Clinical trial results:
A Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel Group Trial to Evaluate the Safety and Efficacy of Delamanid (OPC-67683) Administered Orally as 200 mg Total Daily Dose for Six Months in Patients With Pulmonary Sputum Culture-positive, Multidrug-resistant Tuberculosis

Summary

EudraCT number	2010-022271-59
Trial protocol	LV EE LT
Global end of trial date	04 July 2016

Results information

Result version number	v1 (current)
This version publication date	24 October 2017
First version publication date	24 October 2017

Trial information

Trial identification

Sponsor protocol code	242-09-213

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01424670
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Otsuka Pharmaceutical Development & Commercialization,Inc.
Sponsor organisation address	2440 Research Boulevard, Rockville, United States, MD 20850
Public contact	Senior Medical Director, Otsuka Pharmaceutical Development & Commercialization, Inc., +1 4155330152, rajesh.gupta@otsuka-us.com
Scientific contact	Senior Medical Director, Otsuka Pharmaceutical Development & Commercialization, Inc., +1 4155330152, rajesh.gupta@otsuka-us.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	30 January 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	04 July 2016
Global end of trial reached?	Yes
Global end of trial date	04 July 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of delamanid administered orally as 100 mg twice daily (BID) for 2 months followed by 200 mg once daily (QD) for 4 months in combination with an optimized background treatment regimen (OBR) versus placebo with OBR.

Protection of trial subjects:

The study was conducted according to the International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) Consolidated Guideline and the applicable local laws and regulatory requirements of the countries in which the trial was conducted. Informed consent was obtained from all subjects in writing before any trial related procedures were performed. Prior to start, copies of the protocol, any amendments, and the informed consent form (ICF) were reviewed and approved by the governing institutional review broad (IRB) or independent ethics committee (IEC). Essential information was fully explained in layman's language to the subject by the investigator or a qualified designee.
Note: All subjects were 18 to 69 years of age, inclusive, at time of informed consent.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	02 September 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Moldova, Republic of: 43
Country: Number of subjects enrolled	Peru: 157
Country: Number of subjects enrolled	Philippines: 127
Country: Number of subjects enrolled	South Africa: 101
Country: Number of subjects enrolled	Estonia: 13
Country: Number of subjects enrolled	Latvia: 30
Country: Number of subjects enrolled	Lithuania: 40
Worldwide total number of subjects	511
EEA total number of subjects	83

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	510
From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Out of 714 screened subjects, only 511 (with multidrug-resistant tuberculosis [MDR TB]) were randomized to Delamanid + OBR (341) & Placebo (170). The study was conducted at 17 sites in 7 countries (Estonia, Latvia, Lithuania, Moldova, Peru, Philippines and South Africa).

Pre-assignment

Screening details:

Pretreatment Period: Days -21 to -1. In this period, Screening and baseline safety, electrocardiogram (ECG), and baseline microbiologic assessments were performed.

Period 1

Period 1 title	Overall study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Delamanid+OBR

Arm description:

On Day 1, patients were randomized to treatment Group 1- Delamanid + OBR and received orally 100 mg Delamanid BID (morning & evening) + OBR for 2 months (Intensive Treatment Period) followed by 200 mg Delamanid QD (morning) + OBR for 4 months.

Arm type	Experimental
Investigational medicinal product name	Delamanid
Investigational medicinal product code	OPC-67683
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Patients received orally 100 mg Delamanid BID (morning & evening) + OBR for 2 months (Intensive Treatment Period) followed by 200 mg Delamanid QD (morning) + OBR for 4 months.

Arm title	Placebo + OBR

Arm description:

On Day 1, patients were randomized to treatment Group 2 - Placebo+OBR and received orally 2 tablets of placebo (morning & evening) exactly matching the 50-mg tablet of Delamanid for 2 months (Intensive Treatment Period) followed by 4 tablets of matching placebo for 4 months.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Patients received orally 2 tablets of placebo (morning & evening) exactly matching the 50-mg tablet of Delamanid for 2 months (Intensive Treatment Period) followed by 4 tablets of matching placebo for 4 months.

Number of subjects included in analysis	327
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8951
Method	Cochran-Mantel-Haenszel
Parameter estimate	Relative ratio of probability
Point estimate	0.991
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.872
upper limit	1.127

Secondary: Treatment outcomes assessed by principal investigators at the end of treatment with OBR

End point title	Treatment outcomes assessed by principal investigators at the end of treatment with OBR

End point description:

Final treatment outcomes was assessed by the investigator (or managing clinician) at the end of treatment with OBR (i.e., 24 months post randomization) according to the WHO outcome definitions for treating patients with MDR TB. Frequency counts and percentage of patients achieving each treatment outcome (Cured, Treatment Completed, Died,Treatment Failed, Defaulted) was provided by treatment group.

End point type	Secondary

End point timeframe:

Post-treatment Follow-up: Month 24

End point values	Delamanid+OBR	Placebo + OBR		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	226	101		
Units: Participants				
number (not applicable)				
Favorable outcome	182	85		
Unfavorable outcome	42	16		

Statistical analyses

Statistical analysis title	Stat. comp. of treatment outcomes assessed by PI

Statistical analysis description:

Frequency counts and percentage of patients achieving each treatment outcome (Cured, Treatment Completed, Died, Treatment Failed, Defaulted) was provided by treatment group as per favorable and unfavorable outcome.

Comparison groups	Delamanid+OBR v Placebo + OBR

Number of subjects included in analysis	327
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5269
Method	Cohran-Mantel-Haenzel Test
Parameter estimate	Relative ratio of probability
Point estimate	0.965
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.869
upper limit	1.073

Secondary: Proportion of subjects who developed resistance to Delamanid.

End point title	Proportion of subjects who developed resistance to Delamanid.

End point description:

Acquired resistance was defined as a post-baseline resistant result at any time point after a baseline susceptible result. The overall resistance to Delamanid during the trial was assessed.

End point type	Secondary

End point timeframe:

Pre-treatment: Day -1
Intensive Treatment (Delamanid+OBR): Week 1, 16, 18, 20, 22, 24 and 26
Continuation treatment (OBR alone): Month 7, 8, 9, 10, 11, 12, 15 and 18
Post-treatment Follow-up: Month 21 and 24
Post-treatment Follow-up: Month 27 and 30

End point values	Delamanid+OBR	Placebo + OBR		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	341	170		
Units: Participants				
number (not applicable)	4	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean area under the concentration-time curve (AUC) of change from baseline

End point title	Mean area under the concentration-time curve (AUC) of change from baseline

End point description:

The AUC of the change from baseline for Time to detection (TTD), (from baseline to Month 6 [Week 26]) summarizes the overall subject response for the treatment period. A larger AUC of change from baseline for TTD strongly suggested a clinical response with the reduction of the burden of MTB organisms in sputum. The analysis of average change from baseline in original time to detection of MGIT positive signal up to 6 months was performed using using AUC in MGIT sample was presented. The baseline was

defined as the average of Day −1 and Day 1 values if cultures on both days were positive; if only one culture was positive, the value for TTD for the positive culture was used as the baseline.

End point type	Secondary

End point timeframe:

Pre-treatment: Day 1
Intensive Treatment (Delamanid+OBR): Week 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26

End point values	Delamanid+OBR	Placebo + OBR		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	221	98		
Units: Mean				
arithmetic mean (standard deviation)	21.9 (± 9.44)	23.3 (± 8.93)		

Statistical analyses

Statistical analysis title	Stat. Comp. of mean AUC of change from baseline
Comparison groups	Delamanid+OBR v Placebo + OBR
Number of subjects included in analysis	319
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0.6986
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.9
upper limit	1.3

Notes:

[3] - Descriptive statistics and the summary of pair wise treatment comparisons from the analysis of covariance model (ANCOVA) were presented for the average AUC of change from baseline to Day 182. Note that the baseline was defined as the average of Day −1 and Day 1 values if cultures on both days were positive; if only one culture was positive, the value for TTD for the positive culture was used as the baseline.

Secondary: Mean change from baseline in TTD using the MGIT system

End point title	Mean change from baseline in TTD using the MGIT system

End point description:

The value for TTD was defined (in days) as the time interval from inoculation until a MGIT machine detects a positive signal for a sputum culture during the routine 42-day
incubation period. TTD analysis was based on only with the corresponding qualitative sputum results of pure positive and pure negative cultures in days and hours of the first positive signal for TTD from the MGIT printout.
The original TTD recorded by the MGIT machine was used in statistical analyses:
1) When a MGIT culture result was negative for MTB complex, TTD was set to 42 days (the value for time-to-result with negative culture). 2) If the MGIT sputum culture result was positive for MTB complex and if the value for time to result in days was less than or equal to 45, then TTD was set to time to result in Days + Hours/24. If the original TTD was greater than 45, then TTD was set to missing.

End point type	Secondary

End point timeframe:

Intensive Treatment: Week 1 to 26
Continuation Treatment: Month 7 to 18

End point values	Delamanid+OBR	Placebo + OBR		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	226	101		
Units: Mean				
arithmetic mean (standard deviation)				
At baseline (n= 222, 98)	16.7 (± 7.9)	15.4 (± 7.7)		
At week 1 (n= 204, 94)	20.8 (± 10.3)	19.9 (± 11.1)		
Change at week 1 (n= 204, 94)	4.3 (± 7.9)	4.8 (± 7.8)		
At week 2 (n= 206, 87)	24.6 (± 11.5)	23.1 (± 11.4)		
Change at week 2 (n= 206, 87)	7.7 (± 8.9)	7.5 (± 7.8)		
At week 3 (n= 209, 89)	28.4 (± 11.8)	25.5 (± 12.4)		
Change at week 3 (n= 209, 89)	11.6 (± 9.8)	10.4 (± 9.6)		
At week 24 (n= 195, 80)	40.4 (± 6.6)	41.3 (± 3.9)		
Change at week 24 (n= 195, 80)	23.4 (± 10.2)	25.5 (± 8.3)		
At week 26 (n= 188, 82)	40.6 (± 5.9)	40.5 (± 5.5)		
Change at week 26 (n= 188, 82)	23.8 (± 9.5)	24.6 (± 9.4)		
At last visit (n= 222, 98)	39.4 (± 8.4)	40.3 (± 6.3)		
Change at last visit (n= 222, 98)	22.7 (± 10.7)	24.9 (± 9.5)		

Statistical analyses

Statistical analysis title	Statistical analysis for week 1
Comparison groups	Delamanid+OBR v Placebo + OBR
Number of subjects included in analysis	327
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6825
Method	ANCOVA

Statistical analysis title	Statistical analysis for week 2
Comparison groups	Delamanid+OBR v Placebo + OBR
Number of subjects included in analysis	327
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.807
Method	ANCOVA

Statistical analysis title	Statistical analysis for week 3
Comparison groups	Delamanid+OBR v Placebo + OBR
Number of subjects included in analysis	327
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.269
Method	ANOVA

Statistical analysis title	Statiscal analysis for week 24
Comparison groups	Delamanid+OBR v Placebo + OBR
Number of subjects included in analysis	327
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2333
Method	ANCOVA

Statistical analysis title	Statistical analysis for week 26
Comparison groups	Delamanid+OBR v Placebo + OBR
Number of subjects included in analysis	327
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9397
Method	ANCOVA

Secondary: Distribution of time to SCC using solid culture at month 6	
End point title	Distribution of time to SCC using solid culture at month 6
End point description: To evaluate the distribution of time to SCC by 6 months using solid culture media and the proportion of patients with SCC at 6 months using the solid culture was derived as a single representative culture result for a patient that was negative using the solid culture system, followed by at least one confirmatory single representative negative culture result at least 25 days after the first negative and not followed by a confirmed positive (defined as 2 or more observed positive single representative culture results not taking into account intermittent, missing, or contaminated results). The analysis was carried out using MITT (SOLID) sample population.	
End point type	Secondary
End point timeframe: Intensive Treatment: Month 6	

End point values	Delamanid+OBR	Placebo + OBR		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	167	81		
Units: Days				
median (confidence interval 95%)	36 (29 to 43)	42 (29 to 51)		

Statistical analyses

Statistical analysis title	Statistical analysis at 6 months

Statistical analysis description:

The proportion of patients with SCC at 6 months using the solid culture was derived as a single representative culture result for a patient that was negative using the MGIT culture system, followed by at least one confirmatory single representative negative culture result at least 25 days after the first negative and not followed by a confirmed positive (defined as 2 or more observed positive single representative culture results not taking into account intermittent, missing, or contaminated).

Comparison groups	Delamanid+OBR v Placebo + OBR
Number of subjects included in analysis	248
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3975
Method	Modified peto-peto test

Secondary: Final outcome at month 30 as a treatment success or failure (including relapse)

End point title	Final outcome at month 30 as a treatment success or failure (including relapse)

End point description:

Treatment success was defined as achieving SCC by 6 months, completing the trial out to 30 months with sustained SCC and alive at the last contact for follow-up. All other patients were treatment failures who failed to achieve SCC by week 26, achieved SCC but have a confirmed positive, early terminate from the trial prior to the Month 30 visit but are alive at the last contact for follow-up, lost to follow-up and vital status unknown and death. Analysis of Treatment Success and failure at 30 months Based on MGIT in MGIT Sample.

End point type	Secondary

End point timeframe:

Continuation Treatment: Month 30

End point values	Delamanid+OBR	Placebo + OBR		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	226	101		
Units: Participants				
number (not applicable)				
Success	173	78		
Failure	53	23		

Statistical analyses

Statistical analysis title	Stat. comp. of treatment success at month 30

Statistical analysis description:

The proportions of Treatment success at Month 30 between treatment groups was statistically compared with the Cochran-Mantel-Haenszel test stratified by risk strata
(Low Risk/High Risk). The analysis of treatment success at month 30 was calculated using relative ratio of probability of success between Delamanid+OBR and Placebo+OBR, produced using Proc Freq procedure with CMH option.

Comparison groups	Delamanid+OBR v Placebo + OBR
Number of subjects included in analysis	327
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8951
Method	Treatment comparison using CMH
Parameter estimate	Relative ratio of probability
Point estimate	0.991
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.872
upper limit	1.127

Secondary: Sustained SCC using solid culture at Month 18, Month 24, and Month 30

End point title	Sustained SCC using solid culture at Month 18, Month 24, and Month 30

End point description:

Sustained SCC was defined as SCC achieved by Month 6 and not followed by a “confirmed positive” thereafter, where confirmed positive was defined as 2 or more observed positive single representative culture results, not taking into account intermittent, missing, or contaminated results.
Sustained SCC using solid culture was analyzed at month 18 to 30 using MITT (solid) sample.

End point type	Secondary

End point timeframe:

Continuation Treatment (OBR Alone): Month 18, Continuation treatment (OBR alone) or Post- treatment Follow up: Month 24, Post-treatment Follow-up: Month 30

End point values	Delamanid+OBR	Placebo + OBR		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	167	81		
Units: Participants				
number (not applicable)				
At month 18	130	61		

At month 24	130	60		
At month 30	125	57		

Statistical analyses

Statistical analysis title	Stat. comparison of sustained SCC at month 18
Comparison groups	Delamanid+OBR v Placebo + OBR
Number of subjects included in analysis	248
Analysis specification	Pre-specified
Analysis type	superiority

Number of subjects included in analysis	248
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4729
Method	Cochran-Mantel-Haenszel
Parameter estimate	Relative ratio of probability
Point estimate	1.061
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.899
upper limit	1.253

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Adverse events were collected throughout the study (30 Months)	
Adverse event reporting additional description:	
Adverse events were collected for randomized patients who received any amount of study drug, regardless of any protocol deviation or violation.	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups	
Reporting group title	Delamanid + Optimized background regimen (OBR)
Reporting group description:	
On Day 1, patients were randomized to treatment Group 1- Delamanid + OBR and received orally 100 mg. Delamanid BID (morning & evening) + OBR for 2 months (Intensive Treatment Period) followed by 200 mg Delamanid QD (morning) + OBR for 4 months.	
Reporting group title	Placebo + OBR
Reporting group description:	
On Day 1, patients were randomized to treatment Group 2 - Placebo+OBR and received orally 2 tablets. Placebo (morning & evening) exactly matching the 50-mg tablet of Delamanid for 2 months (Intensive Treatment Period) followed by 4 tablets of matching placebo for 4 months.	

Serious adverse events	Delamanid + Optimized background regimen (OBR)	Placebo + OBR	
Total subjects affected by serious adverse events			
subjects affected / exposed	89 / 341 (26.10%)	47 / 170 (27.65%)	
number of deaths (all causes)	15	6	
number of deaths resulting from adverse events	15	6	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Brain neoplasm			
subjects affected / exposed	1 / 341 (0.29%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung adenocarcinoma metastatic			
subjects affected / exposed	0 / 341 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Malignant neoplasm of unknown primary site			

subjects affected / exposed	1 / 341 (0.29%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Meningioma			
subjects affected / exposed	1 / 341 (0.29%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma of lung			
subjects affected / exposed	1 / 341 (0.29%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Squamous cell carcinoma of the oral cavity			
subjects affected / exposed	0 / 341 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	3 / 341 (0.88%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	1 / 341 (0.29%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	1 / 341 (0.29%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	2 / 341 (0.59%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Hypothermia			
subjects affected / exposed	1 / 341 (0.29%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Multiple organ dysfunction syndrome			
subjects affected / exposed	1 / 341 (0.29%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 341 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	2 / 341 (0.59%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Asphyxia			
subjects affected / exposed	1 / 341 (0.29%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Asthma			
subjects affected / exposed	1 / 341 (0.29%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchiectasis			
subjects affected / exposed	0 / 341 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bullous lung disease			
subjects affected / exposed	1 / 341 (0.29%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 341 (0.29%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	3 / 341 (0.88%)	2 / 170 (1.18%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 1	
Pneumothorax			
subjects affected / exposed	0 / 341 (0.00%)	2 / 170 (1.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax spontaneous			
subjects affected / exposed	1 / 341 (0.29%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	1 / 341 (0.29%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pulmonary fibrosis			
subjects affected / exposed	2 / 341 (0.59%)	2 / 170 (1.18%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary haematoma			
subjects affected / exposed	0 / 341 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary haemorrhage			
subjects affected / exposed	1 / 341 (0.29%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			

subjects affected / exposed	0 / 341 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory failure			
subjects affected / exposed	1 / 341 (0.29%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Restrictive pulmonary disease			
subjects affected / exposed	0 / 341 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Acute psychosis			
subjects affected / exposed	2 / 341 (0.59%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Alcohol abuse			
subjects affected / exposed	2 / 341 (0.59%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anxiety			
subjects affected / exposed	1 / 341 (0.29%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anxiety disorder			
subjects affected / exposed	1 / 341 (0.29%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Completed suicide			
subjects affected / exposed	1 / 341 (0.29%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Confusional state			

subjects affected / exposed	1 / 341 (0.29%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Delirium tremens			
subjects affected / exposed	1 / 341 (0.29%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			
subjects affected / exposed	1 / 341 (0.29%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Major depression			
subjects affected / exposed	1 / 341 (0.29%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Panic attack			
subjects affected / exposed	0 / 341 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychotic disorder			
subjects affected / exposed	3 / 341 (0.88%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reactive psychosis			
subjects affected / exposed	1 / 341 (0.29%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Substance-induced psychotic disorder			
subjects affected / exposed	2 / 341 (0.59%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicidal ideation			

subjects affected / exposed	1 / 341 (0.29%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicide attempt			
subjects affected / exposed	1 / 341 (0.29%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 341 (0.29%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 341 (0.29%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrocardiogram QT prolonged			
subjects affected / exposed	6 / 341 (1.76%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	4 / 6	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 341 (0.29%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transaminases increased			
subjects affected / exposed	1 / 341 (0.29%)	3 / 170 (1.76%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Abdominal injury			

subjects affected / exposed	1 / 341 (0.29%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Alcohol poisoning			
subjects affected / exposed	2 / 341 (0.59%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Ankle fracture			
subjects affected / exposed	0 / 341 (0.00%)	2 / 170 (1.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest injury			
subjects affected / exposed	0 / 341 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral neck fracture			
subjects affected / exposed	1 / 341 (0.29%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foot fracture			
subjects affected / exposed	1 / 341 (0.29%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaw fracture			
subjects affected / exposed	1 / 341 (0.29%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Kidney contusion			
subjects affected / exposed	1 / 341 (0.29%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower limb fracture			

subjects affected / exposed	0 / 341 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal compression fracture			
subjects affected / exposed	1 / 341 (0.29%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haematoma			
subjects affected / exposed	1 / 341 (0.29%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 341 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Atrial fibrillation			
subjects affected / exposed	0 / 341 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac arrest			
subjects affected / exposed	0 / 341 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac failure acute			
subjects affected / exposed	1 / 341 (0.29%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	1 / 341 (0.29%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiopulmonary failure			

subjects affected / exposed	0 / 341 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiovascular insufficiency			
subjects affected / exposed	1 / 341 (0.29%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cor pulmonale			
subjects affected / exposed	1 / 341 (0.29%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolic cardiomyopathy			
subjects affected / exposed	1 / 341 (0.29%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	1 / 341 (0.29%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial ischaemia			
subjects affected / exposed	1 / 341 (0.29%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Nervous system disorders			
Brain oedema			
subjects affected / exposed	0 / 341 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cerebral infarction			
subjects affected / exposed	1 / 341 (0.29%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			

subjects affected / exposed	1 / 341 (0.29%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	1 / 341 (0.29%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tremor			
subjects affected / exposed	1 / 341 (0.29%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 341 (0.29%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia macrocytic			
subjects affected / exposed	1 / 341 (0.29%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia of chronic disease			
subjects affected / exposed	1 / 341 (0.29%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	1 / 341 (0.29%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	1 / 341 (0.29%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	1 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			

Deafness			
subjects affected / exposed	1 / 341 (0.29%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deafness bilateral			
subjects affected / exposed	4 / 341 (1.17%)	4 / 170 (2.35%)	
occurrences causally related to treatment / all	0 / 4	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Glaucoma			
subjects affected / exposed	1 / 341 (0.29%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 341 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	1 / 341 (0.29%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	2 / 341 (0.59%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroduodenitis			
subjects affected / exposed	1 / 341 (0.29%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrooesophageal reflux disease			
subjects affected / exposed	2 / 341 (0.59%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Ileal perforation			
subjects affected / exposed	1 / 341 (0.29%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	1 / 341 (0.29%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedematous pancreatitis			
subjects affected / exposed	1 / 341 (0.29%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatic pseudocyst			
subjects affected / exposed	1 / 341 (0.29%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	1 / 341 (0.29%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	2 / 341 (0.59%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 341 (0.29%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	1 / 341 (0.29%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholestasis			

subjects affected / exposed	0 / 341 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug-induced liver injury			
subjects affected / exposed	0 / 341 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis acute			
subjects affected / exposed	1 / 341 (0.29%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis alcoholic			
subjects affected / exposed	0 / 341 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis toxic			
subjects affected / exposed	2 / 341 (0.59%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatotoxicity			
subjects affected / exposed	3 / 341 (0.88%)	2 / 170 (1.18%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertransaminasaemia			
subjects affected / exposed	1 / 341 (0.29%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaundice			
subjects affected / exposed	1 / 341 (0.29%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Diabetic foot			

subjects affected / exposed	0 / 341 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug eruption			
subjects affected / exposed	0 / 341 (0.00%)	2 / 170 (1.18%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug reaction with eosinophilia and systemic symptoms			
subjects affected / exposed	1 / 341 (0.29%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urticaria			
subjects affected / exposed	0 / 341 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	3 / 341 (0.88%)	5 / 170 (2.94%)	
occurrences causally related to treatment / all	0 / 3	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Azotaemia			
subjects affected / exposed	0 / 341 (0.00%)	2 / 170 (1.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephropathy toxic			
subjects affected / exposed	1 / 341 (0.29%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal impairment			
subjects affected / exposed	1 / 341 (0.29%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Endocrine disorders			

Goitre			
subjects affected / exposed	1 / 341 (0.29%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypothyroidism			
subjects affected / exposed	1 / 341 (0.29%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Appendicitis			
subjects affected / exposed	1 / 341 (0.29%)	2 / 170 (1.18%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis perforated			
subjects affected / exposed	1 / 341 (0.29%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	1 / 341 (0.29%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Empyema			
subjects affected / exposed	1 / 341 (0.29%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	2 / 341 (0.59%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung abscess			
subjects affected / exposed	1 / 341 (0.29%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis			

subjects affected / exposed	1 / 341 (0.29%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			
subjects affected / exposed	1 / 341 (0.29%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	3 / 341 (0.88%)	2 / 170 (1.18%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 1	
Pneumonia necrotising			
subjects affected / exposed	0 / 341 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pneumonia viral			
subjects affected / exposed	1 / 341 (0.29%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary tuberculoma			
subjects affected / exposed	1 / 341 (0.29%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary tuberculosis			
subjects affected / exposed	2 / 341 (0.59%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 341 (0.29%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tuberculoma of central nervous system			

subjects affected / exposed	1 / 341 (0.29%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tuberculosis			
subjects affected / exposed	11 / 341 (3.23%)	3 / 170 (1.76%)	
occurrences causally related to treatment / all	0 / 11	0 / 3	
deaths causally related to treatment / all	0 / 3	0 / 0	
Tuberculous pleurisy			
subjects affected / exposed	1 / 341 (0.29%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 341 (0.29%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			
subjects affected / exposed	1 / 341 (0.29%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Cachexia			
subjects affected / exposed	1 / 341 (0.29%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrolyte imbalance			
subjects affected / exposed	2 / 341 (0.59%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypocalcaemia			
subjects affected / exposed	1 / 341 (0.29%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypochloraemia			

subjects affected / exposed	1 / 341 (0.29%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	9 / 341 (2.64%)	3 / 170 (1.76%)	
occurrences causally related to treatment / all	0 / 9	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypomagnesaemia			
subjects affected / exposed	3 / 341 (0.88%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	0 / 341 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Delamanid + Optimized background regimen (OBR)	Placebo + OBR	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	335 / 341 (98.24%)	165 / 170 (97.06%)	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	27 / 341 (7.92%)	10 / 170 (5.88%)	
occurrences (all)	33	14	
Chest pain			
subjects affected / exposed	22 / 341 (6.45%)	8 / 170 (4.71%)	
occurrences (all)	23	9	
Injection site pain			
subjects affected / exposed	24 / 341 (7.04%)	20 / 170 (11.76%)	
occurrences (all)	33	28	
Psychiatric disorders			

Adjustment disorder			
subjects affected / exposed	8 / 341 (2.35%)	9 / 170 (5.29%)	
occurrences (all)	11	11	
Alcohol abuse			
subjects affected / exposed	14 / 341 (4.11%)	15 / 170 (8.82%)	
occurrences (all)	32	23	
Anxiety			
subjects affected / exposed	28 / 341 (8.21%)	21 / 170 (12.35%)	
occurrences (all)	39	32	
Depression			
subjects affected / exposed	26 / 341 (7.62%)	19 / 170 (11.18%)	
occurrences (all)	37	22	
Insomnia			
subjects affected / exposed	87 / 341 (25.51%)	46 / 170 (27.06%)	
occurrences (all)	145	66	
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	22 / 341 (6.45%)	10 / 170 (5.88%)	
occurrences (all)	26	11	
Cardiac disorders			
Palpitations			
subjects affected / exposed	19 / 341 (5.57%)	12 / 170 (7.06%)	
occurrences (all)	21	14	
Nervous system disorders			
Dizziness			
subjects affected / exposed	51 / 341 (14.96%)	23 / 170 (13.53%)	
occurrences (all)	62	34	
Headache			
subjects affected / exposed	104 / 341 (30.50%)	39 / 170 (22.94%)	
occurrences (all)	165	68	
Neuropathy peripheral			
subjects affected / exposed	28 / 341 (8.21%)	18 / 170 (10.59%)	
occurrences (all)	33	24	
Tremor			
subjects affected / exposed	21 / 341 (6.16%)	5 / 170 (2.94%)	
occurrences (all)	27	6	

Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	17 / 341 (4.99%)	9 / 170 (5.29%)	
occurrences (all)	21	11	
Ear and labyrinth disorders			
Deafness bilateral			
subjects affected / exposed	15 / 341 (4.40%)	9 / 170 (5.29%)	
occurrences (all)	17	11	
Hypoacusis			
subjects affected / exposed	15 / 341 (4.40%)	15 / 170 (8.82%)	
occurrences (all)	16	15	
Tinnitus			
subjects affected / exposed	71 / 341 (20.82%)	36 / 170 (21.18%)	
occurrences (all)	102	52	
Eye disorders			
Vision blurred			
subjects affected / exposed	13 / 341 (3.81%)	10 / 170 (5.88%)	
occurrences (all)	14	11	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	33 / 341 (9.68%)	21 / 170 (12.35%)	
occurrences (all)	42	24	
Abdominal pain upper			
subjects affected / exposed	35 / 341 (10.26%)	28 / 170 (16.47%)	
occurrences (all)	62	35	
Constipation			
subjects affected / exposed	12 / 341 (3.52%)	13 / 170 (7.65%)	
occurrences (all)	14	14	
Diarrhoea			
subjects affected / exposed	62 / 341 (18.18%)	33 / 170 (19.41%)	
occurrences (all)	92	51	
Dyspepsia			
subjects affected / exposed	33 / 341 (9.68%)	14 / 170 (8.24%)	
occurrences (all)	42	17	
Gastritis			
subjects affected / exposed	76 / 341 (22.29%)	27 / 170 (15.88%)	
occurrences (all)	133	46	

Gastrooesophageal reflux disease			
subjects affected / exposed	19 / 341 (5.57%)	11 / 170 (6.47%)	
occurrences (all)	20	11	
Nausea			
subjects affected / exposed	95 / 341 (27.86%)	56 / 170 (32.94%)	
occurrences (all)	133	80	
Toothache			
subjects affected / exposed	29 / 341 (8.50%)	17 / 170 (10.00%)	
occurrences (all)	32	25	
Vomiting			
subjects affected / exposed	92 / 341 (26.98%)	39 / 170 (22.94%)	
occurrences (all)	150	62	
Hepatobiliary disorders			
Hepatotoxicity			
subjects affected / exposed	20 / 341 (5.87%)	11 / 170 (6.47%)	
occurrences (all)	33	15	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	28 / 341 (8.21%)	14 / 170 (8.24%)	
occurrences (all)	35	21	
Rash			
subjects affected / exposed	27 / 341 (7.92%)	9 / 170 (5.29%)	
occurrences (all)	30	11	
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	18 / 341 (5.28%)	7 / 170 (4.12%)	
occurrences (all)	24	10	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	116 / 341 (34.02%)	65 / 170 (38.24%)	
occurrences (all)	192	121	
Back pain			
subjects affected / exposed	44 / 341 (12.90%)	31 / 170 (18.24%)	
occurrences (all)	62	43	
Musculoskeletal pain			

subjects affected / exposed	21 / 341 (6.16%)	10 / 170 (5.88%)	
occurrences (all)	24	13	
Myalgia			
subjects affected / exposed	31 / 341 (9.09%)	14 / 170 (8.24%)	
occurrences (all)	43	18	
Pain in extremity			
subjects affected / exposed	24 / 341 (7.04%)	16 / 170 (9.41%)	
occurrences (all)	29	21	
Infections and infestations			
Bronchitis			
subjects affected / exposed	19 / 341 (5.57%)	13 / 170 (7.65%)	
occurrences (all)	20	15	
Influenza			
subjects affected / exposed	21 / 341 (6.16%)	6 / 170 (3.53%)	
occurrences (all)	34	8	
Nasopharyngitis			
subjects affected / exposed	71 / 341 (20.82%)	43 / 170 (25.29%)	
occurrences (all)	121	84	
Pharyngitis			
subjects affected / exposed	32 / 341 (9.38%)	23 / 170 (13.53%)	
occurrences (all)	45	30	
Rhinitis			
subjects affected / exposed	13 / 341 (3.81%)	10 / 170 (5.88%)	
occurrences (all)	18	10	
Upper respiratory tract infection			
subjects affected / exposed	49 / 341 (14.37%)	21 / 170 (12.35%)	
occurrences (all)	114	38	
Urinary tract infection			
subjects affected / exposed	36 / 341 (10.56%)	15 / 170 (8.82%)	
occurrences (all)	48	16	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	26 / 341 (7.62%)	9 / 170 (5.29%)	
occurrences (all)	33	11	
Hyperuricaemia			

subjects affected / exposed	34 / 341 (9.97%)	22 / 170 (12.94%)	
occurrences (all)	45	25	
Hypokalaemia			
subjects affected / exposed	53 / 341 (15.54%)	29 / 170 (17.06%)	
occurrences (all)	111	71	
Hypomagnesaemia			
subjects affected / exposed	20 / 341 (5.87%)	7 / 170 (4.12%)	
occurrences (all)	24	13	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 March 2011	Amendment 1 (version 3.0): Decreased dose to 100 mg BID for 2 months and 200 mg QD for 4 months; Increased follow-up period to 12 months; Increased the number of subjects to be enrolled.
12 May 2011	Amendment 2 (version4.0): Addition of safety data and addition of a second ICF for subjects with HIV co-infection.
01 September 2011	Amendment 3 (version 5.0): The protocol was divided into 2 protocols - trial and HIV sub trial.
01 September 2011	Amendment 3 (version 5.1): The protocol was divided into 2 protocols - trial and HIV subtrial. Added optional genetic testing for HIV-positive subjects.
25 September 2012	