



Clinical trial results:

A 24-week, open-label, parallel-group, interventional Phase IV study comparing Tobramycin Inhalation Powder (TIP) administered once daily continuously versus TIP administered BID in 28 day on / 28 day off cycles for the treatment of pulmonary Pseudomonas aeruginosa in patients with cystic fibrosis

Summary

EudraCT number	2016-004318-82
Trial protocol	Outside EU/EEA
Global end of trial date	11 December 2014

Results information

Result version number	v1 (current)
This version publication date	14 October 2017
First version publication date	14 October 2017

Trial information

Trial identification

Sponsor protocol code	CTBM100CUS03
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02015663
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma AG, 41 61321111,
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, 41 61324111,

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	11 December 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	11 December 2014
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To estimate the difference in mean (absolute) change from baseline in forced expiratory volume in 1 second (FEV1) % predicted at Day 168 (Visit 9) with Tobramycin Inhalation Powder (TIP) 112 mg once daily (continuous) vs TIP 112 mg BID in 28 day on / 28 day off cycles.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	24 January 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 32
Worldwide total number of subjects	32
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)	0
Children (2-11 years)	1
Adolescents (12-17 years)	2
Adults (18-64 years)	28
From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

The study was discontinued by Novartis on 14-11-2014 due to recruitment challenges. The study intended to randomize 200 patients within 18 months, after 9 months, only 32 patients were successfully randomized, with a screen fail rate of 50%.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm 1

Arm description:

Tobramycin Inhalation Powder (112 mg) once daily during 168 days

Arm type	Experimental
Investigational medicinal product name	Tobramycin Inhalation Powder
Investigational medicinal product code	TBM100
Other name	Tobramycin
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

112 mg. once daily during 168 days

Arm title	Arm 2
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Arm description:

Tobramycin Inhalation Powder (112 mg) twice daily on days 1-28, days 57-84 and days 113-140

Arm type	Active comparator
Investigational medicinal product name	Tobramycin Inhalation Powder
Investigational medicinal product code	TBM100
Other name	Tobramycin
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

112 mg. twice daily on days 1-28, days 57-84 and days 113-140.

Number of subjects in period 1	Arm 1	Arm 2
Started	16	16
Completed	1	4
Not completed	15	12
Consent withdrawn by subject	1	-

Adverse event, non-fatal	3	-
Administrative problems	10	11
unsatisfactory therapeutic effect	1	-
Protocol deviation	-	1

Baseline characteristics

Reporting groups

Reporting group title	Arm 1
Reporting group description: Tobramycin Inhalation Powder (112 mg) once daily during 168 days	
Reporting group title	Arm 2
Reporting group description: Tobramycin Inhalation Powder (112 mg) twice daily on days 1-28, days 57-84 and days 113-140	

Reporting group values	Arm 1	Arm 2	Total
Number of subjects	16	16	32
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	1	1
Adolescents (12-17 years)	1	1	2
Adults (18-64 years)	14	14	28
From 65-84 years	1	0	1
85 years and over	0	0	0
Age Continuous Units: year			
arithmetic mean	34.9	26.5	
standard deviation	± 14.31	± 11.09	-
Gender, Male/Female Units: Subjects			
Female	6	8	14
Male	10	8	18

End points

End points reporting groups

Reporting group title	Arm 1
Reporting group description:	
Tobramycin Inhalation Powder (112 mg) once daily during 168 days	
Reporting group title	Arm 2
Reporting group description:	
Tobramycin Inhalation Powder (112 mg) twice daily on days 1-28, days 57-84 and days 113-140	

Primary: Change from baseline in Forced Expiratory Volume in 1 second (FEV1) percent predicted

End point title	Change from baseline in Forced Expiratory Volume in 1 second (FEV1) percent predicted ^[1]
End point description:	
The Forced Expiratory Volume in 1 second (FEV1) percent predicted expresses FEV1 as a percentage of the "predicted values" for participants of similar characteristics (height, age, sex, and sometimes race and weight). A positive change from baseline in FEV1 percent predicted indicates improvement in lung function.	
End point type	Primary
End point timeframe:	
Baseline and Day 168	

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: Only safety data analyzed. No data met pre-specified powering of 200 patients needed for analysis.

End point values	Arm 1	Arm 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0 ^[2]	0 ^[3]		
Units: percentage of FEV1				
arithmetic mean (standard deviation)	()	()		

Notes:

[2] - Only safety data analyzed. No data met pre-specified powering of 200 patients needed for analysis.

[3] - Only safety data analyzed. No data met pre-specified powering of 200 patients needed for analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Percent change from baseline in Forced Expiratory Volume in 1 second (FEV1) percent predicted

End point title	Percent change from baseline in Forced Expiratory Volume in 1 second (FEV1) percent predicted
End point description:	
The Forced Expiratory Volume in 1 second (FEV1) percent predicted expresses FEV1 as a percentage of the "predicted values" for participants of similar characteristics (height, age, sex, and sometimes race and weight). A positive change from baseline in FEV1 percent predicted indicates improvement in lung function.	
End point type	Secondary

End point timeframe:

Baseline and Day 168

End point values	Arm 1	Arm 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0 ^[4]	0 ^[5]		
Units: percentage change of FEV1				
arithmetic mean (standard deviation)	()	()		

Notes:

[4] - Only safety data analyzed. No data met pre-specified powering of 200 patients needed for analysis.

[5] - Only safety data analyzed. No data met pre-specified powering of 200 patients needed for analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Percent change from baseline in Forced Vital Capacity (FVC) percent predicted

End point title	Percent change from baseline in Forced Vital Capacity (FVC) percent predicted
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End point description:

Forced Vital Capacity (FVC) is the amount of air which can be forcibly exhaled from the lungs after taking the deepest breath possible. FVC was assessed via spirometry. A positive change from baseline in FVC indicates improvement in lung function.

End point type	Secondary
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End point timeframe:

Baseline and Day 168

End point values	Arm 1	Arm 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0 ^[6]	0 ^[7]		
Units: percentage change of FVC				
arithmetic mean (standard deviation)	()	()		

Notes:

[6] - Only safety data analyzed. No data met pre-specified powering of 200 patients needed for analysis.

[7] - Only safety data analyzed. No data met pre-specified powering of 200 patients needed for analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Percent change from baseline in forced expiratory flow (FEF) 25%-75% predicted

End point title	Percent change from baseline in forced expiratory flow (FEF) 25%-75% predicted
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End point description:

The Forced Expiratory Flow (FEF) 25%-75% measurement describes the amount of air expelled from the lungs during the middle half (25% - 75%) of the forced vital capacity test and is measured using

spirometry. A positive change from baseline in FEF indicates improvement in lung function. The predicted percent will be assessed.

End point type	Secondary
End point timeframe:	
Baseline and day 168	

End point values	Arm 1	Arm 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0 ^[8]	0 ^[9]		
Units: percengate change of FEF				
arithmetic mean (standard deviation)	()	()		

Notes:

[8] - Only safety data analyzed. No data met pre-specified powering of 200 patients needed for analysis.

[9] - Only safety data analyzed. No data met pre-specified powering of 200 patients needed for analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in Pseudomonas aeruginosa sputum density

End point title	Change from baseline in Pseudomonas aeruginosa sputum density
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End point description:

Change from baseline in Pseudomonas aeruginosa sputum density was supposed to be measured by log10 colony forming units per gram of sputum.

End point type	Secondary
End point timeframe:	
Baseline and day 168	

End point values	Arm 1	Arm 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0 ^[10]	0 ^[11]		
Units: log10 colony forming units per gram of s				
arithmetic mean (standard deviation)	()	()		

Notes:

[10] - Only safety data analyzed. No data met pre-specified powering of 200 patients needed for analysis.

[11] - Only safety data analyzed. No data met pre-specified powering of 200 patients needed for analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Time to first hospitalization due to respiratory-related events

End point title	Time to first hospitalization due to respiratory-related events
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End point description:	
Time to the first hospitalization due to respiratory-related events (number of days) per patient.	
End point type	Secondary
End point timeframe:	
Day 1 to day 168	

End point values	Arm 1	Arm 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0 ^[12]	0 ^[13]		
Units: Days				
median (full range (min-max))	(to)	(to)		

Notes:

[12] - Only safety data analyzed. No data met pre-specified powering of 200 patients needed for analysis.

[13] - Only safety data analyzed. No data met pre-specified powering of 200 patients needed for analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of patients with hospitalizations due to respiratory-related events

End point title	Percentage of patients with hospitalizations due to respiratory-related events
End point description:	
Percentage of patients with hospitalization due to respiratory-related events	
End point type	Secondary
End point timeframe:	
Day 1 to day 168	

End point values	Arm 1	Arm 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0 ^[14]	0 ^[15]		
Units: Percentage of participants				
number (not applicable)				

Notes:

[14] - Only safety data analyzed. No data met pre-specified powering of 200 patients needed for analysis.

[15] - Only safety data analyzed. No data met pre-specified powering of 200 patients needed for analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Length of hospital stay due to respiratory-related events

End point title	Length of hospital stay due to respiratory-related events
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End point description:

The number of days in length of hospital stay per patient due to respiratory-related events will be measured.

End point type	Secondary
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End point timeframe:

Day 1 to day 168

End point values	Arm 1	Arm 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0 ^[16]	0 ^[17]		
Units: Days				
median (full range (min-max))	(to)	(to)		

Notes:

[16] - Only safety data analyzed. No data met pre-specified powering of 200 patients needed for analysis.

[17] - Only safety data analyzed. No data met pre-specified powering of 200 patients needed for analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Time to first usage of anti-pseudomonal antibiotic

End point title	Time to first usage of anti-pseudomonal antibiotic
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End point description:

Time to first usage of anti-pseudomonal antibiotic per patient will be assessed by number of days

End point type	Secondary
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End point timeframe:

Day 1 to day 168

End point values	Arm 1	Arm 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0 ^[18]	0 ^[19]		
Units: Days				
median (full range (min-max))	(to)	(to)		

Notes:

[18] - Only safety data analyzed. No data met pre-specified powering of 200 patients needed for analysis.

[19] - Only safety data analyzed. No data met pre-specified powering of 200 patients needed for analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of patients who use anti-pseudomonal antibiotic

End point title	Percentage of patients who use anti-pseudomonal antibiotic
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End point description:	
Percentage of patients who use anti-pseudomonal antibiotic will be assessed.	
End point type	Secondary
End point timeframe:	
Day 1 to day 168	

End point values	Arm 1	Arm 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0 ^[20]	0 ^[21]		
Units: Percentage of patients				
number (not applicable)				

Notes:

[20] - Only safety data analyzed. No data met pre-specified powering of 200 patients needed for analysis.

[21] - Only safety data analyzed. No data met pre-specified powering of 200 patients needed for analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of use of anti-pseudomonal antibiotic

End point title	Duration of use of anti-pseudomonal antibiotic
End point description:	
Number of days of use of anti-pseudomonal antibiotic per patient will be assessed.	
End point type	Secondary
End point timeframe:	
Day 1 to day 168	

End point values	Arm 1	Arm 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0 ^[22]	0 ^[23]		
Units: Days				
median (full range (min-max))	(to)	(to)		

Notes:

[22] - Only safety data analyzed. No data met pre-specified powering of 200 patients needed for analysis.

[23] - Only safety data analyzed. No data met pre-specified powering of 200 patients needed for analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in tobramycin minimal inhibitory concentration for *Pseudomonas aeruginosa*

End point title	Change from baseline in tobramycin minimal inhibitory concentration for <i>Pseudomonas aeruginosa</i>
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End point description:

Change from baseline in tobramycin minimal inhibitory concentration for *Pseudomonas aeruginosa* will be measured by laboratory testing.

End point type	Secondary
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End point timeframe:

Baseline and day 168

End point values	Arm 1	Arm 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0 ^[24]	0 ^[25]		
Units: Micrograms/milliliters				
arithmetic mean (standard deviation)	()	()		

Notes:

[24] - Only safety data analyzed. No data met pre-specified powering of 200 patients needed for analysis.

[25] - Only safety data analyzed. No data met pre-specified powering of 200 patients needed for analysis.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All Adverse events are reported in this record from First Patient First Treatment until Last Patient Last Visit.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	17.1
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Reporting groups

Reporting group title	Tobramycin Inhalation Powder Once Daily
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Reporting group description:

Tobramycin Inhalation Powder (112 mg) once daily during 168 days

Reporting group title	Tobramycin Inhalation Powder Twice Daily
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Reporting group description:

Tobramycin Inhalation Powder (112 mg) twice daily on days 1-28, days 57-84 and days 113-140

Serious adverse events	Tobramycin Inhalation Powder Once Daily	Tobramycin Inhalation Powder Twice Daily	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 16 (18.75%)	1 / 15 (6.67%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Reproductive system and breast disorders			
Endometriosis			
subjects affected / exposed	1 / 16 (6.25%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Infective pulmonary exacerbation of cystic fibrosis			
subjects affected / exposed	2 / 16 (12.50%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Tobramycin Inhalation Powder Once Daily	Tobramycin Inhalation Powder Twice Daily	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	13 / 16 (81.25%)	12 / 15 (80.00%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Benign ovarian tumour			
subjects affected / exposed	1 / 16 (6.25%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 16 (6.25%)	2 / 15 (13.33%)	
occurrences (all)	1	3	
Chest discomfort			
subjects affected / exposed	2 / 16 (12.50%)	0 / 15 (0.00%)	
occurrences (all)	2	0	
Chills			
subjects affected / exposed	0 / 16 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	2	
Fatigue			
subjects affected / exposed	1 / 16 (6.25%)	1 / 15 (6.67%)	
occurrences (all)	1	1	
Pain			
subjects affected / exposed	0 / 16 (0.00%)	2 / 15 (13.33%)	
occurrences (all)	0	2	
Pyrexia			
subjects affected / exposed	1 / 16 (6.25%)	1 / 15 (6.67%)	
occurrences (all)	1	1	
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	1 / 16 (6.25%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Reproductive system and breast disorders			
Cervical dysplasia			
subjects affected / exposed	1 / 16 (6.25%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Fallopian tube cyst			

subjects affected / exposed	1 / 16 (6.25%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Haemorrhagic ovarian cyst			
subjects affected / exposed	1 / 16 (6.25%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Ovarian cyst			
subjects affected / exposed	1 / 16 (6.25%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	10 / 16 (62.50%)	9 / 15 (60.00%)	
occurrences (all)	20	19	
Dry throat			
subjects affected / exposed	1 / 16 (6.25%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Dysphonia			
subjects affected / exposed	0 / 16 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	3	
Dyspnoea			
subjects affected / exposed	2 / 16 (12.50%)	3 / 15 (20.00%)	
occurrences (all)	2	3	
Haemoptysis			
subjects affected / exposed	2 / 16 (12.50%)	1 / 15 (6.67%)	
occurrences (all)	3	1	
Nasal congestion			
subjects affected / exposed	1 / 16 (6.25%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Oropharyngeal pain			
subjects affected / exposed	3 / 16 (18.75%)	1 / 15 (6.67%)	
occurrences (all)	3	3	
Pharyngeal oedema			
subjects affected / exposed	1 / 16 (6.25%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Productive cough			

subjects affected / exposed	0 / 16 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Prolonged expiration			
subjects affected / exposed	0 / 16 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Pulmonary congestion			
subjects affected / exposed	1 / 16 (6.25%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Rhonchi			
subjects affected / exposed	0 / 16 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Sinus congestion			
subjects affected / exposed	1 / 16 (6.25%)	1 / 15 (6.67%)	
occurrences (all)	1	2	
Sputum increased			
subjects affected / exposed	1 / 16 (6.25%)	2 / 15 (13.33%)	
occurrences (all)	1	2	
Throat irritation			
subjects affected / exposed	1 / 16 (6.25%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Wheezing			
subjects affected / exposed	0 / 16 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 16 (0.00%)	2 / 15 (13.33%)	
occurrences (all)	0	2	
Depression			
subjects affected / exposed	0 / 16 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Investigations			
Hepatic enzyme increased			
subjects affected / exposed	1 / 16 (6.25%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Liver function test abnormal			

subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0	1 / 15 (6.67%) 1	
Oxygen saturation decreased subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0	1 / 15 (6.67%) 1	
Pulmonary function test decreased subjects affected / exposed occurrences (all)	3 / 16 (18.75%) 3	1 / 15 (6.67%) 1	
Weight decreased subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1	0 / 15 (0.00%) 0	
Injury, poisoning and procedural complications			
Anaemia postoperative subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1	0 / 15 (0.00%) 0	
Gastrointestinal disorder postoperative subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1	0 / 15 (0.00%) 0	
Procedural pain subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1	0 / 15 (0.00%) 0	
Vaccination complication subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1	0 / 15 (0.00%) 0	
Cardiac disorders			
Palpitations subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0	1 / 15 (6.67%) 1	
Nervous system disorders			
Aphonia subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1	0 / 15 (0.00%) 0	
Dizziness subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0	2 / 15 (13.33%) 2	
Dysgeusia			

subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0	1 / 15 (6.67%) 1	
Neuralgia subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0	1 / 15 (6.67%) 1	
Ear and labyrinth disorders			
Hypoacusis subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1	0 / 15 (0.00%) 0	
Tinnitus subjects affected / exposed occurrences (all)	2 / 16 (12.50%) 2	1 / 15 (6.67%) 1	
Gastrointestinal disorders			
Abdominal discomfort subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0	1 / 15 (6.67%) 1	
Abdominal pain subjects affected / exposed occurrences (all)	2 / 16 (12.50%) 2	1 / 15 (6.67%) 1	
Abdominal pain upper subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0	2 / 15 (13.33%) 2	
Constipation subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1	1 / 15 (6.67%) 1	
Diarrhoea subjects affected / exposed occurrences (all)	2 / 16 (12.50%) 2	1 / 15 (6.67%) 1	
Dry mouth subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0	1 / 15 (6.67%) 3	
Nausea subjects affected / exposed occurrences (all)	3 / 16 (18.75%) 3	0 / 15 (0.00%) 0	
Post-tussive vomiting			

subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0	1 / 15 (6.67%) 2	
Vomiting subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1	1 / 15 (6.67%) 1	
Skin and subcutaneous tissue disorders Dry skin subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0	1 / 15 (6.67%) 1	
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0	1 / 15 (6.67%) 2	
Back pain subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0	1 / 15 (6.67%) 1	
Muscle spasms subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0	1 / 15 (6.67%) 1	
Infections and infestations Infective pulmonary exacerbation of cystic fibrosis subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0	4 / 15 (26.67%) 8	
Otitis media subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1	0 / 15 (0.00%) 0	
Urinary tract infection subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1	0 / 15 (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.

Due to premature termination, many of the summaries and analyses planned in the protocol were eliminated in the statistical analysis plan prior to database lock. Data were summarized descriptively and no inferential analysis will be provided

Notes: