Clinical trial results:
A Phase 2, Randomized, Double-blind, Controlled Study to Evaluate the Safety and Efficacy of VX-440 Combination Therapy in Subjects Aged 12 Years and Older With Cystic Fibrosis

Summary

EudraCT number	2016-000454-36
Trial protocol	GB AT DK DE BE ES NL IT
Global end of trial date	09 August 2017

Results information

Result version number	v1
This version publication date	14 December 2018
First version publication date	14 December 2018

Trial information

Trial identification

Sponsor protocol code	VX15-440-101

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02951182
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Vertex Pharmaceuticals Incorporated
Sponsor organisation address	50 Northern Avenue, Massachusetts, Boston, United States, 02210-1862
Public contact	Medical Monitor, Vertex Pharmaceuticals Incorporated, +1 617-341-6777, medicalinfo@vrtx.com
Scientific contact	Medical Monitor, Vertex Pharmaceuticals Incorporated, +1 617-341-6777, medicalinfo@vrtx.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	07 September 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	09 August 2017
Global end of trial reached?	Yes
Global end of trial date	09 August 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the safety, tolerability and efficacy of VX-440 in dual and triple combination with tezacaftor (TEZ) and ivacaftor (IVA)

Protection of trial subjects:

The study was conducted in accordance with the ethical principles stated in the Declaration of Helsinki and the International Council on Harmonization (ICH) Guideline for Good Clinical Practice (GCP).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	09 November 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 1
Country: Number of subjects enrolled	United Kingdom: 3
Country: Number of subjects enrolled	Austria: 2
Country: Number of subjects enrolled	Belgium: 3
Country: Number of subjects enrolled	Denmark: 2
Country: Number of subjects enrolled	Germany: 6
Country: Number of subjects enrolled	Australia: 6
Country: Number of subjects enrolled	Canada: 4
Country: Number of subjects enrolled	Italy: 2
Country: Number of subjects enrolled	United States: 45
Worldwide total number of subjects	74
EEA total number of subjects	19

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)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	74
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Four parts were planned for the study, but only Parts 1 and 2 were conducted. Part 3 was removed from the protocol in Version 2.0. Part 4 was not conducted at the Sponsor’s discretion.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Part 1: Placebo - Cohort 1A and 1B Combined

Arm description:

Subjects received placebo matched to VX-440, placebo matched to tezacaftor (TEZ; VX-661) and placebo matched to ivacaftor (IVA, VX-770) triple combination administered orally for 4 weeks in part 1.

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

Dosage and administration details:

Subjects received placebo matched with VX-440, TEZ, and IVA triple combination in part 1.

Arm title	Part 1 Cohort 1A: Triple Combination (TC)

Arm description:

Subjects received VX-440 at a dose of 200 milligram (mg) along with TEZ 100 mg and IVA 150 mg triple combination administered orally up to Week 4.

Arm type	Experimental
Investigational medicinal product name	VX-440
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received VX-440 at a dose of 200 mg administered every 12 hours (q12h) up to 4 weeks.

Investigational medicinal product name	TEZ
Investigational medicinal product code	VX-661
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received TEZ at a dose of 100 mg administered once daily (qd) up to 4 weeks.

Investigational medicinal product name	IVA
Investigational medicinal product code	VX-770
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received IVA at a dose of 150 mg administered q12h up to 4 weeks.

Arm title	Part 1 Cohort 1B: TC Low Dose

Arm description:

Subjects received VX-440 at a dose of 200 mg along with TEZ 50 mg and IVA 150 mg triple combination administered orally up to Week 4.

Arm type	Experimental
Investigational medicinal product name	VX-440
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received VX-440 at a dose of 200 mg administered q12h up to 4 weeks.

Investigational medicinal product name	TEZ
Investigational medicinal product code	
Other name	VX-661
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received TEZ at a dose of 50 mg administered every q12h up to 4 weeks.

Investigational medicinal product name	IVA
Investigational medicinal product code	
Other name	VX-770
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received IVA at a dose of 150 mg administered q12h up to 4 weeks.

Arm title	Part 1 Cohort 1B: TC High Dose

Arm description:

Subjects received VX-440 at a dose of 600 mg along with TEZ 50 mg and IVA 300 mg triple combination administered orally up to Week 4.

Arm type	Experimental
Investigational medicinal product name	VX-440
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received VX-440 at a dose of 600 mg administered q12h up to 4 weeks.

Investigational medicinal product name	TEZ
Investigational medicinal product code	VX-661
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received TEZ at a dose of 50 mg administered every q12h up to 4 weeks.

Investigational medicinal product name	IVA
Investigational medicinal product code	VX-770
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received IVA at a dose of 300 mg administered q12h up to 4 weeks.

Arm title	Part 2: TEZ/IVA

Arm description:

Following a 4-week run-in period on TEZ/IVA, subjects received TEZ 100 mg and IVA 150 mg administered orally up to Week 8.

Arm type	Active comparator
Investigational medicinal product name	TEZ
Investigational medicinal product code	VX-661
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received TEZ at a dose of 100 mg administered once daily up to 12 weeks.

Investigational medicinal product name	IVA
Investigational medicinal product code	VX-770
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received IVA at a dose of 150 mg administered q12h up to 12 weeks.

Arm title	Part 2: TC-2

Arm description:

Following a 4-week run-in period on TEZ/IVA, subjects received VX-440 at a dose of 600 mg for 4 weeks along with TEZ 50 mg and IVA 300 mg administered orally up to Week 8.

Arm type	Experimental
Investigational medicinal product name	TEZ
Investigational medicinal product code	VX-661
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received TEZ at a dose of 50 mg administered q12 up to 12 weeks.

Investigational medicinal product name	IVA
Investigational medicinal product code	VX-770
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received IVA at a dose of 300 mg administered q12h up to 12 weeks.

Investigational medicinal product name	VX-440
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received VX-440 at a dose of 600 mg administered q12h up to 4 weeks.

Number of subjects in period 1[1]	Part 1: Placebo - Cohort 1A and 1B Combined	Part 1 Cohort 1A: Triple Combination (TC)	Part 1 Cohort 1B: TC Low Dose
Started	11	9	9
Completed	11	9	9

Number of subjects in period 1[1]	Part 1 Cohort 1B: TC High Dose	Part 2: TEZ/IVA	Part 2: TC-2
Started	18	6	20
Completed	18	6	20

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Of the 74 subjects enrolled (47 subjects in Part 1 and 27 subjects in Part 2 Run-in Period), 1 subject from Run-in period discontinued before randomization at the start of the Treatment Period because continuation criteria were not met.

Baseline characteristics

Reporting groups	
Reporting group title	Part 1: Placebo - Cohort 1A and 1B Combined
Reporting group description:	
Subjects received placebo matched to VX-440, placebo matched to tezacaftor (TEZ; VX-661) and placebo matched to ivacaftor (IVA, VX-770) triple combination administered orally for 4 weeks in part 1.	
Reporting group title	Part 1 Cohort 1A: Triple Combination (TC)
Reporting group description:	
Subjects received VX-440 at a dose of 200 milligram (mg) along with TEZ 100 mg and IVA 150 mg triple combination administered orally up to Week 4.	
Reporting group title	Part 1 Cohort 1B: TC Low Dose
Reporting group description:	
Subjects received VX-440 at a dose of 200 mg along with TEZ 50 mg and IVA 150 mg triple combination administered orally up to Week 4.	
Reporting group title	Part 1 Cohort 1B: TC High Dose
Reporting group description:	
Subjects received VX-440 at a dose of 600 mg along with TEZ 50 mg and IVA 300 mg triple combination administered orally up to Week 4.	
Reporting group title	Part 2: TEZ/IVA
Reporting group description:	
Following a 4-week run-in period on TEZ/IVA, subjects received TEZ 100 mg and IVA 150 mg administered orally up to Week 8.	
Reporting group title	Part 2: TC-2
Reporting group description:	
Following a 4-week run-in period on TEZ/IVA, subjects received VX-440 at a dose of 600 mg for 4 weeks along with TEZ 50 mg and IVA 300 mg administered orally up to Week 8.	

Reporting group values	Part 1: Placebo - Cohort 1A and 1B Combined	Part 1 Cohort 1A: Triple Combination (TC)	Part 1 Cohort 1B: TC Low Dose
Number of subjects	11	9	9
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	38.2	36.3	30.6
standard deviation	± 9.2	± 13.2	± 13.3
Gender categorical			
Units: Subjects			
Female	2	1	3
Male	9	8	6

Reporting group values	Part 1 Cohort 1B: TC High Dose	Part 2: TEZ/IVA	Part 2: TC-2
Number of subjects	18	6	20
Age categorical			
Units: Subjects			

Age continuous Units: years arithmetic mean standard deviation	29.3 ± 6.7	33.2 ± 3.7	30.8 ± 5.9
Gender categorical Units: Subjects			
Female	1	0	4
Male	17	6	16

Reporting group values	Total		
Number of subjects	73		
Age categorical Units: Subjects			

Age continuous Units: years arithmetic mean standard deviation	- -		
Gender categorical Units: Subjects			
Female	11		
Male	62		

End points

End points reporting groups

Reporting group title	Part 1: Placebo - Cohort 1A and 1B Combined

Reporting group description:

Subjects received placebo matched to VX-440, placebo matched to tezacaftor (TEZ; VX-661) and placebo matched to ivacaftor (IVA, VX-770) triple combination administered orally for 4 weeks in part 1.

Reporting group title	Part 1 Cohort 1A: Triple Combination (TC)

Reporting group description:

Subjects received VX-440 at a dose of 200 milligram (mg) along with TEZ 100 mg and IVA 150 mg triple combination administered orally up to Week 4.

Reporting group title	Part 1 Cohort 1B: TC Low Dose

Reporting group description:

Subjects received VX-440 at a dose of 200 mg along with TEZ 50 mg and IVA 150 mg triple combination administered orally up to Week 4.

Reporting group title	Part 1 Cohort 1B: TC High Dose

Reporting group description:

Subjects received VX-440 at a dose of 600 mg along with TEZ 50 mg and IVA 300 mg triple combination administered orally up to Week 4.

Reporting group title	Part 2: TEZ/IVA

Reporting group description:

Following a 4-week run-in period on TEZ/IVA, subjects received TEZ 100 mg and IVA 150 mg administered orally up to Week 8.

Reporting group title	Part 2: TC-2

Reporting group description:

Following a 4-week run-in period on TEZ/IVA, subjects received VX-440 at a dose of 600 mg for 4 weeks along with TEZ 50 mg and IVA 300 mg administered orally up to Week 8.

Subject analysis set title	Part 1: TC-1A/ TC-1B-low Pooled
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Sub-group analysis for primary efficacy endpoint: All subjects pooled together for Part 1: TC-1A arm and Part 1: TC-1B low dose arm.

Primary: Number of Subjects With Treatment-Emergent Adverse Events (AEs) and Serious Adverse Events (SAEs)

End point title	Number of Subjects With Treatment-Emergent Adverse Events (AEs) and Serious Adverse Events (SAEs)[1]

End point description:

End point type	Primary

End point timeframe:

From first dose of Study Drug in the Treatment Period through Safety Follow-up Visit

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 descriptive data was planned to be analysed for this endpoint. No statistical comparisons were planned.

End point values	Part 1: Placebo - Cohort 1A and 1B Combined	Part 1 Cohort 1A: Triple Combination (TC)	Part 1 Cohort 1B: TC Low Dose	Part 1 Cohort 1B: TC High Dose
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	11	9	9	18
Units: Subjects				
number (not applicable)				
AEs	9	9	9	15
SAEs	0	0	0	2

End point values	Part 2: TEZ/IVA	Part 2: TC-2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	20		
Units: Subjects				
number (not applicable)				
AEs	6	15		
SAEs	2	1		

Statistical analyses

No statistical analyses for this end point

Primary: Absolute Change From Baseline in Percent Predicted Forced Expiratory Volume in 1 Second (ppFEV1) Through Day 29

End point title	Absolute Change From Baseline in Percent Predicted Forced Expiratory Volume in 1 Second (ppFEV1) Through Day 29[2][3]

End point description:

FEV1 is the volume of air that can forcibly be blown out in first second, after full inspiration.

End point type	Primary

End point timeframe:

Baseline, Through Day 29

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: Pooled Data for Part 1: TC-1A arm and Part 1: TC-1B low dose arm was planned to be reported for primary efficacy end point.
[3] - 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: Pooled Data for Part 1: TC-1A arm and Part 1: TC-1B low dose arm was planned to be reported for primary efficacy end point.

End point values	Part 1: Placebo - Cohort 1A and 1B Combined	Part 1 Cohort 1B: TC High Dose	Part 2: TEZ/IVA	Part 2: TC-2
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	11	18	6	19
Units: Percentage of predicted FEV1				
least squares mean (confidence interval	1.4 (-2.5 to	12.0 (8.8 to	-2.5 (-7.2 to	9.5 (6.9 to

95%)	5.5)	15.2)	2.2)	12.2)

End point values	Part 1: TC-1A/ TC-1B-low Pooled			
Subject group type	Subject analysis set			
Number of subjects analysed	18			
Units: Percentage of predicted FEV1				
least squares mean (confidence interval 95%)	10.0 (6.9 to 13.2)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: From first dose of Study Drug in the Treatment Period through Safety Follow-up Visit	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	20
Reporting groups	
Reporting group title	Part 1: Placebo - Cohort 1A and 1B Combined
Reporting group description: -	
Reporting group title	Part 1 Cohort 1A: Triple Combination (TC)
Reporting group description: -	
Reporting group title	Part 1 Cohot 1B: TC Low Dose
Reporting group description: -	
Reporting group title	Part 1 Cohort 1B: TC High Dose
Reporting group description: -	
Reporting group title	Part 2: TEZ/IVA
Reporting group description: -	
Reporting group title	Part 2: TC-2
Reporting group description: -	

Serious adverse events	Part 1: Placebo - Cohort 1A and 1B Combined	Part 1 Cohort 1A: Triple Combination (TC)	Part 1 Cohot 1B: TC Low Dose
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	0 / 9 (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
Distal intestinal obstruction syndrome			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	0 / 9 (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
Psychiatric disorders			
Adjustment disorder			

subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	0 / 9 (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			
Infective pulmonary exacerbation of cystic fibrosis			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	0 / 9 (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	Part 1 Cohort 1B: TC High Dose	Part 2: TEZ/IVA	Part 2: TC-2
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 18 (11.11%)	2 / 6 (33.33%)	1 / 20 (5.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	1 / 18 (5.56%)	0 / 6 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Distal intestinal obstruction syndrome			
subjects affected / exposed	1 / 18 (5.56%)	0 / 6 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Adjustment disorder			
subjects affected / exposed	0 / 18 (0.00%)	1 / 6 (16.67%)	0 / 20 (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
Infections and infestations			
Infective pulmonary exacerbation of cystic fibrosis			
subjects affected / exposed	1 / 18 (5.56%)	1 / 6 (16.67%)	1 / 20 (5.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Part 1: Placebo - Cohort 1A and 1B Combined	Part 1 Cohort 1A: Triple Combination (TC)	Part 1 Cohot 1B: TC Low Dose
Total subjects affected by non-serious adverse events			
subjects affected / exposed	9 / 11 (81.82%)	9 / 9 (100.00%)	9 / 9 (100.00%)
Vascular disorders			
Hot flush			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	2 / 9 (22.22%)
occurrences (all)	0	0	2
Chills			
subjects affected / exposed	1 / 11 (9.09%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Influenza like illness			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Pain			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Pyrexia			
subjects affected / exposed	1 / 11 (9.09%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Hypersensitivity			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Reproductive system and breast disorders			
Testicular cyst			

subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	4 / 11 (36.36%)	3 / 9 (33.33%)	1 / 9 (11.11%)
occurrences (all)	4	3	1
Sputum increased			
subjects affected / exposed	3 / 11 (27.27%)	1 / 9 (11.11%)	1 / 9 (11.11%)
occurrences (all)	3	1	1
Haemoptysis			
subjects affected / exposed	1 / 11 (9.09%)	0 / 9 (0.00%)	1 / 9 (11.11%)
occurrences (all)	1	0	1
Dyspnoea			
subjects affected / exposed	2 / 11 (18.18%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	2	0	0
Nasal congestion			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Oropharyngeal pain			
subjects affected / exposed	2 / 11 (18.18%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	2	0	0
Paranasal sinus hypersecretion			
subjects affected / exposed	1 / 11 (9.09%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	2	0	0
Respiration abnormal			
subjects affected / exposed	2 / 11 (18.18%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	2	0	0
Dysphonia			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Lower respiratory tract congestion			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Productive cough			

subjects affected / exposed	1 / 11 (9.09%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Rhinorrhoea			
subjects affected / exposed	1 / 11 (9.09%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Wheezing			
subjects affected / exposed	0 / 11 (0.00%)	1 / 9 (11.11%)	1 / 9 (11.11%)
occurrences (all)	0	1	1
Dyspnoea exertional			
subjects affected / exposed	1 / 11 (9.09%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Increased viscosity of bronchial secretion			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Paranasal sinus discomfort			
subjects affected / exposed	0 / 11 (0.00%)	1 / 9 (11.11%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Pulmonary pain			
subjects affected / exposed	1 / 11 (9.09%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Rales			
subjects affected / exposed	1 / 11 (9.09%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Sinus disorder			
subjects affected / exposed	1 / 11 (9.09%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Sinus pain			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Throat irritation			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Anxiety			

subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Insomnia			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Mood swings			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 11 (9.09%)	0 / 9 (0.00%)	1 / 9 (11.11%)
occurrences (all)	1	0	1
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 11 (9.09%)	0 / 9 (0.00%)	1 / 9 (11.11%)
occurrences (all)	1	0	1
Blood urine present			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
International normalised ratio increased			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Activated partial thromboplastin time prolonged			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Blood bicarbonate decreased			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Blood bilirubin increased			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Blood bilirubin unconjugated increased			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Blood chloride increased			

subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Blood creatinine increased			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Blood glucose increased			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Blood pressure increased			
subjects affected / exposed	0 / 11 (0.00%)	1 / 9 (11.11%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Crystal urine present			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Lipase decreased			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Monocyte count increased			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Prothrombin time prolonged			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Pulmonary function test decreased			
subjects affected / exposed	1 / 11 (9.09%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Weight decreased			
subjects affected / exposed	0 / 11 (0.00%)	1 / 9 (11.11%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Injury, poisoning and procedural complications			
Anaesthetic complication neurological			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Contusion			

subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Joint injury			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Ligament rupture			
subjects affected / exposed	1 / 11 (9.09%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Post procedural swelling			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Post-traumatic neck syndrome			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Procedural nausea			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Procedural pain			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Sunburn			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 11 (9.09%)	1 / 9 (11.11%)	1 / 9 (11.11%)
occurrences (all)	1	1	1
Dizziness			
subjects affected / exposed	2 / 11 (18.18%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	2	0	0
Lethargy			
subjects affected / exposed	1 / 11 (9.09%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Presyncope			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1

Syncope			
subjects affected / exposed	0 / 11 (0.00%)	1 / 9 (11.11%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	1 / 11 (9.09%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Eye disorders			
Eye pruritus			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 11 (9.09%)	1 / 9 (11.11%)	1 / 9 (11.11%)
occurrences (all)	1	1	1
Abdominal pain			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Abdominal pain upper			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Abnormal faeces			
subjects affected / exposed	1 / 11 (9.09%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	2	0	0
Flatulence			
subjects affected / exposed	1 / 11 (9.09%)	1 / 9 (11.11%)	0 / 9 (0.00%)
occurrences (all)	1	1	0
Anorectal discomfort			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Dyspepsia			
subjects affected / exposed	0 / 11 (0.00%)	1 / 9 (11.11%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Faeces pale			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Nausea			

subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Alopecia			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Blister			
subjects affected / exposed	1 / 11 (9.09%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Hyperhidrosis			
subjects affected / exposed	1 / 11 (9.09%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Night sweats			
subjects affected / exposed	1 / 11 (9.09%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Pruritus			
subjects affected / exposed	1 / 11 (9.09%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Skin disorder			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	0 / 11 (0.00%)	1 / 9 (11.11%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal and connective tissue disorders			
Musculoskeletal chest pain			
subjects affected / exposed	1 / 11 (9.09%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Arthralgia			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Back pain			

subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Flank pain			
subjects affected / exposed	1 / 11 (9.09%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Muscle twitching			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Myalgia			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Neck pain			
subjects affected / exposed	0 / 11 (0.00%)	1 / 9 (11.11%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Tendon discomfort			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Tendonitis			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Infective pulmonary exacerbation of cystic fibrosis			
subjects affected / exposed	2 / 11 (18.18%)	6 / 9 (66.67%)	0 / 9 (0.00%)
occurrences (all)	2	7	0
Viral upper respiratory tract infection			
subjects affected / exposed	1 / 11 (9.09%)	0 / 9 (0.00%)	2 / 9 (22.22%)
occurrences (all)	1	0	2
Upper respiratory tract infection			
subjects affected / exposed	0 / 11 (0.00%)	2 / 9 (22.22%)	0 / 9 (0.00%)
occurrences (all)	0	2	0
Folliculitis			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Gastroenteritis			

subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Influenza			
subjects affected / exposed	0 / 11 (0.00%)	1 / 9 (11.11%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Pharyngitis			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Hypoglycaemia			
subjects affected / exposed	1 / 11 (9.09%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Hyperglycaemia			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Increased appetite			
subjects affected / exposed	1 / 11 (9.09%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0

Non-serious adverse events	Part 1 Cohort 1B: TC High Dose	Part 2: TEZ/IVA	Part 2: TC-2
Total subjects affected by non-serious adverse events			
subjects affected / exposed	15 / 18 (83.33%)	6 / 6 (100.00%)	15 / 20 (75.00%)
Vascular disorders			
Hot flush			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Chills			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Influenza like illness			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1

Pain			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Pyrexia			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Hypersensitivity			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Reproductive system and breast disorders			
Testicular cyst			
subjects affected / exposed	1 / 18 (5.56%)	0 / 6 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 18 (5.56%)	0 / 6 (0.00%)	5 / 20 (25.00%)
occurrences (all)	1	0	5
Sputum increased			
subjects affected / exposed	1 / 18 (5.56%)	1 / 6 (16.67%)	3 / 20 (15.00%)
occurrences (all)	1	1	3
Haemoptysis			
subjects affected / exposed	1 / 18 (5.56%)	0 / 6 (0.00%)	1 / 20 (5.00%)
occurrences (all)	1	0	2
Dyspnoea			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Nasal congestion			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	2 / 20 (10.00%)
occurrences (all)	0	0	2
Oropharyngeal pain			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1

Paranasal sinus hypersecretion			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Respiration abnormal			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Dysphonia			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	2
Lower respiratory tract congestion			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	2 / 20 (10.00%)
occurrences (all)	0	0	2
Productive cough			
subjects affected / exposed	1 / 18 (5.56%)	0 / 6 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
Rhinorrhoea			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Wheezing			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Dyspnoea exertional			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Increased viscosity of bronchial secretion			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Paranasal sinus discomfort			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Pulmonary pain			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Rales			

subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Sinus disorder			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Sinus pain			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Throat irritation			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 18 (5.56%)	0 / 6 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
Insomnia			
subjects affected / exposed	0 / 18 (0.00%)	1 / 6 (16.67%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Mood swings			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	2 / 18 (11.11%)	0 / 6 (0.00%)	2 / 20 (10.00%)
occurrences (all)	2	0	2
Aspartate aminotransferase increased			
subjects affected / exposed	2 / 18 (11.11%)	0 / 6 (0.00%)	1 / 20 (5.00%)
occurrences (all)	2	0	1
Blood urine present			
subjects affected / exposed	1 / 18 (5.56%)	0 / 6 (0.00%)	0 / 20 (0.00%)
occurrences (all)	2	0	0
International normalised ratio increased			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Activated partial thromboplastin time prolonged			

subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Blood bicarbonate decreased			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Blood bilirubin increased			
subjects affected / exposed	1 / 18 (5.56%)	0 / 6 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
Blood bilirubin unconjugated increased			
subjects affected / exposed	1 / 18 (5.56%)	0 / 6 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
Blood chloride increased			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Blood creatinine increased			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Blood glucose increased			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Blood pressure increased			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Crystal urine present			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Lipase decreased			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Monocyte count increased			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Prothrombin time prolonged			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0

Pulmonary function test decreased			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Weight decreased			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Anaesthetic complication neurological			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Contusion			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Joint injury			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Ligament rupture			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Post procedural swelling			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Post-traumatic neck syndrome			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Procedural nausea			
subjects affected / exposed	1 / 18 (5.56%)	0 / 6 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
Procedural pain			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Sunburn			
subjects affected / exposed	1 / 18 (5.56%)	0 / 6 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
Nervous system disorders			

Headache			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Dizziness			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Lethargy			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Presyncope			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Syncope			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Eye disorders			
Eye pruritus			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	2 / 18 (11.11%)	0 / 6 (0.00%)	4 / 20 (20.00%)
occurrences (all)	5	0	4
Abdominal pain			
subjects affected / exposed	2 / 18 (11.11%)	1 / 6 (16.67%)	0 / 20 (0.00%)
occurrences (all)	2	1	0
Abdominal pain upper			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Abnormal faeces			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Flatulence			

subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Anorectal discomfort			
subjects affected / exposed	0 / 18 (0.00%)	1 / 6 (16.67%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Dyspepsia			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Faeces pale			
subjects affected / exposed	1 / 18 (5.56%)	0 / 6 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
Nausea			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Alopecia			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Blister			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Hyperhidrosis			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Night sweats			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Pruritus			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Skin disorder			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0

Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Musculoskeletal chest pain			
subjects affected / exposed	1 / 18 (5.56%)	0 / 6 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
Arthralgia			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Back pain			
subjects affected / exposed	1 / 18 (5.56%)	0 / 6 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
Flank pain			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Muscle twitching			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Myalgia			
subjects affected / exposed	1 / 18 (5.56%)	0 / 6 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
Neck pain			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Tendon discomfort			
subjects affected / exposed	0 / 18 (0.00%)	1 / 6 (16.67%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Tendonitis			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Infections and infestations			
Infective pulmonary exacerbation of cystic fibrosis			
subjects affected / exposed	2 / 18 (11.11%)	0 / 6 (0.00%)	2 / 20 (10.00%)
occurrences (all)	2	0	3

Viral upper respiratory tract infection			
subjects affected / exposed	2 / 18 (11.11%)	2 / 6 (33.33%)	1 / 20 (5.00%)
occurrences (all)	2	2	1
Upper respiratory tract infection			
subjects affected / exposed	2 / 18 (11.11%)	0 / 6 (0.00%)	2 / 20 (10.00%)
occurrences (all)	2	0	2
Folliculitis			
subjects affected / exposed	0 / 18 (0.00%)	1 / 6 (16.67%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Gastroenteritis			
subjects affected / exposed	1 / 18 (5.56%)	0 / 6 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
Influenza			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Pharyngitis			
subjects affected / exposed	0 / 18 (0.00%)	1 / 6 (16.67%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Metabolism and nutrition disorders			
Hypoglycaemia			
subjects affected / exposed	1 / 18 (5.56%)	0 / 6 (0.00%)	0 / 20 (0.00%)
occurrences (all)	2	0	0
Hyperglycaemia			
subjects affected / exposed	1 / 18 (5.56%)	0 / 6 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
Increased appetite			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
31 May 2016	- Sample size was reduced - Clarification in the study drug interruption and discontinuation - Modified contraception requirements

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported