Clinical trial results:
Long Term Administration of Inahled Mannitol in Cystic Fibrosis - A Safety and Efficacy Study

Summary

EudraCT number	2008-002740-42
Trial protocol	DE BE FR NL
Global end of trial date	25 October 2010

Results information

Result version number	v1 (current)
This version publication date	03 June 2021
First version publication date	03 June 2021

Trial information

Trial identification

Sponsor protocol code	DPM-CF-302

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00630812
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)	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	25 October 2010
Is this the analysis of the primary completion data?	Yes
Primary completion date	12 April 2010
Global end of trial reached?	Yes
Global end of trial date	25 October 2010
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine whether inhaled mannitol compared to control improves FEV1 in patients with Cystic Fibrosis.

Protection of trial subjects:

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	03 September 2008
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
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	Canada: 20
Country: Number of subjects enrolled	Argentina: 82
Country: Number of subjects enrolled	United States: 146
Country: Number of subjects enrolled	Netherlands: 5
Country: Number of subjects enrolled	Belgium: 16
Country: Number of subjects enrolled	France: 25
Country: Number of subjects enrolled	Germany: 24
Worldwide total number of subjects	318
EEA total number of subjects	70

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)	62
Adolescents (12-17 years)	99
Adults (18-64 years)	157
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, A screening test with inhaled mannitol (MTT) was administered at Visit 0 to identify subjects with hyperresponsive airways.

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	Subject, Investigator, Monitor, 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:

The 400 mg treatment dose was
contained in 10 x 40 mg capsules and was administered via the RS01 dry-powder inhaler device after pre-medication but before physiotherapy or exercise. Inhaled Bronchitol was encapsulated prior to blister packing in aluminum foil. Blisters were packaged in 2 week supply cartons with 2 RS01 inhaler devices and instructions for use, Appendix 16.1.10.8. Capsules were loaded into the inhaler device, punctured, then inhaled in a deep, controlled manner; followed by a five second breath hold. Each consecutive capsule followed the previous immediately. The process was repeated until the contents of ten capsules had been inhaled. The standard premedication was four puffs of albuterol five to fifteen minutes pre treatment, though an alternative with subject contact bronchodilator could be substituted if preferred.

Arm title	Control

Arm description:

Low dose mannitol (50mg)

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:

The treatment dose was 50 mg B.I.D. for 26
weeks. The 50 mg treatment dose was contained in 10 x 5 mg capsules and was administered via the RS01 dry-powder inhaler after pre-medication but before physiotherapy or exercise. As with the active study drug, control capsules were blister packaged. Capsules were loaded into the inhaler device, punctured, and then inhaled in a deep, controlled manner, each followed by a five

second breath hold. Each consecutive capsule followed the previous immediately. The process was repeated until the contents of ten capsules had been inhaled. The standard premedication was the same as described for the active study drug.
The control product (10 x 5mg capsules) inhaled mannitol was administered using the same methodology as the active treatment.

Number of subjects in period 1	Bronchitol	Control
Started	192	126
Treated	184	121
Completed	153	107
Not completed	39	19
Consent withdrawn by subject	15	10
Physician decision	2	1
Adverse event, non-fatal	14	6
wanted to take drug as she wished not as protocol	1	-
Non-compliance	-	1
Lost to follow-up	2	-
Protocol deviation	5	1

Baseline characteristics

Reporting groups	
Reporting group title	Bronchitol
Reporting group description: -	
Reporting group title	Control
Reporting group description: Low dose mannitol (50mg)	

Reporting group values	Bronchitol	Control	Total
Number of subjects	192	126	318
Age categorical Units: Subjects			
Children (2-11 years)	37	25	62
Adolescents (12-17 years)	58	41	99
Adults (18-64 years)	97	60	157
Age continuous Units: years			
arithmetic mean	19.7	20.3	
standard deviation	± 9.50	± 10.23	-
Gender categorical Units: Subjects			
Female	93	60	153
Male	99	66	165

Subject analysis sets	
Subject analysis set title	FAS Bronchitol
Subject analysis set type	Modified intention-to-treat
Subject analysis set description: Randomised and treated	
Subject analysis set title	FAS Control
Subject analysis set type	Modified intention-to-treat
Subject analysis set description: Randomised and treated	

Reporting group values	FAS Bronchitol	FAS Control	
Number of subjects	184	121	
Age categorical Units: Subjects			
Children (2-11 years)	35	24	
Adolescents (12-17 years)	56	39	
Adults (18-64 years)	93	58	
Age continuous Units: years			
arithmetic mean	19.6	20.4	
standard deviation	± 9.29	± 10.23	

Gender categorical Units: Subjects			
Female	90	58	
Male	94	63	

End points

End points reporting groups

Reporting group title	Bronchitol
Reporting group description: -	
Reporting group title	Control
Reporting group description: Low dose mannitol (50mg)	
Subject analysis set title	FAS Bronchitol
Subject analysis set type	Modified intention-to-treat
Subject analysis set description: Randomised and treated	
Subject analysis set title	FAS Control
Subject analysis set type	Modified intention-to-treat
Subject analysis set description: Randomised and treated	

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 6, 14 and 26 weeks) was compared between the 2 treatment groups using 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	177[1]	120[2]		
Units: mL				
least squares mean (confidence interval 95%)	106.53 (62.43 to 150.62)	52.38 (2.09 to 102.68)		

Notes:

[1] - Only subjects with post-baseline FEV1 are included

[2] - Only subjects with post-baseline FEV1 are included

Statistical analyses

Statistical analysis title	Primary analysis: MMRM
Comparison groups	FAS Bronchitol v FAS Control

Number of subjects included in analysis	297
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.059
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	54.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.97
upper limit	110.26

Secondary: Change in FEV1 % predicted

End point title	Change in FEV1 % predicted
End point description:	
change from baseline to 26 weeks. Those with missing data at 26 weeks are imputed using baseline observation carried forward (BOCF)	
End point type	Secondary
End point timeframe:	
At 26 weeks	

End point values	FAS Bronchitol	FAS Control		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	184	121		
Units: % of predicted				
least squares mean (confidence interval 95%)	3.14 (1.49 to 4.78)	0.72 (-1.18 to 2.62)		

Statistical analyses

Statistical analysis title	ANCOVA with BOCF
Comparison groups	FAS Bronchitol v FAS Control
Number of subjects included in analysis	305
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.024
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	2.42

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.33
upper limit	4.51

Secondary: Change in FEV1 from baseline over 26 weeks - dornase users

End point title	Change in FEV1 from baseline over 26 weeks - dornase users

End point description:

In the subset of dornase users, the mean absolute change from baseline FEV1 (mL) averaged 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.

Change from baseline over 26 weeks (measured at 6,14, 26 weeks) in subset of dornase users

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	137	92		
Units: mL				
least squares mean (confidence interval 95%)	78.60 (27.64 to 129.56)	35.11 (-20.99 to 91.21)		

Statistical analyses

Statistical analysis title	MMRM
Comparison groups	FAS Bronchitol v FAS Control
Number of subjects included in analysis	229
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.177
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	43.49
Confidence interval	
level	95 %
sides	2-sided
lower limit	-19.8
upper limit	106.78

Secondary: Rate of Protocol Defined Pulmonary Exacerbations (PDPEs)

End point title	Rate of Protocol Defined Pulmonary Exacerbations (PDPEs)

End point description:

Exacerbations treated with IV antibiotics and with at least 4 signs and symptoms according to Fuchs criteria (1994). Summary table presents the number with 0, 1,2 and 3 PDPEs during the 26 week treatment period.

End point type	Secondary

End point timeframe:

26 weeks

End point values	FAS Bronchitol	FAS Control		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	184	121		
Units: Participants				
0 PDPEs	156	98		
1 PDPE	21	18		
2 PDPEs	6	4		
3 PDPEs	1	1		

Statistical analyses

Statistical analysis title	Poisson regression of count data
Comparison groups	FAS Bronchitol v FAS Control
Number of subjects included in analysis	305
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0.52
Method	Poisson regression
Parameter estimate	Rate Ratio
Point estimate	0.85
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.51
upper limit	1.41

Notes:

[3] - Rate ratio for Mannitol/Control

Secondary: Hospitalisation associated with PDPEs

End point title	Hospitalisation associated with PDPEs

End point description:

End point type	Secondary

End point timeframe:

26 weeks

End point values	FAS Bronchitol	FAS Control		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	184	121		
Units: Participants				
0 hospitalisations	162	102		
1 hospitalisation	18	14		
2 hospitalisations	3	5		
3 hospitalisations	1	0		

Statistical analyses

Statistical analysis title	Poisson regression
Comparison groups	FAS Bronchitol v FAS Control
Number of subjects included in analysis	305
Analysis specification	Pre-specified
Analysis type	superiority[4]
P-value	= 0.328
Method	Poisson Regression
Parameter estimate	Rate Ratio
Point estimate	0.75
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.42
upper limit	1.33

Notes:

[4] - Analysis of rate ratio Mannitol/Control

Secondary: Antibiotic use associated with PDPEs

End point title	Antibiotic use associated with PDPEs

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	184	121		
Units: participants				
0 Courses	156	98		
1 Course	22	19		
2 Courses	5	2		
3 Courses	1	2		

Statistical analyses

Statistical analysis title	Poisson Regression
Comparison groups	FAS Bronchitol v FAS Control
Number of subjects included in analysis	305
Analysis specification	Pre-specified
Analysis type	superiority[5]
P-value	= 0.368
Method	Poisson regression
Parameter estimate	Rate Ratio
Point estimate	0.89
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.69
upper limit	1.15

Notes:

[5] - Rate ratio Mannitol / Control

Secondary: Change in FVC

End point title	Change in FVC

End point description:

Change from baseline in forced vital capacity (FVC) across 26 weeks (measured at 6,14 and 26 weeks). Analysed using the same methodology as the primary endpoint

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	120		
Units: mL				
least squares mean (confidence interval 95%)	136.33 (88.54 to 184.11)	64.98 (10.58 to 119.37)		

Statistical analyses

Statistical analysis title	MMRM
Comparison groups	FAS Bronchitol v FAS Control
Number of subjects included in analysis	297
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.022
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	71.35
Confidence interval	
level	95 %
sides	2-sided
lower limit	10.57
upper limit	132.13

Secondary: Change from baseline FEF25-75

End point title	Change from baseline FEF25-75

End point description:

Change from baseline in forced expiratory flow at 25-75% of forced vital capacity (FEF25-75) (mL/s) averaged over 26 weeks (measured at 6,14 and 26 weeks) The mean absolute change from baseline 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	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	120		
Units: mL/s				
least squares mean (confidence interval 95%)	84.65 (6.66 to 162.63)	50.31 (-38.24 to 138.86)		

Statistical analyses

Statistical analysis title	MMRM
Comparison groups	FAS Bronchitol v FAS Control
Number of subjects included in analysis	297
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.49
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	34.34
Confidence interval	
level	95 %
sides	2-sided
lower limit	-63.47
upper limit	132.14

Secondary: Sputum weight after first dose	
End point title	Sputum weight after first dose
End point description:	
End point type	Secondary
End point timeframe:	
After first dose of trial medication	

End point values	FAS Bronchitol	FAS Control		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	180[6]	114[7]		
Units: gram				
arithmetic mean (standard deviation)	4.9 (± 6.18)	3.5 (± 4.40)		

Notes:

[6] - Randomised and treated with sputum weight data available

[7] - Randomised and treated with sputum weight data available

Statistical analyses

Statistical analysis title	wilcoxon
Comparison groups	FAS Bronchitol v FAS Control
Number of subjects included in analysis	294
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.042
Method	Wilcoxon (Mann-Whitney)

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
26 weeks	
Adverse event reporting additional description:	
Double blind phase only	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	11

Reporting groups	
Reporting group title	Mannitol - safety
Reporting group description:	
All treated	
Reporting group title	Control - safety
Reporting group description:	
All treated	

Serious adverse events	Mannitol - safety	Control - safety	
Total subjects affected by serious adverse events			
subjects affected / exposed	31 / 184 (16.85%)	30 / 121 (24.79%)	
number of deaths (all causes)	0	1	
number of deaths resulting from adverse events	0	1	
General disorders and administration site conditions			
Condition aggravated			
subjects affected / exposed	27 / 184 (14.67%)	20 / 121 (16.53%)	
occurrences causally related to treatment / all	2 / 35	1 / 25	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Pancreatitis			
subjects affected / exposed	1 / 184 (0.54%)	0 / 121 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Distal intestinal obstruction syndrome			
subjects affected / exposed	0 / 184 (0.00%)	1 / 121 (0.83%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Intestinal obstruction			
subjects affected / exposed	0 / 184 (0.00%)	1 / 121 (0.83%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	0 / 184 (0.00%)	1 / 121 (0.83%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 184 (0.00%)	1 / 121 (0.83%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Haemoptysis			
subjects affected / exposed	2 / 184 (1.09%)	0 / 121 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthmatic crisis			
subjects affected / exposed	0 / 184 (0.00%)	1 / 121 (0.83%)	
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 / 184 (0.00%)	1 / 121 (0.83%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pleuritic pain			
subjects affected / exposed	0 / 184 (0.00%)	1 / 121 (0.83%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 184 (0.54%)	0 / 121 (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			
Bronchopneumonia			
subjects affected / exposed	1 / 184 (0.54%)	0 / 121 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	0 / 184 (0.00%)	3 / 121 (2.48%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute tonsillitis			
subjects affected / exposed	0 / 184 (0.00%)	1 / 121 (0.83%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	0 / 184 (0.00%)	1 / 121 (0.83%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 184 (0.00%)	1 / 121 (0.83%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia bacterial			
subjects affected / exposed	0 / 184 (0.00%)	1 / 121 (0.83%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	0 / 184 (0.00%)	1 / 121 (0.83%)	
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 / 184 (0.54%)	0 / 121 (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 - safety	Control - safety	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	165 / 184 (89.67%)	106 / 121 (87.60%)	
Nervous system disorders			
Headache			
subjects affected / exposed	26 / 184 (14.13%)	22 / 121 (18.18%)	
occurrences (all)	54	29	
General disorders and administration site conditions			
Condition aggravated			
subjects affected / exposed	57 / 184 (30.98%)	50 / 121 (41.32%)	
occurrences (all)	75	55	
Pyrexia			
subjects affected / exposed	17 / 184 (9.24%)	13 / 121 (10.74%)	
occurrences (all)	22	20	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	14 / 184 (7.61%)	8 / 121 (6.61%)	
occurrences (all)	28	8	
Abdominal pain upper			
subjects affected / exposed	6 / 184 (3.26%)	7 / 121 (5.79%)	
occurrences (all)	7	10	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	28 / 184 (15.22%)	16 / 121 (13.22%)	
occurrences (all)	32	18	
Pharyngolaryngeal pain			
subjects affected / exposed	19 / 184 (10.33%)	13 / 121 (10.74%)	
occurrences (all)	26	14	
Haemoptysis			

subjects affected / exposed	11 / 184 (5.98%)	3 / 121 (2.48%)	
occurrences (all)	17	6	
Nasopharyngitis			
subjects affected / exposed	11 / 184 (5.98%)	6 / 121 (4.96%)	
occurrences (all)	13	8	
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	10 / 184 (5.43%)	11 / 121 (9.09%)	
occurrences (all)	11	16	
Sinusitis			
subjects affected / exposed	8 / 184 (4.35%)	7 / 121 (5.79%)	
occurrences (all)	9	10	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 April 2008	Planned subject numbers increased from 250 to 300, expected attrition changes from 20% to 30%, MTT protocol changed to closer resemble a test dose of Bronchitol

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/22198974