Clinical trial results:
A randomised, multicentre, double-blind, placebo-controlled, crossover trial determining the efficacy of dry powder mannitol in improving lung function in subjects with Cystic Fibrosis aged six to seventeen years

Summary

EudraCT number	2012-002699-14
Trial protocol	GB FR BE NL IT
Global end of trial date	15 October 2015

Results information

Result version number	v1 (current)
This version publication date	20 December 2019
First version publication date	20 December 2019
Summary attachment (see zip file)	DPM-CF-204 CSR Synopsis (DPM-CF-204_Synopsis.pdf)

Trial information

Trial identification

Sponsor protocol code	DPM-CF-204

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01883531
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	23 May 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 October 2015
Global end of trial reached?	Yes
Global end of trial date	15 October 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine the effect of eight weeks of twice-daily treatment with inhaled dry powder mannitol on lung function (FEV1) in subjects with CF who are aged six to seventeen years

Protection of trial subjects:

This study was conducted utilising practices that ensured adherence to GCP and protection of the patients, as required by the following Guidelines, Regulations and Directives in operation at the time:
• Declaration of Helsinki, concerning medical research in humans ('Recommendations Guiding Physicians in Biomedical Research Involving Human Patients', Helsinki 1964, amended Tokyo 1975, Venice 1983, Hong Kong 1989, Somerset West 1996, Edinburgh 2000).
• US 21 Code of Federal Regulations dealing with clinical studies, parts 50 and 56, concerning Informed Patient Consent and IRB approval.
• European Directive 75/318/EEC (as amended) on the approximation of laws of Member States relating to analytical, pharmacotoxicological and clinical standards and protocols in respect of the testing of medicinal products.
• ICH Guideline for Good Clinical Practice, May 9, 1997

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	13 June 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 8
Country: Number of subjects enrolled	United Kingdom: 16
Country: Number of subjects enrolled	Belgium: 13
Country: Number of subjects enrolled	France: 13
Country: Number of subjects enrolled	Germany: 13
Country: Number of subjects enrolled	Italy: 10
Country: Number of subjects enrolled	Canada: 11
Country: Number of subjects enrolled	Switzerland: 8
Worldwide total number of subjects	92
EEA total number of subjects	73

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)	39
Adolescents (12-17 years)	53
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients recruited at 39 Sites in 8 countries (Belgium 4; Canada 6; France 5; Germany 7; Italy 3; Switzerland 3; the Netherlands 2; United Kingdom 9).

Pre-assignment

Screening details:

Diagnosis and main criteria for inclusion: Confirmed diagnosis of cystic fibrosis; aged ≥ 6 years and < 18 years; who have a screening percentage of predicted FEV1 of ≥ 30% and ≤ 90% based upon Wang criteria (if less than 8 years old) or NHanes III criteria. Eligible subjects had to pass mannitol tolerance test (MTT). 117 subjects underwent MTT.

Period 1

Period 1 title	Run-in/Screening/Baseline
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Run-in - MTT screening

Arm description:

Screening and MTT testing (117 patients) and then subjects randomised (95 patients). 92 patients went on to receive at least one dose of medication FAS)

Arm type	Tolerance test - single dose
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:

Up to 400mg (tolerance test)

Number of subjects in period 1	Run-in - MTT screening
Started	92
Completed	92

Period 2

Period 2 title	Treatment Phase A
Is this the baseline period?	No
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 - Placebo

Arm description:

Mannitol 400mg bid (Phase A) followed by Non-respirable Mannitol (Phase B)

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 for 8 weeks in Phase A

Arm title	Placebo - Mannitol

Arm description:

Non-respirable mannitol bid for 8 weeks (phase A) followed by mannitol for 8 weeks in phase B

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

Dosage and administration details:

Non-respirable, 10 capsules, bid

Number of subjects in period 2	Mannitol - Placebo	Placebo - Mannitol
Started	48	44
Completed	47	43
Not completed	1	1
Consent withdrawn by subject	1	-
Adverse event, non-fatal	-	1

Period 3	
Period 3 title	Washout
Is this the baseline period?	No
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 - Placebo
Arm description: -	
Arm type	Washout - no treatment
No investigational medicinal product assigned in this arm	
Arm title	Placebo - Mannitol
Arm description: -	
Arm type	Washout - no treatment
No investigational medicinal product assigned in this arm	

Number of subjects in period 3	Mannitol - Placebo	Placebo - Mannitol
Started	47	43
Completed	45	41
Not completed	2	2
Consent withdrawn by subject	1	1
Adverse event, non-fatal	1	-
Sponsor decision	-	1

Period 4	
Period 4 title	Treatment Phase B
Is this the baseline period?	No
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 - Placebo
Arm description: -	
Arm type	Experimental

Investigational medicinal product name	Non-respirable mannitol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder, hard capsule
Routes of administration	Inhalation use

Dosage and administration details:

Non-respirable, 10 capsules, bid for 8 weeks in Phase B

Arm title	Placebo - Mannitol

Arm description: -

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 for 8 weeks in Phase B

Number of subjects in period 4	Mannitol - Placebo	Placebo - Mannitol
Started	45	41
Completed	43	41
Not completed	2	0
Consent withdrawn by subject	1	-
Adverse event, non-fatal	1	-

Baseline characteristics

Reporting groups

Reporting group title	Run-in/Screening/Baseline

Reporting group description: -

Reporting group values	Run-in/Screening/Baseline	Total	
Number of subjects	92	92	
Age categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	39	39	
Adolescents (12-17 years)	53	53	
Adults (18-64 years)	0	0	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous			
Units: years			
arithmetic mean	12.0		
standard deviation	± 3.0	-	
Gender categorical			
Units: Subjects			
Female	55	55	
Male	37	37	
Screening % Predicted FEV1			
Units: Subjects			
mild >70%	59	59	
moderate >40% to <=70%	32	32	
severe <=40%	1	1	

Subject analysis sets

Subject analysis set title	FAS
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

Randomised and received at least one dose of trial treatment

Subject analysis set title	Mannitol treated
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

These patients were those who received at least one dose of mannitol in either Period A (if randomised to Mannitol - Placebo arm) or Period B (if randomised to Placebo-Mannitol arm).

Subject analysis set title	Placebo treated
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

These patients were those who received at least one dose of placebo in either Period A (if randomised to Placebo - Mannitol arm) or Period B (if randomised to Mannitol - Placebo arm).

Reporting group values	FAS	Mannitol treated	Placebo treated
Number of subjects	92	87	87
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over	53		
Age continuous Units: years arithmetic mean standard deviation	±	±	±
Gender categorical Units: Subjects			
Female	55		
Male	37		
Screening % Predicted FEV1 Units: Subjects			
mild >70%	59		
moderate >40% to <=70%	32		
severe <=40%	1		

End points

End points reporting groups

Reporting group title	Run-in - MTT screening
Reporting group description:	
Screening and MTT testing (117 patients) and then subjects randomised (95 patients). 92 patients went on to receive at least one dose of medication FAS)	
Reporting group title	Mannitol - Placebo
Reporting group description:	
Mannitol 400mg bid (Phase A) followed by Non-respirable Mannitol (Phase B)	
Reporting group title	Placebo - Mannitol
Reporting group description:	
Non-respirable mannitol bid for 8 weeks (phase A) followed by mannitol for 8 weeks in phase B	
Reporting group title	Mannitol - Placebo
Reporting group description: -	
Reporting group title	Placebo - Mannitol
Reporting group description: -	
Reporting group title	Mannitol - Placebo
Reporting group description: -	
Reporting group title	Placebo - Mannitol
Reporting group description: -	
Subject analysis set title	FAS
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
Randomised and received at least one dose of trial treatment	
Subject analysis set title	Mannitol treated
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
These patients were those who received at least one dose of mannitol in either Period A (if randomised to Mannitol - Placebo arm) or Period B (if randomised to Placebo-Mannitol arm).	

Subject analysis set title	Placebo treated
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
These patients were those who received at least one dose of placebo in either Period A (if randomised to Placebo - Mannitol arm) or Period B (if randomised to Mannitol - Placebo arm).	

Primary: Change in FEV1 % predicted

End point title	Change in FEV1 % predicted
End point description:	

End point type	Primary
End point timeframe:	
8 weeks	

End point values	Mannitol treated	Placebo treated		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	87	87		
Units: Percentage				
least squares mean (confidence interval 95%)	3.59 (1.81 to 5.37)	0.17 (-1.60 to 1.95)		

Statistical analyses

Statistical analysis title	Crossover ANCOVA

Statistical analysis description:

Repeated analysis of covariance (ANCOVA) model including terms for patient, period, baseline within each period and treatment. Missing values were imputed using BOCF

Comparison groups	Mannitol treated v Placebo treated
Number of subjects included in analysis	174
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.0041
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	3.42
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.12
upper limit	5.71

Notes:

[1] - 92 distinct patients (crossover study) - 87 were treated with mannitol, 87 with placebo. BOCF for missing values

Secondary: Change in FVC % predicted

End point title	Change in FVC % predicted

End point description:

End point type	Secondary

End point timeframe:

8 weeks

End point values	Mannitol treated	Placebo treated		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	87	87		
Units: Percentage				
least squares mean (confidence interval 95%)	2.20 (0.32 to 4.08)	0.40 (-1.48 to 2.28)		

Statistical analyses

Statistical analysis title	Crossover ANCOVA
Comparison groups	Placebo treated v Mannitol treated
Number of subjects included in analysis	174
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1578
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	1.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.71
upper limit	4.32

Secondary: Change in FEF % predicted	
End point title	Change in FEF % predicted
End point description:	
End point type	Secondary
End point timeframe:	
8 weeks	

End point values	Mannitol treated	Placebo treated		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	87	87		
Units: Percentage				
least squares mean (confidence interval 95%)	5.85 (2.70 to 9.00)	0.10 (-3.04 to 3.24)		

Statistical analyses

Statistical analysis title	Crossover ANCOVA
Comparison groups	Mannitol treated v Placebo treated

Number of subjects included in analysis	174
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0047
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	5.75
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.82
upper limit	9.69

Secondary: Sputum weight

End point title	Sputum weight
End point description:	

End point type	Secondary
End point timeframe:	
After first dose	

End point values	Mannitol treated	Placebo treated		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	87	87		
Units: grams				
least squares mean (confidence interval 95%)	2.63 (1.72 to 3.55)	1.30 (0.39 to 2.21)		

Statistical analyses

Statistical analysis title	Crossover ANCOVA
Comparison groups	Mannitol treated v Placebo treated
Number of subjects included in analysis	174
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0124
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	1.33

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.3
upper limit	2.37

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From start of study medication	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	16.0

Reporting groups	
Reporting group title	Mannitol treated
Reporting group description: -	
Reporting group title	Placebo treated
Reporting group description: -	

Serious adverse events	Mannitol treated	Placebo treated	
Total subjects affected by serious adverse events			
subjects affected / exposed	10 / 87 (11.49%)	13 / 87 (14.94%)	
number of deaths (all causes)	0	1	
number of deaths resulting from adverse events	0	1	
Nervous system disorders			
Convulsion			
subjects affected / exposed	0 / 87 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Anal fistula			
subjects affected / exposed	1 / 87 (1.15%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	2 / 87 (2.30%)	2 / 87 (2.30%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			

subjects affected / exposed	0 / 87 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Respiratory tract infection			
subjects affected / exposed	0 / 87 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Productive cough			
subjects affected / exposed	0 / 87 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bronchopulmonary aspergillosis allergic			
subjects affected / exposed	1 / 87 (1.15%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infective pulmonary exacerbation of cystic fibrosis			
subjects affected / exposed	7 / 87 (8.05%)	8 / 87 (9.20%)	
occurrences causally related to treatment / all	0 / 8	0 / 11	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pneumonia			
subjects affected / exposed	1 / 87 (1.15%)	0 / 87 (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	0 / 87 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
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	Placebo treated	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	67 / 87 (77.01%)	59 / 87 (67.82%)	
Nervous system disorders			
Headache			
subjects affected / exposed	6 / 87 (6.90%)	7 / 87 (8.05%)	
occurrences (all)	8	10	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	17 / 87 (19.54%)	20 / 87 (22.99%)	
occurrences (all)	19	21	
Nasopharyngitis			
subjects affected / exposed	6 / 87 (6.90%)	6 / 87 (6.90%)	
occurrences (all)	7	7	
Infections and infestations			
Infective pulmonary exacerbation of cystic fibrosis	Additional description: Includes serious and non-serious numbers		
subjects affected / exposed	8 / 87 (9.20%)	13 / 87 (14.94%)	
occurrences (all)	9	15	
Lung infection			
subjects affected / exposed	2 / 87 (2.30%)	5 / 87 (5.75%)	
occurrences (all)	2	5	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 September 2013	Changes to study design that included deletion of home spirometry, adding of visit windows and inclusion of 5 additional telephone contacts

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/28258928