Clinical trial results:
Long Term Administration of Inhaled Dry Powder Mannitol In Cystic Fibrosis – A Safety and Efficacy Study

Summary

EudraCT number	2007-001412-23
Trial protocol	IE GB DE
Global end of trial date	24 April 2009

Results information

Result version number	v1 (current)
This version publication date	07 April 2021
First version publication date	07 April 2021

Trial information

Trial identification

Sponsor protocol code	DPM-CF-301

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00446680
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 Pty Ltd., Brett.Charlton@pharmaxis.com.au
Scientific contact	Brett Charlton, Pharmaxis Pty Ltd., Brett.Charlton@pharmaxis.com.au

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-000436-PIP01-08
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	15 September 2009
Is this the analysis of the primary completion data?	Yes
Primary completion date	24 April 2009
Global end of trial reached?	Yes
Global end of trial date	24 April 2009
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine the effect of IDPM compared to control on FEV1 in patients with CF.

Protection of trial subjects:

DMC, use of Mannitol Tolerance test at screening to identify hyper-responsiveness to exclude susceptible patients.

Background therapy:

Usual standard of care

Evidence for comparator:

Comparator was low dose mannitol (50mg) - chosen to ensure blinding.

Actual start date of recruitment	05 April 2007
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	12 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 193
Country: Number of subjects enrolled	Ireland: 19
Country: Number of subjects enrolled	Australia: 97
Country: Number of subjects enrolled	New Zealand: 15
Worldwide total number of subjects	324
EEA total number of subjects	212

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)	52

Adolescents (12-17 years)	63
Adults (18-64 years)	209
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Following enrolment and prior to randomisation, subjects were administered an abbreviated version of the Aridol bronchial provocation test (MTT) to exclude those with bronchial hyper-responsiveness.

Period 1

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

Blinding implementation details:

Use of low dose inhaled mannitol as control (ie identical in appearance and taste). Both active and control treatments consisted of ten identical opaque capsules with indistinguishable taste.

Arms

Are arms mutually exclusive?	Yes
Arm title	Bronchitol

Arm description: -

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

Dosage and administration details:

400mg Twice daily. Administered via a RS01 dry-powder inhaler device, after pre-medication but before physiotherapy or exercise. Capsules were loaded into the inhaler device, punctured, then inhaled in a deep, controlled manner; followed by a 5-second breath hold. Each consecutive capsule followed the previous immediately. The process was repeated until the contents of ten capsules had been inhaled.

Arm title	Control

Arm description: -

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

Dosage and administration details:

50mg Twice daily. Administered via a RS01 dry-powder inhaler device, after pre-medication but before physiotherapy or exercise. Capsules were loaded into the inhaler device, punctured, then inhaled in a deep, controlled manner; followed by a 5-second breath hold. Each consecutive capsule followed the previous immediately. The process was repeated until the contents of ten capsules had been inhaled.

Number of subjects in period 1	Bronchitol	Control
Started	192	132
Completed	112	86
Not completed	80	46
Physician decision	7	-
Consent withdrawn by subject	28	22
Discountinued study prior to commencing trtment	15	-
Adverse event, non-fatal	29	10
Discontinued prior to commencing trt	-	14
Unspecified reasons	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Bronchitol
Reporting group description: -	
Reporting group title	Control
Reporting group description: -	

Reporting group values	Bronchitol	Control	Total
Number of subjects	192	132	324
Age categorical Units: Subjects			
Children (2-11 years)	33	19	52
Adolescents (12-17 years)	35	28	63
Adults (18-64 years)	124	85	209
Gender categorical Units: Subjects			
Female	81	70	151
Male	111	62	173
FEV1 % predicted at baseline			
Forced Expiratory Volume in 1 second (FEV1) percentage of predicted value at week 0, start of treatment.			
Units: precentage			
arithmetic mean	62.33	62.06	
standard deviation	± 16.37	± 16.04	-

Subject analysis sets	
Subject analysis set title	FAS randomised and treated
Subject analysis set type	Modified intention-to-treat
Subject analysis set description: All subjects randomised and receiving at least one dose of study medication	
Subject analysis set title	FAS - Bronchitol
Subject analysis set type	Modified intention-to-treat
Subject analysis set description: All subjects who were randomised and received at least one dose	
Subject analysis set title	FAS - Control
Subject analysis set type	Modified intention-to-treat
Subject analysis set description: All randomised subjects who received at least one dose of trial treatment	
Subject analysis set title	Completers - Bronchitol
Subject analysis set type	Per protocol
Subject analysis set description: Completers are those who remained on trt to the 26 week time point	
Subject analysis set title	Completers - Control
Subject analysis set type	Per protocol
Subject analysis set description: Subjects completing 6 months of trial treatment	

Reporting group values	FAS randomised and treated	FAS - Bronchitol	FAS - Control
Number of subjects	295	177	118
Age categorical Units: Subjects			
Children (2-11 years)	48	31	17
Adolescents (12-17 years)	57	32	25
Adults (18-64 years)	190	114	76
Gender categorical Units: Subjects			
Female	132	71	61
Male	163	106	57
FEV1 % predicted at baseline			
Forced Expiratory Volume in 1 second (FEV1) percentage of predicted value at week 0, start of treatment.			
Units: precentage			
arithmetic mean		62.4	61.4
standard deviation	±	± 16.45	± 16.13

Reporting group values	Completers - Bronchitol	Completers - Control	
Number of subjects	116	89	
Age categorical Units: Subjects			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
Gender categorical Units: Subjects			
Female			
Male			
FEV1 % predicted at baseline			
Forced Expiratory Volume in 1 second (FEV1) percentage of predicted value at week 0, start of treatment.			
Units: precentage			
arithmetic mean			
standard deviation	±	±	

End points

End points reporting groups

Reporting group title	Bronchitol
Reporting group description: -	
Reporting group title	Control
Reporting group description: -	
Subject analysis set title	FAS randomised and treated
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
All subjects randomised and receiving at least one dose of study medication	
Subject analysis set title	FAS - Bronchitol
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
All subjects who were randomised and received at least one dose	
Subject analysis set title	FAS - Control
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
All randomised subjects who received at least one dose of trial treatment	
Subject analysis set title	Completers - Bronchitol
Subject analysis set type	Per protocol
Subject analysis set description:	
Completers are those who remained on trt to the 26 week time point	
Subject analysis set title	Completers - Control
Subject analysis set type	Per protocol
Subject analysis set description:	
Subjects completing 6 months of trial treatment	

Primary: Change in FEV1

End point title	Change in FEV1

End point description:

Mean Change in FEV1 (mL) From Baseline (Visit 1) Over the 26-week Treatment Period (to Visit 4).

The mean absolute change from baseline FEV1 (mL) over 26 weeks (measured at week 6, 14 and 26) was compared between the two treatment groups with a REML (restricted maximum likelihood) based repeated measures approach.

Least square means presented are for the average change over the 6, 14, and 26 week visits.

End point type	Primary

End point timeframe:

Over 26 weeks

End point values	FAS - Bronchitol	FAS - Control		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	160[1]	112[2]		
Units: mL				
least squares mean (confidence interval 95%)	118.01 (87.94 to 148.07)	34.87 (0.59 to 69.15)		

Notes:

[1] - Only those with post-baseline FEV1 measures included

[2] - Only those with post-baseline FEV1 measures included

Statistical analyses

Statistical analysis title	Primary analysis : MMRM
Comparison groups	FAS - Bronchitol v FAS - Control
Number of subjects included in analysis	272
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	83.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	39.49
upper limit	126.79

Secondary: Change in FEV1 in rhDNase users

End point title	Change in FEV1 in rhDNase users

End point description:

For the subset of rhDNase users, the mean change in FEV1 (mL) From Baseline (Visit 1) Over the 26-week Treatment Period (to Visit 4).

The mean absolute change from baseline FEV1 (mL) over 26 weeks (measured at week 6, 14 and 26) will be compared between the two treatment groups with a REML (restricted maximum likelihood) based repeated measures approach.

Least square means presented are for the average change over the 6, 14, and 26 week visits.

End point type	Secondary

End point timeframe:

Over 26 weeks

End point values	FAS - Bronchitol	FAS - Control		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	160[3]	112[4]		
Units: mL				
least squares mean (confidence interval 95%)	86.01 (45.47 to 126.54)	8.39 (-38.30 to 55.07)		

Notes:

[3] - Effect in rhDNase users estimated in model with all 272 patients (users were 147)

[4] - Effect in rhDNase users estimated in model with all 272 patients (users were 147)

Statistical analyses

Statistical analysis title	MMRM with trt by rhDNase interaction
Comparison groups	FAS - Bronchitol v FAS - Control
Number of subjects included in analysis	272
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.011
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	77.62
Confidence interval	
level	95 %
sides	2-sided
lower limit	18.16
upper limit	137.08

Secondary: Change in FEV1 in rhDNase non-users

End point title	Change in FEV1 in rhDNase non-users

End point description:

In the subset of rhDNase non-users, the mean change in FEV1 (mL) From Baseline (Visit 1) Over the 26-week Treatment Period (to Visit 4).

The mean absolute change from baseline FEV1 (mL) over 26 weeks (measured at week 6, 14 and 26) will be compared between the two treatment groups with a REML (restricted maximum likelihood) based repeated measures approach.

Least square means presented are for the average change over the 6, 14, and 26 week visits.

End point type	Secondary

End point timeframe:

Over 26 weeks

End point values	FAS - Bronchitol	FAS - Control		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	160[5]	112[6]		
Units: mL				
least squares mean (confidence interval 95%)	150.29 (107.45 to 193.14)	60.74 (10.78 to 110.71)		

Notes:

[5] - Effect in rhDNase users estimated in model with all 272 patients (non-users were 125)

[6] - Effect in rhDNase users estimated in model with all 272 patients (non-users were 125)

Statistical analyses

Statistical analysis title	MMRM with trt by rhDNase interaction
Comparison groups	FAS - Control v FAS - Bronchitol
Number of subjects included in analysis	272
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.006
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	89.55
Confidence interval	
level	95 %
sides	2-sided
lower limit	25.35
upper limit	153.75

Secondary: FEV1 Responder

End point title	FEV1 Responder
End point description:	
Responders were classified as those who had an absolute increase in FEV1 from baseline to Week 26 of at least 100mL	
End point type	Secondary
End point timeframe:	
at 26 weeks	

End point values	Completers - Bronchitol	Completers - Control		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	116	89		
Units: Number of Patients	62	33		

Statistical analyses

Statistical analysis title	Logistic regression
Comparison groups	Completers - Bronchitol v Completers - Control
Number of subjects included in analysis	205
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.026
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.97
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.08
upper limit	3.58

Secondary: FEV1 Responder - rhDNase users

End point title	FEV1 Responder - rhDNase users
End point description:	
Response is increase of more than 100mL from baseline in FEV1	
End point type	Secondary
End point timeframe:	
At week 26	

End point values	Completers - Bronchitol	Completers - Control		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	61	50		
Units: Number of Patients	30	12		

Statistical analyses

Statistical analysis title	Logistic regression
Comparison groups	Completers - Bronchitol v Completers - Control
Number of subjects included in analysis	111
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.017
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.89

Confidence interval	
level	95 %
sides	2-sided
lower limit	1.21
upper limit	6.94

Secondary: FEV1 Responder - rhDNase non-users

End point title	FEV1 Responder - rhDNase non-users
End point description:	
Response is increase >=100mL from baseline in FEV1	
End point type	Secondary
End point timeframe:	
At week 26	

End point values	Completers - Bronchitol	Completers - Control		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	55	39		
Units: Number of Patients	32	21		

Statistical analyses

Statistical analysis title	Logistic regression
Comparison groups	Completers - Bronchitol v Completers - Control
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.422
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.44
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.59
upper limit	3.47

Secondary: QoL responder

End point title	QoL responder
End point description:	
Responders have 5 point or higher improvement from baseline in SGRQ respiratory score	

End point type	Secondary
End point timeframe:	
At 26 weeks	

End point values	Completers - Bronchitol	Completers - Control		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	114	87		
Units: Number of Patients	45	34		

Statistical analyses

Statistical analysis title	Logistic regression
Comparison groups	Completers - Bronchitol v Completers - Control
Number of subjects included in analysis	201
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.385
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.74
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.38
upper limit	1.46

Secondary: PDPE rate

End point title	PDPE rate
End point description:	
PDPE is a protocol defined pulmonary exacerbation defined by Fuchs criteria	
End point type	Secondary
End point timeframe:	
Over 26 weeks	

End point values	FAS - Bronchitol	FAS - Control		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	177	118		
Units: rate per subject per year				
arithmetic mean (standard deviation)	0.78 (± 1.976)	1.05 (± 2.148)		

Statistical analyses

Statistical analysis title	Negative Binomial model
Comparison groups	FAS - Control v FAS - Bronchitol
Number of subjects included in analysis	295
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.205
Method	Negative Binomial Model
Parameter estimate	Rate ratio
Point estimate	0.74
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.47
upper limit	1.18

Secondary: PDPE rate - rhDNase users

End point title	PDPE rate - rhDNase users
End point description:	
PDPE is a protocol defined pulmonary exacerbation defined by Fuchs criteria	
End point type	Secondary
End point timeframe:	
Over 26 weeks	

End point values	FAS - Bronchitol	FAS - Control		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	96	67		
Units: rate per person per year				
arithmetic mean (standard deviation)	0.52 (± 1.144)	0.6 (± 1.152)		

Statistical analyses

Statistical analysis title	Negative Binomial model
Comparison groups	FAS - Bronchitol v FAS - Control

Number of subjects included in analysis	163
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.29
Method	Negative Binomial Model
Parameter estimate	Rate ratio
Point estimate	0.76
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.45
upper limit	1.27

Secondary: PDPE rate - rhDNase non-users

End point title	PDPE rate - rhDNase non-users
End point description:	
PDPE is a protocol defined pulmonary exacerbation defined by Fuchs criteria	
End point type	Secondary
End point timeframe:	
Over 26 weeks	

End point values	FAS - Bronchitol	FAS - Control		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	81	51		
Units: rate per person per year				
arithmetic mean (standard deviation)	0.17 (± 0.495)	0.29 (± 0.576)		

Statistical analyses

Statistical analysis title	Negative Binomial model
Comparison groups	FAS - Bronchitol v FAS - Control
Number of subjects included in analysis	132
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.259
Method	Negative Binomial Model
Parameter estimate	Rate ratio
Point estimate	0.59
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.24
upper limit	1.47

Secondary: Change in CFQ-R respiratory score

End point title	Change in CFQ-R respiratory score

End point description:

The CFQ-R respiratory domain score is a scale from 0 to 100. Higher scores are a more favourable response.

End point type	Secondary

End point timeframe:

at week 26

End point values	Completers - Bronchitol	Completers - Control		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	114	87		
Units: score				
least squares mean (standard deviation)	1.3 (± 15.95)	-2.5 (± 17.55)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of days of rescue antibiotic use

End point title	Number of days of rescue antibiotic use

End point description:

End point type	Secondary

End point timeframe:

Over 26 weeks

End point values	FAS - Bronchitol	FAS - Control		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	177	118		
Units: days				
arithmetic mean (standard deviation)	5.72 (± 20.616)	12.3 (± 44.142)		

Statistical analyses

Statistical analysis title	Negative Binomial model
Comparison groups	FAS - Bronchitol v FAS - Control
Number of subjects included in analysis	295
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.407
Method	Negative Binomial Model
Parameter estimate	Rate ratio
Point estimate	0.66
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.25
upper limit	1.76

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	FAS - Bronchitol	FAS - Control		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	177	118		
Units: days				
arithmetic mean (standard deviation)	2.41 (± 6.962)	2.38 (± 5.791)		

Statistical analyses

Statistical analysis title	Negative Binomial model
Comparison groups	FAS - Bronchitol v FAS - Control
Number of subjects included in analysis	295
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.924
Method	Negative Binomial Model
Parameter estimate	Rate ratio
Point estimate	0.94

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.26
upper limit	3.42

Adverse events

Adverse events information

Timeframe for reporting adverse events:

During 26 week double blind treatment period. Subjects who withdrew prematurely were followed for AEs for a period of 7 days after the last dose

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	9.1

Reporting groups

Reporting group title	Bronchitol
Reporting group description: -	
Reporting group title	Control

Reporting group description: -

Serious adverse events	Bronchitol	Control	
Total subjects affected by serious adverse events			
subjects affected / exposed	46 / 177 (25.99%)	35 / 118 (29.66%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Investigations			
Bacteria sputum identified			
subjects affected / exposed	1 / 177 (0.56%)	0 / 118 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Postoperative ileus			
subjects affected / exposed	0 / 177 (0.00%)	1 / 118 (0.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Treatment noncompliance			
subjects affected / exposed	0 / 177 (0.00%)	1 / 118 (0.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Catheterisation venous			

subjects affected / exposed	2 / 177 (1.13%)	0 / 118 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Antibiotic prophylaxis			
subjects affected / exposed	1 / 177 (0.56%)	0 / 118 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hospitalisation			
subjects affected / exposed	1 / 177 (0.56%)	0 / 118 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
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 condition aggravated		
subjects affected / exposed	33 / 177 (18.64%)	25 / 118 (21.19%)	
occurrences causally related to treatment / all	1 / 40	0 / 31	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	1 / 177 (0.56%)	0 / 118 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	0 / 177 (0.00%)	2 / 118 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal Pain			
subjects affected / exposed	0 / 177 (0.00%)	1 / 118 (0.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Distal intestinal obstruction syndrome			

subjects affected / exposed	2 / 177 (1.13%)	0 / 118 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	0 / 177 (0.00%)	1 / 118 (0.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tooth impacted			
subjects affected / exposed	1 / 177 (0.56%)	0 / 118 (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	6 / 177 (3.39%)	2 / 118 (1.69%)	
occurrences causally related to treatment / all	4 / 6	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchospasm			
subjects affected / exposed	1 / 177 (0.56%)	0 / 118 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nasal polyps			
subjects affected / exposed	0 / 177 (0.00%)	1 / 118 (0.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 177 (0.56%)	0 / 118 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleuritic pain			
subjects affected / exposed	1 / 177 (0.56%)	0 / 118 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			

subjects affected / exposed	0 / 177 (0.00%)	1 / 118 (0.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Polymyositis			
subjects affected / exposed	0 / 177 (0.00%)	1 / 118 (0.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Lower respiratory tract infection			
subjects affected / exposed	4 / 177 (2.26%)	2 / 118 (1.69%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	1 / 177 (0.56%)	0 / 118 (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	0 / 177 (0.00%)	1 / 118 (0.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Otitis media			
subjects affected / exposed	0 / 177 (0.00%)	1 / 118 (0.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pilonidal cyst			
subjects affected / exposed	1 / 177 (0.56%)	0 / 118 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 177 (0.00%)	1 / 118 (0.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Viral infection			
subjects affected / exposed	0 / 177 (0.00%)	1 / 118 (0.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 177 (0.00%)	1 / 118 (0.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Diabetes mellitus			
subjects affected / exposed	1 / 177 (0.56%)	0 / 118 (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	Bronchitol	Control	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	154 / 177 (87.01%)	109 / 118 (92.37%)	
Investigations			
Bacteria sputum identified			
subjects affected / exposed	33 / 177 (18.64%)	21 / 118 (17.80%)	
occurrences (all)	40	32	
Nervous system disorders			
Headache			
subjects affected / exposed	38 / 177 (21.47%)	28 / 118 (23.73%)	
occurrences (all)	102	79	
General disorders and administration site conditions			
Condition Aggravated			
subjects affected / exposed	27 / 177 (15.25%)	21 / 118 (17.80%)	
occurrences (all)	38	27	
Abdominal pain			
subjects affected / exposed	6 / 177 (3.39%)	7 / 118 (5.93%)	
occurrences (all)	6	26	
Gastrointestinal disorders			

Abdominal pain upper			
subjects affected / exposed	12 / 177 (6.78%)	7 / 118 (5.93%)	
occurrences (all)	21	10	
Vomiting			
subjects affected / exposed	13 / 177 (7.34%)	4 / 118 (3.39%)	
occurrences (all)	20	4	
Toothache			
subjects affected / exposed	9 / 177 (5.08%)	3 / 118 (2.54%)	
occurrences (all)	12	3	
Constipation			
subjects affected / exposed	6 / 177 (3.39%)	4 / 118 (3.39%)	
occurrences (all)	6	6	
Diarrhoea			
subjects affected / exposed	9 / 177 (5.08%)	1 / 118 (0.85%)	
occurrences (all)	14	1	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	45 / 177 (25.42%)	24 / 118 (20.34%)	
occurrences (all)	62	37	
Haemoptysis			
subjects affected / exposed	16 / 177 (9.04%)	8 / 118 (6.78%)	
occurrences (all)	25	9	
Pharyngolaryngeal pain			
subjects affected / exposed	24 / 177 (13.56%)	5 / 118 (4.24%)	
occurrences (all)	36	6	
Upper respiratory tract infection			
subjects affected / exposed	14 / 177 (7.91%)	8 / 118 (6.78%)	
occurrences (all)	16	11	
Productive cough			
subjects affected / exposed	12 / 177 (6.78%)	7 / 118 (5.93%)	
occurrences (all)	14	11	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	12 / 177 (6.78%)	7 / 118 (5.93%)	
occurrences (all)	12	7	
Back pain			

subjects affected / exposed	7 / 177 (3.95%)	7 / 118 (5.93%)	
occurrences (all)	7	9	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	25 / 177 (14.12%)	17 / 118 (14.41%)	
occurrences (all)	35	23	
Lower respiratory tract infection			
subjects affected / exposed	12 / 177 (6.78%)	18 / 118 (15.25%)	
occurrences (all)	14	24	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 August 2007	No. of subjects increased to 340 (previously 250). Interim analysis added.
16 November 2008	Additional Open label extension period added (for a further 26 weeks)

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/21478216