faustini A, Hall AJ, Perucci CA. Risk factors for multidrug resistant tuberculosis in Europe: a systematic review. Thorax. 2006;61(2):158-163. doi:10.1136/thx.2005.045963".

[7] "Samuels JP, Sood A, Campbell JR, Ahmad Khan F, Johnston JC. Comorbidities and treatment outcomes in multidrug resistant tuberculosis: a systematic review and meta-analysis. Scientific reports. 2018 Mar 21;8(1):4980.".

[8] "JOINN Laboratories M12 43-2CD. 28 Day Oral Dose-Range Finding Study in CD-1 Mice.".

[9] "MPI Research 1408-017. 13 Week Oral Toxicity and Toxicokinetic Study in CD-1 Mice.".

[10] "BioReliance AC30JU.2G3R.BTL. 28 Day Oral Toxicity and Toxicokinetic Study in CByB6F1 Mice.".

[11] "Covance 7504-101. 14 Day Oral Toxicity and Toxicokinetic Study.".

[12] "Covance 7504-110. 2-Week Oral Toxicity and Toxicokinetic Study with a 2 Week Recovery Period.".

[13] "MPI Research 1408-002. 3 Month Oral Toxicity Study with a 3 Month Recovery Period.".

[14] "Covance 7504-170. 26 Week Oral Toxicity and Toxicokinetic Study with a 13-Week Component to Evaluate".

[15] "MPI Research 1408-003. 3 Month Oral Toxicity and Toxicokinetic Study with a 3 Month Recovery Period.".

[16] "SRI M962-12. A 39 Week Oral Toxicity and Toxicokinetic Study with a 12 Week Recovery Period.".

[17] "CRL QTC00007. Fertility and General Reproduction in Rats.".

[18] "SNBL 269.01. 13-Week Oral Study to Evaluate Reproductive Function and Lenticular Lesions in Male Monkeys with a 20-Week Recovery Period.".

[19] "Sirturo® SmPC, 2019. https://www.ema.europa.eu/en/documents/product-information/sirturo-epar-productinformation_en.pdf Available at: Accessed: 2020 Feb 18.".

[20] "Zyvox® SmPC, 2018. Pfizer limited. Available at: https://www.medicines.org.uk/emc/product/1688/smpc/print Accessed: 2018 Dec 21.".

[21] "Quinn DK, Stern TA. Linezolid and serotonin syndrome. Primary care companion to the Journal of clinical psychiatry. 2009;11(6):353."