PASS information

Title	A Multicentre, EU-wide, Non-Interventional Post-Authorisation Study to Assess the Safety and Usage of Delamanid in Routine Medical Practice in Multidrug-Resistant Tuberculosis Patients
Version identifier of the final study report	Final Report v2.0
Date of last version of the final study report	04 May 2023
EU PAS register number	ENCEPP/SDPP/10618
Active substance	Delamanid ATC code J04AK06 (J04AK Other drugs for treatment of tuberculosis) Delamanid, a nitro-dihydroimidazo-oxazole derivative
Medicinal product	Deltyba
Product reference	EMEA/H/C/2552
Procedure number	EMEA/H/C/002552/MEA/002
Marketing authorisation holder(s)	Otsuka Novel Products GmbH Erika-Mann-Str. 21 80636 Munich, Germany
Joint PASS	No
Research question and objectives	This post-authorisation safety study (PASS) is a non-interventional treatment registry for Deltyba use in routine medical practice and aims to assess compliance with the recommendations in the authorised product information to collect further information on Deltyba usage, treatment outcomes as assessed per WHO[1] definition and / or national guidelines and safety of Deltyba. No hypothesis was tested in this study.

	Treatment, all assessments and patient monitoring were performed according to the existing practices and / or treatment centre's local / national tuberculosis programme (NTP) guidelines. The primary objective was: • To monitor the usage of Deltyba in a real-life setting when prescribed as part of an appropriate combination regimen (ACR) designed by the treating physician. The secondary objectives were: • To evaluate treatment outcomes (including clinical effectiveness) as defined by the World Health Organization (WHO)[1] and / or national guidelines for patients at the end of a full treatment period for MDR-TB up to 30 months or earlier if patients were cured. • To monitor the safety of Deltyba in a real-life setting when prescribed as part of an ACR designed by the treating physician.
Country(-ies) of study	Countries of the study (launch date): • At start of the EU-PASS: o United Kingdom (30 May 2014) o Germany (17 June 2014). • At later stage: o Estonia (28 September 2016) o France (06 June 2016) o Latvia (03 July 2015) Lithuania (02 May 2016).
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1. ABSTRACT

Title

Protocol No. 242-12-402: A Multicentre, EU-wide, Non-Interventional Post-Authorisation Study to Assess the Safety and Usage of Delamanid in Routine Medical Practice in Multidrug-Resistant Tuberculosis Patients

Keywords

Delamanid, pulmonary Multidrug-Resistant Tuberculosis, PASS

Rationale and background

Delamanid is a synthesised nitrodihydroimidazo-oxazole derivative developed by the Otsuka Pharmaceutical Company.[2] It acts by inhibiting the biosynthesis of mycolic acid, a critical component of the tuberculosis (TB) bacterium cell wall. 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 Appropriate Combination Regimen (ACR) for the treatment of multi-drug resistant tuberculosis (MDR-TB) patients receiving delamanid-containing regimens experienced an approximately 50% increase in sputum culture conversion from growth of Mycobacterium tuberculosis (MTB) to no growth over the first 2 months of treatment compared to those receiving an ACR plus placebo.

Deltyba received a conditional marketing authorisation within the European Union (EU) as of 28 Apr 2014 based on a favourable benefit-risk ratio assessment derived from Phase II trial data. The benefits of the treatment with Deltyba were shown for patients with MDR-TB affecting the lung. The safety profile was considered manageable, and several measures were introduced to minimise the risks, including educational materials for health care professionals and patients.

This post-authorisation safety study (PASS) was a non-interventional treatment registry for Deltyba use in routine medical practice and aimed:

- To assess compliance with the recommendations in the authorised product information
- To collect further information on safety
- To collect further information on treatment outcomes as assessed per World Health Organisation (WHO) definition[1] and / or national guidelines.

Research question and objectives

Study design

This was an EU-wide, multicentre, non-interventional prospective study of MDR-TB patients prescribed Deltyba. The total duration of the study per patient was up to 30 months after receiving first dose of Deltyba or until completion of MDR-TB treatment. The total duration of the Deltyba PASS was planned to be 6.5 years (4-years enrolment period). The ACR was designed by the treating physician. According to the summary of product characteristics (SmPC), Deltyba is indicated for use as part of an ACR for pulmonary MDR-TB in adult patients, when an effective treatment regimen cannot otherwise be composed for reasons of resistance or tolerability. The treatment, all assessments, and patient monitoring were performed according to the existing practices and / or treatment centre's local / national TB program (NTP). According to a request of the German Health Authorities, only patients in compliance with the SmPC approved indication should participate in the PASS and therefore, a separate protocol specifying corresponding inclusion and exclusion criteria for patients recruited in Germany had been prepared. The paediatric extension of indication (EMEA/H/C/002552/II/0040 and EMEA/H/C/002552/X/0046/G) were approved after the enrolment for PASS delamanid study stopped.

Setting

The study was planned for 250 patients or 4-year enrolment period (whichever occurred first) with MDR-TB, prescribed Deltyba and treated at specialised sites in the EU.

Patients and study size

A total of 250 MDR-TB patients were planned to be enrolled in this Deltyba PASS. An important consideration that had been taken into account for estimation of the sample size was the incidence of pulmonary MDR-TB in EU countries.[6] MDR-TB is an orphan disease in the EU with low incidence in Germany, UK, and some other EU countries. The restricted indication of Deltyba (according to the SmPC Deltyba is indicated for use as part of an ACR for pulmonary MDR-TB in adult patients, when an effective treatment regimen cannot otherwise be composed for reasons of resistance or tolerability) was also taken into consideration in the sample size estimation. In addition, the dates of anticipated launch were taken into account (initially planned launched in Austria, Estonia, France, Germany, Latvia, Lithuania, UK, Bulgaria, Norway, Poland, Portugal, Romania, Spain, and Sweden).

Variables and data sources

By the nature of this study, the source of the data collected were patient records or documentation used for the NTPs, depending upon local circumstances.

The following data were collected and included in analysis but were not limited to: Deltyba usage, ACR usage, use with directly observed therapy (DOT), duration of Deltyba use, age of the patient, treatment indication, medical history and all medical conditions, all concomitant medications, laboratory tests including drug susceptibility testing (DST), electrocardiogram (ECG) test results, all adverse events (AEs), and final treatment outcomes.

No formal hypotheses were tested in this study.

Descriptive summary statistics for continuous variables included the mean, standard deviation (SD), median, and range. Descriptive summary statistics for categorical variables included frequency counts, and percentages (n [%]).

Results

During the procedure EMEA/H/C/002552/MEA/002.2, the Committee for Medicinal Products for Human Use requested to present real-world usage data grouped by EU (without the inclusion of Germany, considering the German specific inclusion and exclusion criteria) and Germany separately and discuss potential differences between countries in final study report. In the appendices data are presented per site and country while in the body of the report data are presented at the EU aggregate level as well as for Germany versus Non-Germany dataset.

Eighty-eight patients with MDR-TB in the EU were treated with Deltyba and enrolled into PASS. Eighty-six patients were included in analyses set and 2 patients were excluded due to invalid informed consent form (ICF) process.

Deltyba was administered for treatment of MDR-TB in all 86 patients enrolled in the PASS, 85 (98.8%) patients were diagnosed for the approved indication of pulmonary TB and 1 patient (1.2%) for extrapulmonary TB. During the SmPC recommended treatment duration of 24 weeks, all patients received the recommended Deltyba dose 100 mg twice daily (BID). As per physician's decision, treatment with Deltyba continued after the SmPC recommended treatment duration of 24 weeks in 57 (66.3%) patients. During Deltyba extension, 43 of patients received the recommended Deltyba 100 mg BID dose, while in 14 patients the treatment dose or dosing frequency was changed by the treating physician as follows: one patient received the daily 200 mg in a once-daily (QD) application (Lithuania) and 13 patients, all from the same study site in Germany, received Deltyba 100 mg QD.

Overall, 66 (76.7%) of the 86 enrolled patients had a successful treatment outcome. Forty-nine (57.0%) patients were cured, 17 (19.8%) have completed the treatment, 1 (1.2%) was a treatment failure, 11 (12.8%) were lost to follow up (LTFU), 5 (5.8%) were not evaluated and 3 (3.5%) died. In Germany Enrolled set, 2 (10.0%) of 20 patients enrolled in Germany were cured, 14 (70.0%) have completed the treatment, and 4 (20.0%) were LTFU. In Non-Germany Enrolled Set, 47 (71.2%) out of 66 patients enrolled were cured, 3 (4.5%) have completed the treatment, 1 (1.5%) was treatment failure, 7 (10.6%) were LTFU, 5 (7.6%) were not evaluated, and 3 (4.5%) died.

Overall, 79 patients (91.9%) experienced treatment-emergent AEs (TEAEs) and 21 patients (24.4%) had at least 1 serious TEAE of which 6 were assessed as related to delamanid by the PASS physician. Sixteen patients (18.6%) experienced severe TEAEs. Five patients (5.8%) experienced TEAEs leading to treatment discontinuation and 3 patients (3.5%) died. The reported TEAEs observed in this study are in line with the established safety profile of delamanid. No new adverse drug reactions (ADRs) or new safety concerns were detected.

There were no notable trends in clinical laboratory parameters, vital signs, physical examinations, and ECG parameters, including QT interval corrected for heart rate by Bazett's formula (QTcB) and QT interval corrected for heart rate by Fridericia's formula (QTcF).

Discussion

The observational study reveals that Deltyba is used in the approved indication in 85 (98.8%) patients and therefore all but 1 (1.2%) patient (diagnosed as extrapulmonary TB) has been treated in agreement with the labelled indication.

The treatment success rate (defined as the combination of patients who were cured and those who completed treatment) in this study was 76.7% which is similar to estimates reported in published studies[11] (82% [95% confidence interval: 76% to 89%].

Drug resistance against delamanid was reported in 2 patients in Germany. For 1 patient, DST sample taken at baseline before start of delamanid treatment revealed resistance against delamanid. The other event was reported in a patient with pre-existing cavities and extensively resistant TB (XDR-TB) along with a serious AE (SAE) of treatment failure during extended use of 100 mg BID delamanid. The case was reported as recovered/resolved after pneumonectomy and the patient completed the study treatment.

The previously established favourable benefit-risk profile for delamanid has been reconfirmed by the efficacy and safety data that have become available during this study. With respect to important identified risks, analysed data support QT interval prolongation as the most prominent risk related to delamanid use. The risk seems to be well known and was adequately managed with frequent ECG monitoring during the study and PASS physicians were frequently administering delamanid in combination with other QT-prolonging drugs (eg, bedaquiline, clofazimine, moxifloxacin). Too few patients from special patient groups, eg, elderly patients, patients with hepatic impairment, as well as patients with human immunodeficiency virus (HIV) have been included in the PASS for assessing specific risks in these populations.

The AEs reported for the patients treated longer than 24 weeks with delamanid are overall consistent with the AEs observed during the first 24 weeks of delamanid treatment. Based on the reported TEAEs during this study, there are no safety concerns from the use of delamanid longer than 24 weeks. No safety concern is identified in relation with the property of delamanid and its metabolites to covalently bind to plasma proteins.

Study limitations included lower overall patient enrolment than initially anticipated, low number of countries participating with reasonable patient numbers and low number of patients from several subpopulations, like elderly or HIV positive patients. In addition, study outcomes of the

PASS may have to be restricted to Baltic states and Germany as only these countries contributed with reasonable patient number to the PASS.

In addition, country specificities of MDR-TB management in terms of duration of hospitalisation and ensuring adherence to MDR-TB treatment during the outpatient or continuation treatment phase resulted in difficulties for collection of data throughout the entire MDR-TB treatment period for several patients.

2. LIST OF ABBREVIATIONS

Abbreviation	Definition
ACR	Appropriate combination regimen
ADR	Adverse drug reaction
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical classification system
BID	Twice daily
BMI	Body mass index
CI	Confidence interval
CRO	Contract research organisation
CYP	Cytochrome
DOT	Directly observed therapy
DST	Drug susceptibility testing
EBA	Early bactericidal activity
ECDC	European Centre for Disease Prevention and Control
ECG	Electrocardiogram
eCRF	Electronic case report form
EMA	European Medicines Agency
EU	European Union
GGT	Gamma glutamyl transferase
HCP	Healthcare professional
HIV	Human immunodeficiency virus
ICF	Informed consent form
LJ	Lowenstein-Jensen
LTFU	Loss to follow-up
MAH	Marketing Authorisation Holder
MDR-TB	Multidrug-resistant tuberculosis
MedDRA	Medical Dictionary for Regulatory Activities
MGIT	Mycobacterium growth indicator tube
MTB	Mycobacterium tuberculosis
NTP	National tuberculosis programme
OBR	Optimised background regimen
PAS	Para-aminosalicylic acid
PASS	Post-authorisation safety study
PT	Preferred term
QD	Once daily
QTc	Q wave - T wave interval corrected for heart rate
QTcB	QT interval corrected for heart rate by Bazett's formula
QTcF	QT interval corrected for heart rate by Fridericia's formula
RMP	Risk management plan
RR-TB	Rifampicin resistant tuberculosis
SAE	Serious adverse event

Abbreviation	Definition
SAP	Statistical Analysis Plan
SAT	Self-administered therapy
SmPC	Summary of product characteristics
SOC	System Organ Class
TB	Tuberculosis
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal
WHO	World Health Organisation
XDR-TB	Extensively drug-resistant tuberculosis

3. INVESTIGATORS

List of all participating healthcare professionals (HCPs) will be kept in a stand-alone document as listed in Annex 1, and will be available upon request.

4. OTHER RESPONSIBLE PARTIES

Contract Research Organisation (CRO):

Labcorp Clinical and Periapproval Services Limited, Osprey House, Maidenhead Business Park, Westacott Way, Maidenhead SL6 3QH, United Kingdom.

5. MILESTONES

Milestone	Planned date	Actual date	Comments
Start of data collection	Q4 2015	Q3 2016*	12 Aug 2016
End of data collection	Q2 2022	To be confirmed	N/A
Registration in the EU PAS register	Q3 2015	Q3 2015	N/A
Study progress report 1	Q2 2017	20 Jun 2017	N/A
Study progress report 2	Q2 2018	25 Jun 2018	N/A
Study progress report 3	Q4 2019	22 Jul 2019	N/A
Study progress report 4	Q4 2020	06 Nov 2020	N/A
Study progress report 5	Q4 2021	16 Dec 2021	N/A
Final report of study results	Q3 2022	18 Aug 2022	N/A
Study report Amendment 1	Q2 2023	04 May 2023	N/A

*Annual study progress report: yearly from **actual** start of data collection.

6. RATIONALE AND BACKGROUND

Delamanid is a nitrodihydroimidazo-oxazole derivative developed by the Otsuka Pharmaceutical Company.[2] It acts to inhibit the biosynthesis of mycolic acid, a critical component of the Tuberculosis (TB) bacterium cell wall.

Bioavailability of delamanid is approximately 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 lesser extent by cytochrome (CYP) enzymes. Delamanid has an elimination half-life of about 38 hours. Delamanid and metabolites are excreted in faeces, and not significantly via kidneys.

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 Multidrug-resistant TB (MDR-TB) patients receiving delamanid-containing regimens experienced an approximately 50% increase in sputum culture conversion from growth of Mycobacterium tuberculosis (MTB) to no growth over the first 2 months of treatment compared to those receiving OBR plus placebo.[4]

6.1. Non-clinical safety profile and relevance to human usage

Non-clinical data revealed no specific hazard for humans based on conventional studies for genotoxicity and carcinogenic potential.

However, non-clinical data reveal that delamanid and/or its metabolites have the potential to affect cardiac repolarisation via blockade of hERG potassium channels. This non-clinical safety finding has been shown to be of clinical relevance: electrocardiogram (ECG) Q wave – T wave interval corrected for heart rate (QTc) interval prolongation has been identified as the most prominent safety concern. The clinical safety profile is described in Section 6.2.

In rabbit reproductive studies, embryo-foetal toxicity was observed at maternally toxic dosages. As currently no clinical data are available, delamanid is not recommended in pregnant women or in women of childbearing potential unless they are using a reliable form of contraception. Pharmacokinetic data in animals have shown excretion of delamanid or metabolites into breast milk. In lactating rats, the maximum concentration for delamanid in breast milk was 4-fold higher than that of the blood, while corresponding clinical data are currently not available and a potential risk to the breast-feeding infant cannot be ruled out. Therefore, it is recommended that women should not breastfeed during treatment with delamanid.

6.2. Clinical Safety Profile

Deltyba received a conditional marketing authorisation within the European Union (EU) as of 28 Apr 2014 based on a favourable benefit-risk ratio assessment derived from Phase 2 data (last licence renewal date of the conditional marketing authorisation: 13 Apr 2021). The benefits of the treatment with Deltyba were shown in patients with MDR-TB affecting the lung. The safety profile was considered manageable, and several measures were introduced to minimise the risks.

At the time of delamanid approval, the safety profile of delamanid was derived from the frequency of the adverse drug reactions (ADRs) from one double blind controlled clinical trial involving 481 patients with MDR-TB, in which 321 patients received delamanid in combination with an appropriate combination regimen (ACR). Electrocardiogram QTc interval prolongation has been identified as the most prominent safety concern of treatment with delamanid. A major factor contributing to QTc interval prolongation is hypoalbuminaemia (particularly below 2.8 g/dl) (Protocol No. 242-12-402, Final Version 4.0, 15 November 2017).

The following risk minimisation measures were implemented:

- Central order and distribution process to ensure that Deltyba was used only by sites and treating physicians with experience in MDR-TB management according to World Health Organisation (WHO)[5] and/or national guidelines,
- educational materials for health care professionals and patients to inform them about the appropriate usage of Deltyba and potentially associated risks to be closely monitored (such as risk of QTc prolongation and development of resistance to Deltyba),
- this EU-wide post-authorisation safety study (PASS) to monitor usage of the product, to assess treatment outcomes and to obtain further information on safety.

This PASS was a non-interventional treatment registry for Deltyba in routine medical practice and it was aimed to:

- Assess compliance with the recommendations in the authorised product information,
- collect further information on safety,
- collect further information on treatment outcomes as assessed per WHO definition[1] and/or national guidelines.

7. RESEARCH QUESTION AND OBJECTIVES

Non-interventional PASS study did not define a therapeutic strategy and the decision to administer commercially available product fell under the responsibility of the treating physician and his/her medical judgement. The physician's decision to treat a patient with Deltyba was independent of the decision to enrol the patient into the PASS. The study did not require any additional diagnostic, therapeutic or monitoring procedures outside routine medical practice.

7.1. Study Objectives

The primary objective of the study was:

- To monitor the usage of Deltyba in a real-life setting when prescribed as part of an ACR designed by the treating physician.

The secondary objectives of the study were:

- To evaluate treatment outcomes (including clinical effectiveness) as defined by the WHO[1] and/or national guidelines for patients at the end of a full treatment period for MDR-TB up to 30 months, or earlier if patients were cured.

- To monitor the safety of Deltyba in a real-life setting when prescribed as part of an ACR designed by the treating physician.

All adverse events (AEs) (serious and non-serious) were entered into the electronic case report form (eCRF) during the study. At every regular visit of their patient, physicians entered any new information on AEs into the eCRF. The following were monitored as signs and symptoms of special interest, and the incidence was summarised:

- Cardiac disorders (including QT prolongation)

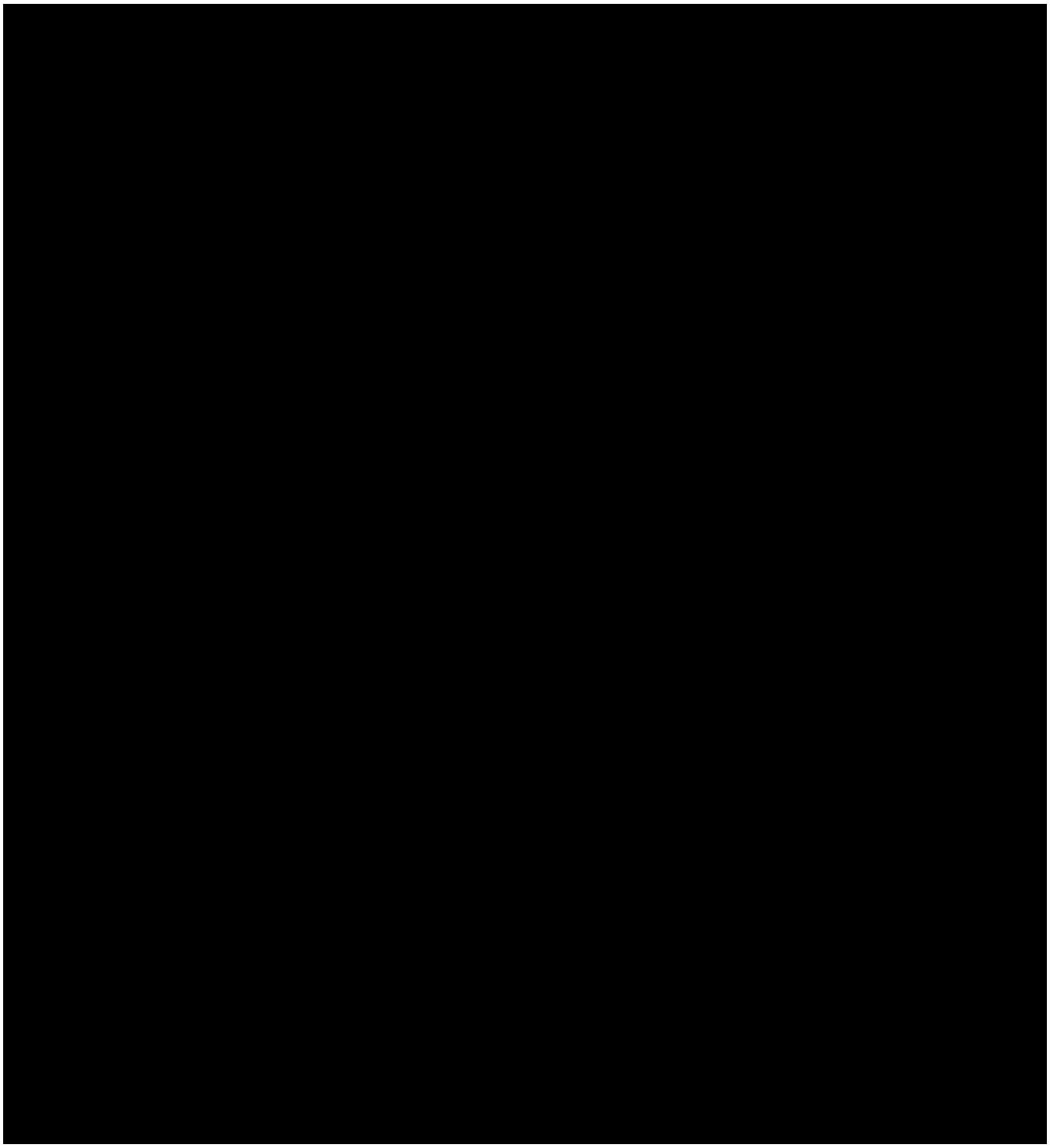
- Suspected delamanid resistance (including lack of delamanid effect).

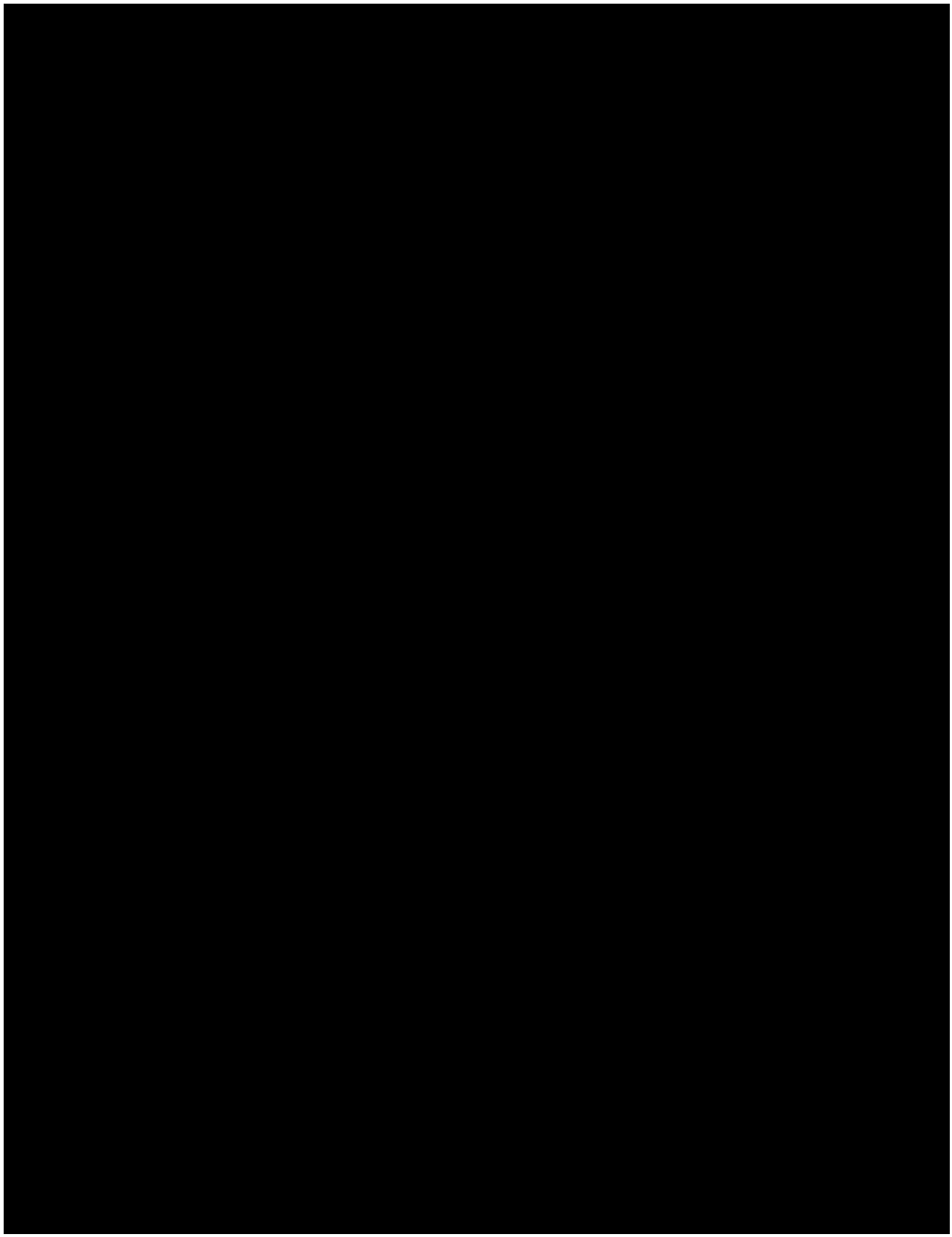
Furthermore, the physicians were asked to monitor any occurring pregnancies and breastfeeding during the study.

For drug resistance surveillance purposes, the physicians were asked to evaluate any signs of suspected delamanid resistance (including lack of drug effect). Delamanid drug susceptibility testing (DST) has been established in several European reference laboratories at the time of launch and can be accessed by any European centre prescribing Deltyba. This enabled the collection of data on the development of resistance to delamanid. The risk for drug resistance development was aimed to be minimised by raising awareness of such risk and by providing appropriate risk minimization measures through educational material for health care professionals.

According to the summary of product characteristics (SmPC), Deltyba shall be only administered with an ACR and directly observed therapy (DOT) is recommended in order to ensure treatment compliance.

All usage and safety data generated from routine medical practice during this PASS, in particular those on closely monitored special events of interest were regularly evaluated in order to add to the product's cumulative safety and usage profile.





9. RESEARCH METHODS

9.1. Study Design

This was an EU-wide, multicentre, non-interventional study of MDR-TB patients who were prescribed Deltyba. The duration of the study per patient was up to 30 months after receiving first dose of Deltyba or until completion of MDR-TB treatment. It is noteworthy that United Kingdom is not a member state of the EU since Feb 2020.

The total duration of the EU PASS 242-12-402 was planned to be 6.5 years (4-year enrolment period). The ACR was designed by the treating physician. According to the SmPC, Deltyba is indicated for use as part of an ACR for pulmonary MDR-TB in adult patients, when an effective treatment regimen cannot otherwise be composed for reasons of resistance or tolerability. The Deltyba recommended dose for adults with pulmonary MDR-TB is 100 mg twice daily for 24 weeks. Treatment, all assessments and patient monitoring were performed according to the existing practices and/or treatment centre's local/national programme.

The PASS collected information routinely documented in patient medical records or in national tuberculosis programme (NTPs).

A central order process had been implemented in Europe; thus, the marketing authorisation holder (MAH) has been aware when Deltyba is ordered by each treatment site in the EU. This procedure included also EU PASS sites. Thus, patient enrolment could occur only after Deltyba had been prescribed and delivered for dispensing to the patient.

The MAH aimed to collect data from patients being treated with Deltyba in a prospective manner. All patients in the PASS were followed up routinely by their physicians/ HCPs at each regular visit according to the existing practices (usually monthly or in the intervals specified on local/ national basis) until the end of patient's participation in the study (up to 30 months after having received the first dose of Deltyba) or until completion of MDR-TB treatment. If the patient was cured or completed his/her full MDR-TB treatment course at a date earlier than month 30 after start of Deltyba, then patient's participation in the study stopped on that date. Patient's participation stopped 30 months after the start of Deltyba treatment, even in the unlikely event that the MDR-TB treatment course continued after this period. Data was documented by the treating physician at each regularly scheduled patient visit until the end of patient's participation in the study.

Physicians assessed patients for the occurrence of AEs with respect to their seriousness, causality and other safety aspects at each visit. Obtained information on safety data was entered into the eCRF by the physician. The MAH followed up AEs and other safety information until the reported conditions were resolved or had returned to normal or baseline status (status prior to the Deltyba intake) or until the conditions stabilised. Pregnancies of patients or their partners were documented via paper safety report form.

Data on the use of Deltyba in a real-world setting were collected in the eCRF of the PASS. These data included but were not limited to: Deltyba usage, ACR usage, use with DOT, duration of Deltyba use, age of the patient, treatment indication, medical history and all medical conditions,

all concomitant medications, laboratory tests including DST, ECG test results, all AEs, and final treatment outcomes.

9.2. Setting

It had been planned to include 250 patients with MDR-TB, prescribed Deltyba and treated at specialised sites in the EU in the Deltyba PASS.

The total duration of the study per patient was up to 30 months after receiving first dose of Deltyba or until completion of MDR-TB treatment. The total duration of the Deltyba PASS was planned to be 6.5 years (4-years enrolment period).

9.3. Patients

Patient eligibility criteria were applied for all countries by the treating physicians according to the SmPC.

The following inclusion/exclusion criteria applied for Germany only:

Inclusion criteria:

Meet the therapeutic indication according to SmPC:

1) Deltyba must be part of an ACR,

2) for pulmonary multi-drug resistant TB,

3) when an effective treatment regimen could not otherwise be composed for reasons of resistance or tolerability.

Exclusion criteria:

1) Age < 18 years

2) Concomitant use of drugs that were strong inducers of CYP3A4

3) Serum albumin < 2.8 g/dL

4) Hypersensitivity to the active substance or to any of the excipients.

9.4. Variables

9.4.1. Extent of Exposure

Length of exposure to Deltyba (number of days) was assessed based on the variables related to Deltyba usage collected in the eCRF.

9.5. Data Sources and Measurement

Data sources were the patient records or documentation used for the NTPs, depending upon local circumstances. The health information of any participating patient was documented by the treating physician at each regularly scheduled patient visit (usually monthly or in the intervals specified on local / national basis) until the end of patient's participation in the study (up to 30 months after receiving first dose of Deltyba) or until completion of MDR-TB treatment.

Coding of the data was performed as follows:

- Indication, co-morbidities, and AEs were coded according to Medical Dictionary for Regulatory Activities (MedDRA) version 24.1.

- All medications were coded according to WHO Drug Dictionary Anatomical Therapeutic Chemical (ATC) classification system using WHODRUG B3G Mar 2021 Dictionary Version.

All mentioned coding was done using a current version of the mentioned dictionaries and/ or recoding, as applicable.

9.6. Bias

Some of the most likely main challenges of conducting such an observational study in different countries were cultural issues, local infrastructure and awareness of the HCPs and community.

Other limitations were:

- Issues regarding confounding comorbidities, concomitant medication, prior TB treatment.

- Data sources and documentation of routine practice as well as schedule of visits on the different settings where the study was conducted.

- Treatment outcomes definitions per HCP.

The data resulting from this PASS might provide valuable information on the usage of Deltyba and its safety profile.

9.6.1. Baseline

The following data captured prior to Deltyba treatment were collected from patient's records as far as available and considered as a baseline:

- Indication for Deltyba use

- Socio-demographics (age, gender, ethnic origin, country of origin)

- Medical history and concurrent conditions including cardiac risk factors and renal or hepatic impairment, human immunodeficiency virus (HIV) co-infection, prior treatment with anti-

TB drugs, outcome of previous anti-TB treatment (cured, treatment completed, failure, default)

- Signs and symptoms of TB
- Dosage and start of treatment with Deltyba
- Physical examination
- Vital signs (temperature, heart rate, systolic blood pressure, diastolic blood pressure), height, weight, and body mass index (BMI)
- Chest X-ray
- Baseline acid-fast bacilli smear (negative / positive) and culture results
- DST to Delamanid, first-line and second-line anti-TB drugs
- Laboratory tests (serum electrolytes, serum chemistry, haematology, pregnancy test for all women of childbearing potential, urinalysis (dipstick))
- Pregnancy or known to be breastfeeding
- DOT information for Deltyba and ACR
- Prior and current concomitant medication and ACR
- ECG (including QT interval corrected for heart rate by Fridericia's formula [QTcF] value).

Routine visits

During the conduct of the study, the following data were collected and analysed:

- AEs (serious / non-serious)
- Deltyba usage (including medication errors such as overdose, missed dose) including information on DOT
- ACR usage (including medication errors such as overdose, missed dose) including information on DOT
- ECG (including QTcF value)
- Laboratory data
- All-cause mortality
- Treatment outcome at the end of MDR-TB treatment

- Microbiologic data
  - Sputum smear microscopy
  - Sputum culture
  - DST (Delamanid and ACR).

Available data, from standard of care medical treatment, were to be recorded in the eCRF.

Drug susceptibility testing results to delamanid and ACR were collected by the MAH as provided by the participating physicians at baseline and all routine visits. Available DST results for ACR and delamanid were captured as sensitive or resistant.

The frequencies and cumulative incidence of all AEs (serious / non-serious) were analysed.

The incidences of grouped conditions and individual AEs were evaluated for new safety signals per each quarter and cumulatively.

9.7. Study Size

It had been planned to include 250 MDR-TB patients in the Deltyba PASS. The sample size estimate was made on pragmatic grounds, whilst taking the following into account: (1) The incidence of pulmonary MDR-TB in EU countries- in other words, MDR-TB as an orphan disease in the EU with low incidence in Germany, UK, and some other EU countries, (2) The restricted indication of Deltyba (ie, according to the SmPC, Deltyba is indicated for use as part of an ACR for pulmonary MDR-TB in adult patients, when an effective treatment regimen cannot otherwise be composed for reasons of resistance or tolerability), and (3) The dates of anticipated launch (ie, firstly in Germany, Estonia, Latvia, UK, Lithuania, and France to be followed by other EU countries at a later stage) (Table 1).

Table 1: Originally estimated number of patients to be treated with delamanid in the European Union by country, 2014 to 2018

Launch country	ECDC 2014 report - MDR-TB notification among all culture positive cases (incidence data from 2012)	Estimated launch date	2014	2015	2016	2017	2018 (half year)	2014-2018
Germany	58	Jun-14	11	6	6	6	3	**32**
Austria	27	Jan-15		3	3	3	1	**10**
Latvia	106	Jan-15		10	10	10	5	**35**
Norway	6	Jan-15		1	1	1	0	**3**
Sweden	14	Jan-15		1	1	1	1	**4**
UK	81	May-15		8	8	8	4	**28**
France	90	Oct-15		9	9	9	4	**31**
Italy	74	Oct-15		7	7	7	4	**25**
Spain	37	Oct-15		4	4	4	2	**14**
Estonia	61	Jan-16			6	6	3	**15**
Lithuania	271	Jan-16			26	26	13	**65**
Portugal	17	Jan-16			2	2	1	**5**
Bulgaria	49	Jan-17				5	2	**7**
Poland	31	Jan-17				3	1	**4**
Romania	530	Jan-17				51	25	**76**
Totals			**11**	**49**	**83**	**142**	**69**	**354**

With the assumption that 70% of Deltyba treated patients would be included in the PASS, a total of 250 patients were anticipated for enrolment into this non-interventional study. The assumption was based on the initial feedback by potential prescribers. Deltyba has been launched in the UK (no longer authorised since Brexit occurred), and Germany, on 30 May and 17 June 2014, respectively. The following countries participated in the PASS afterward (launch date): Estonia (28 September 2016), France (06 June 2016), Latvia (03 July 2015), and Lithuania (02 May 2016).

In accordance with the 242-12-402 study protocol (as approved by the European medicines agency [EMA]), the total duration of the EU PASS should either be limited to 6.5 years, including 4 years of enrolment, or patients' enrolment should be terminated after recruitment of 250 patients, whichever was earlier. Hence, in line with the study protocol, the enrolment for the study was stopped on 12 Aug 2020, which marked the completion of 4 years of active patient recruitment.

The enrolment of the originally targeted patient number (n=250) was not feasible during the protocol pre-specified study duration and the actual achieved number of patients for this study was lower than expected.

Among the 88 patients treated with Deltyba and recruited in PASS in 11 sites, 2 patients were excluded due to lack of evidence that they were consented correctly. Sixty-seven patients completed the EU PASS 242-12-402, and 19 patients discontinued from the study (3 deaths, 11 lost to follow-up [LTFU], and 5 withdrawal of consent). A total of 86 patients were included in the analysis set which is presented in Section 10 RESULTS.

9.8. Data Transformation

9.8.1. Start of Data Collection

Data collection commenced after the patient or his/her legal representative had signed the informed consent form (ICF). Retrospective data could be entered provided that the patient or his/her legal representative had signed the ICF. Post-authorisation safety study relevant information from patient's medical records were entered by HCPs into the appropriate section of the electronic Case Report Form (eCRF).

9.8.2. Data Collection during Deltyba treatment

All participating physicians in the PASS documented pertinent information at each patient visit (usually monthly) or at intervals specified on a local/ national basis. Only data from patients with valid ICFs and treated with Deltyba were collected. Data on Deltyba usage with an ACR were captured. Data concerning concomitant medication, physical examination, any surgical treatment, DOT and/or self-administered therapy (SAT), and laboratory results were collected if available; AEs were collected and reported according to Good Pharmacovigilance Practices.[7] Treatment and management followed the standard of care for pulmonary MDR-TB patients. According to Deltyba SmPC, it is recommended that ECG should be done monthly during the full course of treatment with Deltyba and more frequently if the QTc interval duration exceeds 450/470 ms for male/female patients, respectively. Patients with serum albumin < 3.4 mg/dL at baseline or during Deltyba treatment, as well as patients receiving Deltyba in combination with quinolones or strong CYP P450 3A4 enzyme (CYP3A4) inhibitors had to undergo very frequent monitoring of ECGs throughout the full Deltyba treatment period.

9.8.3. Data Collection after completion of Deltyba treatment

All patients in the PASS were followed up routinely by their physicians at regular visits according to the existing practices (usually monthly or in the intervals specified on local/national basis). Data were collected for a period of up to 30 months after the start of the Deltyba use as a part of an ACR until the end of the MDR-TB treatment. The treating physician selected the most adequate medications comprising ACR based on national or WHO's guidelines for the programmatic management of drug-resistant TB.[5]

9.8.4. End of data collection

The end of data collection was defined as the last contact time point (date of final contact/ preferably visit) with evaluable endpoint for the last patient completing or withdrawing from the study.

9.9. Statistical Methods

9.9.1. Main Summary Measures

No formal hypotheses were tested in this study.

Data were summarised by assessment and visit (where applicable) and displayed by enrolled patients.

Descriptive summary statistics for continuous variables included mean, SD, median and range. Descriptive summary statistics for categorical variables included frequency counts and percentages [n (%)]. Unless stated otherwise in the table shells, the denominator for percentage calculations was the number of enrolled patients. Point estimate and its 95% confidence interval (CI), based binomial distribution assumption, of endpoints were provided. If the sample size was small and made the binomial distribution questionable, the exact CI was to be applied instead.

Baseline was defined as patient status before initiation of Deltyba treatment. Change from baseline was calculated as: Value at relevant time point – baseline value.

9.9.2. Main Statistical Methods

9.9.2.1. Descriptive Statistics

Extent of exposure to Deltyba

Number of days that patients were exposed to Deltyba were summarised by duration categories using counts and frequencies.

Duration of exposure to Deltyba was defined as (date of last dose - date of first dose +1).

Socio-demographics

Socio-demographic data (age, gender, ethnic origin, country of origin, height, weight, and BMI) were presented using descriptive statistics. Age (years) was recorded during baseline.

Medical history

Data on medical history were summarised using descriptive statistics.

Clinical laboratory data

Available laboratory data captured per standard of care was presented using descriptive statistics.

Additional TB-related clinical parameters were collected, if available:

- Haematology
- Serum Chemistry
- C-reactive protein
- Urinalysis (dipstick)
- Thyroid stimulating hormone

- Adrenocorticotropic hormone
- Cortisol.

Descriptive statistics for continuous laboratory variables were presented for all data collection time points as available and change from baseline over time up to the last visit. Last visit was the last scheduled measurement during the study.

If a patient has multiple test results for a particular test at a particular post-baseline visit, and at least 1 result was with potentially clinically significant abnormality by the given criterion, the patient was classified as having a potentially clinically significant abnormal test at that visit for that criterion. Denominator of the percentages in these summaries was the number of patients that could be evaluated for potentially clinically significant abnormalities of the given laboratory test for the time interval (baseline, post-baseline, etc.).

Listings were provided for all laboratory test values outside normal range and all laboratory test results with potentially clinically significant abnormalities.

Physical examination and vital sign data

Available data on physical examination and vital signs captured as performed per standard of care were presented using descriptive statistics.

From physical examination of head, eyes, ears, nose, throat, thorax, abdomen, urogenital, extremities, neurological, skin, and mucosae, data were presented by frequency counts (normal, abnormal clinically significant, abnormal not clinically significant, not done).

Descriptive statistics over time for vital signs (temperature [C], heart rate [bpm], systolic blood pressure [mmHg], diastolic blood pressure [mmHg],) weight [kg], and BMI [kg/m^2] were provided.

ECG assessments

Available ECG data were collected during baseline and all routine visits during the study. The primary focus was on QTcF. However, if QTcF was not done, then physicians were asked to provide ventricular rate, RR interval, QT interval, QT interval corrected for heart rate by Bazett's formula (QTcB), and overall ECG interpretation. A listing was provided for QTcF results (or other parameters if QTcF is not available). Frequency of ECG assessments during the study (overall and for patients with/without abnormalities noted in clinical investigations) were presented using descriptive statistics. In addition, an overall safety evaluation was performed for the patients who developed QTcF > 500 ms during Deltyba treatment. The same procedure would have been applied for patients who entered the study with QTcF > 500 ms at baseline.

Adverse events

All AEs were coded by System Organ Class (SOC) and MedDRA (using MedDRA version 24.1) preferred term (PT). Patients with more than one AE within a particular SOC or with a particular

PT are counted only once for that SOC or PT and the maximum severity was selected. AEs with missing intensity/severity were included in the overall count of patients with AEs but were not included in the counts for severity summary.

The incidence of the following events was summarised:

- Treatment-emergent AEs (TEAEs) by severity
- Potentially drug-related TEAEs
- TEAEs with an outcome of death
- Serious TEAEs
- Discontinuations due to TEAEs.

The incidence of the events of special interest (cardiac disorders including QT prolongation and delamanid resistance, suspected and/or confirmed (including lack of delamanid effect) were summarised.

Other safety assessments

Imaging: Chest X-ray, if available comparison to the baseline chest X-ray.

Final treatment outcome

Final treatment outcome as judged by the treating physician at the end of the study was listed for each patient. The number and percentage of patients and the 95% CI were summarised by certain category of factor of interest for each outcome (Cured / Treatment completed / Treatment failed / Died / Lost to follow-up / Not evaluated / Treatment success) per treating physician's judgement following the definitions outlined by the WHO[1] and/or national guidelines:

- **Cured**: Treatment completed as recommended by the national policy without evidence of failure AND three or more consecutive cultures taken at least 30 days apart were negative after the intensive phase.
- **Treatment completed**: Treatment completed as recommended by the national policy without evidence of failure BUT no record that three or more consecutive cultures taken at least 30 days apart were negative after the intensive phase.
- **Treatment failed**: Treatment terminated or there was a need for permanent regimen change of at least two anti-TB drugs because of:
    - lack of conversion by the end of the intensive phase, or bacteriological reversion in the continuation phase after conversion to negative, or
    - evidence of additional acquired resistance to fluoroquinolones or second-line injectable drugs, or

- adverse drug reactions (ADRs).

- **Died**: A patient who died for any reason during the course of treatment.
- **Lost to follow-up**: A patient whose treatment was interrupted for 2 consecutive months or more.
- **Not evaluated**: A patient for whom no treatment outcome was assigned. (This included cases "transferred out" to another treatment unit and whose treatment outcome was unknown).
- **Treatment success**: The sum of cured and treatment completed

All other data collected during PASS were assessed by adequate descriptive methods.

9.9.3. Missing Values

9.9.3.1. Handling of dropouts or missing data

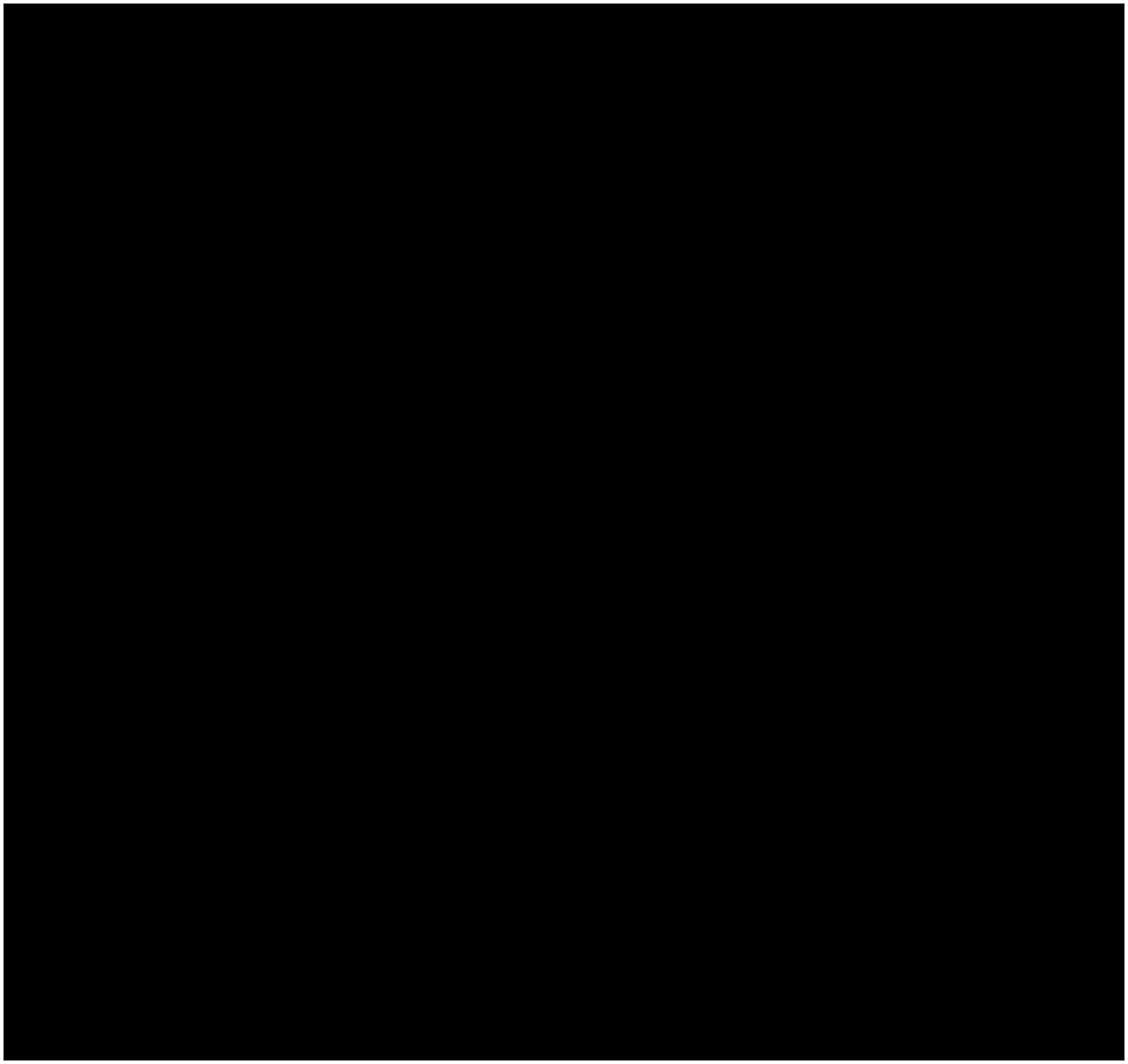
Missing data were not discarded in the study. In line with the nature of the PASS, data that were planned to be collected but not available were assessed as 'not recorded' by the treatingphysician. Data 'not recorded' were included in descriptive and summary statistics. This also applied to final treatment outcomes.

In cases patients withdrew from study by their own decision ("discontinuation with no known reason"), patients were contacted and reasons for withdrawal/discontinuation were asked and documented.

If the attempt of such further contact was not successful, she/he was categorised as "lost to follow-up". If the patient could be contacted but was not willing to, or due to some reasons, could not provide the reason(s) for discontinuation, patient was categorised as "Not evaluated".

9.9.4. Sensitivity Analyses

No sensitivity analyses were planned. For treatment outcome the protocol pre-specified analyses were already based on a conservative approach making further sensitivity analyses unnecessary. Also sensitivity analyses for safety (assuming AEs with missing severity as having high severity grade) deemed unnecessary because for all AEs severity grade had been assessed (PDATA-1-11).



9.10. Quality Control

Information from the source documents was entered by the authorised site staff directly onto the eCRFs, which was compliant with applicable regulatory requirements (authorised access to database, audit trail and system control to ensure only authorised modifications of information on the eCRF).

9.10.1. Monitoring

Monitoring activities were performed by a CRO and Otsuka oversaw these activities. A study specific monitoring plan was used. The HCP had to permit and assist in monitoring PASS files and original patient medical records by Otsuka appointed personnel and authorised government agencies.

9.10.2. Auditing / Inspections

The following audits were performed during PASS study:

- Covance Quality Unit performed an audit at site No. 05001. The scope of audit included but was not limited to: presence of required documents, the informed consent process, and comparison of eCRFs with source documents; the HCP having agreed to participate and support audits and regulatory authority inspections.

- Otsuka's Quality Management Unit conducted study audit [redacted]. The scope of the audit included was not limited to: Quality Management System, Project Management or Monitoring Oversight, Training, Essential Documents, Pharmacovigilance and Data Management or Statistics.

- Otsuka's Quality Management Unit conducted study audit [redacted]. The scope of the audit included was not limited to: Quality Management System, Project Management or Monitoring Oversight, Training, Contract and Vendor Management
  Essential Documents, Pharmacovigilance and Data Management or Statistics.

- Otsuka's Quality Management Unit conducted study audit [redacted]. This was an internal pharmacovigilance system audit.

9.10.3. Record maintenance and archiving

Patient medical records were archived per national/local requirements. All other study records such as: signed version of the protocol and protocol amendments, curricula vitae of participating HCPs, documentation of ethics committee and ICF approval, signed ICFs, datasets, and statistical programming performed to generate the results will be archived for at least 10 years after final report or first publication of study results, whichever comes first.

9.10.4. Records retention at the study site

The HCP did not dispose of any records relevant to this study without either written permission from Otsuka or provision of an opportunity for Otsuka to collect such records. The HCP was responsible to maintain adequate and accurate electronic and hard copy source documents of all observations and data generated during this study. Such documentation being subject to inspection by Otsuka and relevant regulatory agencies. If the investigator withdrew from the study (eg, due to relocation or retirement), all study related records were to be transferred to a mutually agreed upon designee. Notice of such transfer were to be given to Otsuka in writing. Patient records or other source data are to be kept for the maximum period of time mandated by the institution, clinic or hospital, but not less than 10 years after the study end date. This was detailed in the contractual agreement.

If off-site archiving was used, all records were to be retrieved and made available for review at the time of an audit or a regulatory authority inspection.

10. RESULTS

10.1. Participants

10.1.1. Patient disposition

In accordance with the study protocol, a total of 250 MDR-TB patients were planned to be enrolled in this study. The reasons for not reaching the targeted patient number and the lower recruitment rate of the study are manifold.

It has been observed over the last few years that the incidences of MDR-TB patients have declined steadily in some of the EU countries. Since 2017, Estonia, Latvia, and Lithuania were excluded from the list of countries with high Drug-Resistant (DR)-TB burden, and a substantial decrease of TB, including MDR-TB, notification rates were observed in these countries, which had a major impact on the patient enrolment rate observed for the PASS. According to the low enrolment rate observed beginning of 2019, it was not feasible to provide a calculation for beyond 2018.

This could be due to adoption of reformed state-level interference in the fight against TB that paved way for more standardized national TB programs and guidelines, in line with the evolving WHO recommendations. The re-grouping of drugs according to the 2019 WHO guideline on drug-resistant TB treatment assigned delamanid to Group C.[9] Group C included all other medicines that can be used when a regimen cannot be composed with Group A and B agents. The medicines in Group C are ranked by the relative balance of benefit to harm usually expected of each. As a result, the addition of delamanid to ACR required a justification in most study sites and the approval was frequently rejected. This translated into relatively lesser number of patients recruited in the Deltyba PASS.

The COVID-19 pandemic and associated healthcare crisis affected all participating countries within Europe, where TB patients were reportedly finding it extremely challenging to visit healthcare sites that were specialised to treat infectious diseases or other respiratory diseases. Since both TB and SARS-CoV-2 infections primarily affect the lungs and respiratory system, the specialised sites were occupied to manage COVID-19 patients due to the extremely high rate of transmission and lack of standard of care, which made recruitment of TB patients very challenging. For many clinical trials evaluating TB, patient recruitment was temporarily interrupted. Moreover, the specialised physicians/Investigators in this PASS were called up for national duties to address the growing challenges in treating COVID-19 patients in their respective countries. Furthermore, delamanid was in use since 2014 in Europe to treat pulmonary MDR-TB, and patients from more than 100 countries globally received the drug thus far. Since then, through multiple clinical trials worldwide, through real-life clinical-practice data, and through post-authorization studies, a great volume of safety data is available for delamanid, which has reassured the favourable safety profile of the drug in clinical use, and has been extensively discussed throughout numerous peer-reviewed scientific research articles[11], while being evaluated in some of the largest cohorts through multiple dosage-multiple platform regimen cluster clinical studies, such as the endTB study sponsored by the Médecins Sans Frontières.

Finally, successful treatment of MDR-TB patients in the Baltics and ensuring a long-term follow-up observation period after discharge from hospital due to the implementation of a caregiver system contributed to the low recruitment rate of the study.

Twelve specialised sites were initiated and 11 sites actively enrolled patients. All study sites were evaluated in a pre-selection process for their experience in MDR-TB treatment and sites in Baltic countries represented the National TB Reference Centres.

Eighty-eight patients with MDR-TB from the 11 specialised sites in the EU were prescribed and treated with Deltyba and enrolled into PASS. Out of the 88 patients enrolled, 86 patients were included in analyses set because 2 patients were excluded due to invalid ICF process and are discussed further in this study report. It is noteworthy that United Kingdom is not a member state of the EU since Feb 2020.

Sixty-seven patients completed the study and 19 patients discontinued study participation. The disposition of all patients in the study is shown in Table 2. The reasons for patient discontinuation were as follows: 3 patients died during the study, 11 patients were considered LTFU, and 5 patients withdrew their consent. A summary of the reasons for discontinuation is provided in Table 3 and the details are as described in Section 10.4.

Table 2 : **Subject Disposition (Enrolled Set)**

	Deltyba
Number of Subjects:	**n (%)[a]**
Enrolled	86 (100.0)
Treated	86 (100.0)
Completed	67 (77.9)
Discontinued	19 (22.1)

[a]Percentages are based on the number of subjects enrolled.
Source: CT-1-1.1.

Table 3: Reasons for Discontinuation (Enrolled Set)

	Deltyba
Number of Subjects:	**n (%)**
Discontinued	19 (22.1)
Death	3 (3.5)
Lost to follow-up	11 (12.8)
Study Terminated by Sponsor	0 (0.0)
Withdrawal by Subject	5 (5.8)
Physician Decision	0 (0.0)

Note: percentages are based on the number of subjects enrolled.
Source: CT-1-2.1.

10.1.2. Enrolment

Most of the patients were enrolled in Lithuania (31 patients, 36.0%), followed by Germany (20 patients, 23.3%), and Latvia (16 patients, 18.6%). Enrolment by country is provided in Table 4.

Table 4: Enrolment by Country (Enrolled Set)

	Deltyba
Country/ Number of sites	**N/ %**
Estonia/ 1	14/ 16.3
France/ 2	3/ 3.5
Germany/ 3	20/ 23.3
Latvia/ 1	16/ 18.6
Lithuania/ 3	31/ 36
UK/ 1	2/ 2.3

Source: CT-1-1.2.

The majority of patients (83 out of 86, 96.5%) were < 65 years old whereas 3 patients were ≥ 65 years old. One patient was recruited in Estonia, Latvia and Lithuania.

Enrolment of patients by country and by age group is presented in Table 5.

Table 5: **Enrolment by Country By Age Group (Enrolled Set)**

		Deltyba
Age (Years)	**Country**	**N**
< 65	Estonia	13
	France	3
	Germany	20
	Latvia	15
	Lithuania	30
	UK	2
>= 65	Estonia	1
	Latvia	1
	Lithuania	1
Total	Estonia	14
	France	3
	Germany	20
	Latvia	16
	Lithuania	31
	UK	2

Source: CT-1-1.3.

10.2. Descriptive Data

10.2.1. Demographic and Other Baseline Characteristics

The mean age at baseline was 39.8 years and ranged from 18 to 72 years. The majority of patients (55 patients, 64.0%) were male and 31 (36.0%) were female. The majority of patients were white (76 patients, 88.4%) and 6 patients (7.0%) were Asian.

The Deltyba baseline dosage was 100 mg twice daily (BID) for all patients. In accordance with the approved SmPC effective during PASS enrolment, there were no children who were treated with Deltyba.

The Deltyba usage at baseline was by DOT in 83 patients (96.5%) and both DOT/self-administration by 4 patients (4.7%).

At Deltyba treatment initiation, signs and symptoms of TB were evaluated. Chest x-ray was performed in 83 (97.0%) patients, of which 77 out of 83 (92.8%) showed abnormal findings and 2 (2.4%) patients showed normal findings. For 4 out of 83 (4.8%) patients, results were either

missing (4 patients) or were not done (3 patients). Cavities were diagnosed in 49 (59.0%) of the patients.

At baseline MTB in sputum was assessed by Löwenstein-Jensen (LJ) culture in 64 out of 86 (74.4%) patients. For 22 (25.6%) patients, samples were not evaluated. In 49 out of 64 (76.6%) patients the culture was MTB positive and in 15 out of 64 (23.4%) patients the culture was negative. The mycobacterium growth indicator tube (MGIT) was assessed at baseline in 64 out of 86 (74.4%) patients and 22 out of 86 (25.6%) patients were not evaluated. Test results were positive for MTB in 52 out of 64 (81.3%) patients and negative in 12 out of 64 patients (18.8%). Sputum Smear microscopy was performed at baseline in 82 out of 86 (95.3%) patients and not evaluated in 4 (4.7%) patients. MTB was detected in 38 out of 82 (46.3%) patients and not detected in 44 out of 82 (53.7%) patients.

Demographic and other baseline characteristics are summarised in Table 6.

Table 6: Demographic and Baseline Characteristics (Enrolled Set)

Baseline Characteristics		**Deltyba (N=86)**
Age (Years)	N	86
	Mean	39.8
	Median	36.5
	SD	13.7
	Min,Max	18,72
Sex	Male n(%)	55 (64.0%)
	Female n(%)	31 (36.0%)
Race	White n(%)	76 (88.4%)
	Black or African American n(%)	1 (1.2%)
	American Indian or Alaska Native n(%)	0 (0.0%)
	Asian n(%)	6 (7.0%)
	Native Hawaiian or Other Pacific Islander n(%)	0 (0.0%)
	Other n(%)	0 (0.0%)
	Missing n(%)	3 (3.5%)
Ethnicity	Hispanic or Latino n(%)	3 (3.5%)
	Not Hispanic or Latino n(%)	80 (93.0%)
	Other n(%)	0 (0.0%)
	Missing n(%)	3 (3.5%)
Country of Site	Estonia n(%)	14 (16.3%)
	France n(%)	3 (3.5%)
	Germany n(%)	20 (23.3%)
	Latvia n(%)	16 (18.6%)
	Lithuania n(%)	31 (36.0%)
	UK n(%)	2 (2.3%)
Pulmonary MDR-TB	Yes n(%)	85 (98.8%)
	No n(%)	1 (1.2%)

Table 6: Demographic and Baseline Characteristics (Enrolled Set)

Baseline Characteristics		**Deltyba (N=86)**
Further Disease Manifestations	Yes n(%)	6 (7.0%)
	No n(%)	80 (93.0%)
Deltyba Baseline Dosage	100 mg BID n(%)	86 (100.0%)
Dosage Type	DOT n(%)	82 (95.3%)
	Self-Admin n(%)	0 (0.0%)
	Both n(%)	4 (4.7%)
HIV Co-Infection	Yes n(%)	3 (3.5%)
	No n(%)	83 (96.5%)
Most Recent Outcome of Previous Anti-TB Treatment	Cured n(%)	11 (12.8%)
	Treatment Completed n(%)	1 (1.2%)
	Treatment Failed n(%)	15 (17.4%)
	Default n(%)	3 (3.5%)
	Unknown n(%)	28 (32.6%)
	Missing n(%)	28 (32.6%)
Chest X-Ray Result	Normal n(%)	2 (2.3%)
	Abnormal n(%)	77 (89.5%)
	Not Available n(%)	0 (0.0%)
	Not Done n(%)	3 (3.5%)
	Missing n(%)	4 (4.7%)
Cavitation	Yes n(%)	49 (57.0%)
	No n(%)	32 (37.2%)
	Missing n(%)	5 (5.8%)
MGIT Culture	Negative for MTB Complex n(%)	12 (14.0%)
	Positive for MTB Complex n(%)	52 (60.5%)
	No TB Growth, but Positive for Other Mycobacteria n(%)	0 (0.0%)
	Positive for MTB Complex and Contaminated n(%)	0 (0.0%)
	Contaminated n(%)	0 (0.0%)
	Not Done n(%)	17 (19.8%)
	Unknown n(%)	2 (2.3%)
	Missing n(%)	3 (3.5%)
LJ Culture	Negative for MTB Complex n(%)	15 (17.4%)
	TB Growth (1-9 Colonies) n(%)	17 (19.8%)
	TB Growth (10-100 Colonies) n(%)	19 (22.1%)
	TB Growth (More Than 100 Colonies) n(%)	12 (14.0%)
	TB Growth (Innumerable or Confluent Growth) n(%)	1 (1.2%)
	No TB Growth, but Positive for Other Mycobacteria n(%)	0 (0.0%)
	Contaminated n(%)	0 (0.0%)

Table 6: Demographic and Baseline Characteristics (Enrolled Set)

Baseline Characteristics		Deltyba (N=86)
	Positive for MTB Complex and Contaminated n(%)	0 (0.0%)
	Not Done n(%)	11 (12.8%)
	Not Available n(%)	5 (5.8%)
	Unknown n(%)	3 (3.5%)
	Missing n(%)	3 (3.5%)
Smear Result	Negative n(%)	44 (51.2%)
	Rare n(%)	11 (12.8%)
	Few n(%)	8 (9.3%)
	Many n(%)	15 (17.4%)
	Too Numerous to Count n(%)	4 (4.7%)
	Not Done n(%)	1 (1.2%)
	Missing n(%)	3 (3.5%)
Pregnancy Status	Yes n(%)	0 (0.0%)
	No n(%)	17 (19.8%)
	Not Done n(%)	9 (10.5%)
Breastfeeding Status	Yes n(%)	0 (0.0%)
	No n(%)	18 (20.9%)
	Not Done n(%)	8 (9.3%)

Note: percentages are based on the number of subjects enrolled.
Race and ethnicity are not collected for French sites.
DOT: directly/virtually observed therapy; Self-Admin: self-administered treatment.
Source: CT-1-3.1.1.

10.2.2. Medical History

Overall, 76 (88.4%) of patients reported at least 1 condition in their medical history. The most common medical history was in SOCs of infections and infestations (44.2%), metabolism and nutrition disorders (32.6%), gastrointestinal disorders (31.4%), and respiratory, thoracic and mediastinal disorders (27.9%). The most frequent PT in the SOC of infections and infestations was pulmonary TB (15 patients, 17.4%). Six patients (7.0%) were co-infected with chronic hepatitis C, 5 patients (5.8%) with hepatitis C and 3 patients with HIV (3.5%). Further frequent PTs in medical history were anaemia (14 patients, 16.3%), vitamin D deficiency (13 patients, 15.1%), insomnia (10 patients, 11.6%), cough (11 patients, 12.8%), and hypertension (13 patients, 15.1%). One German patient had a medical history of drug hypersensitivity (penicillin allergy). No hypersensitivity to the active substance or to any of the excipients was reported.

Several patients were immigrants for whom records from medical history were not available.

A summary of patient medical history is provided in Table CT-1-3.2.

10.2.3. Anti-TB Treatment History

All anti-TB treatments were coded using the WHO drug dictionary (WHODRUG B3G Mar 2021 Dictionary Version). Data were presented by drug class (ATC2) and medication PT.

Anti-TB treatment history was reported for 61 patients (70.9%). The most commonly used anti-TB medications in medical history were pyrazinamide (47.7%), ethambutol (47.7%), moxifloxacin (39.5%), linezolid (37.2%), protionamide (34.9%), and levofloxacin (33.7%). A summary of prior anti-TB medication is provided in Table 7.

Table 7: Anti-TB Treatment History (Enrolled Set)

	Deltyba (N=86)
Drug Class **Medication Preferred Name**[a]	**n (%)**
Total Using One or More Medications	61 (70.9)
Antibacterials For Systemic Use	54 (62.8)
Amikacin	20 (23.3)
Amoxicillin Trihydrate/clavulanate Potassium	7 (8.1)
Cilastatin/imipenem	4 (4.7)
Kanamycin	3 (3.5)
Levofloxacin	29 (33.7)
Linezolid	32 (37.2)
Meropenem	1 (1.2)
Moxifloxacin	34 (39.5)
Ofloxacin	2 (2.3)
Streptomycin	3 (3.5)
Antimycobacterials	61 (70.9)
Aminosalicylic Acid	17 (19.8)
Bedaquiline	9 (10.5)
Capreomycin	25 (29.1)
Clofazimine	6 (7.0)
Cycloserine	26 (30.2)
Delamanid	5 (5.8)
Ethambutol	41 (47.7)
Ethionamide	4 (4.7)
Isoniazid	26 (30.2)
Protionamide	30 (34.9)
Pyrazinamide	41 (47.7)
Rifabutin	1 (1.2)
Rifampicin	26 (30.2)
Terizidone	19 (22.1)

Note: percentages are based on the number of subjects enrolled.
Table is presented by drug class (ATC2) and preferred term.
[a]Medications are coded using the WHO Drug Dictionary (WHODRUG B3G Mar 2021 dictionary version).
Source: CT-1-3.3.

10.2.4. Concomitant Medications

All concomitant medications were coded using the WHO drug dictionary (WHODRUG B3G Mar 2021 Dictionary Version). Data were presented by drug class (ATC2) and medication PT.

In the Enrolled Set, 82 patients (95.3%) were using one or more concomitant medication other than anti-TB medications during the study treatment phase with delamanid.

In the Enrolled Set, the most frequently used drug classes and concomitant medications were vitamins (52 patients, 60.5%); drugs for functional gastrointestinal disorders (37 patients, 43.0%); drugs for acid related disorders (57 patients, 66.3%); and bile and liver therapy (24 patients, 27.9%) (Table CT-1-4.2).

In the Germany Enrolled Set, 19 patients (95.0%) were using 1 or more concomitant medications (excluding anti-TB medications) during the study treatment phase. The most frequently used drug classes were drugs for acid related disorders (11 patients, 55.0%); drugs for functional gastrointestinal disorders (9 patients, 45.0%), and vitamins (9 patients, 45.0%) (Table CT-2-4.2).

In the Non-Germany Enrolled Set, 63 patients (95.5%) were using 1 or more concomitant medications (excluding anti-TB medications) during the study treatment phase. The most frequently used drug classes were drugs for acid related disorders (46 patients, 69.7%); vitamins (43 patients, 65.2%), drugs for functional gastrointestinal disorders (28 patients, 42.4%) and bile and liver therapy (24 patients, 36.4%) (Table CT-3-4.2).

Overall, the use of concomitant medications was comparable in the Germany and Non-Germany Enrolled Set. The use of Silybum marianum is mainly used in Eastern European countries for the prophylaxis and treatment of hepatic diseases.

The concomitant use of strong CYP3A4 inducers with delamanid was an exclusion criterion in the German version of the protocol. No patients took CYP3A4 inducers during the study treatment phase in the Germany Enrolled Set (Table CT-2-4.2, Table CT-2-7.2.1). Out of 66 patients in the Non-Germany Enrolled Set, 7 (10.6%) patients used strong CYP3A4 inducers: 3 patients used carbamazepine as antiepileptic (4.5%), 1 (1.5%) analgesic, 2 (3%) rifampicin, and 1 (1.5%) dexamethasone during the study treatment phase (Table CT-3-4.2, Table CT-3-7.2.1).

10.3. Outcome Data

10.3.1. Treatment outcome

Final treatment outcome at the end of study was the secondary endpoint to evaluate treatment efficacy. In Enrolled Set, among 86 patients treated with Deltyba, 49 (57.0%) were cured, 17 (19.8%) have completed the treatment, 1 (1.2%) was treatment failure, 11 (12.8%) were LTFU, 5 (5.8%) were not evaluated, and 3 (3.5%) died. The proportion of patients for each outcome is summarised in Table 8.

In the Germany Enrolled Set, 2 (10.0%) were cured, 14 (70.0%) have completed the treatment, and 4 (20.0%) were LTFU (Table CT-2-5.1).

In the Non-Germany Enrolled Set, 47 (71.2%) were cured, 3 (4.5%) have completed the treatment, 1 (1.5%) was treatment failure, 7 (10.6%) were LTFU, 5 (7.6%) were not evaluated, and 3 (4.5%) died (Table CT-3-5.1).

Table 8: Frequency and Percentage of Final Treatment Outcome (Enrolled Set)

	Deltyba (N=86)		
	n (%)		95% CI[a]
Final Treatment Outcome			
Cured	49	(57.0)	46.5 - 67.4
Death	3	(3.5)	0 - 7.4
Lost to Follow-Up	11	(12.8)	5.7 - 19.8
Not Evaluated	5	(5.8)	-
Treatment Completed	17	(19.8)	11.4 - 28.2
Treatment Failed	1	(1.2)	-

[a]The 95% confidence interval is based on Binomial distribution (for example cured vs. not cured) using PROC FREQ procedure.
Source: CT-1-5.1.

10.3.2. Deltyba Usage

A total of 86 patients received Deltyba and were included in the Enrolled Set. Duration of exposure to Deltyba was defined as the difference between the date of last dose of Deltyba and date of first dose +1. Duration of exposure to delamanid was less than 24 weeks in 12 patients (14.0%), 24 weeks in 17 (19.8%) patients, and more than 24 weeks in 57 (66.3%) patients.

The recommended dose for adults is 100 mg BID for 24 weeks according to SmPC. All patients enrolled in the study received Deltyba dose of 100 mg BID during the recommended treatment duration of 24 weeks. In the Enrolled Set, the overall median treatment duration was 182.5 days with a range of 2 to 792 days. For 12 patients (14%), delamanid treatment was less than 24 weeks. Deltyba treatment was terminated after 24 weeks in 17 (19.8%) patients and in 57 (66.3%) patients Deltyba treatment was extended beyond 168 days (Table CT-1-7.1.1 and Table CT-1-7.1.2). Patient exposure in the Enrolled Set to Deltyba by period is summarised in Table 9 and Table CT-1-7.1.2.

Extension of Deltyba treatment occurred in 38 of the 66 (57.6%) patients from non-German sites (Table CT-3-7.1.2), and in 19 of the 20 (95.0%) patients from the German sites (Table CT-2-7.1.2). During the treatment extension beyond 24 weeks, 43 patients received the recommended Deltyba 100 mg BID dose, while in 14 patients treatment dose or dosing frequency was changed by the treating physician. One patient received the daily dose of 200 mg once daily (QD) at site No. 05003 (Lithuania), and 13 patients, all from the same study site in Germany, received Deltyba 100 mg QD (Table CT-1-7.1.4).

Table 9: Duration of Exposure to Deltyba by Period (Enrolled Set)

		Number of Subjects	
Country	**Duration[a]**	**n[b]**	**(%)[c]**
Total (N=86)	< 24 Weeks	12	(14)
	24 Weeks	17	(19.8)
	26 -30 Weeks	18	(20.9)
	> 30 Weeks	39	(45.3)
Estonia (N=14)	< 24 Weeks	0	(0.0)
	24 Weeks	1	(7.1)
	26 - 30 Weeks	9	(64.3)
	> 30 Weeks	4	(28.6)
France (N=3)	< 24 Weeks	2	(66.7)
	24 Weeks	0	(0.0)
	26 - 30 Weeks	0	(0.0)
	> 30 Weeks	1	(33.3)
Germany (N=20)	< 24 Weeks	1	(5.0)
	24 Weeks	0	(0.0)
	26 - 30 Weeks	3	(15.0)
	> 30 Weeks	16	(80.0)
Latvia (N=16)	< 24 Weeks	2	(12.5)
	24 Weeks	0	(0.0)
	26 - 30 Weeks	0	(0.0)
	> 30 Weeks	14	(87.5)
Lithuania (N=31)	< 24 Weeks	6	(19.4)
	24 Weeks	16	(51.6)
	26 - 30 Weeks	6	(19.4)
	> 30 Weeks	3	(9.7)
UK (N=2)	< 24 Weeks	1	(50.0)
	24 Weeks	0	(0.0)
	26 - 30 Weeks	0	(0.0)
	> 30 Weeks	1	(50.0)

[a]Duration of exposure is calculated as date of last Deltyba dose – date of first Deltyba dose + 1.
[b]The number of subjects whose duration of exposure falls into this category. For example, subjects whose duration of exposure to Deltyba is 156 will be counted towards the Week 24 (155 - 168 Days) period. The subjects from each category are mutually exclusive.
[c]This is calculated as a percentage of total number of subjects in the enrolled set for each country.
Source: CT-1-7.1.2.

Patient exposure in the Germany Enrolled Set to Deltyba by period is summarised in Table 10 and Table CT-2-7.1.2. Deltyba treatment was terminated after 10 weeks in 1 (5.0%) patient, and in 19 (95.0%) patients Deltyba treatment was extended up to 26 to > 30 weeks.

Table 10: **Duration of Exposure to Deltyba by Period (Germany Enrolled Set)**

		Number of Subjects	
Country	**Duration[a]**	**n[b]**	**(%)[c]**
Total (N=20)	< 24 weeks	1	(5.0)
	24 Weeks	0	(0.0)
	26 -30 Weeks	3	(15.0)
	> 30 Weeks	16	(80.0)
Germany (N=20)	< 24 Weeks	1	(5.0)
	24 Weeks	0	(0.0)
	26 - 30 Weeks	3	(15.0)
	> 30 Weeks	16	(80.0)

[a]Duration of exposure is calculated as date of last Deltyba dose – date of first Deltyba dose + 1.
[b]The number of subjects whose duration of exposure falls into this category. For example, subjects whose duration of exposure to Deltyba is 156 will be counted towards the Week 24 (155 - 168 Days) period. The subjects from each category are mutually exclusive.
[c]This is calculated as a percentage of total number of subjects in the enrolled set for each country.
Source: CT-2-7.1.2.

Patient exposure in the Non-Germany Enrolled Set to Deltyba by period is summarised in Table 11and Table CT-3-7.1.2. Deltyba treatment was terminated after 24 weeks in 17 (25.8%) patients, and in 38 (57.6%) patients Deltyba treatment was extended up to 26 to > 30 weeks.

Table 11: **Duration of Exposure to Deltyba by Period (Non-Germany Enrolled Set)**

		Number of Subjects	
Country	**Duration[a]**	**n[b]**	**(%)[c]**
Total (N=66)	< 24 Weeks	11	(16.7)
	24 Weeks	17	(25.8)
	26 - 30 Weeks	15	(22.7)
	> 30 Weeks	23	(34.8)
Estonia (N=14)	< 24 Weeks	0	(0.0)
	24 Weeks	1	(7.1)
	26 - 30 Weeks	9	(64.3)
	> 30 Weeks	4	(28.6)
France (N=3)	< 24 Weeks	2	(66.7)
	24 Weeks	0	(0.0)
	26 - 30 Weeks	0	(0.0)
	> 30 Weeks	1	(33.3)
Latvia (N=16)	< 24 Weeks	2	(12.5)
	24 Weeks	0	(0.0)
	26 - 30 Weeks	0	(0.0)
	> 30 Weeks	14	(87.5)
Lithuania (N=31)	< 24 Weeks	6	(19.4)
	24 Weeks	16	(51.6)
	26 - 30 Weeks	6	(19.4)
	> 30 Weeks	3	(9.7)
UK (N=2)	< 24 Weeks	1	(50.0)
	24 Weeks	0	(0.0)
	26 - 30 Weeks	0	(0.0)
	> 30 Weeks	1	(50.0)

[a]Duration of exposure is calculated as date of last Deltyba dose – date of first Deltyba dose + 1.
[b]The number of subjects whose duration of exposure falls into this category. For example, subjects whose duration of exposure to Deltyba is 156 will be counted towards the Week 24 (155 - 168 Days) period. The subjects from each category are mutually exclusive.
[c]This is calculated as a percentage of total number of subjects in the enrolled set for each country.
Source: CT-3-7.1.2.

For the Enrolled Set (n=86 patients), the Deltyba usage during the first 24 weeks was by DOT in 83 patients (96.5%), self-administration by 1 patient, and both DOT/self-administration by 4 patients. The Deltyba usage after the first 24 weeks was by DOT in 55 patients (64.0%), self-administration by 3 patients, and both DOT/self-administration by 11 patients. Three patients from sites based in Germany stopped DOT after 3 months of treatment since in Germany, patients are hospitalised for approximately 3 months and thereafter transferred to an ambulatory care setting.

10.3.3. Appropriate Combination Regimen Usage

All anti-TB treatments were coded using the WHO drug dictionary (WHODRUG B3G Mar 2021 Dictionary Version). Data were presented by drug class (ATC2) and medication PT.

Eighty-five patients (98.8%) used 3 or more anti-TB medications in their ACR during the Deltyba treatment period Listing (PDATA-1-8.3.1). The most commonly used anti-TB medications were linezolid (80.2%), moxifloxacin (53.5%), and cycloserine (48.8%).

For one patient from the UK, data recorded in eCRF are incomplete due to inadvertent deletion. This led to the wrong conclusion that delamanid had been given as monotherapy and no ACR regimen was designed for this patient.

The frequency and percentage of ACR usage during study treatment is provided in Table 12.

Table 12: Frequency and Percentage of ACR Taken During Study Treatment (Enrolled Set)

	Deltyba (N=86)	
ACR Name	**n**	**(%)**
Total Using One or More ACR	85	(98.8)
Amikacin	24	(27.9)
Amoxicillin	1	(1.2)
Amoxicillin/Clavulanate	6	(7.0)
Amoxiclav	3	(3.5)
Bedaquiline	11	(12.8)
Capreomycin	37	(43.0)
Clarithromycin	1	(1.2)
Clofazimine	29	(33.7)
Cycloserine	42	(48.8)
Ertapenem	1	(1.2)
Ethambutol	13	(15.1)
Imipenem/ Cilastatin	5	(5.8)
Isoniazid	1	(1.2)
Kanamycin	1	(1.2)
Levofloxacin	37	(43.0)
Linezolid	69	(80.2)
Meropenem	3	(3.5)
Moxifloxacin	46	(53.5)
Mycobutin	1	(1.2)
PAS	35	(40.7)
Prothionamide	29	(33.7)
Pyrazinamide	30	(34.9)
Rifabutin	3	(3.5)

Table 12: Frequency and Percentage of ACR Taken During Study Treatment (Enrolled Set)

	Deltyba (N=86)	
ACR Name	**n**	**(%)**
Rifampicin	2	(2.3)
Terizidone	33	(38.4)
Thioridazine	1	(1.2)
Trimethoprim/Sulfamethoxazole	3	(3.5)

Note: percentages are based on the number of subjects enrolled.
Source: CT-1-7.2.1.

10.4. Main Results

1. Study objectives/endpoints

The primary objective of this study was to monitor and present the usage of Deltyba in a real-life setting when prescribed as part of an ACR designed by the treating physician.

Deltyba was used for treatment of MDR-TB in all 86 adult patients enrolled in the PASS, 85 (98.8%) patients were diagnosed for the approved indication of pulmonary TB, and 1 patient (1.2%) for extrapulmonary TB.

In the Enrolled Set, 12 patients out of 86 received Deltyba for less than 24 weeks, of these 1 patient died, 2 patients left hospital against medical advice, 1 patient decided to return to his/her home country, 1 patient did not return to the primary site and was registered as loss to follow-up (LTFU), and 4 patients withdrew their consent. In addition, 1 patient out of 12 was resistant to Delamanid at baseline and stopped the intake of delamanid at receipt of the laboratory results, 1 patient was sensitive to Rifampicin and was included in the study by error. Delamanid was discontinued and replaced by Rifampicin. One patient completed the delamanid treatment course and was diagnosed as cured after 133 days.

Out of 74 patients who received Deltyba for 24 weeks, treatment with delamanid continued for 57 patients (26 weeks to > 30 weeks) with a median of 200 days.

Seventeen patients received Deltyba for 24 weeks according to SmPC. Fifty-seven patients were treated with Deltyba for a duration longer than 24 weeks, of these, 39 patients received Deltyba for longer than 30 weeks. Of these, 1 patient was treated with Deltyba for 113 weeks and 1 day.

In the Germany Enrolled Set, 1 patient out 20 received Deltyba for less than 24 weeks (10 weeks). This patient was treated [redacted] and showed a phenotypic resistance. Nineteen patients were treated with Deltyba for a duration longer than 24 weeks, of these, 16 patients received Deltyba for > 30 weeks.

In the Non-Germany Enrolled Set (EU excluding Germany), 11 out 66 patients received Deltyba for less than 24 weeks and 17 patients received Deltyba for 24 weeks according to SmPC. Thirty-eight patients were treated with Deltyba for a duration longer than 24 weeks, of these 23 patients received Deltyba for longer than 30 weeks.

The recommended dose of Deltyba for adults is 100 mg BID for 24 weeks. Seventeen patients received Deltyba 100 mg BID for 24 weeks. During the treatment extension phase (> 168 days), 43 patients received the recommended Deltyba 100 mg BID dose, while in 14 patients, treatment dose or dosing frequency was changed by the treating physician. One patient received the daily dose of 200 mg QD (Lithuania), and 13 patients, all from the same study site in Germany, received Deltyba 100 mg QD.

The secondary objectives of this study were as follows:

- To evaluate treatment outcomes (including clinical effectiveness) as defined by the WHO[1] and / or national guidelines for patients at the end of a full treatment period for MDR-TB up to 30 months, or earlier if patients were cured.
- To monitor the safety of Deltyba in a real-life setting when prescribed as part of an ACR designed by the treating physician.

Following the definitions outlined by the WHO[1], treatment success has been reported for 66 (76.7%, 95% CI [65.6% - 84.6%]) out of 86 patients treated with Deltyba. Forty-nine (57.0%, 95% CI [46.5% - 67.4%]) were cured, 17 (19.8%, 95% CI [11.4% - 28.2%]) have completed the treatment, 1 (1.2%) was a treatment failure, 11 (12.8%, 95% CI [5.7% -19.8%]) were LTFU, 5 (5.8%) were not evaluated, and 3 (3.5%, 95% CI [0.0% - 7.4%]) died.

Cardiac disorders (including QT prolongation) and suspected delamanid resistance were monitored as signs and symptoms of special interest. The results of the safety monitoring of Deltyba use as a part of an ACR in a real-life setting are presented in Section 10.6.7, along with results for all other safety concerns, as specified in Module SVIII: Summary of the Safety Concerns of the currently effective Delamanid EU risk management plan (RMP) v.3.5.

Drug resistance against delamanid has been removed as an important identified risk from the list of safety concerns in the EU RMP v.3.5, as per Health Authority request according to the Assessment Report of the procedure EMEA/H/C/002552/II/0040, where the EMA considered bacterial resistance development against delamanid as an efficacy concern, and not a safety concern. Nevertheless, it remains as an important topic for the benefit-risk balance of the product. As such, drug resistance data is presented here and discussed in Section 11.1.2 (Efficacy) of this final study report.

There were 2 events of drug resistance recorded during the study. Drug resistance was reported in 2 patients in Germany. For 1 patient DST sample taken at baseline before start of delamanid treatment revealed resistance against delamanid. Consequently, delamanid was stopped. The other event was reported in a patient with pre-existing cavities and extensively resistant TB (XDR-TB) along with a serious adverse event (SAE) of treatment failure during extended use of 100 mg BID delamanid. No action was taken with delamanid. The case was reported as recovered/resolved after pneumonectomy and the patient completed the study treatment (see narratives, Appendix 5).

10.5. Other Analyses

No other analyses were performed.

10.6. Adverse Events, Adverse Reactions, and other Safety Assessments

10.6.1. Summary of Adverse Events

Cumulatively, 425 AEs corresponding to 79 patients were reported in the study in the Enrolled set. No AEs were reported for 7 patients. Overall, 79 of 86 patients (91.9%) experienced 391 TEAEs, and 21 patients (24.4%) had at least 1 serious TEAE. Sixteen patients (18.6%) experienced severe TEAEs. Five patients (5.8%) experienced TEAEs leading to treatment discontinuation and 3 patients (3.5%) died. An overall summary of TEAEs reported during the study are presented in Table 13 and Table CT-1-8.1.

Table 13: **Adverse Events (All Causalities) (Enrolled Set)**

	Deltyba
	n (%)[a]
Subjects Treated	86 (100.0)
Subject Days of Drug Exposure	24921
Subjects with Adverse Events	79 (91.9)
Adverse Events	425
Subjects with Treatment-Emergent Adverse Events	79 (91.9)
Treatment-Emergent Adverse Events[b]	391
Subjects with Serious Treatment-Emergent Adverse Events	21 (24.4)
Subjects with Non-Serious Treatment-Emergent Adverse Events	78 (90.7)
Subjects with Severe Treatment-Emergent Adverse Events	16 (18.6)
Subjects Discontinued Investigational Medicinal Product Due to Adverse Events	5 (5.8)
Deaths	3 (3.5)

[a] Percentages are based on the number of subjects treated.
[b] Treatment-emergent adverse event is defined as an adverse event that started after patient started treatment with Deltyba, till the patient completed the study; or if the event was continuous from baseline and was serious, trial drug related, or resulted in death, discontinuation, interruption or reduction of trial therapy during the afore-mentioned period.
Multiple occurrences of treatment-emergent adverse event are counted once per MedDRA preferred term.
Source: CT-1-8.1.

In the Germany Enrolled Set, 104 AEs corresponding to 20 enrolled patients were reported in the study. Overall, 20 patients (100.0%) experienced 99 TEAEs, and 7 patients (35.0%) had at least 1 serious TEAE. Four patients (20.0%) experienced severe TEAEs. Two patients (10.0%) experienced TEAEs leading to treatment discontinuation. There were no deaths. A summary of TEAEs reported in Germany Enrolled Set during the study are provided in Table CT-2-8.1.

Out of 66 enrolled patients in the Non-Germany Enrolled Set, 321 AEs corresponding to 59 patients were reported in the study. There were no AEs reported for 7 patients. Overall, 59 patients (89.4%) experienced 292 TEAEs, and 14 patients (21.2%) had at least 1 serious TEAE. Twelve patients (18.2%) experienced severe TEAEs. Three patients (4.5%) experienced TEAEs leading to treatment discontinuation, and 3 patients (3.5%) died. A summary of TEAEs in Non-Germany Enrolled Set reported during the study are provided in Table CT-3-8.1.

10.6.2. Treatment-Emergent Adverse Events

For Table CT-1-8.2.1.1 (Enrolled Set), Table CT-2-8.2.1.1 (Germany Enrolled Set), and Table CT-3-8.2.1.1 (Non-Germany Enrolled Set) presenting the incidence of TEAEs by SOC and MedDRA PT, the 95% CI were both calculated using Wald and exact methods for all SOC classes and are presented in Table ADHOC 2-1a (Enrolled Set), Table ADHOC-2-2a (Germany Enrolled Set), and Table ADHOC-2-3a (Non-Germany Enrolled Set). As expected because of the lower number of patients, in general, the 95% CIs are wider in the data subsets for Germany and non-Germany.

For the 2 nonserious AEs reported in 2 patients in Germany concerning drug resistance, no 95% CI or exact CI is presented as there was only one acquired drug resistance to delamanid during the study. The nonserious AE was reported in a patient with pre-existing cavities and extensively drug-resistant TB along with a serious AE of treatment failure. For the other patient, the DST sample taken at baseline (before start of delamanid treatment) revealed resistance against delamanid. More details are presented in narratives (Appendix 5).

In the Enrolled set, the most frequently reported TEAEs were reported in SOC of gastrointestinal disorders (32 patients, 37.2%), and metabolism and nutrition disorders (22 patients, 25.6%). The most frequently reported TEAEs were nausea (19 patients, 22.1%), followed by vomiting (10 patients, 11.6%), anaemia (10 patients, 11.6%), and ECG QT prolonged (10 patients, 11.6%) (Table CT-1-8.2.1.2).

In the Germany Enrolled Set, the most frequently reported TEAEs were in SOC of general disorders and administration site conditions (9 patients, 45.0%), SOC of metabolism and nutrition disorders (9 patients, 45.0%) and gastrointestinal disorders (8 patients, 40.0%). The most frequently reported TEAEs were tinnitus (6 patients, 30%), nausea (5 patients, 25.0%), and decreased appetite (5 patients, 25.0%) (Table CT-2-8.2.1.2).

In the Non-Germany Enrolled Set, the most frequently reported TEAEs were in SOC of gastrointestinal disorders (24 patients; 36.4%), blood and lymphatic system disorders (16 patients, 24.2%), and nervous system disorders (16 patients; 24.2%). The most frequently reported TEAEs were nausea (14 patients, 21.2%), vomiting (10 patients, 15.2%), anaemia (10 patients, 15.2%), and ECG QT prolonged (8 patients, 12.1%) (Table CT-3-8.2.1.2).

The TEAEs occurring at a frequency of at least 3% reported during the study are presented by SOC, and PT in Table 14.

Table 14: **Incidence of Treatment-Emergent Adverse Events of at Least 3% by System Organ Class and MedDRA Preferred Term (Enrolled Set)**

	Deltyba (N=86)
System Organ Class Adverse Event (MedDRA Preferred Term)	**n (%)**
Subject With Any Treatment Emergent Adverse Events[a]	79 (91.9)
Blood and Lymphatic System Disorders	18 (20.9)
Anaemia	10 (11.6)
Neutropenia	5 (5.8)
Cardiac Disorders	6 (7.0)
Palpitations	3 (3.5)
Ear and Labyrinth Disorders	13 (15.1)
Hypoacusis	4 (4.7)
Tinnitus	7 (8.1)
Eye Disorders	9 (10.5)
Optic Neuropathy	3 (3.5)
Gastrointestinal Disorders	32 (37.2)
Abdominal Pain Upper	4 (4.7)
Diarrhoea	7 (8.1)
Dyspepsia	3 (3.5)
Nausea	19 (22.1)
Vomiting	10 (11.6)
General Disorders and Administration Site Conditions	21 (24.4)
Asthenia	5 (5.8)
Infections and Infestations	20 (23.3)
Tuberculosis	3 (3.5)
Investigations	19 (22.1)
Blood Uric Acid Increased	3 (3.5)
Electrocardiogram QT Prolonged	10 (11.6)
Metabolism and Nutrition Disorders	22 (25.6)
Decreased Appetite	6 (7.0)
Folate Deficiency	4 (4.7)
Hypokalaemia	5 (5.8)
Vitamin D Deficiency	7 (8.1)
Musculoskeletal and Connective Tissue Disorders	14 (16.3)
Arthralgia	8 (9.3)
Nervous System Disorders	21 (24.4)
Epilepsy	5 (5.8)
Headache	4 (4.7)
Polyneuropathy	5 (5.8)
Psychiatric Disorders	21 (24.4)

Table 14: Incidence of Treatment-Emergent Adverse Events of at Least 3% by System Organ Class and MedDRA Preferred Term (Enrolled Set)

	Deltyba (N=86)
System Organ Class Adverse Event (MedDRA Preferred Term)	**n (%)**
Anxiety	5 (5.8)
Borderline Personality Disorder	3 (3.5)
Depression	3 (3.5)
Insomnia	9 (10.5)
Renal and Urinary Disorders	14 (16.3)
Acute Kidney Injury	3 (3.5)
Renal Failure	7 (8.1)
Respiratory, Thoracic and Mediastinal Disorders	15 (17.4)
Chronic Obstructive Pulmonary Disease	4 (4.7)
Cough	4 (4.7)
Dyspnoea	3 (3.5)
Haemoptysis	4 (4.7)
Skin and Subcutaneous Tissue Disorders	20 (23.3)
Acne	4 (4.7)
Dermatitis Allergic	5 (5.8)
Pruritus	5 (5.8)
Vascular Disorders	6 (7.0)
Hypertension	4 (4.7)

Note: all adverse events which started after patient started treatment with Deltyba, till the patient completed the study; or if the event was continuous from baseline and was serious, study drug related, or resulted in death, discontinuation, interruption or reduction of study therapy during the afore-mentioned period. Subjects are counted once, per term, for the most severe of multiple occurrences of a specific MedDRA preferred term.

[a] Subjects with adverse events in multiple system organ classes were counted only once towards the total.

Source: CT-1-8.2.1.2.

In the Enrolled Set, 33 patients (38.4%) reported at least 1 potentially drug-related TEAE by the PASS physician. The most frequently drug-related TEAEs were in the SOCs of investigations (11 patients, 12.8%), and gastrointestinal disorders (10 patients, 11.6%). In the SOCs of investigations, ECG QT prolonged (9 patients, 10.5%), and blood creatinine increased (2 patients, 2.3%) were the most common potentially drug related TEAEs. In the SOC of gastrointestinal disorders nausea (6 patients, 7.0%), and vomiting (3 patients, 3.5%) were the most common potentially drug related TEAEs (Table CT-1-8.3.1).

In the Germany Enrolled Set, 13 patients (13 out of 20, 65.0%) reported at least 1 potentially drug-related TEAE. The most frequently drug-related TEAEs were in the SOC of investigations (20.0%), of which ECG QT prolonged (2 patients, 10.0%), and blood creatinine increased (2 patients, 10.0%) were the most common TEAEs. Nausea in the SOC of gastrointestinal disorders occurred in 3 (15.0%) patients (Table CT-2-8.3.1).

In the Non-Germany Enrolled Set, twenty patients (20 out of 66, 30.3%) reported at least 1 potentially drug-related TEAE. The most frequent drug-related TEAEs were in the SOC of investigations (10.6%), of which ECG QT prolonged (7 patients, 10.6%) was the reported AE. Gastrointestinal disorders occurred in 10.6% of patients of which nausea (3 patients, 4.5%) and vomiting (3 patients, 4.5%) were the most common (Table CT-3-8.3.1).

Potentially drug-related TEAEs reported during the study are presented by SOC, and PT in Table 15.

Table 15: Incidence of Potentially Drug-Related Treatment-Emergent Adverse Events by System Organ Class and MedDRA Preferred Term (Enrolled Set)

	Deltyba (N=86)
System Organ Class Adverse Event (MedDRA Preferred Term)	**n (%)**
Subject With Any Treatment Emergent Adverse Events[a]	33 (38.4)
Blood and Lymphatic System Disorders	1 (1.2)
Leukopenia	1 (1.2)
Neutropenia	1 (1.2)
Cardiac Disorders	2 (2.3)
Palpitations	2 (2.3)
Ear and Labyrinth Disorders	1 (1.2)
Tinnitus	1 (1.2)
Eye Disorders	2 (2.3)
Eye Pain	1 (1.2)
Optic Neuropathy	1 (1.2)
Gastrointestinal Disorders	10 (11.6)
Glosodynia	1 (1.2)
Nausea	6 (7.0)

Table 15: Incidence of Potentially Drug-Related Treatment-Emergent Adverse Events by System Organ Class and MedDRA Preferred Term (Enrolled Set)

	Deltyba (N=86)
System Organ Class **Adverse Event (MedDRA Preferred Term)**	**n (%)**
Vomiting	3 (3.5)
General Disorders and Administration Site Conditions	5 (5.8)
Asthenia	1 (1.2)
Chills	1 (1.2)
Drug Resistance	1 (1.2)
Fatigue	1 (1.2)
Paradoxical Drug Reaction	1 (1.2)
Hepatobiliary Disorders	2 (2.3)
Hepatic Cytolysis	1 (1.2)
Hepatitis Acute	1 (1.2)
Infections and Infestations	1 (1.2)
Oral Candidiasis	1 (1.2)
Injury, Poisoning and Procedural Complications	1 (1.2)
Incorrect Product Administration Duration	1 (1.2)
Investigations	11 (12.8)
Blood Creatinine Increased	2 (2.3)
Blood Potassium Decreased	1 (1.2)
Electrocardiogram QT Prolonged	9 (10.5)
Metabolism and Nutrition Disorders	4 (4.7)
Decreased Appetite	1 (1.2)
Hypocalcaemia	1 (1.2)
Hypokalaemia	2 (2.3)
Hypomagnesaemia	1 (1.2)
Nervous System Disorders	5 (5.8)
Autonomic Nervous System Imbalance	1 (1.2)
Headache	2 (2.3)
Hypoaesthesia	1 (1.2)
Paraesthesia	1 (1.2)
Psychiatric Disorders	2 (2.3)
Anxiety	1 (1.2)
Depression	1 (1.2)
Renal and Urinary Disorders	1 (1.2)
Renal Failure	1 (1.2)
Skin and Subcutaneous Tissue Disorders	5 (5.8)

Table 15: Incidence of Potentially Drug-Related Treatment-Emergent Adverse Events by System Organ Class and MedDRA Preferred Term (Enrolled Set)

	Deltyba (N=86)
System Organ Class **Adverse Event (MedDRA Preferred Term)**	**n (%)**
Acne	1 (1.2)
Alopecia	1 (1.2)
Dermatitis Acneiform	1 (1.2)
Pruritus	2 (2.3)
Rash	1 (1.2)
Vascular Disorders	1 (1.2)
Hypotension	1 (1.2)

Note: all adverse events which started after patient started treatment with Deltyba, till the patient completed the study; or if the event was continuous from baseline and was serious, study drug related, or resulted in death, discontinuation, interruption or reduction of study therapy during the afore-mentioned period. Subjects are counted once, per term, for the most severe of multiple occurrences of a specific MedDRA preferred term.

Potentially drug-related TEAES includes possibly related, probably related and related treatment-emergent adverse events.

[a] Subjects with adverse events in multiple system organ classes were counted only once towards the total.

Source: CT-1-8.3.1.

10.6.3. Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

Three subjects died due to TEAEs in Enrolled Set (3 out of 86, 3.5%).

No TEAEs had an outcome of death in the Germany Enrolled Set.

Three patients (3 out of 66, 4.5%) died due to TEAEs in the Non-Germany Enrolled set.

The causality for the 3 cases with an outcome "death" was assessed as not related to delamanid by both the investigator and the sponsor. Patient narratives of all fatal cases are provided in Appendix 5. The TEAEs resulting in death are presented by SOC, and PT in Table 16, Table CT-1-8.4, Table CT-2-8.4 and Table CT-3-8.4.

Table 16: Incidence of Death Due to Treatment-Emergent Adverse Events by System Organ Class and MedDRA Preferred Term (Enrolled Set)

	Deltyba (N=86)
System Organ Class Adverse Event (MedDRA Preferred Term)	**n (%)**
Subject With Any Treatment Emergent Adverse Events[a]	3 (3.5)
Cardiac Disorders	1 (1.2)
Myocardial Infarction	1 (1.2)
Infections and Infestations	2 (2.3)
HIV Infection	1 (1.2)
Pneumocystis Jirovecii Pneumonia	1 (1.2)
Pneumonia Cytomegaloviral	1 (1.2)
Tuberculosis	2 (2.3)

Note: all adverse events which started after patient started treatment with Deltyba, till the patient completed the study; or if the event was continuous from baseline and was serious, study drug related, or resulted in death, discontinuation, interruption or reduction of study therapy during the afore-mentioned period. Subjects are counted once, per term, for the most severe of multiple occurrences of a specific MedDRA preferred term.

[a] Subjects with adverse events in multiple system organ classes were counted only once towards the total.

Source: CT-1-8.4.

Overall, 33 serious TEAEs were reported in 21 patients (24.4%). The occurrence of treatment-emergent SAEs reported during the study are presented by SOC, and PT in Table 17. Out of 33 SAEs, 6 SAEs in 6 patients were assessed as causally related to delamanid (optic neuropathy, hepatic cytolysis, hepatitis acute, blood creatinine increased, autonomic nervous system imbalance, and renal failure). Apart from SAE of optic neuropathy, all SAEs assessed as causally related to delamanid were reported as recovered/resolved.

Patient narratives for the patients that experienced SAEs assessed as causally related to delamanid are provided in Appendix 5.

In the German Enrolled Set, 12 SAEs in 7 patients (35.0%) were reported. Of these, 4 SAEs were reported as potentially causally related to delamanid (optic neuropathy, blood creatinine increased, autonomic nervous system imbalance, and renal failure).

In the Non-German Enrolled Set, 21 SAEs in 14 patients (21.2%) were reported. Of these, 2 SAEs in 2 patients were assessed as potentially causally related to delamanid (hepatic cytolysis and acute hepatitis).

Other significant AEs are presented in Section 10.6.7. Adverse Events per Delamanid Safety Concerns.

Table 17: Incidence and Occurrence (Number of Events) of Serious Treatment-Emergent Adverse Events by System Organ Class and MedDRA Preferred Term (Enrolled Set)

	Deltyba (N=86)		
System Organ Class MedDRA Preferred Term	**n[a]**	**%**	**E[b]**
Subject With Any Treatment Emergent Adverse Events[a]	21	(24.4)	33
Cardiac Disorders	1	(1.2)	1
Myocardial Infarction	1	(1.2)	1
Eye Disorders	1	(1.2)	1
Optic Neuropathy	1	(1.2)	1
Gastrointestinal Disorders	1	(1.2)	2
Abdominal Adhesions	1	(1.2)	1
Mechanical Ileus	1	(1.2)	1
General Disorders and Administration Site Conditions	3	(3.5)	3
General Physical Health Deterioration	1	(1.2)	1
Treatment Failure	2	(2.3)	2
Hepatobiliary Disorders	4	(4.7)	4
Hepatic Cytolysis	1	(1.2)	1
Hepatitis	1	(1.2)	1
Hepatitis Acute	1	(1.2)	1
Hepatitis Toxic	1	(1.2)	1
Infections and Infestations	4	(4.7)	8
HIV Infection	1	(1.2)	1
Pneumocystis Jirovecii Pneumonia	1	(1.2)	1
Pneumonia	1	(1.2)	2
Pneumonia Cytomegaloviral	1	(1.2)	1
Tuberculosis	3	(3.5)	3
Injury, Poisoning and Procedural Complications	1	(1.2)	1
Ankle Fracture	1	(1.2)	1
Investigations	2	(2.3)	2
Blood Creatinine Increased	1	(1.2)	1
Weight Decreased	1	(1.2)	1
Metabolism and Nutrition Disorders	1	(1.2)	1
Diabetic Ketoacidosis	1	(1.2)	1
Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps)	1	(1.2)	1
Adenocarcinoma Of Colon	1	(1.2)	1
Nervous System Disorders	3	(3.5)	3
Autonomic Nervous System Imbalance	1	(1.2)	1
Epilepsy	1	(1.2)	1
Generalised Tonic-Clonic Seizure	1	(1.2)	1
Pregnancy, Puerperium and Perinatal Conditions	1	(1.2)	1

Table 17: Incidence and Occurrence (Number of Events) of Serious Treatment-Emergent Adverse Events by System Organ Class and MedDRA Preferred Term (Enrolled Set)

	Deltyba (N=86)		
System Organ Class MedDRA Preferred Term	**n[a]**	**%**	**E[b]**
Imminent Abortion	1	(1.2)	1
Psychiatric Disorders	1	(1.2)	1
Depression	1	(1.2)	1
Renal and Urinary Disorders	2	(2.3)	2
Acute Kidney Injury	1	(1.2)	1
Renal Failure	1	(1.2)	1
Respiratory, Thoracic and Mediastinal Disorders	2	(2.3)	2
Acute Respiratory Failure	1	(1.2)	1
Haemoptysis	1	(1.2)	1

Note: all adverse events which started after patient started treatment with Deltyba, till the patient completed the study; or if the event was continuous from baseline and was serious, study drug related, or resulted in death, discontinuation, interruption or reduction of study therapy during the afore-mentioned period.

[a] Subjects are counted once, per term, for multiple occurrences of a specific MedDRA preferred term.

[b] Number of adverse events were counted as reported.

Source: CT-1-8.5.1.

10.6.4. Adverse Events Leading to Discontinuation of Medicinal Product

In the Enrolled set, 5 patients (5.8%) discontinued the study treatment due to 7 TEAEs (non-serious AEs of tinnitus, eye pain, nausea, chills, drug resistance, ECG QT prolonged, and SAE of hepatic cytolysis).

In Germany Enrolled set, 2 patients (10.0%) discontinued the study treatment due to 2 non-serious TEAEs (tinnitus and drug resistance). One patient reported tinnitus and for the other patient, drug resistance against delamanid was reported which was detected at baseline prior to the initiation of delamanid therapy.

In Non-Germany Enrolled Set, 3 patients (4.5%) discontinued the study treatment due to 4 non-serious TEAEs: chills, eye pain, nausea, ECG QT prolonged, and 1 serious TEAE of hepatic cytolysis.

Adverse events leading to discontinuation from study are presented by SOC, and PT in Table 18, Table CT-1-8.6.1, Table CT-2-8.6.1 and Table CT-3-8.6.1.

Table 18: Incidence of Treatment-Emergent Adverse Events Resulting in Discontinuation from Study Medication by System Organ Class and MedDRA Preferred Term (Enrolled Set)

	Deltyba (N=86)
System Organ Class Adverse Event (MedDRA Preferred Term)	**n (%)**
Subject With Any Treatment Emergent Adverse Events[a]	5 (5.8)
Ear and Labyrinth Disorders	1 (1.2)
Tinnitus	1 (1.2)
Eye Disorders	1 (1.2)
Eye Pain	1 (1.2)
Gastrointestinal Disorders	1 (1.2)
Nausea	1 (1.2)
General Disorders and Administration Site Conditions	2 (2.3)
Chills	1 (1.2)
Drug Resistance	1 (1.2)
Hepatobiliary Disorders	1 (1.2)
Hepatic Cytolysis	1 (1.2)
Investigations	1 (1.2)
Electrocardiogram QT Prolonged	1 (1.2)

Note: all adverse events which started after patient started treatment with Deltyba, till the patient completed the study; or if the event was continuous from baseline and was serious, study drug related, or resulted in death, discontinuation, interruption or reduction of study therapy during the afore-mentioned period. Subjects are counted once, per term, for the most severe of multiple occurrences of a specific MedDRA preferred term.

[a] Subjects with adverse events in multiple system organ classes were counted only once towards the total.

Source: CT-1-8.6.1.

10.6.5. Electrocardiography Data

The absolute number of patients with ECG assessments per month and the corresponding percentage of patients with ECG assessments per month of the total patients still in study are presented in Table ADHOC-1-1 (Enrolled Set), Table ADHOC-1-2 (Germany Enrolled Set), and Table ADHOC-1-3 (Non-Germany Enrolled Set).

According to the non-interventional design of the PASS, no prespecified study visits were foreseen in the study protocol. Therefore, for the following ECG frequency assessment, patients' study participation was divided into monthly intervals for the first 3 months and thereafter every 3 months, and number of patients with ECG measurement per interval was counted.

ECG measurements were performed frequently during the first 6 months of the study in the Enrolled Set. In more detail, the ECG measurements in the Enrolled Set were performed in approximately 90% of the patients during the first 6 months (92.8% of patients at Month 1 and 87% of patients at Month 6). In the Germany Enrolled Set the frequency of ECG measurements was slightly higher (100% of patients at Months 1, 3, and 6) than in the Non-Germany Enrolled

Set (90.5% of patients at Month 1 and 82.5% of patients at Month 6). The relative frequency of ECG measurements decreased from Month 9 to the Month 30 visit in the Enrolled Set as well as in the Germany and Non-Germany Enrolled Set. For almost all patients an ECG measurement was performed at the last documented study visit: 97.6% for the Enrolled Set, 100% for the Germany Enrolled Set, and 96.9% for the Non-Germany Enrolled Set.

For all patients an ECG measurement was documented for baseline in the clinical database (PDATA-1-13). However, the 3 ADHOC tables display the derived baseline, which is defined in the Statistical Analysis Plan (SAP) as patient status before the initiation of Deltyba treatment. As for the 13 patients, delamanid had been already started when baseline ECG measurement was performed, Table ADHOC 1-1, Table ADHOC 1-2, and Table ADHOC 1-3 do not show 100% baseline ECG measurements.

Table 19: Electrocardiogram Measurements per Visit - Overall (Enrolled Set)

Deltyba	Number of Patients with ECG Measurement	Number of Patients in Study	% of Patients with ECG Measurement
Baseline	73	86	84.9
Month 1	77	83	92.8
Month 2	67	83	80.7
Month 3	72	80	90.0
Month 6	67	77	87.0
Month 9	53	72	73.6
Month 12	39	60	65.0
Month 15	25	46	54.3
Month 18	20	37	54.1
Month 21	12	21	57.1
Month 24	6	13	46.2
Month 27	1	5	20.0
Month 30	0	4	0.0
Last Visit	83	85	97.6

Source: ADHOC-1-1.

For 7 out of 10 patients with reported AEs of QT prolongation (all nonserious), additional unscheduled ECG measurements (outside the study visits) were documented (PDATA-1-13).

The data show that during real-world use of delamanid, ECG measurements were performed frequently and regularly with more frequent ECG measurements in patients after QT prolongations were detected.

An analysis of ECG data of all patients from the Enrolled Set revealed that the baseline mean ventricular rate was 78.7 (51 - 117) beats per minute (BPM) and remained constant with minor variations and within normal parameters throughout the duration of the trial. The mean value at the final visit was 73.1 (52 - 140) BPM with a mean change of -6.2 (-41 - 65) BPM. One out of 57 patients (1.8%), and 4 out of 57 patients (7.0%) had potentially clinically relevant

bradycardias (< 50 BPM) or tachycardias (> 100 BPM), respectively. No tachycardia nor bradycardia AEs were assessed as related to delamanid.

The mean RR interval at baseline was estimated to be 687.3 (92 - 1071) ms in 48 patients. By the final visit the mean interval increased marginally to 740.3 (103 - 1131) ms; representing a mean change from baseline of 41.7 (-768 - 782) ms.

Mean values for assessed parameters, QTcB and QTcF showed mild fluctuations above and below baseline values, however remained generally consistent throughout the study. The mean QTcF at baseline was estimated to be 400.3 (330 - 480) ms in 40 patients. At Months 3, 6, 12, 24, and last visit, the mean QTcF was 414.8, 420.5, 425.0, 425.7, and 421.2 ms, with a mean change from baseline of 11.3, 19.1, 17.6, 14.2, and 17.2, respectively. A detailed description of the AEs due to QT prolongation are presented in Section 10.6.7.1.1.

The incidence of clinically significant abnormalities and changes in ECG results is presented in Table 20. In the Enrolled Set, an increase of ≥ 30 and ≤ 60 msec in QTc was the most frequently reported abnormality and was reported in 24 patients with QTcF, and 14 patients with QTcB. QTcF interval prolongation > 60 ms was reported in 10 patients, and QTcB > 60 ms in 2 patients. For 2 patients QTc > 500 ms was reported with QTcB, and for 1 patient with QTcF, respectively (see Section 11.1.3 and Table CT-1-13.2).

In the Germany Enrolled Set, an increase of ≥ 30 and ≤ 60 msec, and new onset > 450 msec in QTc were the most frequently reported abnormality. The increase of ≥ 30 and ≤ 60 msec was reported in 7 patients with QTcF, and 2 patients with QTcB. The new onset > 450 msec was reported in 3 patients with QTcF, and 2 patients with QTcB. For 1 patient QTc > 500 ms was reported with QTcF (Table CT-2-13.2).

In the Non-Germany Enrolled Set, an increase of ≥ 30 and ≤ 60 msec, and new onset > 450 msec in QTc were the most frequently reported abnormality. The increase of ≥ 30 and ≤ 60 msec was reported in 17 patients with QTcF, and 12 patients with QTcB. The new onset > 450 msec was reported in 11 patients with QTcF. For 2 patients QTc > 500 ms was reported with QTcB (Table CT-3-13.2).

Table 20: Incidence of Potential Clinically Significant ECG Measurements (Enrolled Set)

		Deltyba (N=86)		
	Clinical Significant ECG	**Ne[a]**	**n[b]**	**(%)**
HR Outliers	< 50 Bpm And Decrease >= 25%	57	1	(1.8)
	> 100 Bpm And Increase >= 25%	57	4	(7.0)
QTcB	New Onset (> 450 Msec)	34	13	(38.2)
	New Onset (> 480 Msec)	34	2	(5.9)
	New Onset (> 500 Msec)	34	2	(5.9)
	Increase Of > 60 Msec	34	2	(5.9)
	Increase Of >= 30 Msec And <= 60 Msec	34	14	(41.2)
QTcF	New Onset (> 450 Msec)	38	14	(36.8)
	New Onset (> 480 Msec)	38	6	(15.8)
	New Onset (> 500 Msec)	38	1	(2.6)
	Increase Of > 60 Msec	38	10	(26.3)
	Increase Of >= 30 Msec And <= 60 Msec	38	24	(63.2)
QT	New Onset (> 500 Msec)	61	2	(3.3)

Note: criteria for potential clinical relevance are defined in CT-1-13.4.
[a] Ne is the total number of subjects with at least one post-baseline numeric result for the given ECG parameter.
[b] n is the number of subjects with at least one ECG of potential clinical significance.
Source: CT-1-13.2.

10.6.6. Vital signs, Physical Findings and Other Observations Related to Safety

10.6.6.1. Chest X-ray

Chest x-ray was performed in 83 (96.5%) patients, of which 77 (92.8%) showed abnormal findings, and 2 showed (2.4%) normal findings. For 4 out of 83 patients (4.8 %), results were either missing (4 patients), or were not done (3 patients). Cavities were diagnosed in 49 (59.0%) of the patients.

Chest X-rays were evaluated and results over time are presented by frequency and percentage in Table CT-1-9.1.

10.6.6.2. Vital Signs Data

Vital signs were measured during the study and results are presented in Table CT-1-12.1.

There were no trends observed over time in systolic and diastolic blood pressure, heart rate, weight, BMI, and temperature.

The mean heart rate at baseline in 77 patients was 82.1 (52 - 111) BPM and at the last visit was estimated to be 77.9 (52 - 122) BPM with a mean change from baseline of -4.7 (-38 - 42) BPM. The mean systolic blood and diastolic blood pressures were estimated to be 116.4 and 74.2 mmHg, respectively, at baseline with a mean change of +2.6 and +3.5 mmHg, respectively

when compared to the last visit. Very marginal variations were observed in body temperature, weight, and BMI.

10.6.6.3. Clinical Laboratory Results

There were potentially clinically significant findings observed in the study. Test results for a particular test at post-baseline visit are presented in Table CT-1-11.2.

Chemistry laboratory results reported as potentially clinically significant by the PASS physician were increased values of alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma glutamyl transferase (GGT), and total bilirubin in 5 out of 84 (6.0%), 2 out of 76 (2.6%), 3 out of 66 (4.5%), and 4 out of 78 (5.1%) patients, respectively. A detailed description of TEAEs and laboratory results pertaining to liver disorders is presented in Section 10.6.7.2.5.

Potentially clinically significant increased creatinine was observed in 3 out of 83 (3.6%) patients, with a maximum value of 3.18 mg/dL. Two increased creatinine cases were associated with TEAEs (1 SAE) that were assessed as possibly related to the use of delamanid; nevertheless, the creatinine values were not provided. The remaining increased creatinine cases were assessed as not related to the use of delamanid. In 6 out of 47 (12.8%) patients, a low serum calcium was reported and assessed as potentially clinically relevant. One AE of hypocalcaemia were assessed as potentially related to the use of delamanid. Similar results were observed with hyperkalaemia (7 out of 83, 8.4%), hyperglycaemia (1 out of 54, 1.9%), and hyponatremia (10 out of 68, 14.7%). In the case of hypokalemia, 3 out of 83 (3.6%) patients with low serum potassium values were identified.

For 6 enrolled patients (1 German patient, 5 non-German patients), a serum albumin value < 3.4 g/dL at baseline was reported (Listing LAB-1-1.1). A serum albumin value < 2.8 g/dL at baseline was an exclusion criterion in Germany protocol. In the Germany Enrolled Set, there was no patient with serum albumin value < 2.8 g/dL at baseline. In the Non-Germany Enrolled Set, 1 patient had a serum albumin value < 2.8 g/dL at baseline (Table CT-1-11.1.5). No AEs of QTc prolongation were reported in any of these 6 patients. For 2 non-German patients with normal serum albumin values at baseline, serum albumin values < 3.4 g/dL were reported during the study and one of those patients had an AE of QTc prolongation discussed in Section 11.1.3.3.

Haematology parameters revealed decreased haemoglobin in 12 out of 82 (14.6%) patients, leucocytosis in 6 out of 83 (7.2%), leukopenia in 3 out of 83 (3.6%), and thrombocytopenia in 2 out of 83 (2.4%) that were assessed as potentially clinically relevant.

There were generally no trends in the serum chemistry and haematology parameters. The same was observed in the patients of the Germany Enrolled Set and Non-Germany Subset.

For urinalysis, a meaningful analysis cannot be performed due to incomplete record of data and the broad spectrum of units reported.

There were generally no trends in other laboratory tests performed.

Clinical laboratory data were evaluated and results are presented in Tables CT-1-11.1.1, CT-1-11.1.2, CT-1-11.1.3, CT-1-11.1.6, CT-1-11.6, and CT-1-11.1.4.

10.6.7. Adverse Events per Delamanid Safety Concerns

Adverse events pertaining to important identified/potential risks and missing information as per current approved RMP 3.5 are described in detail as follows.

10.6.7.1. Important Identified Risks

10.6.7.1.1. QT interval prolongation (including SOC cardiac disorders)

Results for the SMQ Torsade de pointes/ QT prolongation and TEAEs reported in the SOC Cardiac disorders are presented in this section.

The incidence of TEAEs for Cardiac disorders / QT Prolongation are provided in Table CT-1-8.10.1. Out of 86 patients, 15 (17.4%) patients experienced TEAEs of cardiac disorder or QT interval prolongation. The majority of TEAEs were reported in the SOC of investigations: 10 (11.6%) patients had ECG QT prolonged while 6 patients (7.0%) had TEAEs in the SOC of cardiac disorders (palpitations 3 patients, 3.5%), tachycardia (2 patients, 2.3%), myocardial infarction (1 patient, 1.2%), and Wolff-Parkinson-White syndrome (1 patient, 1.2%). No TEAEs of sudden cardiac death, ventricular extrasystoles or Torsade de pointes were reported.

Apart from the serious and severe TEAE of myocardial infarction with fatal outcome, cardiac TEAEs in remaining 14 patients (16.3%) were reported as non-serious (Table CT-1-8.10.6) and were either mild (10 patients), or moderate (5 patients) (Table CT-1-8.10.2, Table CT-1-8-10.4). For 10 out of 86 (11.6%) patients, 10 non-serious TEAEs of ECG QT prolonged were reported of which 6 were mild and 4 were moderate.

The majority of TEAEs (11 out of 15) have been assessed as related to delamanid (Table CT-1-8.10.3). Nine of 10 (90%) TEAEs of ECG QT prolonged were assessed as related to delamanid. Details for fatal case with SAE of myocardial infarction are provided in the narratives (Appendix 5).

Out of 20 patients in the Germany Enrolled Subset, cardiac TEAEs were reported in 4 patients (20.0%) (palpitations in 2 patients, 10%); and ECG QT prolonged in 2 other patients, (10.0%) which were all reported as non-serious and assessed as related to delamanid (Tables CT-2-8.10.1 to CT-2-8.10.6).

Out of 66 patients of the Non-German Enrolled Subset, cardiac TEAEs were reported in 11 patients (16.7%). Of these, 10 were reported as non-serious and 1 as serious (myocardial infarction). Out of 8 TEAEs of ECG QT prolonged (12.1%), 7 TEAEs were assessed as related to delamanid (Table CT-3-8.10.1 to CT-3-8.10.6).

10.6.7.1.2. Nervous System Disorder: Paraesthesia, Hypoaesthesia and Tremor

In the Enrolled Set, the incidence of TEAEs the risk of paraesthesia, hypoaesthesia, or tremor are provided in Table CT-1-8.11.1. Four patients (4.7%) experienced 4 non-serious TEAEs (2 patients mild hypoaesthesia, and 2 patients moderate paraesthesia) (Table CT-1-8.11.2). No TEAEs of tremor were reported.

In the Germany Enrolled Set, the incidence of TEAEs for the risks of paraesthesia, hypoaesthesia, or tremor are provided in Table CT-2-8.11.1. One patient (5.0%) experienced paraesthesia which was assessed as related to delamanid (Table CT-2-8.3.1).

In the Non-Germany Enrolled Set, the incidence of TEAEs for the risks of paraesthesia, hypoaesthesia, or tremor are provided in Table CT-3-8.11.1. Three patients (4.5%) experienced 2 TEAEs of hypoaesthesia and 1 TEAE of paraesthesia. One TEAE of hypoaesthesia was assessed as related to delamanid (Table CT-3-8.8.3.2).

10.6.7.1.3. Psychiatric disorders: Anxiety, Depression and Insomnia

In the Enrolled Set, the incidence of TEAEs related to the important identified risk of psychiatric disorders (anxiety, depression, and insomnia) by SOC and PT are provided in Table CT-1-8.12.1. Sixteen patients (6 out of 86, 18.6%) experienced 19 TEAEs (5 patients anxiety, 1 patient anxiety disorder, 1 patient generalized anxiety disorder, 3 patients depression, and 9 patients insomnia). Apart from 1 SAE of moderate depression all events were reported as non-serious. The severity was mild for 11, moderate for 5, and severe for 1 (anxiety) TEAEs (Table CT-1-8.12.2). Two patients (2.3%) experienced 2 non-serious TEAEs (anxiety and depression) which were considered related to delamanid (Table CT-1-8.12.3).

In the Germany Enrolled Set, the incidence of TEAEs for the risk of psychiatric disorders by SOC and PT is provided in Table CT-2-8.12.1. Four patients (20.0%) experienced 6 TEAEs (1 patient anxiety, 3 patients depression, and 2 patients insomnia). The severity was mild for 4 and moderate for 2 TEAEs (Table CT-2-8.12.2). One patient (5.0%) experienced a serious TEAE of moderate depression (Table CT-2-8.12.4). Apart from one non-serious TEAE of depression, all TEAEs were assessed as not related to delamanid.

In the Non-Germany Enrolled Set, the incidence of TEAEs for the risk of psychiatric disorders by SOC and PT is provided in Table CT-3-8.12.1. Twelve patients (18.2%) experienced 13 non-serious TEAEs (4 patients anxiety, 1 patient anxiety disorders, 1 patient generalised anxiety disorder, and 7 patients insomnia). The severity was mild for 9, moderate for 3, and severe for 1 TEAEs (Table CT-3-8.12.2). Apart from one non-serious TEAE of anxiety, all TEAEs were assessed as not related to delamanid.

10.6.7.1.4. Gastrointestinal disorders: Nausea, Vomiting and Gastritis

In the Enrolled Set, the incidence of TEAEs related to the important identified risk of gastrointestinal disorders (nausea, vomiting, and gastritis) by SOC and PT is provided in Table CT-1-8.13.1. Twenty-seven patients (31.2%) experienced 33 non-serious TEAEs (19 patients nausea, 10 patients vomiting, 1 patient chronic gastritis, 1 patient erosive

oesophagitis, 1 patient gastroesophageal reflux disease, and 1 helicobacter gastritis). The severity was mild for 18 and moderate for 15 TEAEs (Table CT-1-8.13.2). Nine patients (10.5%) experienced gastrointestinal TEAEs (6 nausea and 3 vomiting) which were considered related to delamanid (Table CT-1-8.13.3).

In the Germany Enrolled Set, the incidence of TEAEs for the risk of gastrointestinal disorders by SOC and PT is provided in Table CT-2-8.13.1. Six patients (30.0%) experienced 6 TEAEs (5 patients nausea and 1 patient helicobacter gastritis). The severity was mild for 4 and moderate for 2 TEAEs. Three events of nausea were assessed as related to delamanid.

In the Non-Germany Enrolled Set, the incidence of TEAEs the risk of Gastrointestinal disorders by SOC and PT is provided in Table CT-3-8.13.1. Twenty-one patients (31.8%) experienced 27 TEAEs (14 patients nausea, 10 patients vomiting, 1 patient chronic gastritis, 1 patient erosive oesophagitis, and 1 patient gastrooesophageal reflux disease). The severity was mild for 14 and moderate for 13 TEAEs. Each 3 events of nausea and vomiting were assessed as related to delamanid.

10.6.7.2. Important Potential Risks

10.6.7.2.1. Tinnitus

In the Enrolled Set, the incidence of TEAEs the risk of tinnitus is provided in Table CT-1-8.15.1. Seven patients (8.1%) experienced tinnitus. All TEAEs were reported as non-serious and mild (Table CT-1-8.15.6).

In the Germany Enrolled Set, the incidence of TEAEs for the risk of tinnitus is provided in Table CT-2-8.15.1. Six patients (30.0%) experienced TEAEs of tinnitus of which one was assessed as causally related to delamanid (Table CT-2-8.15.3).

In the Non-Germany Enrolled Set, the incidence of TEAEs for the risk of tinnitus is provided in Table CT-3-8.15.1. One patient (1.5%) experienced tinnitus which was assessed as not related to delamanid (Table CT-3-8.15.2).

10.6.7.2.2. Blurred vision

In the Enrolled Set, the incidence of TEAEs for the risk of blurred vision is provided in Table CT-1-8.16.1. One patient (1.2%) experienced a mild non-serious TEAE of blurred vision which was assessed as not related to delamanid (Table CT-1-8.16.6).

In the Germany Enrolled Set, no TEAE of blurred vision was reported.

In the Non-Germany Enrolled Set, the incidence of TEAEs for the risk of blurred vision is provided in Table CT-3-8.16.1. One patient (1.5%) experienced a mild non-serious TEAE of blurred vision which was assessed as not related to delamanid (Table CT-3-8.16.6).

10.6.7.2.3. Hypokalaemia

In the Enrolled Set, the incidence of TEAEs for the risk of hypokalaemia is provided in Table CT-1-8.17.1. Five patients (5.8%) experienced a TEAE of hypokalaemia.

In the Germany Enrolled Set, no TEAEs of hypokalaemia were reported.

In the Non-Germany Enrolled Set, the incidence of TEAEs for hypokalaemia by SOC and PT is provided in Table CT-3-8.17.1. Five patients (7.6%) experienced 5 non-serious TEAEs of hypokalaemia (of which 3 were reported as mild, and 2 as moderate). Two TEAEs were assessed as causally related to delamanid.

10.6.7.2.4. Blood cortisol level increase

No TEAE of blood cortisol increased was reported during this study.

10.6.7.2.5. Liver disorders

In the Enrolled Set, the incidence of TEAEs for the important potential risk liver disorders by SOC and PT is provided in Table CT-1-8.19.1. Eight patients (9.3%) experienced 9 (4 serious and 5 non-serious) TEAEs in the SOC of hepatobiliary disorders (5 patients, 5.8%), and in the SOC investigations (3 patients, 3.5%). Four (4 patients, 4.7%) TEAEs were reported as serious of which 2 SAEs (hepatic cytolysis and acute hepatitis) were assessed as causally related to delamanid. The severity was severe for 5, moderate for 1, and mild for 3 TEAEs. Toxic hepatitis was the most common TEAE (2 patients, 2.3%).

For 8 patients AST and/or ALT values > 3x upper limit of normal (ULN) and/or total bilirubin > 2x ULN were reported. Of these, hepatic TEAEs were reported for 5 patients (2 related SAEs of hepatic cytolysis and hepatitis acute, respectively, and 2 not related SAE of hepatotoxicity and hepatitis, respectively and 1 non-serious and not related AE of toxic hepatitis). For 2 patients with AST > 3x ULN and 1 patient with total bilirubin > 2x ULN no TEAEs were reported.

In the Germany Enrolled Set, the incidence of TEAEs for the important potential risk liver disorders by SOC and PT is provided in Table CT-2-8.19.1. Two patients (10.0%) reported 3 non-serious TEAEs in the SOC of investigations, all assessed as not related to delamanid (Table CT-2-8.19.6). In 1 patient 2 TEAEs of severe ALT increased, and 1 severe AST increased were reported. In another patient, 1 TEAE of moderate transaminase increased was reported.

In the Non-Germany Enrolled Set, the incidence of TEAEs for the important potential risk liver disorders by SOC and PT is provided in Table CT-3-8.19.1. Six patients (9.1%) experienced TEAEs in the SOC of hepatobiliary disorders (5 patients, 7.6%); 1 severe SAE of hepatic cytolysis, 1 severe SAE of hepatitis, 1 mild SAE of acute hepatitis, and 2 TEAEs of toxic hepatitis (1 severe and serious, and 1 mild and non-serious), and in the SOC investigations (1 patient, 1.5%); 1 non-serious and mild TEAE of bilirubin increased) (Table CT-3-8.19.6). Of these, the SAEs of hepatic cytolysis and SAE of acute hepatitis were assessed as causally related to delamanid and the narratives are presented in Appendix 5.

10.6.7.2.6. Drug use during pregnancy

Drug use during pregnancy was twice reported in a single patient from Lithuania (see narratives, Appendix 5).

10.6.7.2.7. Drug use during breastfeeding

No drug use in breast feeding patients was reported during this study.

10.6.7.3. Missing Information

10.6.7.3.1. Drug use in paediatric patients

No paediatric patients were included in this clinical study. The protocol was designed to include adult patients only. The paediatric extension was approved after the enrolment for PASS delamanid study was stopped on 12 Aug 2020.

10.6.7.3.2. Drug use in elderly patients (≥ 65 years)

Drug use was reported in 3 elderly patients. For 2 patients, 1 serious TEAE and 14 non-serious TEAEs were reported (Tables CT-3-8.20.1 to CT-3-8.20.6, Table CT-3-8.27.10).

In a [redacted] patient from Estonia, SAE of adenocarcinoma of colon was reported which was assessed as not related to delamanid due to the short latency between the first dose of delamanid (53 days) and the onset of the event, as well as the lack of biological plausibility. In the same patient, 8 non-serious TEAEs were reported, all assessed as not related to delamanid.

In a [redacted] patient from Latvia, 6 non-serious TEAEs were reported of which 3 (oral candidiasis, hypotension, and ECG QT prolonged) were assessed as causally related to delamanid.

For a [redacted] patient from Lithuania who withdrew his consent (treatment duration 8 weeks), no TEAEs were reported.

10.6.7.3.3. Drug use in patients with HIV

Three patients with a medical history of HIV infection were enrolled in the study (Table CT-1-8.21.1).

Four severe and not related SAEs of pneumocystis jirovecii pneumonia, cytomegalovirus pneumonia, TB-, and HIV infection were reported as fatal in a 25-year-old female patient from Latvia (see narratives, Appendix 5). Further 8 non-serious TEAEs in this patient were assessed as not related to delamanid.

One non-serious and not related TEAE of mild tinnitus along with a non-serious related TEAE of drug resistance were reported in a 39-year-old male patient from Germany. The drug resistance against delamanid was present at baseline (see narratives, Appendix 5).

Six non-serious and not related TEAE of severe toothache, moderate gastroesophageal reflux disease, moderate hypoacusis, mild galactorrhea, mild dry eye, and severe anxiety were reported in a 32-year-old female patient from Latvia.

10.6.7.3.4. Drug use in patients with severe renal impairment

No patients with a medical history of severe renal impairment were included in this clinical study (Table CT-1-8.22.1).

10.6.7.3.5. Drug use in patients with severe hepatic impairment

One [redacted] patient with a medical history of severe hepatic impairment was enrolled in the study. The medical history recorded toxic hepatitis due to previous MDR-TB treatment, which included an ACR with pyrazinamide, moxifloxacin, prothionamide, terizidone, linezolid, para-aminosalicyclic acid (PAS), and bedaquiline; which all were stopped and the patient recovered in Oct 2016. No event of hepatotoxicity was reported while the patient was treated with delamanid starting Dec 2016, during the study. The patient was reported as cured of MDR-TB [redacted] Jan 2018. For this patient 15 non serious, causally not related TEAEs were reported (Tables CT-1-8.23.1 to CT-1-8.23.6).

10.6.7.3.6. Drug-drug interactions

No drug-drug interactions were reported during this study.

10.6.7.3.7. Extended use (> 168 days)

As per PASS physicians' decision, 57 patients were treated with delamanid after 24 weeks during this study. During the treatment extension (beyond 24 weeks), 13 patients in a German site received 100 mg delamanid QD instead of 100 mg BID.

For 30 (52.6%) out of 57 patients receiving delamanid more than 168 days, TEAEs with an onset > 168 days were reported (Table CT-1-8.25.1). For 2 of these patients (both delamanid use of 169 days), delamanid was interrupted resulting in a real delamanid use of 156 and 160 days, respectively. Time to onset ranged from 169 to 792 days since the first administration of delamanid. The majority of TEAEs were mild (24 patients, 42.1%) or moderate (18 patients, 31.6%); in 4 patients (7.0%) TEAEs were reported as severe (Table CT-1-8.25.2). For 9 patients (15.8%) TEAEs were assessed as related to delamanid by the PASS physician with ECG QT prolonged being the most frequently reported event (6 patients, 10.5%). Thirteen SAEs in 8 patients (14.0%) were reported (Table CT-1-8.25.4, Appendix 5 Narratives). Thereof, 2 SAEs in 2 patients (3.5%) (optic neuropathy and blood creatinine increased) were assessed as potentially related to delamanid (Table CT-1-8.25.5; Appendix 5 Narratives).
Seventy-nine non-serious TEAEs with an onset > 168 days were reported in 30 out of 57 patients (52.6%) receiving delamanid more than 168 days (Table CT-1-8.25.6).

In the Germany Enrolled Set, TEAEs with an onset > 168 days were reported in Table CT-2-8.25.1. Out of 19 patients of the German subset, the majority of TEAEs were mild (9 patients, 47.4%), or moderate (7 patients, 36.8%). In 2 patients (10.5%) TEAEs were reported as severe (Table CT-2-8.25.2). For 5 patients (26.3%) TEAEs were assessed as related to

delamanid by the PASS physician with ECG QT prolonged being the most frequently reported event (2 patients, 10.5%). Seven SAEs in 5 patients (26.3%) were reported (Table CT-2-8.25.4, Appendix 5 Narratives). Thereof, 2 SAEs in 2 patients (10.5%) (optic neuropathy and blood creatinine increased) were assessed as potentially related to delamanid (Table CT-2-8.25.5; Appendix 5 Narratives). 34 non-serious TEAEs with an onset > 168 days were reported in 10 out of 19 patients (52.6%) receiving delamanid more than 168 days (Table CT-2-8.25.6).

In the Non-Germany Enrolled Set, TEAEs with an onset > 168 days were reported in Table CT-3-8.25.1. Out of 38 patients of the Non-German Subset, the majority of TEAEs were mild (15 patients, 39.5%), or moderate (11 patients, 28.9%). In 2 patients (5.3%) TEAEs were reported as severe (Table CT-3-8.25.2). For 4 patients (10.5%) TEAEs were assessed as related to delamanid by the PASS physician with ECG QT prolonged being the only reported event (4 patients; 10.5%). Six SAEs in 3 patients (7.9%) were reported (Table CT-3-8.25.4, Appendix 5 Narratives). None of SAEs were assessed as potentially related to delamanid (Table CT-3-8.25.5; Appendix 5 Narratives). Forty-five non-serious TEAEs with an onset > 168 days were reported in 20 out of 38 patients (52.6%) receiving delamanid more than 168 days (Table CT-3-8.25.6).

An SAE of treatment failure along with non-serious drug resistance against delamanid was reported for one patient during extended use of delamanid (100 mg BID, > 24 weeks). The patient was already diagnosed with cavitary disease left lung at baseline of the study. Since medical treatment did not lead to sputum conversion, pneumonectomy was performed and ACR including delamanid treatment continued. The treatment outcome was reported as “treatment completed”. The causality for the SAE treatment failure and non-serious TEAE drug resistance was assessed as not related to delamanid considering patient's underlying difficult to treat MDR-TB or XDR-TB as a significant confounding factor (see Section 10.4 and Appendix 5 Narratives).

With respect to the open signal covalent binding, which is usually discussed with the periodic safety update reports, data have been cumulatively assessed for EU PASS. Out of 30 patients with TEAEs with an onset > 168 days, 8 TEAEs could potentially be related to covalent binding. No safety concern is identified in relation with the property of delamanid and its metabolites to covalently bind to plasma proteins.

11. DISCUSSION

11.1. Key Results

11.1.1. Deltyba Real World Usage

The objectives of this study were to monitor and document the drug-use pattern of Deltyba (delamanid) in medical practice when prescribed as part of an ACR designed by the treating physician for the treatment of MDR-TB, evaluate treatment outcomes and to collect safety information. A German specific protocol was used for the PASS following the request of the BfArM, for defining inclusion and exclusion criteria based on the approved SmPC while in the other countries concerned observations of deviations from the SmPC were the focus of the competent authorities.

Eleven active clinical sites, specialised for TB, enrolling 86 patients, were involved in the PASS. Countries with study sites participating were Lithuania (31 patients, 36.0%), Germany (20 patients, 23.3%), Latvia (16 patients, 18.6%), Estonia (14 patients, 16.3%), France (3 patients, 3.5%), and the UK (2 patients, 2.3%).

Deltyba was used for treatment of MDR-TB in all 86 patients enrolled in the PASS, 85 (98.8%) patients were diagnosed for the approved indication of pulmonary TB, and 1 patient (1.2%) for extrapulmonary TB. During the SmPC recommended treatment duration of 24 weeks, all patients received the recommended Deltyba dose 100 mg BID. As per physician's decision, treatment with Deltyba continued after the SmPC recommended treatment duration of 24 weeks in 57 (66.3%) patients. During Deltyba treatment extension, 43 patients received the recommended Deltyba 100 mg BID dose, while in 14 patients the treatment dose or dosing frequency was changed by the treating physician as follows: 1 patient received the daily 200 mg in a once-daily (QD) application (Lithuania) and 13 patients, all from the same study site in Germany, received Deltyba 100 mg QD. The mean age of the patients enrolled was 39.8 years (standard deviation =1.7 years), the age ranged from 18 to 72 years. In agreement with the approved SmPC effective during the PASS enrolment period, no children were treated with Deltyba. At Deltyba treatment initiation, 3 patients (3.3%) were ≥ 65 years, 1 (1.2%) patient was recruited in each of the following countries: Estonia, Lithuania, and Latvia.

Concomitant use of drugs that are strong inducers of CYP3A4 and serum albumin < 2.8 g/dL are contraindicated for Deltyba treatment as per SmPC. Seven out of the 66 patients, all in the Non-Germany Enrolled Set, used strong CYP3A4 inducers and 1 patient in the Non-Germany Enrolled Set had a serum albumin value < 2.8 g/dL at baseline.

No violation of Germany specific inclusion and exclusion criteria has been observed.

The patients were diagnosed with pulmonary TB at the time of study entry. At baseline, MTB in sputum was assessed by LJ culture in 64 out of 86 (74.4%) patients. Thereof, 49 out of 64 (76.6%) were MTB positive, and 15 out of 64 (23.4%) were negative. For 22 out of 86 (25.6%) patients, samples were not evaluated. The MGIT was assessed at baseline in 64 out of 86 (74.4%) of the patients, test results were positive in 52 out of 64 (81.3%) patients, and negative in 12 out of 64 patients (18.8%). Sputum smear microscopy was performed at baseline

in 82 out of 86 (95.3%) patients, MTB was detected in 38 out of 82 (46.3%) patients, not detected in 44 out of 82 patients (53.7%), and not evaluated in 4 (4.7%) patients.

The most frequently (in more than 10% of the patients) used anti-TB medication for the composition of patients' MDR-TB regimen in combination with Deltyba were Amikacin (24 patients, 27.9%), Bedaquiline (11 patients, 12.8%), Capreomycin (37 patients, 43.0%), Clofazimine (29 patients, 33.7%), Cycloserine (42 patients, 48.8%), Ethambutol (13 patients, 15.1%), Levofloxacin (37 patients, 43.0%), Linezolid (69 patients, 80.2%), Moxifloxacin (46 patients, 53.5%), PAS (35 patients, 40.7%), Prothionamide (29 patients, 33.7%), Pyrazinamide (30 patients, 34.9%), and Terizidone (33 patients, 38.4%).

11.1.2. Efficacy

Efficacy was assessed according to the WHO criteria for treatment outcome: of the 86 enrolled patients, 49 (57.0%) patients were cured, 17 (19.8%) patients completed treatment, 11 patients (12.8%) were LTFU, 1 patient (1.2%) was a treatment failure, and 3 (3.5%) patients died. In 5 patients (5.8%) treatment outcome was not evaluated. Overall, 66 (76.7%, 95% CI [65.6% - 84.6%]) of the enrolled patients had a positive treatment outcome per WHO definition. The 95% CI for the positive treatment effect of 76.7% calculated for a patient number of 250 patients results in [70.2% - 81.2%] compared to [65.6% - 84.6%] based on 86 patients. Thus, the originally planned higher patient number of 250 would have moderately improved the precision of the estimate for this secondary response variable, but it is questionable whether such improved precision would have outweighed the necessary much longer duration of the PASS study, particularly when also considering the generally lower evidence of results generated by non-interventional treatment registries as compared to double-blind controlled clinical trials data. In the Non-Germany Enrolled Set, 47 (71.2%) patients were cured, 3 (4.5%) completed the treatment, 1 (1.5%) was a treatment failure, 7 (10.6%) were LTFU, 5 (7.6%) were not evaluated, and 3 (4.5%) died. Overall, 50 (75.8%) of the enrolled non-German patients had a positive treatment outcome. In the German sites, 2 (10.0%) patients were cured, 4 (20.0%) LTFU, 14 (70.0%) completed treatment, and no treatment failure was observed. Overall, 16 (80.0%) of the enrolled German patients had a positive treatment outcome.

The reasons for LTFU patients were the long duration of hospitalisation for the Baltic states (up to 6 months) that was not tolerated by several patients and resulted in preliminary study discontinuation. In Germany, patients are hospitalized for approximately 3 months and transferred to an ambulatory care setting thereafter, as there is no network of caregivers in place observing dose administration. The latter may lead to patient non-compliance and impact the treatment outcome. In addition, there is a risk that patients do not return to the ambulance and become LTFU. Furthermore, the social status and alcohol abuse triggered the decision to leave the hospital prior to completion of the treatment regimen. The data cleaning process indicated that 3 patients died during the study, 11 patients were recorded as LTFU, and 5 patients withdrew their consent which did not fulfil the criteria of LTFU. It is noteworthy that most of the patient dropouts occurred after 24 weeks of treatment, and the dropout rate in the follow-up phase shows real-world usage of delamanid for TB treatment. Six patients recorded as LTFU completed the 24 weeks treatment course and were treated with delamanid for a duration of > 24 weeks.

Suboptimal antibiotic dosing with corresponding exposure not reaching the pharmacodynamics targets pose a potential risk for the development of delamanid resistance by MTB. All patients who completed 24 weeks treatment schedule as per SmPC received delamanid 100 mg BID for 6 months in agreement with posology. However, in 13 patients the treating physician extended delamanid treatment up to 24 months with reduced doses of 100 mg delamanid QD following the initial 6-month delamanid 100 mg BID therapy. In all those 13 patients, following 6 months of delamanid 100 mg BID and prior to continuation treatment with 100 mg QD sputum culture were negative for MTB. Eleven out of 13 patients had a negative MGIT, and negative smear result at Month 6 or at Month 3. All 13 patients were treated in the German site [redacted]

There were 2 events of delamanid resistance recorded during the study. These 2 drug resistance cases did not occur with the reduced dose (1 event was present before start of delamanid treatment, whereas 1 other event was reported along with an SAE of treatment failure with extended use of 100 mg BID delamanid).

11.1.3. Safety

11.1.3.1. Adverse Events/Adverse Reactions

Cumulatively during the EU PASS study, 79 patients (91.9%) experienced 391 TEAEs, and 21 patients (24.4%) had at least 1 serious TEAE (33 SAEs). In the Enrolled Set, 33 patients (38.4%) reported at least 1 potentially drug related TEAE.

The most frequently drug related TEAEs was ECG QT prolonged (9 out of 86 patients, 10.5%) followed by nausea (6 out of 86 patients, 7.0%), and vomiting (3 out of 86 patients, 3.5%). Out of 33 SAEs, 6 SAEs in 6 patients (18.2%) were assessed causally related to delamanid (optic neuropathy, hepatic cytolysis, hepatitis acute, blood creatinine increased, and renal failure). As described further in the Germany versus non-Germany data set discussion, medical history, concurrent conditions, and concomitant use anti-TB drugs are considered to be confounding factors.

The percentage of potentially related TEAEs in the Germany Enrolled set (65.0%) is significantly higher compared to the non-Germany Enrolled set (30.3%) as well as the percentage of potentially related SAEs in the Germany Enrolled set (20.0%) versus the Non-Germany Enrolled set (3.0%).

In the Germany Enrolled Set, among the 27 potentially drug-related TEAEs (reported in 13 patients), the most frequently reported were nausea (3 patients, 15.0%) followed by ECG QT prolonged, palpitations, and blood creatinine increased (2 patients, 10.0% each). The related SAEs were optic neuropathy, autonomic nervous system imbalance, renal failure, and blood creatinine increased. The related SAE of optic neuropathy was confounded by the medical history of hypertension and use of ethambutol as well as the concurrent condition of visual impairment, and concomitant administration of linezolid, amikacin, and clofazimine. In the related SAE of psychovegetative exhaustion, social circumstances, the patient's underlying MDR-TB, and concomitant medications were possible confounding factors. The underlying

chronic alcohol abuse, historical and concomitant use of amikacin, clarithromycin, linezolid, and moxifloxacin are contributing factors to the SAE of renal failure. For the SAE of blood creatinine increased the underlying exsiccosis was the main trigger for the SAE and concomitant use of moxifloxacin, linezolid, and metoclopramide are possible contributing factors. The non-serious TEAE of blood creatinine increased was confounded by medical history of treatment with amikacin as well as concomitant administration of moxifloxacin, linezolid, and metoclopramide. All other reported non-serious related TEAEs are in line with the undesirable effects listed EU SmPC.

In the Non-Germany Enrolled Set, among the 31 potentially drug-related TEAEs (reported in 20 patients), the most frequently reported were ECG QT prolonged (7 patients, 10.6%), followed by nausea and vomiting (3 patients, 4.5% each). The related SAEs were acute hepatitis and hepatic cytolysis. For the SAE acute hepatitis, underlying chronic hepatitis C, and use of concomitant anti-TB drugs with hepatotoxic potential are considered confounding factors. For the SAE of hepatic cytolysis co-administration of pyrazinamide, moxifloxacin, and clofazimine is considered a confounding factor.

Overall, 5.8% (5 out of 86) patients experienced TEAEs leading to treatment discontinuation and 3.5% (3 out of 86) patients died. In the Germany Enrolled Set, the percentage of patients with TEAEs leading to treatment discontinuation is higher (2 out of 20 patients, 10.0%) compared to the Non-Germany Enrolled set (3 out of 66 patients, 4.5%). However, this difference is not significant due to a very low number of discontinuations. For 1 of the German patients, delamanid was discontinued due to delamanid resistance present at baseline. The other German patient was discontinued due to TEAE of tinnitus while treated with amikacin. In the non-Germany dataset delamanid was discontinued due to a non-serious TEAE of ECG QT prolonged in one patient, due to 3 non-serious TEAEs of chills, eye pain, and nausea in another patient as well as due to a SAE of hepatic cytolysis in a third patient discussed above.

All events leading to death were reported in the Non-Germany enrolled set and assessed as not related to delamanid (see narratives, Appendix 5).

For 7 patients, there were no AEs reported. Two of these patients withdrew their consent, and 3 were LTFU. Furthermore, 2 patients completed the study without reported TEAEs.

Overall, safety data reported from this EU PASS are in line with the known safety profile of delamanid.

11.1.3.2. Electrocardiograms, Laboratory Evaluations, and Vital Signs

For most patients, ECG parameters (heartbeat and RR interval) were within in the normal range with slight variation for the duration of the study. Reported potentially significant abnormalities were assessed not related to delamanid. The QT interval discussion is provided in Section 11.1.3.3.

The analysis of the laboratory tests (blood chemistry, haematology, and urine) conducted during study revealed that apart from the 2 TEAEs of hypokalaemia, 6 TEAEs of liver disorders (2 SAEs), 2 TEAEs of blood creatinine increased (one of which SAE), and 1 TEAE of leukopenia and neutropenia assessed as causally related to delamanid, only marginal variations

were observed in chemical and haematological laboratory tests and vital signs. For 8 patients, AST and/or ALT values > 3x ULN, and/or total bilirubin > 2x ULN were reported (see below for a detailed discussion of liver disorders). These results are in line with the known safety profile of delamanid.

Vital signs showed no clinically significant variations during the study.

11.1.3.3. Important Identified and Potential Risks

With respect to important identified and potential risks, analysed data support QT interval prolongation as the most prominent risk related to delamanid use.

Out of 10 patients (11.6%) with 10 non-serious TEAEs of ECG QT prolonged reported, 9 were assessed as related to delamanid. There were no TEAEs of 'Torsades de Pointes', ventricular extrasystoles, or sudden cardiac deaths.

All TEAEs were either mild or moderate. There were 3 AEs of QT prolongation above 500ms. All TEAEs occurred during the delamanid treatment phase. The onset latency was between 11 and 315 days after delamanid start. The outcome for 9 events was recovered/resolved (5 without any action taken with delamanid), and for 1 not recovered/not resolved.

Delamanid was withdrawn in 1 patient with a mild QT interval prolongation (QTc < 500ms). The QTc was still elevated 3 months after delamanid was stopped and no action was taken with regards to 3 other concomitant anti-TB drugs with QT prolonging potential. Delamanid was interrupted in 3 patients. In 2 patients, the event recovered/resolved within a couple of days. In the other patient, the AE outcome was 'not recovered/resolved' (QT interval prolongation > 500ms persisted for the next 3 months after delamanid suspension while the patient was continuously treated with clofazimine, and the QT interval remained at the same level after delamanid was restarted). In 6 patients (1 with QTc > 500ms), no action was taken with delamanid of which 5 were reported as recovered or resolved. For 1 of these patients with QTc > 500ms and the history of alcohol abuse, hepatic impairment, and chronic pancreatitis the AE of QTc prolongation was assessed as not related to delamanid. Diarrhoea, due to the chronic pancreatitis, was reported as a possible causal and/or confounding factor for hypokalaemia, which was reported as additional risk factor for QTc prolongation. The patient had a serum albumin value < 3.4 g/dL at the Month 18 visit. The available remaining albumin values from baseline to Month 21 visit were within normal ranges. The AE was reported at the Month 1 visit and was reported as resolved at the month 21 visit with normal QT values. No action was taken with delamanid or any other ACR drugs in response to the AE.

The cases with TEAE of QT interval prolongation were equally distributed between men and women with the age range between 30 and 72 years. Previous medical history included dyspepsia, cardiovascular diseases (hypertension, arrhythmia, coronary artery disease, and angina pectoris), alcohol abuse, drug dependence, and psychiatric disorders (anxiety and depression). For all the patients ECG recording was done before delamanid was initiated and during the treatment, as per SmPC. Baseline serum albumin was reported for all but 1 of the patients, while serum electrolytes were monitored in all of them. All patients were administered

with at least fluoroquinolone concomitantly, while most of them additionally received 1 to 2 other anti-TB drugs with QT prolonging effect (clofazimine, bedaquiline, and/or moxifloxacin).

The data show that QT interval prolongation could be detected with frequent ECG monitoring and managed by electrolyte monitoring and substitution. No TEAEs of 'Torsades de Pointes', ventricular extrasystoles, or sudden cardiac deaths were reported.

In the group of nervous system disorders, 4 patients (4.7%) experienced 4 non-serious TEAEs (2 patients mild hypoaesthesia, and 2 patients moderate paraesthesia) of which 1 AE of paraesthesia, and 1 event of hypoaesthesia were assessed as related to delamanid. Time-to-onset of all TEAEs ranged from 10 to 450 days after delamanid start. For the causally related AE of paraesthesia, delamanid was interrupted and the event was reported as recovered. For all other TEAEs no action was taken with delamanid and apart from 1 event all were reported as recovered/resolved. The ACR of all patients included linezolid.

In the group of psychiatric disorders in 16 patients (18.6%), 18 non-serious, and 1 serious TEAEs were reported of which 17 were assessed as not related to delamanid. The SAE of depression was assessed as not related to delamanid in view of the patient's psychosocial status and the concomitant use of terizidone. The only severe non-serious TEAE of anxiety with reported verbatim worsening of anxiety was assessed as not related considering the patient's underlying anxiety in medical history. Time-to-onset of all TEAEs ranged from 10 to 322 days after delamanid start. No action was taken with delamanid in response to any psychiatric TEAE. The outcome for 17 events was recovered/resolved, for 1 unknown and for 1 not recovered/not resolved. The ACR of the majority of patient included 1 to 2 anti-TB drugs with potential psychiatric effects (cycloserine, terizidone, and/or fluoroquinolones). Furthermore, 1 TEAE of non-serious and moderate hallucination was reported which was assessed as not related to delamanid. No further psychiatric TEAEs were reported for this patient. The patient had a medical history of anxiety and depression and the ACR included terizidone and PAS. The event recovered without any action taken with delamanid.

In the group of gastrointestinal disorders 33 mild or moderate non-serious gastrointestinal TEAEs were reported in 27 patients (31.4%) of which 9 were assessed as related to delamanid. Time-to-onset of all TEAEs ranged from 2 to 329 days after delamanid start. All events were reported as recovered/resolved. Delamanid was withdrawn in 2 and interrupted in 4 patients. The ACR for all patients included more than 1 anti-TB drug with known gastrointestinal side effects, eg, pyrazinamide, clofazamine, linezolid or PAS. Concurrent medical conditions or medical history were alcohol abuse, chronic hepatitis C, diabetes mellitus, and nausea.

Tinnitus was reported in 7 patients (8.1%). All events were non-serious and mild. One TEAE of tinnitus was assessed as related to delamanid which was withdrawn in response to the event. Reportedly, 3 events are not recovered/not resolved, and 4 events were recovered/resolved. The time-to-onset of the AEs ranged from 6 to 201 days after delamanid start. Delamanid dose was not changed in response to any of the TEAEs. The ACR and/or the TB treatment history for all patients included amikacin.

For 1 patient (1.2%) a non-serious and mild TEAE of blurred vision was co-reported with mild and non-serious TEAE of optic neuropathy. The onset latency was 93 days after start of

delamanid. Both events were assessed as not related to delamanid and recovered without any action taken with delamanid. Historic anti-TB drugs included ethambutol, linezolid, and capreomycin; the ACR contained linezolid and clofazimine. The patient had a concurrent condition of hypertension and diabetes mellitus.

For 5 patients (5.8%), 5 non-serious TEAEs (3 mild and 2 moderate) of hypokalemia were reported of which 2 were assessed as related to delamanid. Time-to-onset of all TEAEs ranged from 10 to 161 days after delamanid start. All events were reported as recovered/resolved. Apart from 1 patient where delamanid was interrupted, no action was taken with delamanid. The medical history of patients included hypokalemia, electrolyte disturbances, alcohol abuse, and HIV. All patients were concomitantly treated with at least one anti-TB drug with electrolyte disturbing potential, eg, linezolid, bedaquiline, and/or capreomycin and 1 patient additionally received anti-retroviral drugs.

No TEAE of blood cortisol increased was reported during this study.

Eight patients (9.3%) experienced 9 hepatic TEAEs which all were reported as recovered/resolved. Apart from the 2 SAEs of hepatic cytolysis and acute hepatitis, all events were assessed as not related to delamanid. Time-to-onset of all TEAEs ranged from 12 to 647 days after delamanid start. All patients were treated with at least 1 or more concomitant anti-TB drugs with known hepatotoxic potential. Four patients had a history of hepatic conditions (hepatic impairment, chronic hepatitis C), or alcohol abuse. Delamanid was withdrawn in 1 patient and interrupted in 3 patients. For 4 patients no action was taken with delamanid.

For 8 patients AST and/or ALT values >3x ULN, and/or total bilirubin >2x ULN were reported. Of these, hepatic TEAEs were reported for 5 patients (as further discussed below: SAEs: hepatitis, hepatotoxicity, acute hepatitis, hepatic cytolysis; non-serious TEAE toxic hepatitis). Out of 3 patients with AST or ALT > 3x ULN, or bilirubin > 2x ULN, for whom no hepatic AEs were reported 2 had a medical history explaining elevated transaminases (one with hepatic impairment, one with alcoholism). For the third patient elevated AST > 3x ULN was reported at the month 6 visit. Delamanid was administered during 168 days and AST returned to normal after delamanid treatment completion.

In the Germany Enrolled set, delamanid was interrupted due to a non-serious TEAE of transaminases increased. The event occurred during the extended use of delamanid (100 mg BID) and was assessed as not related to delamanid as the patient had a medical history of intermittent alcohol abuse. In another patient with a medical history of hepatic impairment, 2 TEAEs of severe ALT increased and 1 severe AST increased were reported. The events occurred under ACR treatment approximately 2 months after delamanid treatment was completed.

In the Non-Germany Enrolled set, delamanid was interrupted in the not related SAE of hepatitis. The event resolved after withdrawal of moxifloxacin, terizidone, and delamanid. However, only delamanid was restarted 11 days before the resolution of the event, hence the causality was assessed as not related to delamanid but related to moxifloxacin and terizidone. The not related SAE of hepatotoxicity occurred during extended use of delamanid (100 mg BID). Protionamide

and delamanid were stopped. The re-challenge with delamanid was negative. Liver enzymes remained normal after restarting delamanid. Prothionamide was not restarted and it was reported that the event was related to prothionamide. In the patient with a related SAE of hepatic cytolysis delamanid was withdrawn together with all other ACR drugs. De-challenge was positive not only to delamanid, but to all concomitant ACR drugs. Re-challenge was not applicable as anti-TB drugs have not been resumed. Co-administration of pyrazinamide, moxifloxacin, and clofazimine is considered a confounding factor for this SAE. For 3 hepatic TEAEs no action was taken with delamanid. The related SAE acute hepatitis resolved without any action taken with delamanid or any other concomitant anti-TB drugs. Confounding factors were underlying chronic hepatitis C and use of concomitant anti-TB drugs with hepatotoxic potential. For the TEAE of toxic hepatitis reported as non-serious other anti-TB drugs and alcohol abuse were confounders. The non-serious and not related TEAE of bilirubin increased was reported in a patient on study day 12 and resolved without any action taken with delamanid. The event was co-reported with not related SAE of acute kidney injury which was confounded by concurrent conditions of diabetes mellitus and hypertension as well as historical use of injectable anti-TB drugs.

Drug use during pregnancy was twice reported ('imminent abortion', as well as 'abortion missed') in a [redacted] patient [redacted]. Both events were assessed as serious and not related to delamanid. Medical history included [redacted] children and tobacco use. The first pregnancy was diagnosed [redacted] after treatment with delamanid was completed and was terminated (abrasion performed) due to recurrent bleeding. The second pregnancy was detected at the End of Study Visit, [redacted] after completion of delamanid treatment and ended by elected abortion due to non-developing pregnancy.

There were no reports of a new-born after exposure during pregnancy or exposure via semen.

No drug use in breastfeeding patients was reported.

11.1.3.4. Missing information

As the paediatric extension was approved after the enrolment for PASS study no paediatric patients were included.

Drug use was reported in 3 elderly patients. TEAEs observed in the age group ≥ 65 years were in line with those reported in the age group < 65 years.

Drug use in patients with HIV was reported in 3 patients. For 2 patients, 8 non-serious TEAEs were reported. Apart from the non-serious event of drug resistance against delamanid present at baseline all were assessed as not related to delamanid and no action was taken with delamanid. In response to the event drug resistance, delamanid was stopped as the patient was resistant against delamanid before the start of the study (see narratives, Appendix 5). One patient died due to worsening of MDR-TB, progression of HIV, Pneumocystis jirovecii pneumonia, and cytomegalovirus pneumonia; all assessed as not related to delamanid. The patient did not take [redacted] antiretroviral drugs and was in a severely immunocompromised condition (see narratives, Appendix 5).

No patients with a medical history of severe renal impairment or renal failure were included in the study.

For the single patient with a medical history of severe hepatic impairment, no drug related TEAEs and no SAEs were reported.

No drug-drug interactions were reported.

As per physician's decision, 57 patients (66.3%) were treated with delamanid longer than 24 weeks during this study. During the treatment extension, the majority of patients received 100 mg delamanid BID. In a German site, 13 patients received 100 mg delamanid QD instead of 100 mg BID. The AEs reported for the patients longer than 24 weeks with delamanid are overall consistent with the AEs observed during the first 24 weeks of treatment. Based on the reported TEAEs during this study, there are no safety concerns from the use of delamanid longer than 24 weeks. No safety concern is identified in relation with the property of delamanid and its metabolites to covalently bind to plasma proteins. The dose reduction to 100 mg delamanid QD did not lead to the development of drug resistance. The high number of patients treated with delamanid beyond 24 weeks reflects the need for use of new anti-TB drugs in second-line all oral treatment regimens for the most difficult to treat patients with MDR-TB.

With regards to important identified or important potential risks and missing information no relevant differences were observed between Germany versus the non-Germany dataset.

11.1.3.5. Evaluation of Effectiveness of additional Risk Minimization Measures

Additional risk minimisation measures as per Annex II D of Deltyba Product Information: Conditions or Restrictions about the safe and effective use of the medicinal product and per Deltyba RMP include educational material for healthcare providers and for patients.

Risk management plan defined objectives of educational materials for HCPs (QT interval prolongation, drug resistance, drug use during pregnancy, and breastfeeding) were the following:

To inform the health care professionals about the appropriate usage and to minimize potentially associated risks from use of delamanid and to inform HCPs that delamanid should be used according to WHO/National guidelines for MDR TB management.

The RMP defined objective of educational materials for patients was to reinforce and/or supplement the information on delamanid use during pregnancy and breast feeding provided in the patient information leaflet.

With respect to the implementation of educational materials:

The educational materials for HCPs and Patients and their distribution plan have been agreed with each national Health Authority of the respective EU/EEA member state prior to every launch of delamanid. Educational materials for patients are distributed via the HCPs.

The distribution was not specially described in clinical study protocol and followed the distribution plan agreed with the respective national Health Authority.

In France, there was a Health Authority requirement for a prelaunch shipment of educational materials to treatment sites likely to prescribe delamanid for management of patients with MDR-TB.

After the launch in all countries educational materials were shipped with each product supply. At the end of 2018 and in 2019, educational material handling for orders from France, Germany, and the UK were amended with the possibility to select whether educational materials were already received by the treating physician as well as the patient. Subsequently, educational materials were only included into the shipment when the treating physician and/or patient had not received the respective materials.

The educational materials were delivered to HCPs via email or the treatment site pharmacy with the exception of the Baltic countries which have a centralised procurement system where product and the educational materials are distributed to treatment sites via the local wholesaler.

In general, confirmation of receipt was received by many of the treating physicians if the educational materials were sent via email to them.

As it cannot be tracked whether the order for delamanid by a study site was for a study patient or another patient not enrolled in the PASS, no numbers will be presented in this report.

The educational material for patients explains the important potential risks of Drug Use during Pregnancy and Drug Use during Breastfeeding in lay language and was provided as a source of counselling in addition to the ICF signed before the study participation.

With respect to safety outcomes for the risks presented in the educational materials, QT prolongation, drug use in pregnancy and breastfeeding are presented and discussed in Sections 10.6.7 and 11.1.3.3.

The assessment of AEs pertinent to the SMQ “Torsade de pointes/QT prolongation” indicates that the EU PASS physicians were aware of the risk of QT interval prolongation and implemented ECG and electrolyte monitoring, in particular when delamanid was given with other medications with QTc prolonging effect, including CYP3A4 inhibitors. The frequency, nature, and the outcomes of the reported AEs of QT prolongation indicate that the risk was successfully managed.

Two pregnancies in a single patient were reported from this PASS. Both pregnancies occurred after the end of delamanid treatment. One pregnancy was terminated by abrasion due to recurrent bleeding. The second pregnancy ended by elected abortion due to non-developing pregnancy.

No events of delamanid exposure via semen, in a new-born exposed to delamanid during pregnancy or during breastfeeding have been reported.

Drug resistance against delamanid has been removed as the important identified risk from the list of safety concerns in the EU RMP v.3.5, as per Health Authority request.

With respect to prevention of drug resistance, DST was performed for all PASS patients for the purpose of the ACR selection at the baseline visit and during the treatment to monitor treatment effectiveness. Drug susceptibility testing to delamanid was usually not a part of the baseline testing, however, most sites performed it for the treatment monitoring purposes. All PASS patients were hospitalised for the initial phase of the treatment and their anti-TB medications were administered as DOT. In the continuation phase, most of the sites were able to implement DOT, however, no delamanid resistance occurred also in patients who practiced delamanid self-administration. Only 1 case of treatment-emergent resistance to delamanid was reported, which was not related to extended use. The reported low incidence is in line with the results from the controlled clinical trials with delamanid and suggests well managed efficacy risk.

Overall assessment of the risks covered by the educational materials for HCPs and patients reveals that the PASS patients were treated by health professionals well trained for drug-resistant TB management. The implemented practices were certainly mostly driven by the WHO guidelines for the management of drug-resistant TB, which provide detailed guidance on prevention of new drug-resistance, appropriate selection of the treatment regimens, implementation of DOT and management of side effects and risks related to administration of individual medications, including delamanid. PASS HCPs demonstrated that they were well aware of the information provided in Deltyba label which describes QT prolongation as the most prominent safety risk, drug resistance as the main efficacy risk, while drug use is not recommended during pregnancy and breastfeeding.
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11.2. Limitations

Observational studies play an increasing important role in the evaluation of risks and benefits of medicinal products. The main focus of this observational study was on collecting information on how Deltyba is used in real-life setting as well as collecting safety data.

This observational study was not defining strict inclusion or exclusion criteria, nor were strict requirement for treatment posology, visits or investigation schedule required, rather than documentation of the day-to-day practice in a mixed hospital, and out-patient setting and data documented might be not have been that accurate as in controlled randomized clinical trials.

Data collection and assessments in this non-interventional study were different from a clinical trial. No fixed visits were scheduled but visits could be done in a time frame of several weeks as per decision of the treating physician. Not all examinations were mandatory to be done for each patient during each study visit. Follow-up investigations after an AE was reported were not always done, eg, ECG or laboratory investigations. For patients who were LTFU or withdrew consent no follow up on AEs was possible. Hence, the data set is less complete compared to a clinical trial. For several investigations different methods and ranges were used, eg, ranges for laboratory values or no standardized urine test.

The population included into the study was limited to the approved label at the time of the start of the study. No paediatric patients were included, and pregnant or breastfeeding patients were not allowed to be included. Due to the low number of patients enrolled information regarding

missing information, eg, elderly patients, patients with HIV, or hepatic/renal impairment is limited.

Study limitations were the overall lower than estimated patient number, the lower than expected overall number of EU countries participating in the PASS, the rather low total number of patients recruited in several countries participating in the PASS, different structure of health care systems and maximum of length of stay of the flat rate defined for hospitalisation of MDR-TB patients at least in Germany and the availability of an outpatient care service facility network system in some countries to ensure patients were compliant after discharge from hospital. Further study limitations were the very low number of patients for several subpopulations, like elderly or HIV positive patients.

11.2.1. Lower than Estimated Overall Patient Number

The number of patients enrolled (n=86) during the 4-year enrolment period was considerably lower than the originally targeted number (n=250). Although the originally planned patient number was only an estimation of patients treated with Deltyba in the EU countries after launch, and this observational study did not intent statistical testing but rather present the data descriptively, higher patient numbers might have delivered more meaningful results.

Baltic countries within Europe with the highest MDR-TB rates experienced declining TB and MDR-TB rates for the last 10 years, having an impact of considerably lowering enrolment into this study. Furthermore, Deltyba's re-grouping to Group C in the 2019 WHO Guidelines recommending its use only in instances when a regimen cannot be composed with Groups A and B agents, required a specific justification for the use of Deltyba in the MDR-TB regimen in some of the EU countries, and the approval was frequently rejected by the hospital board (in the UK] and Estonia). In addition, the COVID-19 pandemic and associated healthcare crisis affected all participating countries within Europe, where TB patients were reportedly finding it extremely challenging to visit healthcare sites that were specialised to treat infectious diseases or other respiratory diseases. Since both TB and SARS-CoV-2 infections primarily affect the lungs and respiratory system, the specialised sites were occupied to manage COVID-19 patients due to the extremely high rate of transmission and lack of standard of care, which made recruitment of TB patients very challenging.

11.2.2. Overall Low Number of EU Countries Enrolled in Deltyba PASS

Decisions for including European countries in PASS were dependent from the timepoints for reimbursement and launch, from countries' estimated absolute number of MDR-TB patients and incidences, regulatory feasibility, and the possibility of data exchange between primary treatment centre (hospital) and healthcare professional that followed patients after discharge.

Applying these criteria for country selection, the number of countries qualifying for participating in the Deltyba PASS was lower than anticipated. The vast majority (94.2%) of patients had been recruited in the Baltic states ([total 70.9%]; Lithuania 36%, Latvia 18.6%, and Estonia 16.3%) and Germany (23.3%). The only 2 other countries with centres including MDR-TB patients in the PASS were France (3 patients, 3.5%) and the UK (2 patients, 2.3%). Country specific reasons

for low recruitment or for not participating were as follows: In France all MDR-TB patients are initially assessed and their treatment regimen is decided by 2 main healthcare centres in Paris and thereafter patients are transferred to secondary centres. Following the MAH's evaluation process, it was very challenging to ensure individual patients' data transfer between main healthcare centre and secosndary sites involving labour intensive administrative procedures that were not appreciated by these secondary centres due to already existing heavy workload.

After reimbursement approval and launch in Italy (Q2 2017) and Spain (Q2 2018), the number of patients prescribed Deltyba was overall small and furthermore distributed to several centres, suggesting very poor contribution of patient numbers per centre or meaningful information on real-world use of Deltyba in these countries. In Italy, additional regulatory impracticability caused difficulties to recruit centres for the PASS, including the complexity of the submission process to the Health Authority and Ethics Committees.

Low absolute patient number causing similar restricted country specific information or not contributing meaningfully to the overall PASS patient number were expected for the Nordic countries.

Although Deltyba's launch in Romania (Q1 2019) was rather late, the MAH put much effort in including Romania in the PASS, specifically for increasing the PASS patient number reasonably when considering Romania's high MDR-TB incidence and absolute patient numbers. Following launch of Deltyba, all necessary arrangements for the participation of the only centre qualified for treatment of MDR-TB, patients in Romania had progressed to almost final when due to upcoming COVID crises the centre had been requested by the government to concentrate exclusively on the COVID pandemic.

With respect to the primary objective of the study aiming to monitor and document the real-life usage of Deltyba in medical practice in Europe, outcomes of the PASS may therefore have to be restricted to Baltic states and Germany as a consequence of the limited European country participation.

11.2.3. Different Structure of Health Care Systems and Maximum of Length of Stay of the Flat Rate Defined for Hospitalisation of MDR-TB Patients at least in Germany

As the vast majority of patients have been recruited in the Baltic states and Germany (94.2%), the following comparisons may have to be restricted to these countries.

In Baltic states individual patients' resistance status is reviewed and composition of patients' MDR-TB regimen is decided by a central board (Concilium) in Latvia and Estonia, or 3 such boards in Lithuania. The duration of hospitalisation is generally up to 6 months; following discharge from hospital and directly observed therapy is usually ensured by a network of caregivers until the end of the patients' MDR-TB therapy. This network includes regular exchange between ambulatory care and the Concilium until the end of patients' MDR-TB treatment. Results for DST during treatment and assessment of final treatment outcome therefore are known by the Concilium representing the study investigator for the PASS, and from there data could be provided for the Deltyba PASS. A 6-month hospital stay has, however, not always

been tolerated by patients and resulted in preliminary study interruption (next to social status and alcohol abuse, also triggering the decision to leave the hospital) by several patients.

In Germany, patients are hospitalised for approximately 3 months and thereafter transferred to an ambulatory care setting, provided their sputum assessment is negative for mycobacterium tuberculosis at that timepoint. In Germany, a network of ambulatory caregivers, resident doctors, and the original treatment initiating hospital is not in place. Instead, patients' follow-up is monitored by regional/local Health Authority. As a consequence, patients' compliance to treatment throughout the MDR-TB treatment duration and final treatment outcome is routinely not known by the initial treatment centre, representing the study site for PASS. The MAH therefore invited the initial centre participating in PASS to contact resident doctors (if known) in order to receive patients' final treatment outcome for PASS documentation. This approach was successful for most of the patients.

The impact of the different structure of health care systems described above seems of minor influence on Deltyba's appropriate use for the approved indication of pulmonary MDR-TB, but rather for the follow-up of patients after release from hospital. This becomes apparent when comparing the rates for 'LTFU', 'cure', and 'treatment completed' between the German and non-German centres. Higher LTFU rates (20.0%) have been observed in the Germany subset as compared to the non-Germany centres (10.6%). Treatment outcome 'cure' requires measurements of > 3 negative sputa at the end of MDR-TB treatment and was reported in 71.2% of the patients in non-Germany centres by the sites of central boards. In German centres, cure has been reported for only 10% of the patients while treatment completion by 70% of patients. Presumably, this is because the data exchange between the primary outpatient unit (where the patients were treated in the continuation phase of the MDR-TB treatment) and the secondary level treatment centre (where they were treated in the initial phase) was focused on obtaining the information on treatment completion rather than on collecting the necessary sputum culture results to confirm the outcome 'cured'.

Comparable results for successful treatment outcome (sum of cure + treatment completed, 80% [95% CI (62.5% - 97.5%)] for German and 75.8% [95% CI (65.4% - 86.1%)] for non-German centres) between both follow-up scenarios agree with such an assumption (Table ADHOC 3 1, Table ADHOC 3-2, and Table ADHOC 3-3).

11.2.4. Limited Generalizability of Results

For estimation of the treatment efficacy the overall patient number n = 86 in the Deltyba PASS was considerably lower than the anticipated number of n = 250 patients, and therefore this study result is of limited overall significance. Furthermore, data were collected primarily only from centres of the Baltic states and Germany and this circumstance clearly limits the generalization of results. However, treatment success rate of the PASS study (76.7%, 95% CI [67.8% - 85.7%]) falls well within the range of that reported in meta-analysis[11] across 6 studies conducted in Europe (82% [95% CI: 76% – 89%]), where Deltyba has been used for the treatment of MDR-TB. When compared to overall treatment success rate (52.4%) for Rifampicin resistant/MDR-TB patients starting treatment in 2018 in EU/European Economic Area as presented by the WHO European Centre for Disease Prevention and Control (ECDC) in *Tuberculosis surveillance and monitoring in Europe 2022,*[12] results reported in PASS show a higher efficacy rate. When broken

down to countries largely contributing to PASS, treatment success rate for PASS (76.7%) is very similar to that for Estonia (74.2%), and higher than that for Germany (63.4%) or Lithuania (54.5%). Data for Latvia were not presented in the ECDC report. Nevertheless, these findings are not qualified to gain any evidence for concluding the contribution of Deltyba to efficacy in MDR-TB regimens.

Only very limited results became available for subpopulations like elderly or HIV positive patients with MDR-TB. Three (3.5%) patients were of age > 65 years and also only 3 (3.5%) patients were HIV positive. The low absolute numbers of these subpopulations presumably are primarily a consequence of the low total number of patients recruited in the PASS study. As neither the prevalence for patients co-infected with MDR-TB and HIV nor for MDR-TB patients > 65 years of age is available allowing for a comparison with corresponding rates in PASS, it cannot be decided whether these subpopulations were underrepresented in PASS. In any case, the low number of patients recruited in the PASS does not provide meaningful information on Deltyba's efficacy or safety for these subpopulations of interest.

11.3. Interpretation

The current SmPC for Deltyba defines the following therapeutic indication: "Deltyba is indicated for use as part of an ACR for pulmonary MDR-TB in adult patients, when an effective treatment regimen cannot otherwise be composed for reasons of resistance or tolerability treatment". The recommended dose and duration that delamanid is administered is 100 mg twice daily for 24 weeks. The observational study reveals that Deltyba was used in this approved indication in 85 (98.8%) patients and therefore all but one (1.2%) patient (diagnosed as extrapulmonary TB) has been treated in agreement with the labelled indication. During the recommended Deltyba treatment duration of 24 weeks, all patients received the approved dose of 100 mg BID. In 66.3% of the patients, treatment with Deltyba was extended up to > 30 weeks.

The data collected from EU PASS are supported by 2 recent publications regarding the endTB study. During 2015 to 2019, the endTB (Expand New Drug markets for Tuberculosis)[13] Consortium supported National Tuberculosis (TB) programs to introduce new and repurposed TB drugs in regimens to treat MDR and XDR TB at sites in 17 countries. As part of the endTB project and observational study (2015 to 2019), rigorous post-marketing safety surveillance for all patients (referred to as "endTB patients") who began MDR/rifampicin resistant-TB (RR-TB) regimens containing bedaquiline or delamanid was performed. In total 2,906 patients were exposed to delamanid (760 patients, 26%) or combination/sequential use of bedaquiline and delamanid (460 patients, 16%). A total of 967 SAEs were reported in 621 patients (21%). Many patients who experienced fatal or life-threatening SAEs had important co-morbidities such as diabetes, HIV, and hepatitis C. The authors discuss that polypharmacy is common in the treatment of MDR- and XDR-TB patients and that QT prolongation can be caused by other TB drugs, such as clofazimine or moxifloxacin, as well as many non-TB drugs.

The UNITAID funded endTB project, comprising an observational study and 2 randomized controlled clinical trials, included consecutively all patients who started a bedaquiline- or delamanid-containing MDR/RR-TB regimen between 2015 and 2018 in 16 countries and evaluated the safety of longer MDR/RR-TB regimens containing bedaquiline and/or delamanid.[14] Out of 2296 patients, 904 patients (39.4%) received delamanid and 238 (10.4%)

patients received both, delamanid and bedaquiline. Clinically relevant QT interval prolongation was detected in a low proportion of patients (3%), occurring only 2.6 times per 1000 patient-months of exposure to bedaquiline or delamanid. This low event rate is especially noteworthy since 96% of patients received at least one other QT-prolonging anti-TB drug. Despite the fact that electrolyte depletion (hypokalaemia or hypomagnesemia) was experienced by over a quarter of patients the results show QT interval prolongation is one of the least frequently reported clinically relevant AEs.

Based on the data collected in these larger study cohorts, delamanid presented a safety profile similar or even more favourable compared to many other TB drugs. The main conclusions of endTB project are in line with the conclusions of this report.

11.4. Generalisability

This study reported data from 86 patients in the Deltyba PASS. Patients were recruited at 11 TB specialised study sites across 6 European countries; data collection began in August 2016 and ended at the last patient last visit on 30 September 2021. There were no inclusion or exclusion criteria imposed in the PASS that would have affected the approved labelling or have impacted the generalisability of the study results; hence the population of patients in the study was representative of a real-life setting. However, it is possible that a selection bias occurred due to individual physician decisions at some or all sites. There are differences in real-life clinical practice of medical care for patients with TB in different European countries or clinical sites mainly with respect to duration of hospitalisation stay versus transfer of medical care from in-hospital stay to ambulatory care setting, to other clinics or general practitioners which might have resulted in higher LTFU and consequently lower treatment success rates compared to clinical trials. The cure rate in the non-Germany patients (71.2%) was markedly higher compared to that of the German patients (10%), however, the study completion rates showed reversed rates (4.5% for non-German versus 70% for German patients). Hence, the overall rates for successful treatment outcome according to WHO is comparable between non-German and German patients. The most probable explanation for these findings might be the differences in patients care with respect to duration of hospitalisation and follow-up of patients after discharge from hospital. In general, in non-German sites, patients stay longer in hospital and are closely monitored during continued ambulatory MDR-TB therapy, MTB measurement for assessing sustained sputum negativity and enabling the diagnosis for cure are performed regularly, in particular in the Baltic sites. The patients in Germany leave hospital earlier and are looked after by hospital ambulatory and/or external pulmonologists during treatment completion whereby the necessary MTB assessments for defining cure were often not transmitted to the primary hospital and therefore only treatment completion could be confirmed and not the diagnosis of cure. Higher LTFU rates for German patients compared to non-German patients (20% versus 10.8%) are in support of these differences in follow-up. With regards to safety, no differences were observed between the Germany versus the Non-Germany data set. The established favourable safety profile for delamanid as described in the SmPC has been confirmed in this study.

12. OTHER INFORMATION

None.

13. CONCLUSION

The objectives of this study were met as the aim of the study was to monitor and document the real-life usage of Deltyba in medical practice and to collect safety data.

Deltyba was used as per the labelled indication. Dosing was in agreement with the SmPC posology during the recommended Deltyba treatment of 24 weeks' duration. In the majority of patients, treatment with Deltyba was extended until completion of patients' MDR-TB treatment. During the Deltyba treatment extension, delamanid dose was reduced in 65% of patients at one German site from 100 mg BID to 100 mg QD. These appear as the major differences for real-life use of Deltyba between the German and non-German sites.

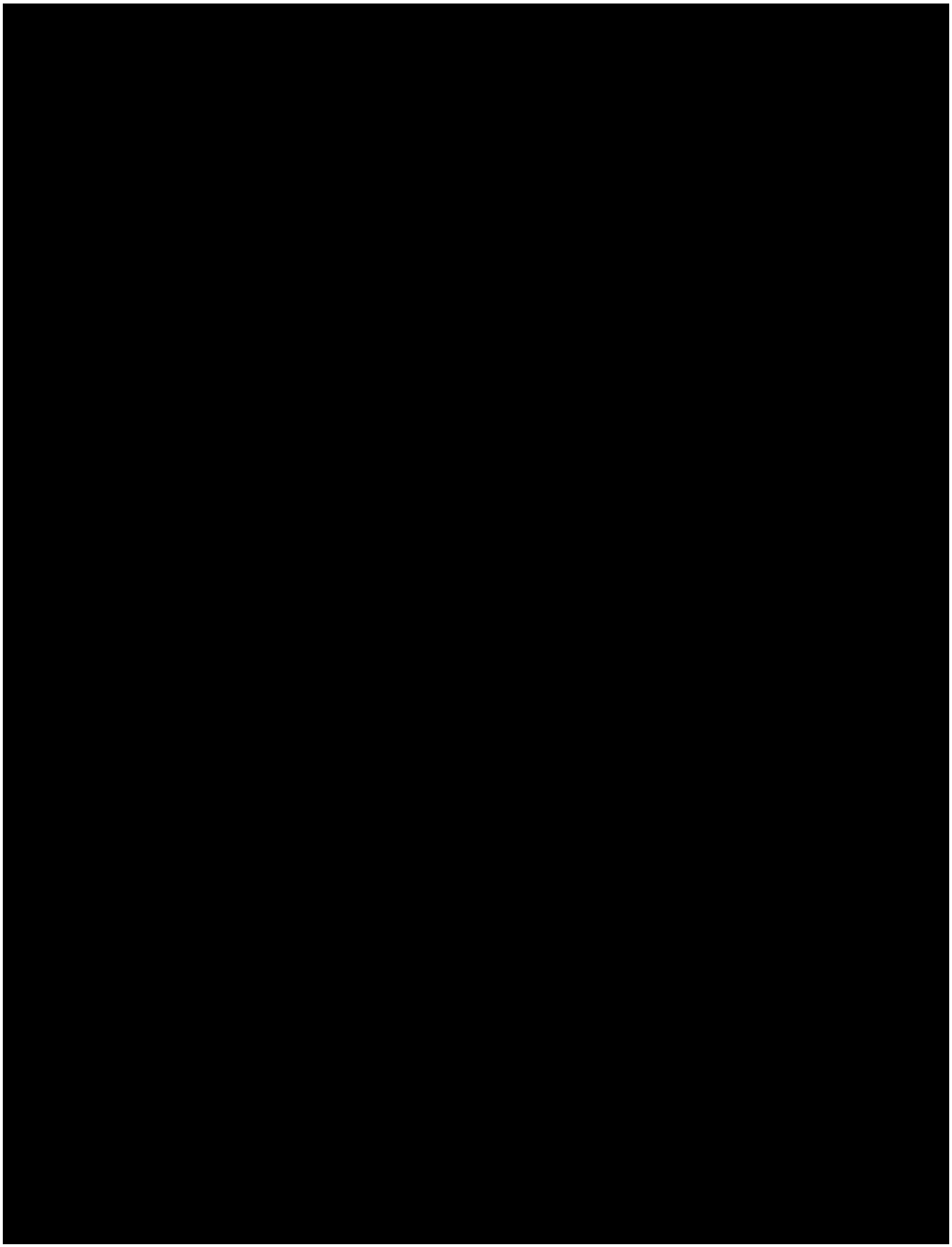
Treatment success has been reported for 76.7% of the patients and efficacy results are comparable with results from published studies with Deltyba usage.

Deltyba was well tolerated.

The reported TEAEs observed in this study are in line with the established safety profile of delamanid. No new ADRs or new safety concerns were detected. QT interval prolongation remains the most frequently reported AE related to delamanid use. The risk was successfully managed with the implementation of ECG monitoring and the correction of electrolyte abnormalities. The AEs reported for delamanid use beyond 24 weeks demonstrated not to be a safety concern.

Overall, available data for the Deltyba PASS suggests that the PASS patients were treated in TB/MDR-TB specialised sites by health care professionals well trained for drug-resistant TB management and well informed about the delamanid label. Composition of patients' MDR-TB regimen was based on DST and treatment was largely applied under DOT conditions. Accordingly, treatment was successful in almost all patients that could be followed up until their end of MDR-TB treatment. Primary reason for non-successful treatment outcome was due to patients lost-to-follow up after intended or unintended discharge from hospital.

The previously established favourable benefit-risk profile for delamanid has been reconfirmed by the efficacy and safety data that have become available during this non-interventional study.



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Appendix 3 Tables

Appendix 4 Data Listings

Appendix 5 Narratives