Clinical trial results:
Long Term Administration of Inhaled Mannitol in Cystic Fibrosis – A Safety and Efficacy Trial in Adult Cystic Fibrosis Subjects

Summary

EudraCT number	2013-005357-79
Trial protocol	CZ HU IT BE SK GR BG SE
Global end of trial date	21 February 2017

Results information

Result version number	v1 (current)
This version publication date	19 December 2019
First version publication date	19 December 2019
Summary attachment (see zip file)	DPM-CF-303 Abbreviated Synopsis (DPM-CF-303 CSR Abbreviated Synopsis Final 13Sep2019.pdf)

Trial information

Trial identification

Sponsor protocol code	DPM-CF-303

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Pharmaxis Pty Ltd
Sponsor organisation address	20 Rodborough Road, Frenchs Forest, Australia, 2086
Public contact	Brett Charlton, Pharmaxis Limited, +61 2 9454 7210 , Brett.Charlton@pharmaxis.com.au
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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 November 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	21 February 2017
Global end of trial reached?	Yes
Global end of trial date	21 February 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine whether inhaled mannitol (400 mg b.i.d.) is superior to control (50mg b.i.d.) for improving lung function as measured by mean change from baseline FEV1 (mL) over the 26-week treatment period in adult subjects with cystic fibrosis (CF).

Protection of trial subjects:

DMC monitoring of Safety profile

Background therapy:

Standard CF therapy (excluding maintenance hypertonic saline

Evidence for comparator: -

Actual start date of recruitment	11 July 2014
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	Poland: 44
Country: Number of subjects enrolled	Romania: 10
Country: Number of subjects enrolled	Slovakia: 17
Country: Number of subjects enrolled	Spain: 11
Country: Number of subjects enrolled	Belgium: 6
Country: Number of subjects enrolled	Bulgaria: 13
Country: Number of subjects enrolled	Czech Republic: 1
Country: Number of subjects enrolled	Greece: 7
Country: Number of subjects enrolled	Hungary: 17
Country: Number of subjects enrolled	Italy: 15
Country: Number of subjects enrolled	Argentina: 6
Country: Number of subjects enrolled	Australia: 4
Country: Number of subjects enrolled	Canada: 13
Country: Number of subjects enrolled	Israel: 11
Country: Number of subjects enrolled	Mexico: 5
Country: Number of subjects enrolled	New Zealand: 5
Country: Number of subjects enrolled	Russian Federation: 41
Country: Number of subjects enrolled	South Africa: 10
Country: Number of subjects enrolled	United States: 116
Country: Number of subjects enrolled	Ukraine: 63

Country: Number of subjects enrolled	Turkey: 8
Worldwide total number of subjects	423
EEA total number of subjects	141

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)	420
From 65 to 84 years	3
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details: -

Pre-assignment period milestones

Number of subjects started	486[1]
Number of subjects completed	423

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Other inclusion/exclusion criteria not met: 31
Reason: Number of subjects	Failed or incomplete mannitol tolerance test: 32

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same. Justification: Patients were required to undergo a mannitol tolerance test (MTT) prior to entry and randomisation into the trial itself. As the MTT was a trial procedure have included this period in the reporting. However patients who failed or had incomplete MTT were not enrolled into the study itself.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Mannitol

Arm description:

Mannitol 400mg bid

Arm type	Experimental
Investigational medicinal product name	Mannitol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder, hard capsule
Routes of administration	Inhalation use

Dosage and administration details:

400mg bid

Arm title	Control

Arm description:

Control - mannitol 50mg bid

Arm type	Low dose control
Investigational medicinal product name	Mannitol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder, hard capsule
Routes of administration	Inhalation use

Dosage and administration details:

50mg bid

Number of subjects in period 1	Mannitol	Control
Started	209	214
Completed	183	190
Not completed	26	24
Adverse event, serious fatal	-	1
Consent withdrawn by subject	12	13
Adverse event, non-fatal	10	6
Pregnancy	-	1
Patient's choice - prefer to be on alternative trt	-	1
relocation	1	-
Lost to follow-up	1	1
Lack of efficacy	2	1

Baseline characteristics

Reporting groups	
Reporting group title	Mannitol
Reporting group description: Mannitol 400mg bid	
Reporting group title	Control
Reporting group description: Control - mannitol 50mg bid	

Reporting group values	Mannitol	Control	Total
Number of subjects	209	214	423
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	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	209	211	420
From 65-84 years	0	3	3
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	26.8	28.6	
standard deviation	± 7.63	± 10.75	-
Gender categorical Units: Subjects			
Female	92	107	199
Male	117	107	224
PE hospitalisations in 12 months before screening Units: Subjects			
00	121	135	256
01	57	43	100
02	20	23	43
03	11	9	20
04	0	3	3
>4	0	1	1
rhDNase use at screening Units: Subjects			
yes	144	142	286
no	65	72	137
Lung function at Screening Units: % of predicted			
arithmetic mean	63.72	64.01	
standard deviation	± 14.161	± 12.933	-

End points

End points reporting groups

Reporting group title	Mannitol
Reporting group description: Mannitol 400mg bid	
Reporting group title	Control
Reporting group description: Control - mannitol 50mg bid	

Primary: Change in FEV1

End point title	Change in FEV1
End point description:	
End point type	Primary
End point timeframe: Over 26 weeks	

End point values	Mannitol	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	205[1]	212[2]		
Units: Litres				
least squares mean (confidence interval 95%)	0.063 (0.025 to 0.100)	0.008 (-0.027 to 0.044)		

Notes:

[1] - Trial withdrawals related to safety/eff of trt imputed using BOCF (others not imputed)

[2] - Trial withdrawals related to safety/eff of trt imputed using BOCF (others not imputed)

Statistical analyses

Statistical analysis title	MMRM using BOCF
Comparison groups	Mannitol v Control
Number of subjects included in analysis	417
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.02
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.054
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.008
upper limit	0.1
Variability estimate	Standard error of the mean
Dispersion value	0.023

Secondary: Change in FVC

End point title	Change in FVC

End point description:

End point type	Secondary

End point timeframe:

Over 26 weeks

End point values	Mannitol	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	205[3]	212[4]		
Units: Litres				
least squares mean (confidence interval 95%)	0.028 (-0.014 to 0.070)	-0.012 (-0.053 to 0.029)		

Notes:

[3] - Trial withdrawals related to safety/eff of trt imputed using BOCF (others not imputed)

[4] - Trial withdrawals related to safety/eff of trt imputed using BOCF (others not imputed)

Statistical analyses

Statistical analysis title	MMRM using BOCF
Comparison groups	Control v Mannitol
Number of subjects included in analysis	417
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.128
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.012
upper limit	0.092
Variability estimate	Standard error of the mean
Dispersion value	0.026

Secondary: Time to first Protocol Defined Pulmonary Exacerbation

End point title	Time to first Protocol Defined Pulmonary Exacerbation

End point description:

Median not reached in either group - have reported number with an event in each group.

End point type	Secondary

End point timeframe:
During treatment period (up to 36 weeks)

End point values	Mannitol	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	209	214		
Units: Weeks				
number (not applicable)	28	29		

Statistical analyses

Statistical analysis title	Cox PH model
Comparison groups	Mannitol v Control
Number of subjects included in analysis	423
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.877
Method	Cox proportional hazards
Parameter estimate	Hazard ratio (HR)
Point estimate	1.029
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.719
upper limit	1.472

Secondary: Number of days on Antibiotics due to PDPE

End point title	Number of days on Antibiotics due to PDPE
End point description:	
End point type	Secondary
End point timeframe:	
Over 26 weeks	

End point values	Mannitol	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	209	214		
Units: Number of days				
00	181	185		
1-7	1	2		

8-14	0	2		
15-21	1	2		
22-28	3	3		
29-35	7	6		
36-42	5	2		
50-56	2	5		
57-63	0	2		
64-70	2	1		
>71	7	4		

Statistical analyses

Statistical analysis title	Negative Binomial model
Comparison groups	Mannitol v Control
Number of subjects included in analysis	423
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.67
Method	Negative Binomial Model
Parameter estimate	Adjusted Rate Ratio
Point estimate	0.75
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.198
upper limit	2.846

Secondary: Number of days in Hospital due to PDPE

End point title	Number of days in Hospital due to PDPE
End point description:	
End point type	Secondary
End point timeframe:	
Over 26 weeks	

End point values	Mannitol	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	209	214		
Units: Number of days				
00	192	199		
1-7	1	4		
8-14	4	6		
15-21	5	3		

22-28	3	2		
29-35	3	0		
>35	1	0		

Statistical analyses

Statistical analysis title	Negative Binomial model
Comparison groups	Mannitol v Control
Number of subjects included in analysis	423
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.737
Method	Negative Binomial Model
Parameter estimate	Adjusted Rate Ratio
Point estimate	1.273
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.315
upper limit	5.154

Secondary: Rate of PDPE

End point title	Rate of PDPE
End point description:	
End point type	Secondary
End point timeframe:	
Over 26 weeks	

End point values	Mannitol	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	209	214		
Units: Number of PDPEs				
00	181	185		
01	24	29		
02	3	0		
>2	1	0		

Statistical analyses

Statistical analysis title	Negative Binomial model - with imputation
Comparison groups	Mannitol v Control
Number of subjects included in analysis	423
Analysis specification	Pre-specified
Analysis type	superiority[5]
P-value	= 0.057
Method	Negative Binomial Model
Parameter estimate	Adjusted Rate ratio
Point estimate	1.545
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.99
upper limit	2.411

Notes:

[5] - Imputation of historical rate of exacerbations for those withdrawing from study

Statistical analysis title	Negative Binomial model - no imputation
Statistical analysis description:	
Pre-specified sensitivity.	
Comparison groups	Mannitol v Control
Number of subjects included in analysis	423
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.246
Method	Negative Binomial Model
Parameter estimate	Adjusted Rate ratio
Point estimate	1.357
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.81
upper limit	2.275

Secondary: Incidence of PDPE

End point title	Incidence of PDPE

End point description:

End point type	Secondary

End point timeframe:

Over 26 weeks

End point values	Mannitol	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	209	214		
Units: Number of Patients	28	29		

Statistical analyses

Statistical analysis title	Logistic regression
Comparison groups	Mannitol v Control
Number of subjects included in analysis	423
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.976
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.009
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.555
upper limit	1.836

Secondary: Change in Ease of Expectoration VAS score

End point title	Change in Ease of Expectoration VAS score
End point description:	
End point type	Secondary
End point timeframe:	
Over 26 weeks	

End point values	Mannitol	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	209	214		
Units: cm				
least squares mean (confidence interval 95%)	0.795 (0.556 to 1.034)	0.537 (0.306 to 0.767)		

Statistical analyses

Statistical analysis title	MMRM using BOCF
Comparison groups	Mannitol v Control

Number of subjects included in analysis	423
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.083
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.259
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.034
upper limit	0.551

Secondary: Change in CFQ-R Respiratory Domain scaled score

End point title	Change in CFQ-R Respiratory Domain scaled score
End point description:	

End point type	Secondary
End point timeframe:	
Over 26 weeks	

End point values	Mannitol	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	209	214		
Units: Points on scale				
least squares mean (confidence interval 95%)	0.308 (-1.554 to 2.169)	-0.562 (-2.357 to 1.234)		

Statistical analyses

Statistical analysis title	MMRM using BOCF
Comparison groups	Mannitol v Control
Number of subjects included in analysis	423
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.453
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.87
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.406
upper limit	3.145

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Over 26 weeks

Adverse event reporting additional description:

Treatment emergent (after start of treatment and within 28 days of permanent discontinuation of study drug) are reported.

Summaries were performed for all and serious adverse events - no separate summary for non-serious events - therefore the summaries for non-serious also include serious.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	11.1

Reporting groups

Reporting group title	Mannitol treated
Reporting group description: -	
Reporting group title	Control treated

Reporting group description:

Received at least one dose of control treatment

Serious adverse events	Mannitol treated	Control treated	
Total subjects affected by serious adverse events			
subjects affected / exposed	31 / 207 (14.98%)	29 / 213 (13.62%)	
number of deaths (all causes)	0	1	
number of deaths resulting from adverse events	0	1	
Injury, poisoning and procedural complications			
Intentional overdose			
subjects affected / exposed	1 / 207 (0.48%)	0 / 213 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Guillan-Barre syndrome			
subjects affected / exposed	0 / 207 (0.00%)	1 / 213 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Condition Aggravated	Additional description: Pulmonary exacerbations were coded to this event term for consistency with other Phase 3 trials		

subjects affected / exposed	20 / 207 (9.66%)	15 / 213 (7.04%)	
occurrences causally related to treatment / all	1 / 25	0 / 15	
deaths causally related to treatment / all	0 / 0	1 / 1	
Gastrointestinal disorders			
Pancreatitis acute			
subjects affected / exposed	1 / 207 (0.48%)	2 / 213 (0.94%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	1 / 207 (0.48%)	1 / 213 (0.47%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Distal intestinal obstruction syndrome			
subjects affected / exposed	1 / 207 (0.48%)	0 / 213 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Haemoptysis			
subjects affected / exposed	1 / 207 (0.48%)	3 / 213 (1.41%)	
occurrences causally related to treatment / all	1 / 1	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	1 / 207 (0.48%)	0 / 213 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumomediastinum			
subjects affected / exposed	0 / 207 (0.00%)	1 / 213 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	0 / 207 (0.00%)	1 / 213 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pulmonary embolism			
subjects affected / exposed	0 / 207 (0.00%)	1 / 213 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 207 (0.00%)	2 / 213 (0.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Subcutaneous emphysema			
subjects affected / exposed	0 / 207 (0.00%)	1 / 213 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 207 (0.00%)	1 / 213 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug abuse			
subjects affected / exposed	0 / 207 (0.00%)	1 / 213 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	1 / 207 (0.48%)	0 / 213 (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			
Lung Infection			
subjects affected / exposed	1 / 207 (0.48%)	2 / 213 (0.94%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			

subjects affected / exposed	1 / 207 (0.48%)	2 / 213 (0.94%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
bronchitis			
subjects affected / exposed	0 / 207 (0.00%)	1 / 213 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lobar pneumonia			
subjects affected / exposed	0 / 207 (0.00%)	1 / 213 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection viral			
subjects affected / exposed	1 / 207 (0.48%)	0 / 213 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection pseudomonal			
subjects affected / exposed	1 / 207 (0.48%)	0 / 213 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis bacterial			
subjects affected / exposed	1 / 207 (0.48%)	0 / 213 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia bacterial			
subjects affected / exposed	0 / 207 (0.00%)	1 / 213 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia viral			
subjects affected / exposed	0 / 207 (0.00%)	1 / 213 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			

subjects affected / exposed	0 / 207 (0.00%)	1 / 213 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal bacteraemia			
subjects affected / exposed	1 / 207 (0.48%)	0 / 213 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	1 / 207 (0.48%)	0 / 213 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Mannitol treated	Control treated	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	144 / 207 (69.57%)	140 / 213 (65.73%)	
Nervous system disorders			
headache			
subjects affected / exposed	12 / 207 (5.80%)	22 / 213 (10.33%)	
occurrences (all)	41	47	
General disorders and administration site conditions			
Condition aggravated	Additional description: Includes serious events as well (summaries were done for all events only not just non-serious) Pulmonary exacerbations were coded to this term for consistency with previous Phase III trials		
subjects affected / exposed	56 / 207 (27.05%)	59 / 213 (27.70%)	
occurrences (all)	84	75	
Pyrexia			
subjects affected / exposed	13 / 207 (6.28%)	8 / 213 (3.76%)	
occurrences (all)	18	9	
Respiratory, thoracic and mediastinal disorders			
cough			
subjects affected / exposed	23 / 207 (11.11%)	21 / 213 (9.86%)	
occurrences (all)	25	25	
Haemoptysis	Additional description: Includes serious AEs also (summaries done for serious and all events - no separate summary for non-serious)		

subjects affected / exposed	21 / 207 (10.14%)	11 / 213 (5.16%)	
occurrences (all)	28	36	
Upper respiratory tract infection	Additional description: Includes serious AEs also (summaries done for all and serious adverse events - no separate summary for non-serious)		
subjects affected / exposed	15 / 207 (7.25%)	11 / 213 (5.16%)	
occurrences (all)	18	12	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	12 / 207 (5.80%)	10 / 213 (4.69%)	
occurrences (all)	17	11	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 October 2014	Addition of IMP discontinuation visit for subjects who discontinue study treatment but continue their participation in the trial. Disclosing the identity of the control. Clarification on bronchodilator use.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported