**PASS information**

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| **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 v1.0 |
| **Date of last version of the final study report** | 18 August 2022 |
| **EU PAS register number** | ENCEPP/SDPP/10618 |
| **Active substance** | Delamanid<br>ATC code J04AK06<br>(J04AK Other drugs for treatment of tuberculosis)<br>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<br>Erika-Mann-Str. 21<br>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.<br>No hypothesis was tested in this study. |

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| | Treatment, all assessments and patient monitoring were performed according to the existing practices and / or treatment centre's local / national tuberculosis programme (NTP) guidelines.<br><br>The primary objective was:<br>• 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.<br>The secondary objectives were:<br>• 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.<br>• 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):<br>• At start of the EU-PASS:<br>o United Kingdom (30 May 2014)<br>o Germany (17 June 2014).<br>• At later stage:<br>o Estonia (28 September 2016)<br>o France (06 June 2016)<br>o Latvia (03 July 2015)<br>Lithuania (02 May 2016). |
| **Author** | Medical Writer<br>Labcorp Drug Development |

## Marketing authorisation holder

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| **Marketing authorisation holder** | Otsuka Novel Products GmbH<br>Erika-Mann-Str. 21<br>80636 Munich, Germany |
| **MAH contact** | Otsuka Novel Products GmbH<br>Erika-Mann-Str. 21 80636 Munich, Germany |

## 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.[3] 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[4] (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.

Overall, 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). Delamanid use in special patient groups, eg, elderly patients, patients with hepatic impairment, as well as delamanid use in patients with human immunodeficiency virus (HIV) does not suggest any specific risks based on the limited data in this study.

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 patient enrolment than initially anticipated. 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. 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, et al. OPC-67683, a nitro-dihydroimidazo-oxazole derivative with promising action against tuberculosis in vitro and in mice. PLoS Med 2006; 3(11): e466.

3 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.

4 Javad Nasiri M, Zangiabadian M, Arabpour E, Amini S, Khalili F, Centis R, et al. Delamanid-containing regimens and multidrug-resistant tuberculosis: A systematic review and meta-analysis. Int J Infect Dis. 2022 Mar 2; S1201-9712(22).