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
Protocol version identifier	Protocol No. 242-12-402, version 3.0 FINAL
Date of last version of protocol	30 October 2015
EU PAS register number	ENCEPP/SDPP/10618
Active substance	ATC code J04AK06 delamanid (J04AK Other drugs for treatment of tuberculosis) Delamanid, a nitro-dihydroimidazo-oxazole derivative
Medicinal product	Deltyba
Product reference	EU/1/13/875/001, EU/1/13/875/002, EU/1/13/875/003, EU/1/13/875/004
Procedure number	EMEA/H/C/2552
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 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 is being tested in this study. Treatment, all assessments and patient monitoring will be performed according to the existing practices and / or treatment centre's local / national tuberculosis programme (NTP). Primary objective: • To monitor the usage of Deltyba in a real-life setting when prescribed as part of an ACR designed by the treating physician. Secondary objective: • 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 are 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	Deltyba was launched in Germany and the UK in May / June 2014. It is anticipated that the following countries will participate in the PASS: Austria, Bulgaria, Estonia, France, Germany, Italy, Latvia, Lithuania, Norway, Poland, Portugal, Romania, Spain, Sweden and the UK. This protocol version (final version 3.0) is not applicable for Germany.

Author	Barbara Eschenbach
	Otsuka Novel Products GmbH
	Erika-Mann-Str. 21
	80636 Munich, Germany
	Phone: + 49 89 2060 205 81
	Fax: + 49 89 2060 205 15
	E-mail: beschenbach@otsuka-onpg.com

Marketing authorisation holder

Marketing authorisation holder (MAH)	Otsuka Novel Products GmbH Erika-Mann-Str. 21 80636 Munich, Germany
MAH contact person	Dr. Petra Brunner Senior Manager, Deputy Head Regulatory Affairs Europe Otsuka Europe Development & Commercialisation Europa-Allee 52 60327 Frankfurt am Main Tel: +49 69 955044-374 Fax: +49 69 955044-50 E-mail: PBrunner@otsuka-europe.com

1 Table of Contents

List of In-text Tables

2 List of Abbreviations

Abbreviation	Definition
ACR	Appropriate combination regimen
ACTH	Adrenocorticotropic hormone
ADR	Adverse drug reaction
AE	Adverse event
AFB	Acid-fast bacilli
ATC	Anatomical Therapeutic Chemical classification system
BMI	Body mass index
CD4	Cluster of differentiation 4
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
C_{max}	Maximum concentration
CRO	Contract research organisation
DOT	Directly observed therapy
DST	Drug susceptibility testing
EBA	Early bactericidal activity
EC	Ethics Committee
ECG	Electrocardiogram
ECDC	European Centre for Disease Prevention and Control
eCRF	Electronic case report form
EU	European Union
EMA	European Medicines Agency
GVP	Good Pharmacovigilance Practice
HCP	Healthcare professional
HEENT	Head, eyes, ears, nose and throat examination
HIV	Human immunodeficiency virus
ICF	Informed consent form
MAH	Marketing Authorisation Holder
MDR-TB	Multidrug-resistant tuberculosis
MTB	Mycobacterium tuberculosis
MedDRA	Medical Dictionary for Regulatory Activities
NTP	National tuberculosis programme
OBR	Optimised background regimen
PASS	Post-authorisation safety study
PT	Preferred term
PVRE	Pharmacovigilance Region Europe
QTc	Q wave - T wave interval corrected for heart rate
RAP	Responsible access programme
RMP	Risk management plan
SAE	Serious adverse event
SAT	Self-administered therapy
SCC	Sputum culture conversion
SD	Standard deviation

SR	Safety report
SmPC	Summary of product characteristics
SOC	System Organ Class
TEAE	Treatment-emergent adverse event
TB	Tuberculosis
WHO	World Health Organization

3 Responsible parties

Marketing authorisation holder (MAH): Otsuka Novel Products GmbH, Erika-Mann-Str. 21, 80636 Munich, Germany

Contract research organisation (CRO): Covance Clinical and Periapproval Services Limited, Osprey House Maidenhead Business Park, Westacott Way, Maidenhead SL6 3QH, United Kingdom

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

4 Abstract

Title

Protocol No. 242-12-402, Final Version 3.0, 30 October 2015: 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

Author

Barbara Eschenbach Otsuka Novel Products GmbH

Rationale and background

Delamanid is a newly synthesised 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. Mycobacteria-specific antibacterial activity in vitro and potent anti-TB activity in vivo by oral administration have been confirmed. Delamanid shows potent activity in vitro against pansensitive, drug-resistant and multi-drug-resistant strains of Mycobacterium tuberculosis (MTB). It also has potent in vitro activity against intracellular mycobacteria and both growing and hypoxia-induced dormant strains. Delamanid has no in vitro activity against bacterial species other than mycobacteria[2 3]. Clinical studies in drug-sensitive TB patients demonstrated robust early bactericidal activity (EBA) of delamanid during the first two weeks of treatment. When co-administered with an optimised background regimen (OBR) for the treatment of multi-drug resistant tuberculosis (MDR-TB) patients receiving delamanid-containing regimens experienced an approximately 50% increase in sputum culture conversion (SCC) from growth of MTB to no growth over the first 2

months of treatment compared to those receiving OBR plus placebo[4]. To date delamanid has not shown cross-resistance with any of the currently used anti-TB drugs.

Deltyba received a conditional marketing authorisation within the European Union (EU) as of 28 April 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 a Responsible Access Programme (RAP) as part of the pharmacovigilance activities included in the Risk Management Plan (RMP). The RAP for Deltyba consists of the following elements: 1. a central order and distribution process, 2. educational materials for health care professionals and patients, 3. this EU-wide Post-Authorisation Safety Study (PASS) to monitor usage of the product and to obtain further information on treatment outcomes and safety.

This PASS is a non-interventional treatment registry for Deltyba in routine medical practice and aims

- 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

PASS is a key element to generate data on usage of Deltyba in patients with MDR-TB treated in routine medical practice in order to add to the product safety profile. Furthermore, the safety of Deltyba will be monitored and treatment outcomes (clinical effectiveness) will be assessed as per WHO revised definitions[1] and / or national guidelines.

The primary objective of the study is:

- To monitor 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 objective of the study is:

- 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 are cured.
- To monitor the safety of Deltyba in a real-life setting when prescribed as part of an appropriate combination regimen (ACR) designed by the treating physician.

Study design

This is an EU-wide, multicentre, non-interventional study of MDR-TB patients prescribed Deltyba. The total duration of the study per patient is up to 30 months after receiving first dose of Deltyba or until completion of MDR-TB treatment. The total duration of the Deltyba PASS is planned to be 6.5 years (4 years enrolment). The ACR will be 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.

Treatment, all assessments and patient monitoring will be performed according to the existing practices and / or treatment centre's local / national tuberculosis programme (NTP).

This protocol version (final version 3.0) is not applicable for Germany.

Population

It is planned that 250 patients with MDR-TB, prescribed Deltyba and treated at specialised centres in the EU will be included in the Deltyba PASS.

Variables

Data on the use of Deltyba in a real world setting will be collected in the eCRF of the PASS. These data include, but are 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.

Data sources

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

Study size

It is planned to include 250 MDR-TB patients in the Deltyba PASS. An important consideration taken into account for calculation of the sample size is 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 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) has also been taken into consideration in the sample size calculation. In addition, the dates of anticipated launch have been taken into account (launched in Germany and UK, to be followed by other EU countries at a later stage).

Data analysis

No formal hypotheses are to be tested in this study.

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

Milestones

- Registration in the EU PAS register: Q3 - 2015, prior to start of data collection.
- Start of data collection: Q4 - 2015
- End of data collection: Q2 - 2022
- Final report of study results: Q4 - 2022

5 Amendments and updates

None

6 Milestones

Milestone	Planned date

Registration in the EU PAS register	Q3 2015
Start of data collection	Q4 2015
End of data collection	Q2 2022
Annual study progress report*	Q2 2017 and yearly afterwards (Q2 2018, Q4 2019, Q4 2020, Q4 2021)
Final report of study results	Q4 2022

*Annual study progress report until final report will include updated information that study plans to collect and data cut-off will be 3 months prior to annual submission.

7 Rationale and background

Delamanid is a newly synthesised nitrodihydroimidazo-oxazole derivative developed by the Otsuka Pharmaceutical Company[2]. It acts to inhibit the biosynthesis of mycolic acid, a critical component of the TB bacterium cell wall. Mycobacteria-specific antibacterial activity in vitro and potent anti-TB activity in vivo by oral administration have been confirmed. Delamanid shows potent activity in vitro against pansensitive, drug-resistant and multi-drug-resistant strains of MTB. It also has potent in vitro activity against intracellular mycobacteria and both growing and hypoxia-induced dormant strains. Delamanid has no in vitro activity against bacterial species other than mycobacteria[2 3].

Bioavailability of delamanid is 2-fold higher when taken with a standard meal compared to ingestion under fasting conditions. Delamanid extensively binds to plasma proteins and has a large volume of distribution. Metabolism of delamanid primarily takes place in plasma by albumin and to a less extent by 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 EBA of delamanid during the first two weeks of treatment. When co-administered with an OBR for the treatment of MDR-TB patients receiving delamanid-containing regimens experienced an approximately 50% increase in SCC from growth of MTB to no growth over the first 2 months of treatment compared to those receiving OBR plus placebo[4]. To date delamanid has not shown cross-resistance with any of the currently used anti-TB drugs.

Non-clinical safety profile and relevance to human usage

Non-clinical data reveal 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 Q wave – T wave interval corrected for heart rate (QTc) interval prolongation has been identified as the most prominent safety concern, see clinical safety profile below.

In the dog, foamy macrophages were observed in lymphoid tissue of various organs during repeat-dose toxicity studies. The finding was shown to be partially reversible; the clinical relevance of this finding is unknown.

Repeat-dose toxicity studies in rabbits revealed an inhibitory effect of delamanid and/or its metabolites on vitamin K-dependent blood clotting. To date the clinical relevance of this finding is unknown.

In rabbits reproductive studies, embryo-foetal toxicity was observed at maternally toxic dosages. Clinical data is currently not available. Therefore 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 /metabolites into breast milk. In lactating rats, the the maximum concentration (C_{max}) for delamanid in breast milk was 4-fold higher than that of the blood. Clinical data is currently not available. 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.

Clinical safety profile

The safety profile of delamanid is currently derived from the frequency of the adverse drug reactions from one double blind controlled clinical trial involving 481 patients with MDR-TB, in which 321 patients received delamanid in combination with an OBR. 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). Other important adverse drug reactions are anxiety, paraesthesia, and tremor.

The most frequently observed adverse drug reactions in patients treated with delamanid (i.e. incidence > 10%) are nausea (38.3%), vomiting (33%), and dizziness (30.2%).

Deltyba received a conditional marketing authorisation within the EU as of 28 April 2014 based on a favourable benefit-risk ratio assessment derived from Phase II 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 a RAP as part of the pharmacovigilance activities included in the RMP. The RAP for Deltyba includes

- central order and distribution process to ensure that Deltyba is used only by centres and treating physicians with experience in MDR-TB management according to 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 PASS to monitor usage of the product, to assess treatment outcomes and to obtain further information on safety.

Consequently this PASS is a non-interventional treatment registry for Deltyba in routine medical practice and aims

- 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 WHO definition[1] and / or national guidelines.

Intended as a non-interventional study the PASS protocol does not define a therapeutic strategy and the decision to administer commercially available product falls under the responsibility of the treating physician according to the product's SmPC and his/her medical judgement. The physician's decision to treat a patient with Deltyba is independent of the decision to enrol the patient into the PASS. The study does not require any additional diagnostic, therapeutic or monitoring procedures outside routine medical practice.

8 Research questions and objectives

Given the conditional approval granted within the EU, the safety profile of Deltyba was assessed as manageable and several measures were introduced to minimise the risks, including the RAP (as outlined in section 7). Thereof the PASS is a key element to generate data on usage of Deltyba in patients with MDR-TB treated in routine medical practice in order to add to the product safety profile.

Furthermore, the safety of Deltyba will be monitored and treatment outcomes (clinical effectiveness) will be assessed as per WHO revised definitions[1] and / or national guidelines.

Study Objectives

The primary objective of the study is:

- 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 objective of the study is:

- 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 are 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 (serious and non-serious) will be entered into the eCRF during the study. At every regular visits of their patient, physicians will enter into the eCRF any new information on adverse events. The following are monitored as signs and symptoms of special interest, and will also be assessed with regard to AE and laboratory data:

- Cardiac disorders (including QT prolongation)
- Suspected delamanid resistance (including lack of delamanid effect)

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

For drug resistance surveillance purposes, the physicians are asked to evaluate any signs of suspected delamanid resistance (including lack of drug effect). Delamanid 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 will enable the collection of data on the development of resistance to delamanid. The risk of drug resistance development is aimed to be minimised by raising awareness of the risk and appropriate minimization measures through educational material for health care professionals.

According to the SmPC Deltyba shall be only administered with an ACR and 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 will be regularly evaluated in order to add to the products cumulative safety and usage profile.

9 Research methods

9.1 Study design

This is an EU-wide, multicentre, non-interventional study of MDR-TB patients prescribed Deltyba. The duration of the study per patient is up to 30 months after receiving first dose of Deltyba or until completion of MDR-TB treatment.

The total duration of the Deltyba PASS is planned to be 6.5 years (4 years enrolment). The ACR will be 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. Treatment, all assessments and patient monitoring will be performed according to the existing practices and / or treatment centre's local / national programme.

The PASS will collect information routinely documented in patient medical records or in NTPs.

The RAP involves a central order process; thus the MAH is aware when Deltyba is ordered by each prescribing centre for each patient. This process allows centre initiation and patient recruitment to occur after Deltyba has been prescribed and delivered for dispensing to the patient.

The MAH aims to collect data from patients who are treated with Deltyba in a prospective manner.

All patients in the PASS will be followed up routinely by their physicians / healthcare professionals (HCPs) at each regular visits 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 has been cured or completed his full MDR-TB treatment course at a date earlier than month 30 after start of Deltyba, then patient participation in the study will stop on that date. The patient's participation will stop 30 months after the start of Deltyba, even in the unlikely event that the MDR-TB treatment course continues after this period. Data will be documented by the treating physician at each regularly scheduled patient visit until the end of patient's participation in the study.

Physicians will assess patients for the occurrence of adverse events (serious and non-serious) and other safety related aspects at each visit. Obtained information on safety related data will be entered into the eCRF by the physician. The MAH will follow up adverse events and other safety related information until the reported conditions are resolved or have returned to normal or baseline status (status prior to the Deltyba intake) or until the conditions have stabilised. Pregnancies of patients or their partners will be followed-up until delivery.

Data on the use of Deltyba in a real world setting will be collected in the eCRF of the PASS. These data include, but are 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.

Endpoints

Primary:

- Usage incl. dosage, compliance and treatment duration of Deltyba

Secondary:

- AEs (serious / non-serious)
- Treatment outcomes at the end of observation period (cured, treatment completed, failed, lost to follow-up, died, not evaluated, treatment success)

At the end of the treatment period, the treatment outcomes of MDR-TB patients will be assessed by physician according to the definitions outlined in national guidelines or by the WHO[1] as applicable.

If the MAH terminates or suspends the study, prompt notification will be given to HCPs, ECs, and the Competent Authorities in accordance with regulatory requirements. All patients have the right to withdraw at any point during the study without prejudice. The HCP will notify the MAH promptly when a patient is withdrawn.

9.2 Setting

The MAH has set up a RAP for Deltyba use within the scope of its European Marketing Authorisation. The RAP includes:

- a central order and distribution process to ensure that delamanid is used only by centres and treating physicians with experience in MDR-TB management according to WHO[5] and / or national guidelines,
- educational materials for health care professionals and patients to inform them about the appropriate usage of delamanid and potentially associated risks to be closely monitored,
- as well as this EU-wide PASS to monitor usage of the product, treatment outcomes and to obtain further information on safety.

In line with the non-interventional nature of the study, patients will only be recruited once the decision on treatment with Deltyba has been made.

By utilising a central ordering process it will be possible to identify treatment centres and treating physicians prescribing Deltyba who will then be asked to participate in the PASS.

Physicians will be contacted either by phone or in writing and a PASS information leaflet will be sent out to treating physicians.

Deltyba was launched in Germany and the UK in May/June 2014. It is anticipated that the following countries will participate in the PASS: Austria, Bulgaria, Estonia, France, Germany, Italy, Latvia, Lithuania, Norway, Poland, Portugal, Romania, Spain, Sweden and the UK. Wherever possible, the MAH will include each prescribing centre in the PASS. As a consequence, a wide variety of centres ranging from tertiary referral centres through to non-TB specialist centres in an ambulatory care setting depending on national treatment practice is expected. It is likely that treating physicians will include specialists from either respiratory or infectious disease medicine.

It is planned that 250 patients with MDR-TB, prescribed Deltyba and treated at specialised centres in the EU will be included in the Deltyba PASS.

Patients will be informed about the intended use of their medical data. Only patients who give consent for documentation, transfer and evaluation of their data will be enrolled in the study. Data from patients who participate in any interventional clinical trial will not be included in the study.

Treatment management

Patients participating in the PASS are not required to have any study-related visits. Treatment management will follow the standard of care for pulmonary MDR-TB patients. Deltyba treatment should comply with the recommendations in the authorised product information, including all examinations and / or other procedures such as ECG, which is recommended before initiation of treatment and monthly during the full course of treatment with Deltyba. Any critical assessment (e.g. ECG at baseline and as required per SmPC, DST to delamanid and other anti-TB drugs) will be done according to the existing practices at the clinical sites.

9.3 Variables

Extent of exposure

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

Baseline

The following data captured prior to Deltyba treatment will be 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 (AFB) 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 QTcF value)

Routine visits

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

- AEs (serious / non-serious)
- Deltyba usage (including medication errors such as overdose, missed dose) incl. 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, are to be recorded in the eCRF.

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

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

Reporting of AEs or other safety related information which pertain to conditions under close monitoring will trigger standardised questions to the physician to fully evaluate the associated detailed circumstances.

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

9.4 Data sources

Data sources will be the patient records or documentation used for the NTPs, depending upon local circumstances. The health information of any participating patient will be 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 will be done as follows:

- Indication, co-morbidities, AEs will be coded according to Medical Dictionary for Regulatory Activities (MedDRA).
- All medications will be coded according to WHO Drug Dictionary Anatomical Therapeutic Chemical (ATC) classification system.

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

9.5 Study size

No hypothesis is being tested in this study.

It is planned to include 250 MDR-TB patients in the Deltyba PASS. This sample size estimate was made on pragmatic grounds taking the following into account: an important consideration taken into account for calculation of the sample size is 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 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) has also been taken into consideration in the sample size calculation. In addition, the dates of anticipated launch have been taken into account (launched in Germany and UK, to be followed by other EU countries at a later stage).

Table 1 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 will be included in the PASS, a total of 250 patients is anticipated for enrolment into this non-interventional study. The assumption is based on the initial feedback by potential prescribers.

9.6 Data management

All source documents pertaining to this study will be maintained on-site at the patient's records and made available for direct inspection by authorised persons. HCPs / hospital / clinic(s) will permit study-related monitoring, audits, EC review, and regulatory inspection(s) by providing direct access to source data / documents by authorised persons.

Start of data collection

Data collection will commence after the patient or his/her legal representative has signed the informed consent form (ICF). Retrospective data can be entered provided that the patient or his/her legal representative has signed the ICF. PASS relevant information from patient's medical records will be entered by HCPs into the appropriate section of the electronic Case Report Form (eCRF).

Data collection during Deltyba treatment

All participating physicians in the PASS will document pertinent information at each patient visit (usually monthly) or at intervals specified on a local / national basis. Data on Deltyba usage with an ACR will be captured. Data concerning concomitant medication, physical examination, any surgical treatment, DOT and / or self-administered therapy (SAT), and laboratory results will be collected if available; AEs will be collected and reported according to Good Pharmacovigilance Practices (GVP). Treatment and management will follow 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. 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 Cytochrome P450 3A4 enzyme (CYP3A4) inhibitors should undergo very frequent monitoring of ECGs throughout the full Deltyba treatment period.

Data collection after completion of Deltyba treatment

All patients in the PASS will be 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 will be 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 will select the most adequate medications comprising ACR based on national or WHO's guidelines for the programmatic management of drug-resistant TB[5].

End of data collection

The end of data collection is 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.

Statistical Software

All data processing and summarisation will be performed using version 9. 3 or higher of the SAS® statistical software package.

9.7 Data analysis

No formal hypotheses are to be tested in this study.

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

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

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

Extent of exposure to Deltyba

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

Duration of exposure to Deltyba will be 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, BMI) will be presented using descriptive statistics.

Age (years) will be recorded during baseline.

Medical history

Data on medical history will be summarised using descriptive statistics.

Clinical laboratory data

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

Additional TB-related clinical parameters will be collected, if available:

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

Descriptive statistics for continuous laboratory variables will be presented for all data collection time points as available, and change from baseline over time up to the last visit. Last visit will be 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 one result is with potentially clinically significant abnormality by the given criterion, the patient will be classified as having a potentially clinically significant abnormal test at that visit for that criterion. Denominator of the percentages in these summaries will be 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 will be 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 done per standard of care will be presented using descriptive statistics.

From physical examination of head, eyes, ears, nose and throat (HEENT), thorax, abdomen, urogenital, extremities, neurological, skin and mucosae, data will be 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], BMI [kg/m^2] will be provided.

ECG assessments

Available ECG data will be collected during baseline and all routine visits during the study. Primary focus is on QTcF, however if QTcF has not been done, physicians are asked to provide ventricular rate, RR interval, QT interval, QTcB interval and overall ECG interpretation. A listing will be 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) will be presented using descriptive statistics. In addition, an overall safety evaluation will be done for those who enter the study with QTcF>500 ms at baseline or who develop QTcF>500 ms during Deltyba treatment.

Adverse events

All adverse events will be coded by System Organ Class (SOC) and MedDRA (using a current version and / or recoding, as applicable) 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 will be selected. AEs with missing intensity/severity will be included (as severe) in the overall count of patients with AEs, but will not be included in the counts for severity summary.

The incidence of the following events will be 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)) will be summarized.

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 will be listed for each patient. The number and percentage of patients and the 95% CI will be 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 are 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 are negative after the intensive phase.
- **Treatment failed:** Treatment terminated or 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 dies 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 is assigned. (This includes cases "transferred out" to another treatment unit and whose treatment outcome is unknown).
- **Treatment success:** The sum of cured and treatment completed

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

Handling of dropouts or missing data

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

It is expected that there will be cases when patients are withdrawn from study by themselves. In such cases of "discontinuation with no known reason" patients will be contacted and reasons for withdrawal/discontinuation will be asked and documented.

If the patient cannot be further contacted, she/he will be in the "lost to follow-up" categories, if the patient could be contacted but is not willing to, or due to some reasons, could not provide the reason(s) for discontinuation, those patients should be put in "Not evaluated" category.

Compliance analysis

Patient compliance data will be collected and analysed.

Treatment compliance will be measured using the recommended prescribing information. Patient compliance will be measured over a period of time and reported as a percentage. Non-compliance is defined as inadequate intake of Deltyba and will be analysed with respect to the recommended prescribing information (timing, dosage, duration of use, DOT or not observed therapy, taking Deltyba with ACR, etc.)

9.8 Quality control

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

Monitoring

Monitoring activities will be performed by a CRO and Otsuka will oversee these activities. Study specific monitoring plan will be used. The HCP must permit and assist in monitoring PASS files and original patient medical records by Otsuka appointed personnel and authorised government agencies.

Auditing / Inspections

Otsuka's Quality Management Unit (or representative) may conduct study site audits. Audits will include, but are not be limited to: presence of required documents, the informed consent process, and comparison of eCRFs with source documents. The HCP agrees to participate and support audits and regulatory authority inspections.

Record maintenance and archiving

Patient medical records will be archived per national / local requirements. All other study records such as: signed version of the protocol and protocol amendments (if applicable), curricula vitae of participating HCPs, documentation of EC 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.

Records retention at the study site

The HCP must 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 will be responsible to maintain adequate and accurate electronic and hard copy source documents of all observations and data generated during this study. Such documentation is subject to inspection by Otsuka and relevant regulatory agencies. If the investigator withdraws from the study (e.g. due to relocation or retirement), all study related records should be transferred to a mutually agreed upon designee. Notice of such transfer will be given to Otsuka in writing. Patient records or other source data must 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 should be detailed in the contractual agreement.

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

9.9 Limitations of the research methods

Most likely one of the main challenges conducting an observational study in different countries is cultural issues, local infrastructure and awareness of the HCPs and community. In order to minimise bias and / or errors, the MAH is setting up a RAP to support and monitor the adequate usage of Deltyba.

Other limitations are:

- The bias resulting from the assessment of causal relationship of an AE to the use of Deltyba.

- 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 is conducted.
- Treatment outcomes definitions per HCP

The data from this non-interventional PASS cannot be considered alone to support changes to the product label, if applicable. However, the data resulting from this PASS may provide valuable information on the usage of Deltyba and its safety profile.

9.10 Other aspects

Protocol deviations

In the event of a significant deviation from the protocol (i.e. violation of informed consent process), the HCP or designee must contact Otsuka immediately. A joint decision shall be taken and documented regarding patient's continuation in the study.

Restrictions

Deltyba shall be used according to the SmPC.

10 Protection of human subjects

This study will be conducted in compliance with the protocol and in accordance with Good Pharmacoepidemiology Practices (GPP), local national laws and regulations applicable to non-interventional studies, GVP (in EU countries) and ethical principles that have their origins in the Declaration of Helsinki. The EC will evaluate the ethical and scientific appropriateness of the study. If an EC vote is required per local regulations, the HCP / hospital must have written and dated approval / favourable opinion from the EC for the study protocol / amendment(s), written data consent form, and any data consent form updates before initiating a study. The EC approval must identify the protocol version as well as the documents reviewed.

Informed consent

Written informed consent will be obtained from all patients (or their guardian or legal representative, as applicable) authorising release of medical information prior to inclusion in the PASS in accordance with country-specific requirements for patient data

protection. Once appropriate essential information has been provided and fully explained in layman's language to the patient by the HCP (or a qualified designee), the ICF will be signed and dated by both the patient and the person obtaining consent (HCP or designee), as well as by any other parties required by the EC. The patient will receive a copy of the signed ICF; the original shall be kept on-site, in the patient's records.

This consent will also address the transfer of the data to other entities and their processing for scientific, medical, and statistical research.

Confidentiality

All information obtained during the conduct of the study with respect to the patient's state of health will be regarded as confidential. The HCP must ensure that each patient's anonymity is maintained. On eCRFs and other documents submitted to Otsuka or the CRO, patients must not be identified by name. Instead, patients will be identified only by unique patient numbers on the eCRFs and on all study documentation. The HCP will keep a separate log of these codes. Documents that are not for submission to Otsuka or the CRO (i.e. consent forms) will be maintained on-site in the patient's records in strict confidence, except to the extent necessary to allow monitoring by Otsuka and the CRO, and auditing by Competent Authorities. Patient identity will remain confidential in all publications related to the study.

Amendment policy

The HCP will not make any changes to this protocol without Otsuka's prior written consent and subsequent approval by / notification to the EC and Regulatory Authority as appropriate. Any permanent change to the protocol, whether it is an overall change or a change for specific study site(s), must be handled as a protocol amendment. Any amendment will be written by Otsuka. Each amendment will be submitted to the EC and Regulatory Authority per applicable local regulations. Except for 'administrative' or 'non-substantial' amendments, HCPs will wait for EC approval (as applicable) of the amended protocol before implementing the change(s). Administrative amendments are defined as having no effect on the safety of patients, the conduct or management of the study, the study design or the quality or safety of drug(s) used in the study. However, a protocol change intended to eliminate an apparent immediate hazard to patients should be implemented immediately, followed by EC notification within 5 working days. Otsuka will submit protocol amendments to regulatory agencies as required.

When the EC, HCPs, and / or Otsuka conclude that the protocol amendment substantially alters the study design and / or increases the potential risk to the patient, the currently approved written ICF will require similar modification. In such cases, an updated informed consent will be obtained from patients enrolled in the study before expecting continued participation.

11 Management and reporting of adverse events

The physician shall adhere to the below given definitions when entering details on AEs (serious / non-serious) on the eCRF. A paper safety report (SR) form will be used to report serious adverse events (SAEs) within the required timelines.

Adverse event (AE): Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavourable and unintended sign (including e.g. an abnormal laboratory finding), symptom or disease temporally associated with the use of a medicinal (investigational) product, whether or not it is considered causally related to the medicinal product or treatment procedures.

Serious adverse event (SAE): An SAE is any untoward medical occurrence that at any dose results in any of the following outcomes:

- Death
- Life-threatening
- Persistent or significant disability/incapacity
- Requires in-patient hospitalisation or prolongs hospitalisation (any hospitalisation concerning standard of care procedures, planned before signing the ICF or for social purposes shall not be considered /reported as SAE)
- Congenital anomaly / birth defect
- Other medically significant events that, based upon appropriate medical judgment, may jeopardise the patient and may require medical or surgical intervention to prevent one of the outcomes listed above, e.g. allergic bronchospasm requiring intensive treatment in an emergency room or home, blood dyscrasias or convulsions that do not result in hospitalisation, or the development of drug dependency or drug misuse.

Safety information comprises any information from any source such as:

- All AEs or suspicion thereof
- SAEs
- Lack of efficacy
- Overdose, abuse, misuse (even without resulting adverse reaction)
- Medication error
- Exposure during pregnancy or lactation (including uneventful) and reports where the embryo or foetus may have been exposed to medicinal products (either through maternal exposure or transmission of a medicinal product via semen following paternal exposure)
- Counterfeit product
- Transfer of infectious disease by the medicinal product concerned
- Product complaint report which includes medically important information
- Paediatric use
- Occupational exposure (i.e. to Deltyba)
- Off-label use

A paper SR form should be completed for all following occurrences:

- SAEs
- Pregnancy, although a normal pregnancy is not an adverse event, it must be reported. This includes pregnancies occurring in female patients and female partner of a male patient.
- All events involving overdose, misuse and abuse. This includes accidental overdose by the HCP or a patient. It also includes all such events, whether the course is symptomless, or whether an AE results.
- Occupational exposure to Deltyba
- Off-label use
- Product complaint report which includes medically important information
- Transfer of an infectious disease by the medicinal product concerned
- Lack of efficacy
- Counterfeit product

Severity (intensity): AEs will be graded on a 3-point scale. The intensity of an adverse experience is defined as follows:

1 = Mild: Discomfort noticed, but no disruption of daily activity.

2 = Moderate: Discomfort sufficient to reduce or affect normal daily activity.

3 = Severe: Inability to work or perform normal daily activity.

Deltyba causality: Assessment of causal relationship of AEs (serious / non-serious) to the use of Deltyba:

Related: The AE and the administration of Deltyba are related in time, and a direct association can be demonstrated.

Probably related: The AE and the administration of Deltyba are reasonably related in time, and the AE is more likely explained by the Deltyba (administration) than by other causes.

Possibly related: The AE and the administration of Deltyba are reasonably related in time, and the AE can be equally well explained by causes other than Deltyba administration. The result of dechallenge is lacking or unclear.

Unlikely related: A temporal relationship to the administration of Deltyba cannot be ruled out, but the AE can be more likely explained by reasons other than the Deltyba administration.

Not related: The AE is clearly explained by another cause not related to the Deltyba administration.

If an AE worsens in severity or changes from non-serious to serious, the AE must be entered again as a new event into the eCRF (see eCRF completion instructions for details).

AEs must be followed up until they have resolved or returned to normal or baseline status (status prior to the medicinal product intake), have stabilised or are explained. An AE cannot be left unresolved in the eCRF unless agreed upon by Otsuka Safety Officer at Otsuka Europe Development & Commercialisation, Pharmacovigilance Region Europe (PVRE).

Reporting of AEs:

All AEs (serious and non-serious) will be collected and documented on the eCRF from the time the informed consent is signed until the end of follow-up period for the patient.

If there are any ongoing AEs at the end of the follow-up period, all efforts will be made to collect outcome information within one month after finalisation of the study. For related AEs there is no time limit on the reportability.

A worsening of symptoms of the patient compared to the patient's health status documented at baseline constitutes an AE. Since one of the PASS objectives is to monitor the safety of Deltyba in a real-life setting, the physician must assess patients for the occurrence of AEs at every visit, whether scheduled or unscheduled during the study. The physician must also promptly review all results of assessments performed as part of the standard of care such as laboratory assessments results, ECGs, physical examination, blood counts, urinalysis, etc.

All AEs occurring during the PASS must be entered into the eCRF. An AE that undergoes a clinically significant worsening in severity, or fulfils a criterion of seriousness must be entered as a new AE.

Safety reporting:

All safety communication is required in English.

E-mail correspondence between Otsuka and the CRO or HCPs clarifying medical details of SRs may not contain any patient identifiers other than the subject identification from the study.

The paper SR form must be sent within 24h of first knowledge via e-mail or fax to:

Covance Pharmacovigilance Department

E-mail: Otsuka402@Covance.com

Fax: +44 (0) 1628 540028

All SAEs must be entered into the eCRF by the physician or study coordinator.

If even reporting via e-mail or fax is not possible, Covance should be informed by telephone at first, in order to allow timely processing of a case. Global reporting requirements will be reflected on the safety reporting plan.

If further information is required, the HCP will be contacted. The physician is responsible for providing any requested further information.

12 Plans for disseminating and communicating study results

In the event of any new safety signal Otsuka will notify Competent Authorities immediately and independently of the timing of progress reports.

The main reporting from the study will be the final report as well as study progress reports.

As new safety signals affecting the current safety profile of the compound could potentially arise from the study before study reports are available, the MAH may in general be required to update the label of the product to comply with GVP Module IX in case safety signals are validated.

A change to the safety profile of the product would necessitate an update to the RMP as well which would be amended in agreement with the European Medicines Agency (EMA) accordingly. Study reports would be referenced as final within the RMP only after approval from the EMA has been received.

Study progress reports will be provided in compliance with GVP guidelines[7]. A final study report will be completed within one year after end of data collection (last patient, last study visit). The final study report will be prepared regardless of whether the study is completed or prematurely terminated. The summary of the final results will be provided to all participating HCPs. The final study report will be submitted to the European Medicines Agency (EMA), the CHMP and to the respective Competent Authorities as applicable.

Dissemination of study results

After completion of the study, the participating physician(s) may prepare a joint publication with Otsuka. The participating physician(s) must undertake not to submit any part of the data from this protocol for publication without the prior consent of Otsuka. The participating physicians agree that they are part of a multicentre study, and shall coordinate in advance any intended disclosure of the results of the study with Otsuka to ensure that the results of individual participating physicians are not published or presented before those of the multicentre study, unless otherwise agreed in writing by Otsuka.

The authors have the final responsibility for the content of publication(s) of their own data and the decision to submit it/them for publication. Any planned manuscript, presentation, abstract, or other intended disclosure of the results of the study or otherwise originating from the study shall be made available for review to Otsuka at least thirty (30) days before submission for publication or any other means of disclosure in order to allow Otsuka to protect its intellectual property.

13 References

1 World Health Organization. Definitions and reporting framework for tuberculosis - 2013 revision. WHO/HTM/TB/2013.2.

2 Matsumoto M, Hashizume H, Tomishige T, Kawasaki M, Tsubouchi H, Sasaki H, Shimokawa Y, Komatsu M. OPC-67683, a nitro-dihydroimidazo-oxazole derivative with promising action against tuberculosis in vitro and in mice. PLoS Med 2006; 3(11): e466

3 Barry PJ, O'Connor TM. Novel agents in the management of mycobacterium tuberculosis disease. Curr Med Chem. 2007; 14: 2000-8

4 Gler MT, Scripconoka V, Sanchez-Garavito E, Xiao H, Cabrera-Rivero J, Vargas-Vasquez D, et al. Delamanid for multidrug- resistant pulmonary tuberculosis. N Engl J Med. 2012; 366:2151-60

5 World Health Organization. Guidelines for the programmatic management of drug-resistant tuberculosis, Update, 2011. Geneva, Switzerland. WHO/HTM/TB/2011.6.

6 European Centre for Disease Prevention and Control/WHO Regional Office for Europe. Tuberculosis surveillance and monitoring in Europe 2014. Stockholm: European Centre for Disease Prevention and Control, 2014.

7 Guideline on good pharmacovigilance practices (GVP) (EMA/781168/2013). Annex 1 - Definitions (EMA/876333/2011 Rev 2).

14 Annex 1. List of stand-alone documents

Number	Document reference number	Date	Title
1			Delamanid Summary of Product Characteristics
2			Signature page: Physician
3			List of participating Healthcare professionals

15 Annex 2. ENCePP checklist for study protocols

16 Annex 3. Additional information