Clinical trial results:
Phase 2, Open-label, Multiple-dose Trial to Assess the Safety, Tolerability, Pharmacokinetics, and Efficacy of Delamanid (OPC-67683) in Pediatric Multidrug-resistant Tuberculosis Patients on Therapy With an Optimized Background Regimen of Antituberculosis Drugs over a 6-Month Treatment Period

Summary

EudraCT number	2012-004620-38
Trial protocol	Outside EU/EEA
Global end of trial date	13 January 2020

Results information

Result version number	v1 (current)
This version publication date	29 July 2020
First version publication date	29 July 2020

Trial information

Trial identification

Sponsor protocol code	242-12-233

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01859923
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Otsuka Pharmaceutical Development & Commercialization, Inc.
Sponsor organisation address	2440 Research Boulevard, Rockville, United States, 20850
Public contact	Global Clinical Development, Otsuka Pharmaceutical Development & Commercialization, Inc., +1 609-524-6788, clinicaltransparency@otsuka-us.com
Scientific contact	Global Clinical Development, Otsuka Pharmaceutical Development & Commercialization, Inc., +1 609-524-6788, clinicaltransparency@otsuka-us.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-001113-PIP01-10
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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	13 January 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	13 January 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of this trial was to assess the safety, tolerability, pharmacokinetics, and efficacy of long-term (6-month) treatment with delamanid plus an optimized background regimen (OBR) of other anti-tuberculosis drugs in paediatric participants who completed Study 242-12-232 (NCT01856634; 2012-004473-25).

Protection of trial subjects:

This study was conducted in accordance with International Conference on Harmonisation (ICH) Good Clinical Practice, and the principles of the Declaration of Helsinki, in addition to following the laws and regulations of the country or countries in which the study was conducted.

Background therapy:

All participants were required to be on a standard-of-care, optimized background regimen (OBR) for at least 2 weeks prior to baseline assessments. Medications for the OBR for Multidrug-resistant tuberculosis (MDR-TB) treatment for each trial participant were procured through the standard mechanisms available for a given site ordinarily used for procurement of OBR medications for treating MDR-TB participants. Selection and administration of the treatment medications were based on World Health Organization's Guidelines for the programmatic management of MDR-TB, in conjunction with national TB program guidelines in each country.

Evidence for comparator:

This study did not include a comparator as it involved only a single investigational therapy (delamanid) that was administered to participants already receiving a standard-of-care OBR for MDR-TB.

Actual start date of recruitment	20 July 2013
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	6 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	South Africa: 12
Country: Number of subjects enrolled	Philippines: 25
Worldwide total number of subjects	37
EEA total number of subjects	0

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	7
Children (2-11 years)	23
Adolescents (12-17 years)	7
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants took part in the study at 3 investigative sites in Philippines and South Africa from July 20, 2013 to January 13, 2020. Participants received delamanid up to Day 182 in the treatment period and were followed up to Day 365 for safety and efficacy and up to Day 730 (Month 24) for treatment outcome.

Pre-assignment

Screening details:

Pediatric participants with a diagnosis of MDR-TB who were on therapy with an optimized background regimen (OBR) of anti-tuberculosis drugs and completed study 242-12-232 (NCT01856634; 2012-004473-25) were enrolled in this extension study 242-12-233 to receive delamanid based on the participant's age and weight.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Group 1: 12 to 17 Years of Age

Arm description:

Participants 12 to 17 years old (inclusive) received adult formulation of delamanid 100 milligrams (mg) (2x50 mg tablets), orally, twice daily (BID) plus optimized background regimen (OBR) up to Day 182. Participants continued to receive OBR up to Day 365.

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

Dosage and administration details:

Participants received adult formulation delamanid as per regimen specified in the arm description. Morning dose of the delamanid BID regimen was given within 30 minutes after the start of a standard breakfast meal. The evening dose of the BID dose regimen was given 10 hours post morning dose and within 30 minutes after the start of a standard dinner meal.

Arm title	Group 2: 6 to 11 Years of Age

Arm description:

Participants 6 to 11 years old (inclusive) received adult formulation delamanid 50 mg (1x50 mg tablet), orally, BID plus OBR up to Day 182. Participants continued to receive OBR up to Day 365.

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

Dosage and administration details:

Participants received adult formulation delamanid as per regimen specified in the arm description. Morning dose of the delamanid BID regimen was given within 30 minutes after the start of a standard breakfast meal. The evening dose of the BID dose regimen was given 10 hours post morning dose and within 30 minutes after the start of a standard dinner meal.

Arm title	Group 3: 3 to 5 Years of Age

Arm description:

Participants 3 to 5 years old (inclusive) received 25 mg pediatric formulation of delamanid (DPF - suspension prepared using dispersible tablet), orally, BID plus OBR up to Day 182. Participants continued to receive OBR up to Day 365.

Arm type	Experimental
Investigational medicinal product name	Delamanid
Investigational medicinal product code	
Other name	OPC-67683, Delamanid Pediatric Formulation (DPF)
Pharmaceutical forms	Dispersible tablet
Routes of administration	Oral use

Dosage and administration details:

Participants received delamanid as an extemporaneous suspension using the delamanid pediatric dispersible tablet formulation. Morning dose of the delamanid BID/once daily (QD) regimen was given within 30 minutes after the start of a standard breakfast meal. The evening dose of the BID dose regimen was given 10 hours post morning dose and within 30 minutes after the start of a standard meal.

Arm title	Group 4: Birth to 2 Years of Age

Arm description:

Participants from birth to 2 years old (inclusive) received DPF (suspension prepared using dispersible tablet) for 182 days plus OBR. Participants continued to receive OBR up to Day 365. The DPF dose was based on the participant's body weight during the baseline visit:

- Participants >10 kilograms (kg) received DPF 10 mg BID plus OBR
- Participants >8 kg and ≤10 kg received DPF 5 mg BID plus OBR
- Participants ≥5.5 kg and ≤8 kg received DPF 5 mg once per day (QD) plus OBR

Delamanid dose was adjusted as needed for Group 4 participants based on the weight measurement at specified study visits [Visits 5 (Day 28), 7 (Day 56), 9 (Day 84), 11 (Day 126) and 12 (Day 154)].

Arm type	Experimental
Investigational medicinal product name	Delamanid
Investigational medicinal product code	
Other name	OPC-67683, Delamanid Pediatric Formulation (DPF)
Pharmaceutical forms	Dispersible tablet
Routes of administration	Oral use

Dosage and administration details:

Participants received delamanid as an extemporaneous suspension using the delamanid pediatric dispersible tablet formulation. Morning dose of the delamanid BID/once daily (QD) regimen was given within 30 minutes after the start of a standard breakfast meal. The evening dose of the BID dose regimen was given 10 hours post morning dose and within 30 minutes after the start of a standard meal.

Number of subjects in period 1	Group 1: 12 to 17 Years of Age	Group 2: 6 to 11 Years of Age	Group 3: 3 to 5 Years of Age
Started	7	6	12
Completed	7	6	11
Not completed	0	0	1
Adverse event, serious fatal	-	-	1

Number of subjects in period 1	Group 4: Birth to 2 Years of Age
Started	12
Completed	11
Not completed	1
Adverse event, serious fatal	1

Baseline characteristics

Reporting groups	
Reporting group title	Group 1: 12 to 17 Years of Age
Reporting group description:	
Participants 12 to 17 years old (inclusive) received adult formulation of delamanid 100 milligrams (mg) (2x50 mg tablets), orally, twice daily (BID) plus optimized background regimen (OBR) up to Day 182. Participants continued to receive OBR up to Day 365.	
Reporting group title	Group 2: 6 to 11 Years of Age
Reporting group description:	
Participants 6 to 11 years old (inclusive) received adult formulation delamanid 50 mg (1x50 mg tablet), orally, BID plus OBR up to Day 182. Participants continued to receive OBR up to Day 365.	
Reporting group title	Group 3: 3 to 5 Years of Age
Reporting group description:	
Participants 3 to 5 years old (inclusive) received 25 mg pediatric formulation of delamanid (DPF - suspension prepared using dispersible tablet), orally, BID plus OBR up to Day 182. Participants continued to receive OBR up to Day 365.	
Reporting group title	Group 4: Birth to 2 Years of Age
Reporting group description:	
Participants from birth to 2 years old (inclusive) received DPF (suspension prepared using dispersible tablet) for 182 days plus OBR. Participants continued to receive OBR up to Day 365. The DPF dose was based on the participant's body weight during the baseline visit: • Participants >10 kilograms (kg) received DPF 10 mg BID plus OBR • Participants >8 kg and ≤10 kg received DPF 5 mg BID plus OBR • Participants ≥5.5 kg and ≤8 kg received DPF 5 mg once per day (QD) plus OBR Delamanid dose was adjusted as needed for Group 4 participants based on the weight measurement at specified study visits [Visits 5 (Day 28), 7 (Day 56), 9 (Day 84), 11 (Day 126) and 12 (Day 154)].	

Reporting group values	Group 1: 12 to 17 Years of Age	Group 2: 6 to 11 Years of Age	Group 3: 3 to 5 Years of Age
Number of subjects	7	6	12
Age categorical Units: Subjects			
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	6	12
Adolescents (12-17 years)	7	0	0
Age continuous Units: years			
arithmetic mean	15.37	9.51	4.37
standard deviation	± 1.63	± 1.49	± 0.98
Gender categorical Units: Subjects			
Female	3	4	6
Male	4	2	6
Race Units: Subjects			
Black or African American	0	0	2
Asian	7	4	8
Other	0	2	2
Ethnicity Units: Subjects			

Not Hispanic or Latino	7	6	12

Reporting group values	Group 4: Birth to 2 Years of Age	Total	
Number of subjects	12	37	
Age categorical Units: Subjects			
Infants and toddlers (28 days-23 months)	7	7	
Children (2-11 years)	5	23	
Adolescents (12-17 years)	0	7	
Age continuous Units: years			
arithmetic mean	1.79		
standard deviation	± 0.59	-	
Gender categorical Units: Subjects			
Female	6	19	
Male	6	18	
Race Units: Subjects			
Black or African American	0	2	
Asian	6	25	
Other	6	10	
Ethnicity Units: Subjects			
Not Hispanic or Latino	12	37	

End points

End points reporting groups

Reporting group title	Group 1: 12 to 17 Years of Age

Reporting group description:

Participants 12 to 17 years old (inclusive) received adult formulation of delamanid 100 milligrams (mg) (2x50 mg tablets), orally, twice daily (BID) plus optimized background regimen (OBR) up to Day 182. Participants continued to receive OBR up to Day 365.

Reporting group title	Group 2: 6 to 11 Years of Age

Reporting group description:

Participants 6 to 11 years old (inclusive) received adult formulation delamanid 50 mg (1x50 mg tablet), orally, BID plus OBR up to Day 182. Participants continued to receive OBR up to Day 365.

Reporting group title	Group 3: 3 to 5 Years of Age

Reporting group description:

Participants 3 to 5 years old (inclusive) received 25 mg pediatric formulation of delamanid (DPF - suspension prepared using dispersible tablet), orally, BID plus OBR up to Day 182. Participants continued to receive OBR up to Day 365.

Reporting group title	Group 4: Birth to 2 Years of Age

Reporting group description:

Participants from birth to 2 years old (inclusive) received DPF (suspension prepared using dispersible tablet) for 182 days plus OBR. Participants continued to receive OBR up to Day 365. The DPF dose was based on the participant's body weight during the baseline visit:

- Participants >10 kilograms (kg) received DPF 10 mg BID plus OBR
- Participants >8 kg and ≤10 kg received DPF 5 mg BID plus OBR
- Participants ≥5.5 kg and ≤8 kg received DPF 5 mg once per day (QD) plus OBR

Delamanid dose was adjusted as needed for Group 4 participants based on the weight measurement at specified study visits [Visits 5 (Day 28), 7 (Day 56), 9 (Day 84), 11 (Day 126) and 12 (Day 154)].

Subject analysis set title	Delamanid
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants received delamanid 25, 50 or 100 mg based on age and weight plus OBR up to Day 182. Participants continued to receive OBR up to Day 365.

Primary: Number of Participants With At Least One Treatment Emergent Adverse Event (TEAE)

End point title	Number of Participants With At Least One Treatment Emergent Adverse Event (TEAE)[1]

End point description:

An adverse event (AE) is defined as any untoward medical occurrence in a clinical trial participant and that does not necessarily have a causal relationship with the treatment. A TEAE is defined as an AE that occurred after the administration of investigational medicinal product (IMP). The Safety Sample included participants who received any amount of IMP in this study, regardless of any protocol deviation or violation.

End point type	Primary

End point timeframe:

From the first dose of study drug up to the end of the Post-treatment Follow-up Period (Up to Day 365)

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Inferential statistical analyses was not performed for the safety endpoints. Descriptive statistics are included (number of participants).

End point values	Group 1: 12 to 17 Years of Age	Group 2: 6 to 11 Years of Age	Group 3: 3 to 5 Years of Age	Group 4: Birth to 2 Years of Age
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	7	6	12	12
Units: subjects	7	6	12	12

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants With Abnormal Physical Examination Values

End point title	Number of Participants With Abnormal Physical Examination Values[2]

End point description:

Physical examination included the examination of the abdomen; extremities; head, eyes, ears, nose (HEENT); neurological; skin and mucosae; thorax; urogenital; audiometry assessment and visual assessment. Participants with abnormal values, as assessed by the investigator were reported. The Safety Sample included participants who received any amount of IMP in this study, regardless of any protocol deviation or violation. Number of participants analysed are the participants with data available for analyses.

End point type	Primary

End point timeframe:

From the first dose of study drug up to the end of the Post-treatment Follow-up Period (Up to Day 365)

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Inferential statistical analyses was not performed for the safety endpoints. Descriptive statistics are included (number of participants).

End point values	Group 1: 12 to 17 Years of Age	Group 2: 6 to 11 Years of Age	Group 3: 3 to 5 Years of Age	Group 4: Birth to 2 Years of Age
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	7	6	12	11
Units: subjects				
Abdomen	1	1	4	2
Extremities	2	0	1	1
HEENT	7	6	12	10
Neurological	1	0	1	1
Skin and Mucosae	2	6	6	8
Thorax	5	2	6	7
Urogenital	0	0	1	3
Audiometry Assessment	4	3	9	7
Visual Assessment	0	1	0	1

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants With Clinically Significant Abnormal Vital Sign Values

End point title	Number of Participants With Clinically Significant Abnormal Vital Sign Values[3]

End point description:

Vital signs included weight (kg), height (cm), body temperature (degree Celsius), heart rate (beats/min), respiratory rate (breaths/minute), systolic and diastolic blood pressure (mm Hg), body mass index (BMI) (kg/m^2). The criteria for clinically significant abnormal value for weight was decrease or increase of >=5% in body weight relative to Baseline. Only categories with data for potentially clinically significant abnormal vital sign parameter values are reported. The Safety Sample included participants who received any amount of IMP in this study, regardless of any protocol deviation or violation. Number of participants analysed are the participants with data available for analyses.

End point type	Primary

End point timeframe:

From the first dose of study drug up to the end of the Post-treatment Follow-up Period (Up to Day 365)

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Inferential statistical analyses was not performed for the safety endpoints. Descriptive statistics are included (number of participants).

End point values	Group 1: 12 to 17 Years of Age	Group 2: 6 to 11 Years of Age	Group 3: 3 to 5 Years of Age	Group 4: Birth to 2 Years of Age
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	7	6	12	11
Units: subjects				
Decrease of >=5% in Body Weight	0	2	0	1
Increase of >=5% in Body Weight	4	2	10	10

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants With Clinically Significant Abnormalities in Electrocardiogram (ECG)

End point title	Number of Participants With Clinically Significant Abnormalities in Electrocardiogram (ECG)[4]

End point description:

Criteria for clinically significant abnormal ECG values were ventricular rate outlier (<50 bpm and decrease of >=25%, >100 bpm and increase of >=25%), PR outlier (increase of >=25% when PR >200 milliseconds (ms), QRS outlier (increase of >=25% when QRS >100 ms), QT (new onset (in treatment period but not at Baseline) [>500 ms]), QT interval corrected by Bazett's formula (QTcB) (new onset [>450, >480, >500 ms], increase of >=30 ms and <= 60 ms or increase of >60 ms), QT interval corrected by Fridericia's formula (QTcF) (new onset [>450, >480, >500 ms], increase of >=30 ms and <= 60 ms or increase of >60 ms), new abnormal U waves, new ST segment changes, new T wave changes, new abnormal rhythm, new conduction abnormality were reported as categories. Only categories with data are reported. Safety Sample included participants who received any amount of IMP, regardless of any protocol deviation or violation. Number of participants analysed are participants with data available for analyses.

End point type	Primary

End point timeframe:

From the first dose of study drug up to the end of the Post-treatment Follow-up Period (Up to Day 365)

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Inferential statistical analyses was not performed for the safety endpoints. Descriptive statistics are included (number of participants).

End point values	Group 1: 12 to 17 Years of Age	Group 2: 6 to 11 Years of Age	Group 3: 3 to 5 Years of Age	Group 4: Birth to 2 Years of Age
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	7	6	12	11
Units: subjects				
Ventricular Rate Outliers, Notable Increases	1	0	1	4
QRS Outliers	1	0	0	0
QTcB, New Onset (>480 ms)	1	1	1	0
QTcB, New Onset (>450 ms)	7	2	8	5
QTcB, New Onset (Change >= 30 and <=60 ms)	5	3	8	9
QTcB, New Onset (Change > 60 ms)	1	0	0	2
QTcF, New Onset (>450 ms)	3	2	0	0
QTcF, New Onset (Change >= 30 and <=60 ms)	5	2	6	9
QTcF, New Onset (Change > 60 ms)	1	0	0	1
New Abnormal Rhythm	5	4	6	1
New Conduction Abnormality	6	5	5	8

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants With Clinically Significant Laboratory Test Abnormalities

End point title	Number of Participants With Clinically Significant Laboratory Test Abnormalities[5]

End point description:

Laboratory assessments included parameters for serum chemistry, hematology and urinalysis along with adrenocorticotropic hormone, serum cortisol, free thyroxine, thyroid stimulating hormone (TSH), and high sensitivity C-reactive protein cell count. The participants were categorized based on the clinically significant laboratory values as per protocol predefined criteria. The categories with at least one participant with clinically significant value outside the normal range for laboratory assessments are reported. The normal ranges for those laboratory parameters were potassium 3.4 - 5.4 milliequivalents per liter (mEq/L, uric acid 3.9 - 8.2 mg/dL, partial thromboplastin time (PTT) 9.7 - 12.3 sec, platelet count 180 - 440 thousands platelets/µL. The Safety Sample included participants who received any amount of IMP in this study, regardless of any protocol deviation or violation.

End point type	Primary

End point timeframe:

From the first dose of study drug up to the end of the Post-treatment Follow-up Period (Up to Day 365)

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Inferential statistical analyses was not performed for the safety endpoints. Descriptive statistics are included (number of participants).

End point values	Group 1: 12 to 17 Years of Age	Group 2: 6 to 11 Years of Age	Group 3: 3 to 5 Years of Age	Group 4: Birth to 2 Years of Age
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	7	6	12	12
Units: subjects				
Elevated Potassium	0	0	0	1
Elevated Uric Acid	1	0	1	0
Elevated PTT	0	1	2	0
Low Platelet Count	0	0	0	1

Statistical analyses

No statistical analyses for this end point

Primary: Population Pharmacokinetic (POPPK) Model Point Estimate for Central Clearance (L) and Inter-compartmental Clearance (Q) of Delamanid

End point title	Population Pharmacokinetic (POPPK) Model Point Estimate for Central Clearance (L) and Inter-compartmental Clearance (Q) of Delamanid[6]

End point description:

Central clearance is defined as plasma volume in the vascular compartment that is cleared of drug per unit of time. Inter-compartmental clearance is defined as a ratio of the drug's distribution rate between the central compartment and the peripheral compartments over its circulating concentration (L/hr). Population point estimates were based on POPPK analysis to find one measure each for both L and Q. The exposure data were pooled across visits and participants to identify POPPK parameter estimates and were reported for delamanid. Population Pharmacokinetic (PK)/Pharmacodynamic (PD) analysis sample included all the participants with data available for PK/PD analysis.

End point type	Primary

End point timeframe:

Predose on Days 1, 56, 154, and 182, 210 and at any time point on Days 14, 98, 189, 196, 203, and 238

Notes:

[6] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Inferential statistical analysis (comparison between groups) was not performed for the PK/PD endpoints.

End point values	Delamanid			
Subject group type	Subject analysis set			
Number of subjects analysed	37			
Units: L/hr				
number (not applicable)				
Central Clearance (L)	18.1			
Inter-compartmental Clearance (Q)	105			

Statistical analyses

No statistical analyses for this end point

Primary: POPPK Model Point Estimate for Central Volume of Distribution (Vc) and Peripheral Volume of Distribution (Vp) of Delamanid

End point title	POPPK Model Point Estimate for Central Volume of Distribution (Vc) and Peripheral Volume of Distribution (Vp) of Delamanid[7]

End point description:

Vc is defined as the theoretical volume that would be necessary to contain the total amount of an administered drug at the same concentration that it is observed in the blood plasma. Vp is defined as the apparent volume needed to account for the total amount of drug in the body if the drug was evenly distributed throughout the body and in the same concentration as the site of sample collection such as peripheral venous plasma. Population point estimates were based on POPPK analysis to find one measure each for both Vc and Vp. The exposure data were pooled across visits and participants to identify POPPK parameter estimates and were reported for delamanid. Population PK/PD analysis sample included all the participants with data available for PK/PD analysis.

End point type	Primary

End point timeframe:

Predose on Days 1, 56, 154, and 182, 210 and at any time point on Days 14, 98, 189, 196, 203, and 238

Notes:

[7] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Inferential statistical analysis (comparison between groups) was not performed for the PK/PD endpoints.

End point values	Delamanid			
Subject group type	Subject analysis set			
Number of subjects analysed				
Units: litres (L)				
Central Volume of Distribution (Vc)	254			
Peripheral Volume of Distribution (Vp)	347			

Statistical analyses

No statistical analyses for this end point

Primary: POPPK Model Point Estimate for Absorption Rate Constant (Ka) of Delamanid

End point title	POPPK Model Point Estimate for Absorption Rate Constant (Ka) of Delamanid[8]

End point description:

Ka is defined as a measure of rate at which a drug enters into the circulatory system. Population point estimate for Ka was based on population PK analysis to find one measure. Population point estimates were based on POPPK analysis to find one measure for Ka. The exposure data were pooled across visits and participants to identify POPPK parameter estimates and were reported for delamanid. Population PK/PD analysis sample included all the participants with data available for PK/PD analysis.

End point type	Primary

End point timeframe:

Predose on Days 1, 56, 154, and 182, 210 and at any time point on Days 14, 98, 189, 196, 203, and 238

Notes:

[8] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Inferential statistical analysis (comparison between groups) was not performed for the PK/PD endpoints.

End point values	Delamanid			
Subject group type	Subject analysis set			
Number of subjects analysed	37			
Units: per hour (1/hr)				
number (not applicable)	0.254			

Statistical analyses

No statistical analyses for this end point

Primary: POPPK Model Point Estimate for Absorption Lag Time (ALAG1) of Delamanid

End point title	POPPK Model Point Estimate for Absorption Lag Time (ALAG1) of Delamanid[9]

End point description:

ALAG1 is defined as the time delay prior to the commencement of drug absorption. Population point estimates were based on POPPK analysis to find one measure for ALAG1. The exposure data were pooled across visits and participants to identify POPPK parameter estimates and were reported for delamanid. Population PK/PD analysis sample included all the participants with data available for PK/PD analysis.

End point type	Primary

End point timeframe:

Predose on Days 1, 56, 154, and 182, 210 and at any time point on Days 14, 98, 189, 196, 203, and 238

Notes:

[9] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Inferential statistical analysis (comparison between groups) was not performed for the PK/PD endpoints.

End point values	Delamanid			
Subject group type	Subject analysis set			
Number of subjects analysed	37			
Units: hour (hr)				
number (not applicable)	1.38			

Statistical analyses

No statistical analyses for this end point

Secondary: Baseline QT Interval Corrected by Bazett’s Formula (QTcB) Effect

End point title	Baseline QT Interval Corrected by Bazett’s Formula (QTcB) Effect

End point description:

The 12-lead ECG was performed to obtain recordings of heart rate (QT interval) to analyze QTcB effect. Population PK/PD analysis sample included all the participants with data available for PK/PD analysis.

End point type	Secondary

End point timeframe:

Baseline (Day -1)

End point values	Delamanid			
Subject group type	Subject analysis set			
Number of subjects analysed	37			
Units: ms				
arithmetic mean (confidence interval 90%)				
Delamanid	0.0318 (-0.113 to 0.177)			
Metabolite DM-6705	0.0309 (-0.112 to 0.174)			

Statistical analyses

No statistical analyses for this end point

Secondary: PK/PD Relationship: POPPK Model Point Estimate for Slope of Linear Mixed Effects Model for Change in QTcB Interval Versus Delamanid Plasma Concentrations

End point title	PK/PD Relationship: POPPK Model Point Estimate for Slope of Linear Mixed Effects Model for Change in QTcB Interval Versus Delamanid Plasma Concentrations

End point description:

The linear mixed effects model was applied to characterize the concentration-QTcB relationship of delamanid/DM-6705 to obtain population slope estimate.

End point type	Secondary

End point timeframe:

Predose on Days 1, 56, 154, and 182, 210 and at any time point on Days 14, 98, 189, 196, 203, and 238

End point values	Delamanid			
Subject group type	Subject analysis set			
Number of subjects analysed	37			
Units: ms/[ng/mL]				
arithmetic mean (confidence interval 90%)				
Delamanid	0.00792 (-0.00132 to 0.0172)			
Metabolite DM-6705	0.0613 (0.016 to 0.107)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Treatment Outcome as Assessed by Principal Investigator

End point title	Number of Participants With Treatment Outcome as Assessed by Principal Investigator

End point description:

Treatment outcome was defined as favorable (cured and completed treatment) and unfavorable (lost to follow-up or died).The Safety Sample included participants who received any amount of IMP in this study, regardless of any protocol deviation or violation.

End point type	Secondary

End point timeframe:

Month 24

End point values	Group 1: 12 to 17 Years of Age	Group 2: 6 to 11 Years of Age	Group 3: 3 to 5 Years of Age	Group 4: Birth to 2 Years of Age
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	7	6	12	12
Units: subjects				
Favorable (Cured + Treatment Completed)	6	6	10	11
Unfavorable (Lost To Follow-up + Died)	1	0	2	1

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Abnormal Chest X-ray

End point title	Number of Participants With Abnormal Chest X-ray

End point description:

The data for the chest X-ray with abnormality, as assessed by investigator is reported. The Safety Sample included participants who received any amount of IMP in this study, regardless of any protocol deviation or violation.

End point type	Secondary

End point timeframe:

From the first dose of study drug up to the end of the Post-treatment Follow-up Period (Up to Day 365)

End point values	Group 1: 12 to 17 Years of Age	Group 2: 6 to 11 Years of Age	Group 3: 3 to 5 Years of Age	Group 4: Birth to 2 Years of Age
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	7	6	12	12
Units: subjects	7	6	12	11

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Investigator-Assessed Signs and Symptoms of Tuberculosis

End point title	Number of Participants With Investigator-Assessed Signs and Symptoms of Tuberculosis

End point description:

The following signs and symptoms of tuberculosis were assessed by the investigator: cough, fever, weight loss, failure to thrive, hemoptysis, dyspnea, chest pain, night sweats and loss of appetite. The Safety Sample included participants who received any amount of IMP in this study, regardless of any protocol deviation or violation.

End point type	Secondary

End point timeframe:

From the first dose of study drug up to the end of the Post-treatment Follow-up Period (Up to Day 365)

End point values	Group 1: 12 to 17 Years of Age	Group 2: 6 to 11 Years of Age	Group 3: 3 to 5 Years of Age	Group 4: Birth to 2 Years of Age
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	7	6	12	12
Units: subjects				
Cough	6	4	3	7
Fever	1	2	2	5
Weight Loss	3	5	7	9
Failure to Thrive	0	1	0	3
Hemoptysis	2	0	0	0
Dyspnea	1	1	3	2
Chest Pain	1	1	0	0
Night Sweats	0	0	1	2
Loss of Appetite	1	2	2	6

Statistical analyses

No statistical analyses for this end point

Secondary: Sputum Culture Conversion (SCC)

End point title	Sputum Culture Conversion (SCC)

End point description:

SCC was defined as a sputum specimen from a participant negative for growth of mycobacterium tuberculosis (MTB), followed by at least one confirmatory negative sputum culture at least 27 days after

the first negative sputum test and not followed by any sputum cultures positive for growth.

End point type	Secondary

End point timeframe:

From the first dose of study drug up to the end of the Post-treatment Follow-up Period (Up to Day 365)

End point values	Group 1: 12 to 17 Years of Age	Group 2: 6 to 11 Years of Age	Group 3: 3 to 5 Years of Age	Group 4: Birth to 2 Years of Age
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[10]	0[11]	0[12]	0[13]
Units: subjects				

Notes:

[10] - Data for SCC could not be collected due to the paucity of sputum production in the participants.

[11] - Data for SCC could not be collected due to the paucity of sputum production in the participants.

[12] - Data for SCC could not be collected due to the paucity of sputum production in the participants.

[13] - Data for SCC could not be collected due to the paucity of sputum production in the participants.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Palatability Score as Assessed by the Investigator

End point title	Number of Participants With Palatability Score as Assessed by the Investigator[14]

End point description:

The palatability of the pediatric formulation was assessed using an age-appropriate visual hedonic scale and clinical assessment (Groups 3 and 4 only). The palatability result was based on 1 of 5 responses: 1="Dislike very much", 2="Dislike a little", 3="Neither liked nor disliked", 4="Like a little", 5="Like very much". Participants were categorized based on different scores. The data per the investigator score are reported. Participants were categorized based on different scores. Participants from the safety sample aged below 5 years (Groups 3 and 4) and who received any amount of IMP in this study, regardless of any protocol deviation or violation were analyzed for this outcome measure. 'n' is the number of participants with data available for analyses at the given time point.

End point type	Secondary

End point timeframe:

Days 1, 28, 56 and 182

Notes:

[14] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint was assessed only in Groups 3 and 4.

End point values	Group 3: 3 to 5 Years of Age	Group 4: Birth to 2 Years of Age		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	12		
Units: subjects				
Day 1: Dislike Very Much (n= 12, 12)	0	0		
Day 1: Dislike a Little (n= 12, 12)	0	2		
Day 1: Neither Liked Nor Disliked (n= 12, 12)	1	0		
Day 1: Like a Little (n= 12, 12)	2	2		

Day 1: Like Very Much (n= 12, 12)	9	8		
Day 28: Dislike Very Much (n= 12, 11)	0	0		
Day 28: Dislike a Little (n= 12, 11)	0	0		
Day 28: Neither Liked Nor Disliked (n= 12, 11)	2	0		
Day 28: Like a Little (n= 12, 11)	1	2		
Day 28: Like Very Much (n= 12, 11)	9	9		
Day 56: Dislike Very Much (n= 12, 11)	0	0		
Day 56: Dislike a Little (n= 12, 11)	0	0		
Day 56: Neither Liked Nor Disliked (n= 12, 11)	0	0		
Day 56: Like a Little (n= 12, 11)	2	0		
Day 56: Like Very Much (n= 12, 11)	10	11		
Day 182: Dislike Very Much (n= 12, 11)	0	0		
Day 182: Dislike a Little (n= 12, 11)	0	1		
Day 182: Neither Liked Nor Disliked (n= 12, 11)	0	0		
Day 182: Like a Little (n= 12, 11)	1	5		
Day 182: Like Very Much (n= 12, 11)	11	5		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Palatability Score as Assessed by the Parent or Participant

End point title	Number of Participants With Palatability Score as Assessed by the Parent or Participant[15]

End point description:

The palatability of the pediatric formulation was assessed using an age-appropriate visual hedonic scale and clinical assessment (Groups 3 and 4 only). The palatability result was based on 1 of 5 responses: 1="Dislike very much", 2="Dislike a little", 3="Neither liked nor disliked", 4="Like a little", 5="Like very much". The data per parent/patient score are reported. Participants were categorized based on different scores. Participants from the safety sample aged below 5 years (Groups 3 and 4) and who received any amount of IMP in this study, regardless of any protocol deviation or violation were analyzed for this outcome measure. 'n' is the number of participants with data available for analyses at the given time point.

End point type	Secondary

End point timeframe:

Days 1, 28, 56 and 182

Notes:

[15] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was assessed only in Groups 3 and 4.

End point values	Group 3: 3 to 5 Years of Age	Group 4: Birth to 2 Years of Age		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	12		
Units: subjects				
Day 1: Dislike Very Much (n= 12, 12)	0	0		
Day 1: Dislike a Little (n= 12, 12)	0	1		

Day 1: Neither Liked Nor Disliked (n= 12, 12)	1	1		
Day 1: Like a Little (n= 12, 12)	2	3		
Day 1: Like Very Much (n= 12, 12)	9	7		
Day 28: Dislike Very Much (n= 12, 11)	0	0		
Day 28: Dislike a Little (n= 12, 11)	1	0		
Day 28: Neither Liked Nor Disliked (n= 12, 11)	0	0		
Day 28: Like a Little (n= 12, 11)	1	3		
Day 28: Like Very Much (n= 12, 11)	10	8		
Day 56: Dislike Very Much (n= 12, 11)	0	0		
Day 56: Dislike a Little (n= 12, 11)	0	0		
Day 56: Neither Liked Nor Disliked (n= 12, 11)	1	0		
Day 56: Like a Little (n= 12, 11)	0	0		
Day 56: Like Very Much (n= 12, 11)	11	11		
Day 182: Dislike Very Much (n= 12, 11)	0	0		
Day 182: Dislike a Little (n= 12, 11)	0	0		
Day 182: Neither Liked Nor Disliked (n= 12, 11)	0	1		
Day 182: Like a Little (n= 12, 11)	1	4		
Day 182: Like Very Much (n= 12, 11)	11	6		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the first dose of study drug up to the end of the Post-treatment Follow-up Period (Up to Day 365)

Adverse event reporting additional description:

The Safety Sample included participants who received any amount of investigational medicinal product (IMP) in this study, regardless of any protocol deviation or violation.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.1

Reporting groups

Reporting group title	Group 1: 12 to 17 Years of Age

Reporting group description:

Participants 12 to 17 years old (inclusive) received adult formulation of delamanid 100 mg (2x50 mg tablets), orally, BID plus OBR up to Day 182. Participants continued to receive OBR up to Day 365.

Reporting group title	Group 2: 6 to 11 Years of Age

Reporting group description:

Participants 6 to 11 years old (inclusive) received adult formulation delamanid 50 mg (1x50 mg tablet), orally, BID plus OBR up to Day 182. Participants continued to receive OBR up to Day 365.

Reporting group title	Group 3: 3 to 5 Years of Age

Reporting group description:

Participants 3 to 5 years old (inclusive) received 25 mg pediatric formulation of delamanid (DPF - suspension prepared using dispersible tablet), orally, BID plus OBR up to Day 182. Participants continued to receive OBR up to Day 365.

Reporting group title	Group 4: Birth to 2 Years of Age

Reporting group description:

Participants from birth to 2 years old (inclusive) received DPF (suspension prepared using dispersible tablet) for 182 days plus OBR. Participants continued to receive OBR up to Day 365. The DPF dose was based on the participant's body weight during the baseline visit:

- Participants >10 kilograms (kg) received DPF 10 mg BID plus OBR
- Participants >8 kg and ≤10 kg received DPF 5 mg BID plus OBR
- Participants ≥5.5 kg and ≤8 kg received DPF 5 mg once per day (QD) plus OBR

Delamanid dose was adjusted as needed for Group 4 participants based on the weight measurement at specified study visits [Visits 5 (Day 28), 7 (Day 56), 9 (Day 84), 11 (Day 126) and 12 (Day 154)].

Serious adverse events	Group 1: 12 to 17 Years of Age	Group 2: 6 to 11 Years of Age	Group 3: 3 to 5 Years of Age
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	2 / 12 (16.67%)
number of deaths (all causes)	0	0	1
number of deaths resulting from adverse events	0	0	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Non-Hodgkin's lymphoma			

subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Lethargy			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Immune thrombocytopenic purpura			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Bronchial hyperreactivity			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Lower respiratory tract infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oral candidiasis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Vulvovaginal candidiasis			

subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Group 4: Birth to 2 Years of Age		
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 12 (41.67%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	1		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Non-Hodgkin's lymphoma			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Lethargy			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Immune thrombocytopenic purpura			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Bronchial hyperreactivity			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Lower respiratory tract infection			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Oral candidiasis			

subjects affected / exposed	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Vulvovaginal candidiasis			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Group 1: 12 to 17 Years of Age	Group 2: 6 to 11 Years of Age	Group 3: 3 to 5 Years of Age
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 7 (100.00%)	6 / 6 (100.00%)	12 / 12 (100.00%)
Vascular disorders			
Haematoma			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	1 / 12 (8.33%)
occurrences (all)	0	1	2
General disorders and administration site conditions			
Infusion site extravasation			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Pain			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Pyrexia			
subjects affected / exposed	2 / 7 (28.57%)	0 / 6 (0.00%)	2 / 12 (16.67%)
occurrences (all)	2	0	2
Social circumstances			
Sexual abuse			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1

Reproductive system and breast disorders			
Menorrhagia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Cough			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Oropharyngeal pain			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Psychiatric disorders			
Abnormal behaviour			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Aggression			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Depression			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Hallucination			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Insomnia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Investigations			
Activated partial thromboplastin time prolonged			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Alanine aminotransferase increased			

subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Blood corticotrophin increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	2 / 12 (16.67%)
occurrences (all)	0	0	2
Coagulation time prolonged			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Hepatic enzyme increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Liver function test increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	2 / 12 (16.67%)
occurrences (all)	0	0	2
Prothrombin time prolonged			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Weight decreased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Injury, poisoning and procedural complications			
Animal bite			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Concussion			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Contusion			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	2
Craniocerebral injury			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Eye injury			

subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Muscle strain			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Skin abrasion			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Skin laceration			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	2 / 12 (16.67%)
occurrences (all)	0	1	2
Tooth injury			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			
Wolff-Parkinson-White syndrome			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Nervous system disorders			
Amnesia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Dizziness			
subjects affected / exposed	2 / 7 (28.57%)	0 / 6 (0.00%)	0 / 12 (0.00%)
occurrences (all)	2	0	0
Headache			
subjects affected / exposed	5 / 7 (71.43%)	3 / 6 (50.00%)	2 / 12 (16.67%)
occurrences (all)	7	3	4
Paraesthesia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Psychomotor hyperactivity			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Blood and lymphatic system disorders			

Anaemia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Eosinophilia			
subjects affected / exposed	2 / 7 (28.57%)	0 / 6 (0.00%)	0 / 12 (0.00%)
occurrences (all)	2	0	0
Immune thrombocytopenic purpura			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Ear and labyrinth disorders			
Cerumen impaction			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Conductive deafness			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 12 (0.00%)
occurrences (all)	0	2	0
Deafness neurosensory			
subjects affected / exposed	2 / 7 (28.57%)	0 / 6 (0.00%)	1 / 12 (8.33%)
occurrences (all)	2	0	1
Middle ear effusion			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Eye disorders			
Conjunctivitis allergic			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Vernal keratoconjunctivitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 7 (14.29%)	1 / 6 (16.67%)	1 / 12 (8.33%)
occurrences (all)	2	1	1
Abdominal pain lower			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Abdominal pain upper			

subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Aphthous ulcer			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Constipation			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Dental caries			
subjects affected / exposed	2 / 7 (28.57%)	0 / 6 (0.00%)	1 / 12 (8.33%)
occurrences (all)	2	0	1
Dyspepsia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Gingival swelling			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Lip dry			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Lip ulceration			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Mouth ulceration			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Oral discomfort			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Toothache			
subjects affected / exposed	0 / 7 (0.00%)	2 / 6 (33.33%)	1 / 12 (8.33%)
occurrences (all)	0	3	1
Vomiting			
subjects affected / exposed	2 / 7 (28.57%)	1 / 6 (16.67%)	2 / 12 (16.67%)
occurrences (all)	2	2	2
Skin and subcutaneous tissue disorders			

Angioedema			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Butterfly rash			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Dermatitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Dermatitis diaper			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Eczema			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Rash maculo-papular			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Rash papular			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Skin discolouration			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Skin fissures			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Skin hyperpigmentation			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Skin lesion			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Urticaria			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0

Urticaria papular			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	2 / 7 (28.57%)	0 / 6 (0.00%)	0 / 12 (0.00%)
occurrences (all)	2	0	0
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	2 / 12 (16.67%)
occurrences (all)	0	1	2
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	3 / 7 (42.86%)	2 / 6 (33.33%)	3 / 12 (25.00%)
occurrences (all)	3	2	4
Arthritis			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Bone pain			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Bursitis			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Costochondritis			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Muscular weakness			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal chest pain			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 12 (0.00%)
occurrences (all)	2	0	0
Myalgia			
subjects affected / exposed	2 / 7 (28.57%)	1 / 6 (16.67%)	0 / 12 (0.00%)
occurrences (all)	4	1	0

Pain in extremity			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Soft tissue swelling			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Infections and infestations			
Acarodermatitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Ascariasis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Bronchitis			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	1 / 12 (8.33%)
occurrences (all)	2	0	1
Folliculitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Gastroenteritis			
subjects affected / exposed	1 / 7 (14.29%)	1 / 6 (16.67%)	1 / 12 (8.33%)
occurrences (all)	1	1	1
Genital candidiasis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Gingivitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Helminthic infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	2
Impetigo			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Lower respiratory tract infection			

subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	2 / 12 (16.67%)
occurrences (all)	0	1	2
Mumps			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Nasopharyngitis			
subjects affected / exposed	3 / 7 (42.86%)	0 / 6 (0.00%)	0 / 12 (0.00%)
occurrences (all)	6	0	0
Oral candidiasis			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Otitis media			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Otitis media acute			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Parasitic gastroenteritis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Pharyngotonsillitis			
subjects affected / exposed	1 / 7 (14.29%)	1 / 6 (16.67%)	1 / 12 (8.33%)
occurrences (all)	1	1	1
Pneumonia			
subjects affected / exposed	1 / 7 (14.29%)	1 / 6 (16.67%)	2 / 12 (16.67%)
occurrences (all)	3	1	2
Pustule			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	2
Pyelonephritis acute			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Pyuria			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Respiratory tract infection			

subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	2
Respiratory tract infection viral			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Rhinitis			
subjects affected / exposed	1 / 7 (14.29%)	2 / 6 (33.33%)	0 / 12 (0.00%)
occurrences (all)	1	4	0
Rubella			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Subcutaneous abscess			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Systemic viral infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Tinea infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Tinea versicolour			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Tooth abscess			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Upper respiratory tract infection			
subjects affected / exposed	4 / 7 (57.14%)	3 / 6 (50.00%)	5 / 12 (41.67%)
occurrences (all)	9	5	9
Urinary tract infection			
subjects affected / exposed	3 / 7 (42.86%)	0 / 6 (0.00%)	0 / 12 (0.00%)
occurrences (all)	4	0	0
Viral infection			
subjects affected / exposed	1 / 7 (14.29%)	1 / 6 (16.67%)	0 / 12 (0.00%)
occurrences (all)	1	1	0
Viral upper respiratory tract infection			

subjects affected / exposed	1 / 7 (14.29%)	1 / 6 (16.67%)	0 / 12 (0.00%)
occurrences (all)	1	2	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Hyperuricaemia			
subjects affected / exposed	2 / 7 (28.57%)	1 / 6 (16.67%)	4 / 12 (33.33%)
occurrences (all)	2	1	5
Hypokalaemia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 12 (0.00%)
occurrences (all)	3	0	0

Non-serious adverse events	Group 4: Birth to 2 Years of Age		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	11 / 12 (91.67%)		
Vascular disorders			
Haematoma			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
General disorders and administration site conditions			
Infusion site extravasation			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Pain			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Pyrexia			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Social circumstances			
Sexual abuse			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Reproductive system and breast disorders			

Menorrhagia subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0		
Respiratory, thoracic and mediastinal disorders Asthma subjects affected / exposed occurrences (all) Cough subjects affected / exposed occurrences (all) Oropharyngeal pain subjects affected / exposed occurrences (all)	 0 / 12 (0.00%) 0 0 / 12 (0.00%) 0 0 / 12 (0.00%) 0		
Psychiatric disorders Abnormal behaviour subjects affected / exposed occurrences (all) Aggression subjects affected / exposed occurrences (all) Depression subjects affected / exposed occurrences (all) Hallucination subjects affected / exposed occurrences (all) Insomnia subjects affected / exposed occurrences (all)	 0 / 12 (0.00%) 0 1 / 12 (8.33%) 1 0 / 12 (0.00%) 0 0 / 12 (0.00%) 0 0 / 12 (0.00%) 0		
Investigations Activated partial thromboplastin time prolonged subjects affected / exposed occurrences (all) Alanine aminotransferase increased subjects affected / exposed occurrences (all)	 0 / 12 (0.00%) 0 0 / 12 (0.00%) 0		

Blood corticotrophin increased			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Coagulation time prolonged			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Hepatic enzyme increased			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Liver function test increased			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Prothrombin time prolonged			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	2		
Weight decreased			
subjects affected / exposed	3 / 12 (25.00%)		
occurrences (all)	3		
Injury, poisoning and procedural complications			
Animal bite			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Concussion			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Contusion			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Craniocerebral injury			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	2		
Eye injury			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Muscle strain			

subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Skin abrasion			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Skin laceration			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Tooth injury			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Cardiac disorders			
Wolff-Parkinson-White syndrome			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Nervous system disorders			
Amnesia			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Dizziness			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Headache			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Paraesthesia			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Psychomotor hyperactivity			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Eosinophilia			

subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Immune thrombocytopenic purpura			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	3		
Ear and labyrinth disorders			
Cerumen impaction			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Conductive deafness			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Deafness neurosensory			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Middle ear effusion			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Eye disorders			
Conjunctivitis allergic			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Vernal keratoconjunctivitis			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Abdominal pain lower			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Abdominal pain upper			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Aphthous ulcer			

subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Constipation			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Dental caries			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Dyspepsia			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Gingival swelling			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Lip dry			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Lip ulceration			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Mouth ulceration			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Oral discomfort			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Toothache			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Vomiting			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		

Butterfly rash				
subjects affected / exposed	1 / 12 (8.33%)			
occurrences (all)	1			
Dermatitis				
subjects affected / exposed	1 / 12 (8.33%)			
occurrences (all)	1			
Dermatitis diaper				
subjects affected / exposed	1 / 12 (8.33%)			
occurrences (all)	1			
Eczema				
subjects affected / exposed	1 / 12 (8.33%)			
occurrences (all)	1			
Rash maculo-papular				
subjects affected / exposed	0 / 12 (0.00%)			
occurrences (all)	0			
Rash papular				
subjects affected / exposed	1 / 12 (8.33%)			
occurrences (all)	1			
Skin discolouration				
subjects affected / exposed	1 / 12 (8.33%)			
occurrences (all)	1			
Skin fissures				
subjects affected / exposed	0 / 12 (0.00%)			
occurrences (all)	0			
Skin hyperpigmentation				
subjects affected / exposed	1 / 12 (8.33%)			
occurrences (all)	1			
Skin lesion				
subjects affected / exposed	0 / 12 (0.00%)			
occurrences (all)	0			
Urticaria				
subjects affected / exposed	1 / 12 (8.33%)			
occurrences (all)	1			
Urticaria papular				
subjects affected / exposed	0 / 12 (0.00%)			
occurrences (all)	0			

Renal and urinary disorders Dysuria subjects affected / exposed occurrences (all)	 0 / 12 (0.00%) 0		
Endocrine disorders Hypothyroidism subjects affected / exposed occurrences (all)	 2 / 12 (16.67%) 2		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) Arthritis subjects affected / exposed occurrences (all) Bone pain subjects affected / exposed occurrences (all) Bursitis subjects affected / exposed occurrences (all) Costochondritis subjects affected / exposed occurrences (all) Muscular weakness subjects affected / exposed occurrences (all) Musculoskeletal chest pain subjects affected / exposed occurrences (all) Myalgia subjects affected / exposed occurrences (all) Pain in extremity subjects affected / exposed occurrences (all)	 0 / 12 (0.00%) 0 0 / 12 (0.00%) 0 0 / 12 (0.00%) 0 0 / 12 (0.00%) 0 0 / 12 (0.00%) 0 1 / 12 (8.33%) 1 0 / 12 (0.00%) 0 0 / 12 (0.00%) 0 1 / 12 (8.33%) 3		

Soft tissue swelling			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Infections and infestations			
Acarodermatitis			
subjects affected / exposed	3 / 12 (25.00%)		
occurrences (all)	3		
Ascariasis			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Bronchitis			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Folliculitis			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Gastroenteritis			
subjects affected / exposed	4 / 12 (33.33%)		
occurrences (all)	4		
Genital candidiasis			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Gingivitis			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Helminthic infection			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Impetigo			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Lower respiratory tract infection			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	2		
Mumps			

subjects affected / exposed	1 / 12 (8.33%)			
occurrences (all)	1			
Nasopharyngitis				
subjects affected / exposed	0 / 12 (0.00%)			
occurrences (all)	0			
Oral candidiasis				
subjects affected / exposed	0 / 12 (0.00%)			
occurrences (all)	0			
Otitis media				
subjects affected / exposed	3 / 12 (25.00%)			
occurrences (all)	3			
Otitis media acute				
subjects affected / exposed	0 / 12 (0.00%)			
occurrences (all)	0			
Parasitic gastroenteritis				
subjects affected / exposed	2 / 12 (16.67%)			
occurrences (all)	2			
Pharyngotonsillitis				
subjects affected / exposed	0 / 12 (0.00%)			
occurrences (all)	0			
Pneumonia				
subjects affected / exposed	0 / 12 (0.00%)			
occurrences (all)	0			
Pustule				
subjects affected / exposed	0 / 12 (0.00%)			
occurrences (all)	0			
Pyelonephritis acute				
subjects affected / exposed	0 / 12 (0.00%)			
occurrences (all)	0			
Pyuria				
subjects affected / exposed	0 / 12 (0.00%)			
occurrences (all)	0			
Respiratory tract infection				
subjects affected / exposed	4 / 12 (33.33%)			
occurrences (all)	9			
Respiratory tract infection viral				

subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Rhinitis			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Rubella			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Subcutaneous abscess			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Systemic viral infection			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Tinea infection			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Tinea versicolour			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Tooth abscess			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Upper respiratory tract infection			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	2		
Urinary tract infection			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Viral infection			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Metabolism and nutrition disorders			

Decreased appetite subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0		
Hyperuricaemia subjects affected / exposed occurrences (all)	3 / 12 (25.00%) 3		
Hypokalaemia subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 March 2013	The following updates were made as per Amendment 01: • Revision of introduction; modification of exclusion criteria • Revision of schedule of assessments • Addition of details regarding several procedures • Clarification of text
14 October 2014	The following updates were made as per Amendment 02: • Modification of inclusion/exclusion criteria • Update of prohibited medications • Addition of PK blood draw at the early termination visit • Clarification of text
29 June 2015	The following updates were made as per Amendment 03: • Addition of information for Groups 3 and 4 • Clarification of safety monitoring • Clarification of text
04 October 2016	Addition of information for Group 4; clarification of text; modification of blood sampling schedule; update of sponsor representative information.
28 February 2019	The following update was made as per Amendment 04: • Addition of an interim analysis

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported