Clinical trial results:
Phase 1, Open-label, Multiple-dose, and Age De-escalation Trial to Assess the Pharmacokinetics, Safety, and Tolerability of Delamanid (OPC-67683) in Pediatric Multidrug-resistant Tuberculosis Patients on Therapy With an Optimized Background Regimen of Antituberculosis Drugs

Summary

EudraCT number	2012-004473-25
Trial protocol	Outside EU/EEA
Global end of trial date	28 December 2017

Results information

Result version number	v1 (current)
This version publication date	02 November 2018
First version publication date	02 November 2018

Trial information

Trial identification

Sponsor protocol code	242-12-232

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01856634
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	Otsuka Transparency Department, Otsuka Pharmaceutical Development & Commercialization, Inc., DT-inquiry@otsuka.jp
Scientific contact	Otsuka Transparency Department, Otsuka Pharmaceutical Development & Commercialization, Inc., DT-inquiry@otsuka.jp

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	28 December 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	28 December 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this trial was to determine the pediatric dose of delamanid equivalent to the adult dose already shown to be effective against multidrug-resistant tuberculosis (MDR-TB).

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 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	14 June 2013
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	1 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Philippines: 25
Country: Number of subjects enrolled	South Africa: 12
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	0

wk	
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	8
Children (2-11 years)	22
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:

Investigators and their staff coordinate with the National TB Program and with different TB treatment centers for referral of pediatric participants diagnosed with MDR-TB.

Pre-assignment

Screening details:

Parents of MDR-TB pediatric participants referred to the sites were invited to visit the research site to learn more about the study. Investigators explained study availability and entry. Informed consent was conducted once interest to join was confirmed. Screening procedures began after the consent and assent forms were signed.

Period 1

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

Blinding implementation details:

This was an open-label trial; blinding procedures were not applicable.

Arms

Are arms mutually exclusive?	Yes
Arm title	Group 1: 12-17 Years

Arm description:

Participants 12-17 years old (inclusive) received 100 milligrams (mg) delamanid twice per day (BID) for 10 days plus OBR.

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 100 mg BID (administered as 2 × 50-mg tablets). The 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: 6-11 Years

Arm description:

Participants 6-11 years old (inclusive) received 50 mg delamanid BID for 10 days plus OBR.

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 50 mg BID (administered as 1 × 50-mg tablet). The 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: 3-5 Years

Arm description:

Participants 3-5 years old (inclusive) received 25 mg delamanid pediatric formulation (DPF) BID for 10 days plus OBR.

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 (25 mg BID) as an extemporaneous suspension using the delamanid pediatric dispersible tablet formulation (administered as 1 × 25-mg tablet). The 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 meal.

Arm title	Group 4: 0-2 Years

Arm description:

Participants from birth to 2 years old (inclusive) received DPF for 10 days plus OBR. The DPF dose was based on the participant's body weight during the baseline visit:
• Participants >10 kilograms (kg) received DPF 10 mg BID + OBR
• Participants >8 kg and ≤10 kg received DPF 5 mg BID + OBR
• Participants ≥5.5 kg and ≤8 kg received DPF 5 mg once per day (QD) + OBR

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. The dose was based on body weight during baseline visit:
• Participants with weight >10 kg received DPF 10 mg BID (administered as 2 × 5-mg dispersible tablets)
• Participants with weight >8 and ≤10 kg received DPF 5 mg BID (administered as 1 × 5-mg dispersible tablet)
• Participants with weight ≥5.5 kg and ≤8 kg received DPF 5 mg QD (administered as 1 × 5-mg dispersible tablet)
The 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. For the QD regimen, delamanid was administered within 30 minutes after the start of a standard breakfast meal.

Number of subjects in period 1	Group 1: 12-17 Years	Group 2: 6-11 Years	Group 3: 3-5 Years
Started	7	6	12
Received at Least 1 Dose of Study Drug	7	6	12
Completed	7	6	12

Number of subjects in period 1	Group 4: 0-2 Years
Started	12
Received at Least 1 Dose of Study Drug	12

Completed	12

Baseline characteristics

Reporting groups	
Reporting group title	Group 1: 12-17 Years
Reporting group description:	
Participants 12-17 years old (inclusive) received 100 milligrams (mg) delamanid twice per day (BID) for 10 days plus OBR.	
Reporting group title	Group 2: 6-11 Years
Reporting group description:	
Participants 6-11 years old (inclusive) received 50 mg delamanid BID for 10 days plus OBR.	
Reporting group title	Group 3: 3-5 Years
Reporting group description:	
Participants 3-5 years old (inclusive) received 25 mg delamanid pediatric formulation (DPF) BID for 10 days plus OBR.	
Reporting group title	Group 4: 0-2 Years
Reporting group description:	
Participants from birth to 2 years old (inclusive) received DPF for 10 days plus OBR. The DPF dose was based on the participant's body weight during the baseline visit: • Participants >10 kilograms (kg) received DPF 10 mg BID + OBR • Participants >8 kg and ≤10 kg received DPF 5 mg BID + OBR • Participants ≥5.5 kg and ≤8 kg received DPF 5 mg once per day (QD) + OBR	

Reporting group values	Group 1: 12-17 Years	Group 2: 6-11 Years	Group 3: 3-5 Years
Number of subjects	7	6	12
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	6	12
Adolescents (12-17 years)	7	0	0
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	15.29	9.42	4.28
standard deviation	± 1.62	± 1.53	± 0.97
Gender categorical Units: Subjects			
Female	3	4	6
Male	4	2	6
Ethnicity Units: Subjects			
Hispanic or Latino	0	0	0
Not Hispanic or Latino	7	6	12
Race Units: Subjects			

Asian	7	4	8
Black or African	0	0	2
White	0	0	0
American Indian or Alaska Native	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Other	0	2	2

Reporting group values	Group 4: 0-2 Years	Total	
Number of subjects	12	37	
Age categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	8	8	
Children (2-11 years)	4	22	
Adolescents (12-17 years)	0	7	
Adults (18-64 years)	0	0	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous			
Units: years			
arithmetic mean	1.64		
standard deviation	± 0.58	-	
Gender categorical			
Units: Subjects			
Female	6	19	
Male	6	18	
Ethnicity			
Units: Subjects			
Hispanic or Latino	0	0	
Not Hispanic or Latino	12	37	
Race			
Units: Subjects			
Asian	6	25	
Black or African	0	2	
White	0	0	
American Indian or Alaska Native	0	0	
Native Hawaiian or Other Pacific Islander	0	0	
Other	6	10	

End points

End points reporting groups

Reporting group title	Group 1: 12-17 Years
Reporting group description:	
Participants 12-17 years old (inclusive) received 100 milligrams (mg) delamanid twice per day (BID) for 10 days plus OBR.	
Reporting group title	Group 2: 6-11 Years
Reporting group description:	
Participants 6-11 years old (inclusive) received 50 mg delamanid BID for 10 days plus OBR.	
Reporting group title	Group 3: 3-5 Years
Reporting group description:	
Participants 3-5 years old (inclusive) received 25 mg delamanid pediatric formulation (DPF) BID for 10 days plus OBR.	
Reporting group title	Group 4: 0-2 Years
Reporting group description:	
Participants from birth to 2 years old (inclusive) received DPF for 10 days plus OBR. The DPF dose was based on the participant's body weight during the baseline visit: • Participants >10 kilograms (kg) received DPF 10 mg BID + OBR • Participants >8 kg and ≤10 kg received DPF 5 mg BID + OBR • Participants ≥5.5 kg and ≤8 kg received DPF 5 mg once per day (QD) + OBR	
Subject analysis set title	Safety Population
Subject analysis set type	Safety analysis
Subject analysis set description:	
Participants who took at least 1 dose of delamanid.	

Primary: Area Under The Plasma-time Concentration Curve From Time Zero To 24 Hours (AUC0-24h) For Delamanid And DM-6705 Metabolite On Day 1 And Day 10

End point title	Area Under The Plasma-time Concentration Curve From Time Zero To 24 Hours (AUC0-24h) For Delamanid And DM-6705 Metabolite On Day 1 And Day 10[1]
End point description:	
The pharmacokinetic (PK) parameter of AUC0-24h for delamanid and its metabolite (DM-6705), in combination with OBR, in pediatric MDR-TB participants on Day 1 and Day 10 is presented. This parameter was calculated using noncompartmental analysis. Blood collection for PK analysis occurred on Days 1 and 10. Approximately 3 milliliters (mL) of blood was collected per PK sample for the participants in Group 1, 2 mL for participants in Groups 2 and 3, and 0.6 mL for participants in Group 4. Plasma samples were analyzed for delamanid and DM-6705 using a specific and validated ultra-performance liquid chromatography-tandem mass spectrometry (UPLC-MS/MS) method. Plasma PK parameter calculations and descriptive statistics were performed using Statistical Analysis System (SAS) version 9.4 or higher. Values of AUC0-24h were estimated using the linear up/log down trapezoidal rule. Results are reported in nanograms times hour/mL (ng*hr/mL).	
End point type	Primary
End point timeframe:	
Day 1, Day 10	

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 analysis was not performed for the PK endpoints. Descriptive statistics are included (median and full range).

End point values	Group 1: 12-17 Years	Group 2: 6-11 Years	Group 3: 3-5 Years	Group 4: 0-2 Years
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	7[2]	6[3]	12[4]	12[5]
Units: ng*hr/mL				
median (full range (min-max))				
Delamanid: Day 1	3910 (1910 to 5270)	4080 (3240 to 7090)	3580 (1940 to 4920)	949 (262 to 1930)
Delamanid: Day 10	9790 (6170 to 13000)	12000 (9810 to 13300)	9290 (5180 to 12900)	2740 (701 to 4910)
DM-6705: Day 1	114 (89.4 to 224)	122 (81.1 to 351)	120 (77.9 to 223)	25.2 (2.49 to 61.8)
DM-6705: Day 10	1780 (1210 to 2010)	1880 (1210 to 2210)	1370 (671 to 2160)	291 (49.6 to 774)

Notes:

[2] - Safety Population

[3] - Safety Population

[4] - Safety Population

[5] - Safety Population

Statistical analyses

No statistical analyses for this end point

Primary: Peak (Maximal) Concentration Of Drug In Plasma (Cmax) For Delamanid And DM-6705 Metabolite On Day 1 And Day 10

End point title	Peak (Maximal) Concentration Of Drug In Plasma (Cmax) For Delamanid And DM-6705 Metabolite On Day 1 And Day 10[6]

End point description:

The PK parameter of Cmax for delamanid and DM-6705, in combination with OBR, in MDR-TB participants on Day 1 and Day 10 is presented. This parameter was calculated using noncompartmental analysis. Blood collection for PK analysis occurred on Days 1 and 10. Approximately 3 mL of blood was collected per PK sample for the participants in Group 1, 2 mL for participants in Groups 2 and 3, and 0.6 mL for participants in Group 4. Plasma samples were analyzed for delamanid and DM-6705 using a specific and validated UPLC-MS/MS method. Plasma PK parameter calculations and descriptive statistics were performed using SAS version 9.4 or higher. Values of Cmax were determined directly from the observed data. Results are reported in ng/mL.

End point type	Primary

End point timeframe:

Day 1, Day 10

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 was not performed for the PK endpoints. Descriptive statistics are included (median and full range).

End point values	Group 1: 12-17 Years	Group 2: 6-11 Years	Group 3: 3-5 Years	Group 4: 0-2 Years
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	7[7]	6[8]	12[9]	12[10]
Units: ng/mL				
median (full range (min-max))				
Delamanid: Day 1	268 (164 to 420)	315 (205 to 454)	207 (150 to 364)	80.3 (26.2 to 121)
Delamanid: Day 10	557 (304 to 803)	573 (485 to 682)	500 (287 to 919)	179 (45.2 to 298)
DM-6705: Day 1	8.60 (6.86 to 15.5)	7.68 (6.07 to 23.1)	8.35 (5.03 to 15.1)	2.01 (0.5 to 4.17)

DM-6705: Day 10	81.7 (52.9 to 93.2)	90.0 (62.4 to 112)	68.7 (33.7 to 95.0)	14.2 (2.38 to 35.9)

Notes:

[7] - Safety Population

[8] - Safety Population

[9] - Safety Population

[10] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Palatability Of The DPF

End point title	Palatability Of The DPF[11]

End point description:

The palatability of the DPF is presented. This parameter was assessed within 25 to 30 minutes after the morning dose on Day 1 and Day 10 using an age-appropriate visual hedonic scale and clinical assessment. Palatability data was assessed only for Groups 3 and 4 (participants between 0-5 years old). The palatability result was based on 1 of 5 responses: "Dislike very much", "Dislike a little", "Neither liked nor disliked", "Like a little", "Like very much". The test result was scored by the investigator and either a parent or participant. The frequency counts for the participants with each score were summarized at visits that palatability were assessed (Day 1 and Day 10). The data for the parent/participant scores are reported.

End point type	Secondary

End point timeframe:

Day 1, Day 10

Notes:

[11] - 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: Palatability testing was assessed only for Groups 3 and 4.

End point values	Group 3: 3-5 Years	Group 4: 0-2 Years		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12[12]	12[13]		
Units: Participants				
Day 1: Dislike Very Much	0	0		
Day 1: Dislike A Little	0	0		
Day 1: Neither Liked Nor Disliked	1	0		
Day 1: Like A Little	1	5		
Day 1: Like Very Much	10	5		
Day 10: Dislike Very Much	0	0		
Day 10: Dislike A Little	0	1		
Day 10: Neither Liked Nor Disliked	0	1		
Day 10: Like A Little	2	5		
Day 10: Like Very Much	10	5		

Notes:

[12] - Safety Population

[13] - Safety Population

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Day 1 through follow-up period (30 days post last dose).	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	20.1

Reporting groups	
Reporting group title	Group 1: 12 to 17 Years
Reporting group description: Participants 12-17 years old (inclusive) received 100 mg delamanid BID for 10 days plus OBR.	
Reporting group title	Group 2: 6 to 11 Years
Reporting group description: Participants 6-11 years old (inclusive) received 50 mg delamanid BID for 10 days plus OBR.	
Reporting group title	Group 3: 3 to 5 Years
Reporting group description: Participants 3-5 years old (inclusive) received 25 mg DPF BID for 10 days plus OBR.	
Reporting group title	Group 4: 0-2 Years
Reporting group description: Participants from birth to 2 years old (inclusive) received DPF for 10 days plus OBR. The DPF dose was based on the participant's body weight during the baseline visit: • Participants >10 kg received DPF 10 mg BID + OBR • Participants >8 kg and ≤10 kg received DPF 5 mg BID + OBR • Participants ≥5.5 kg and ≤8 kg received DPF 5 mg QD + OBR	

Serious adverse events	Group 1: 12 to 17 Years	Group 2: 6 to 11 Years	Group 3: 3 to 5 Years
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 12 (8.33%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Infections and infestations			
Hepatitis A			
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
Lower respiratory tract infection			
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

Serious adverse events	Group 4: 0-2 Years		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 12 (8.33%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Infections and infestations			
Hepatitis A			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Lower respiratory tract infection			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	0 / 1		
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	Group 2: 6 to 11 Years	Group 3: 3 to 5 Years
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 7 (71.43%)	5 / 6 (83.33%)	9 / 12 (75.00%)
Vascular disorders			
Haematoma			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	2 / 7 (28.57%)	0 / 6 (0.00%)	4 / 12 (33.33%)
occurrences (all)	2	0	4
Asthenia			
subjects affected / exposed	3 / 7 (42.86%)	0 / 6 (0.00%)	0 / 12 (0.00%)
occurrences (all)	3	0	0
Catheter site pain			
subjects affected / exposed	0 / 7 (0.00%)	2 / 6 (33.33%)	0 / 12 (0.00%)
occurrences (all)	0	2	0
Crepitations			

subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Injection site pain			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Vessel puncture site pain			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Vessel puncture site pruritus			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			
Bronchial hyperreactivity			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Dyspnoea			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Haemoptysis			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
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
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	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 12 (0.00%)
occurrences (all)	2	0	0
Investigations			
Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	2 / 12 (16.67%)
occurrences (all)	0	0	2
Electrocardiogram PR prolongation			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Electrocardiogram U wave present			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Prothrombin time prolonged			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Craniocerebral injury			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Eye contusion			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			
Cyanosis			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 7 (28.57%)	1 / 6 (16.67%)	1 / 12 (8.33%)
occurrences (all)	7	1	5
Dizziness			
subjects affected / exposed	2 / 7 (28.57%)	0 / 6 (0.00%)	0 / 12 (0.00%)
occurrences (all)	2	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			
Eosinophilia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Neutropenia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	2 / 7 (28.57%)	2 / 6 (33.33%)	3 / 12 (25.00%)
occurrences (all)	5	2	3
Nausea			
subjects affected / exposed	4 / 7 (57.14%)	0 / 6 (0.00%)	1 / 12 (8.33%)
occurrences (all)	7	0	1
Toothache			
subjects affected / exposed	1 / 7 (14.29%)	2 / 6 (33.33%)	2 / 12 (16.67%)
occurrences (all)	3	2	2
Abdominal pain			
subjects affected / exposed	2 / 7 (28.57%)	0 / 6 (0.00%)	0 / 12 (0.00%)
occurrences (all)	2	0	0
Diarrhoea			
subjects affected / exposed	0 / 7 (0.00%)	2 / 6 (33.33%)	0 / 12 (0.00%)
occurrences (all)	0	3	0
Mouth ulceration			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	2 / 12 (16.67%)
occurrences (all)	0	0	2
Abdominal discomfort			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Abdominal pain upper			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Faeces soft			

subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Gastritis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Gingival swelling			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Lip dry			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Oral pain			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Skin and subcutaneous tissue disorders			
Dermatitis diaper			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Pruritus			
subjects affected / exposed	2 / 7 (28.57%)	0 / 6 (0.00%)	0 / 12 (0.00%)
occurrences (all)	3	0	0
Butterfly rash			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Night sweats			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 12 (0.00%)
occurrences (all)	4	0	0
Rash maculo-papular			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Rash papular			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Skin hyperpigmentation			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1

Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 7 (28.57%)	1 / 6 (16.67%)	1 / 12 (8.33%)
occurrences (all)	3	1	3
Muscle spasms			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal pain			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Pain in extremity			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 12 (0.00%)
occurrences (all)	2	0	0
Soft tissue swelling			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Lower respiratory tract infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	3 / 12 (25.00%)
occurrences (all)	0	0	3
Respiratory tract infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Gastroenteritis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Nasopharyngitis			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0

Pneumonia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
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	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Skin candida			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Hyperuricaemia			
subjects affected / exposed	2 / 7 (28.57%)	1 / 6 (16.67%)	0 / 12 (0.00%)
occurrences (all)	2	1	0
Decreased appetite			
subjects affected / exposed	2 / 7 (28.57%)	0 / 6 (0.00%)	0 / 12 (0.00%)
occurrences (all)	2	0	0
Hypokalaemia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Hypomagnesaemia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0

Non-serious adverse events	Group 4: 0-2 Years		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 12 (100.00%)		
Vascular disorders			
Haematoma			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
General disorders and administration site conditions			

Pyrexia			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Asthenia			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Catheter site pain			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Crepitations			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Injection site pain			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Vessel puncture site pain			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Vessel puncture site pruritus			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Bronchial hyperreactivity			
subjects affected / exposed	3 / 12 (25.00%)		
occurrences (all)	3		
Dyspnoea			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Haemoptysis			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Oropharyngeal pain			

subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Psychiatric disorders			
Abnormal behaviour			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Hallucination			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Insomnia			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Investigations			
Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Electrocardiogram PR prolongation			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Electrocardiogram U wave present			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Prothrombin time prolonged			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Craniocerebral injury			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Eye contusion			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Cardiac disorders			
Cyanosis			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		

Nervous system disorders			
Headache			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Dizziness			
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			
Eosinophilia			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Neutropenia			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	2		
Nausea			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Toothache			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Abdominal pain			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Diarrhoea			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		

Mouth ulceration subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0		
Abdominal discomfort subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0		
Abdominal pain upper subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0		
Faeces soft subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0		
Gastritis subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0		
Gingival swelling subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0		
Lip dry subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0		
Oral pain subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0		
Skin and subcutaneous tissue disorders			
Dermatitis diaper subjects affected / exposed occurrences (all)	3 / 12 (25.00%) 3		
Pruritus subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0		
Butterfly rash subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0		
Night sweats			

subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Rash maculo-papular			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Rash papular			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Skin hyperpigmentation			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Muscle spasms			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Musculoskeletal pain			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Pain in extremity			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Soft tissue swelling			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	3 / 12 (25.00%)		
occurrences (all)	3		
Lower respiratory tract infection			

subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Respiratory tract infection			
subjects affected / exposed	3 / 12 (25.00%)		
occurrences (all)	4		
Gastroenteritis			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Nasopharyngitis			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Pneumonia			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
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		
Skin candida			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Viral upper respiratory tract infection			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Hyperuricaemia			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	2		
Decreased appetite			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Hypokalaemia			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		

Hypomagnesaemia 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? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

None reported

Notes: