Clinical trial results:
A randomized double-blind (withdrawal) phase 3 study to evaluate the efficacy and tolerability of pancrelipase MT capsules compared with placebo in the treatment of subjects with cystic fibrosis-dependent exocrine pancreatic insufficiency

Due to a system error, the data reported in v1 is not correct and has been removed from public view.

Summary

EudraCT number	2015-001219-11
Trial protocol	Outside EU/EEA
Global end of trial date	06 February 2009

Results information

Result version number	v2 (current)
This version publication date	16 July 2016
First version publication date	14 August 2015
Version creation reason	• Correction of full data set Review of data

Trial information

Trial identification

Sponsor protocol code	PNCRLPCYS3001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00662675
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Johnson & Johnson Pharmaceutical Research & Development, L.L.C.
Sponsor organisation address	Trenton Harbourton Rd, Titusville (Hopewell Township), NJ 08560, United States,
Public contact	Clinical Registry Group-JB BV, Johnson & Johnson Pharmaceutical Research & Development, L.L.C., ClinicalTrialsEU@its.jnj.com
Scientific contact	Clinical Registry Group-JB BV, Johnson & Johnson Pharmaceutical Research & Development, L.L.C., ClinicalTrialsEU@its.jnj.com

Notes:

Paediatric regulatory details

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

1901/2006 apply to this trial?	

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	06 February 2009
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	06 February 2009
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the effectiveness and safety of oral pancrelipase MT in the treatment of adult and pediatric/adolescent cystic fibrosis (CF) patients with clinical symptoms of exocrine pancreatic insufficiency (EPI).

Protection of trial subjects:

The safety assessments included laboratory measurements (for example hematology, serum biochemistry, and urinalysis), vital sign measurements and physical examinations. Adverse events and vital signs were monitored throughout the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	17 July 2008
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	Canada: 2
Country: Number of subjects enrolled	United States: 47
Worldwide total number of subjects	49
EEA total number of subjects	0

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)	7

Adolescents (12-17 years)	11
Adults (18-64 years)	31
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 49 participants were enrolled and 48 participants were treated with open-label drug, among 40 participants were received either PANCREASE microtablets (MT) or placebo in double-blind phase. All 40 subjects completed the study and included in the intent-to-treat (ITT) population.

Period 1

Period 1 title	Open Label
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	PANCREASE MT - Open Label (OL)

Arm description:

Participants received PANCREASE MT 10.5 or MT 21 capsules per meal or snack for maximum of 10,000 units of lipase per kg per day.

Arm type	Experimental
Investigational medicinal product name	PANCREASE MT
Investigational medicinal product code	SUB124273
Other name	PANCRELIPASE AMYLASE
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Pancrease MT 10.5 or MT 21 capsules orally per meal or snack for maximum dose of 10 000 lipase units / Kg / day.

Number of subjects in period 1	PANCREASE MT - Open Label (OL)
Started	49
Completed	40
Not completed	9
Consent withdrawn by subject	2
Adverse event, non-fatal	1
Other	6

Period 2

Period 2 title	Double Blind
Is this the baseline period?	Yes[1]
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	PLACEBO

Arm description:

Participants who qualified for randomization (based on results of the fecal fat analysis), received Matching PLACEBO capsules orally.

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

Dosage and administration details:

Matching Placebo capsules orally per meal or snack.

Arm title	PANCREASE MT - Double Blind (DB)

Arm description:

Participants who qualified for randomization (based on results of the fecal fat analysis), received PANCREASE MT 10.5 or MT 21 capsules orally per meal or snack.

Arm type	Experimental
Investigational medicinal product name	PANCREASE MT
Investigational medicinal product code	SUB124273
Other name	PANCRELIPASE AMYLASE
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Pancrease MT 10.5 or MT 21 capsules orally per meal or snack.

Notes:

[1] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: Baseline data is available only for treated / randomized participants, hence this period has been created to report the baseline dat

Number of subjects in period 2[2]	PLACEBO	PANCREASE MT - Double Blind (DB)
Started	20	20
Completed	20	20

Notes:

[2] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: Not all the enrolled subjects were treated with study drugs. As baseline only included treated subjects, the worldwide number enrolled in the trial differs with the number of subjects reported in the baseline period

Baseline characteristics

Reporting groups	
Reporting group title	PLACEBO
Reporting group description:	
Participants who qualified for randomization (based on results of the fecal fat analysis), received Matching PLACEBO capsules orally.	
Reporting group title	PANCREASE MT - Double Blind (DB)
Reporting group description:	
Participants who qualified for randomization (based on results of the fecal fat analysis), received PANCREASE MT 10.5 or MT 21 capsules orally per meal or snack.	

Reporting group values	PLACEBO	PANCREASE MT - Double Blind (DB)	Total
Number of subjects	20	20	40
Title for AgeCategorical Units: subjects			
Children (2-11 years)	4	3	7
Adolescents (12-17 years)	4	3	7
Adults (18-64 years)	12	14	26
From 65 to 84 years	0	0	0
85 years and over	0	0	0
Title for AgeContinuous Units: years			
arithmetic mean	23.4	24	
standard deviation	± 11.58	± 13.44	-
Title for Gender Units: subjects			
Female	7	11	18
Male	13	9	22

End points

End points reporting groups

Reporting group title	PANCREASE MT - Open Label (OL)
Reporting group description:	
Participants received PANCREASE MT 10.5 or MT 21 capsules per meal or snack for maximum of 10,000 units of lipase per kg per day.	
Reporting group title	PLACEBO
Reporting group description:	
Participants who qualified for randomization (based on results of the fecal fat analysis), received Matching PLACEBO capsules orally.	
Reporting group title	PANCREASE MT - Double Blind (DB)
Reporting group description:	
Participants who qualified for randomization (based on results of the fecal fat analysis), received PANCREASE MT 10.5 or MT 21 capsules orally per meal or snack.	
Subject analysis set title	Intention-to-treat (ITT)
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
The intent-to-treat (ITT) population included participants who were randomly assigned into the double-blind (withdrawal) phase of the study	

Primary: Change from baseline in the Coefficient of Fat Absorption (COA-fat Percent)

End point title	Change from baseline in the Coefficient of Fat Absorption (COA-fat Percent)
End point description:	
Change in the coefficient of fat absorption (percent COA-fat) from the 72-hour inpatient period in the open-label phase to the 72-hour period inpatient period in the double-blind (withdrawal) phase.	
End point type	Primary
End point timeframe:	
72-hours stool collection in the open-label phase to the end of 72-hours stool collection in the doubleblind withdrawal phase.	

End point values	PLACEBO	PANCREASE MT - Double Blind (DB)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20[1]	20[2]		
Units: percentage				
arithmetic mean (standard deviation)	-34.1 (± 23.03)	-1.5 (± 5.88)		

Notes:

[1] - ITT

[2] - ITT

Statistical analyses

Statistical analysis title	Change in the Coefficient of Fat Absorption
Statistical analysis description:	
An ANCOVA model with treatment as a factor and baseline percent COA-fat as covariate is used.	
Comparison groups	PLACEBO v PANCREASE MT - Double Blind (DB)

Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA

Secondary: Change from baseline in Percent COA-Protein (Nitrogen)

End point title	Change from baseline in Percent COA-Protein (Nitrogen)

End point description:

The change in percent COA-protein from the stool collection period in double-blind phase to open-label phase.

End point type	Secondary

End point timeframe:

72-hours stool collection in the open-label phase to the end of 72-hours stool collection in the doubleblind withdrawal phase.

End point values	PLACEBO	PANCREASE MT - Double Blind (DB)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20[3]	20[4]		
Units: percentage				
arithmetic mean (standard deviation)	-26.5 (± 15.3)	1.3 (± 4.71)		

Notes:

[3] - ITT

[4] - ITT

Statistical analyses

Statistical analysis title	Change in Percent COA-Protein (Nitrogen)

Statistical analysis description:

The p-value is from ANCOVA model with treatment as a factor and baseline percent COA-protein (nitrogen) as a covariate.

Comparison groups	PLACEBO v PANCREASE MT - Double Blind (DB)
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA

Secondary: Percent of Participants Reporting Clinical Signs and Symptoms of Exocrine Pancreatic Insufficiency (EPI) During the Double-Blind Phase

End point title	Percent of Participants Reporting Clinical Signs and Symptoms of Exocrine Pancreatic Insufficiency (EPI) During the Double-Blind Phase

End point description:

Percent of participants reporting nausea, vomiting, bloating, diarrhea, oily/greasy stools, and abdominal pain signs and symptoms reported as Adverse events during the double-blind phase.

End point type	Secondary

End point timeframe:

Entire 7 days double-blind phase.

End point values	PLACEBO	PANCREASE MT - Double Blind (DB)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20[5]	20[6]		
Units: percentage of participants				
number (not applicable)				
% of subjects with at least one EPI symptoms	55	20		
% of subjects with Abdominal pain	30	15		
% of subjects with Bloating	15	5		
% of subjects with Diarrhea	20	0		
% of subjects with Greasy stools	15	0		
% of subjects with Vomiting	0	5		

Notes:

[5] - ITT

[6] - ITT

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
During the 7 days double-blind withdrawal phase	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	11.1

Reporting groups	
Reporting group title	PANCREASE MT - Open Label (OL)
Reporting group description:	
Participants received PANCREASE MT 10.5 or MT 21 capsules per meal or snack for maximum of 10,000 units of lipase per kg per day.	
Reporting group title	PLACEBO
Reporting group description:	
Participants who qualified for randomization (based on results of the fecal fat analysis), received Matching PLACEBO capsules orally.	
Reporting group title	PANCREASE MT - Double Blind (DB)
Reporting group description:	
Participants who qualified for randomization (based on results of the fecal fat analysis), received PANCREASE MT 10.5 or MT 21 capsules orally per meal or snack.	

Serious adverse events	PANCREASE MT - Open Label (OL)	PLACEBO	PANCREASE MT - Double Blind (DB)
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 40 (0.00%)	0 / 20 (0.00%)	0 / 20 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	PANCREASE MT - Open Label (OL)	PLACEBO	PANCREASE MT - Double Blind (DB)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	15 / 40 (37.50%)	12 / 20 (60.00%)	8 / 20 (40.00%)
Vascular disorders			
Pallor			
subjects affected / exposed	0 / 40 (0.00%)	1 / 20 (5.00%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			

Headache			
subjects affected / exposed	2 / 40 (5.00%)	0 / 20 (0.00%)	1 / 20 (5.00%)
occurrences (all)	2	0	1
Dizziness			
subjects affected / exposed	1 / 40 (2.50%)	0 / 20 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 40 (2.50%)	2 / 20 (10.00%)	0 / 20 (0.00%)
occurrences (all)	1	2	0
Asthenia			
subjects affected / exposed	0 / 40 (0.00%)	1 / 20 (5.00%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Pain			
subjects affected / exposed	1 / 40 (2.50%)	0 / 20 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
Thirst			
subjects affected / exposed	0 / 40 (0.00%)	1 / 20 (5.00%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Feeling Cold			
subjects affected / exposed	0 / 40 (0.00%)	1 / 20 (5.00%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
Abdominal Distension			
subjects affected / exposed	1 / 40 (2.50%)	1 / 20 (5.00%)	0 / 20 (0.00%)
occurrences (all)	1	1	0
Abdominal Discomfort			
subjects affected / exposed	1 / 40 (2.50%)	1 / 20 (5.00%)	0 / 20 (0.00%)
occurrences (all)	1	1	0
Abdominal Pain Upper			
subjects affected / exposed	3 / 40 (7.50%)	3 / 20 (15.00%)	1 / 20 (5.00%)
occurrences (all)	7	7	1
Constipation			
subjects affected / exposed	3 / 40 (7.50%)	0 / 20 (0.00%)	0 / 20 (0.00%)
occurrences (all)	3	0	0
Abnormal Faeces			

subjects affected / exposed	1 / 40 (2.50%)	3 / 20 (15.00%)	0 / 20 (0.00%)
occurrences (all)	1	3	0
Abdominal Pain			
subjects affected / exposed	2 / 40 (5.00%)	3 / 20 (15.00%)	2 / 20 (10.00%)
occurrences (all)	2	4	3
Diarrhoea			
subjects affected / exposed	0 / 40 (0.00%)	4 / 20 (20.00%)	0 / 20 (0.00%)
occurrences (all)	0	5	0
Flatulence			
subjects affected / exposed	1 / 40 (2.50%)	3 / 20 (15.00%)	1 / 20 (5.00%)
occurrences (all)	1	3	1
Dyspepsia			
subjects affected / exposed	1 / 40 (2.50%)	0 / 20 (0.00%)	1 / 20 (5.00%)
occurrences (all)	5	0	1
Haematochezia			
subjects affected / exposed	1 / 40 (2.50%)	0 / 20 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
Gastric Disorder			
subjects affected / exposed	0 / 40 (0.00%)	0 / 20 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Gastrointestinal Pain			
subjects affected / exposed	1 / 40 (2.50%)	0 / 20 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
Vomiting			
subjects affected / exposed	0 / 40 (0.00%)	0 / 20 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Reproductive system and breast disorders			
Dysmenorrhoea			
subjects affected / exposed	0 / 40 (0.00%)	0 / 20 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal disorders			
Postnasal Drip			
subjects affected / exposed	1 / 40 (2.50%)	0 / 20 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
Haemoptysis			

subjects affected / exposed	1 / 40 (2.50%)	0 / 20 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
Cough			
subjects affected / exposed	2 / 40 (5.00%)	0 / 20 (0.00%)	0 / 20 (0.00%)
occurrences (all)	2	0	0
Wheezing			
subjects affected / exposed	1 / 40 (2.50%)	0 / 20 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
Respiratory Disorder			
subjects affected / exposed	0 / 40 (0.00%)	0 / 20 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Skin and subcutaneous tissue disorders			
Skin Lesion			
subjects affected / exposed	1 / 40 (2.50%)	0 / 20 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 40 (0.00%)	0 / 20 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 40 (2.50%)	1 / 20 (5.00%)	0 / 20 (0.00%)
occurrences (all)	1	1	0
Muscle Spasms			
subjects affected / exposed	1 / 40 (2.50%)	0 / 20 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
Pain in Extremity			
subjects affected / exposed	2 / 40 (5.00%)	1 / 20 (5.00%)	0 / 20 (0.00%)
occurrences (all)	2	1	0
Back Pain			
subjects affected / exposed	1 / 40 (2.50%)	0 / 20 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
Infections and infestations			
Influenza			
subjects affected / exposed	0 / 40 (0.00%)	0 / 20 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1

Viral Upper Respiratory Tract Infection			
subjects affected / exposed	1 / 40 (2.50%)	0 / 20 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
Metabolism and nutrition disorders			
Decreased Appetite			
subjects affected / exposed	0 / 40 (0.00%)	1 / 20 (5.00%)	0 / 20 (0.00%)
occurrences (all)	0	1	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 April 2008	The overall reason for the amendment was to give more flexibility in diet restrictions, administration of either PANCREASE MT 10.5 or 21 (not a combination of both), decrease in total blood volume draw, clarifications of screening and open-label time periods, clarification of exclusion criteria, removal of fasting prior to screening procedures, clarification of the timing of fecal elastase testing, clarification of age groups, clarification of the blinding procedure, addition of pregnancy inclusion, removal of milk as a dietary restriction, changes in the time of serum uric acid collection, prohibition of additional anti-diarrheal medications, clarification of laxative use.
22 May 2008	The overall reason for the amendment was to clarification of protocol elements for stool collection, clarification of PERT regimen during screening and study drug initiation during run-in, clarification of double-blind medication dispensing, replacement of Study Design diagram to accompany changes.
08 January 2009	The overall reason for the amendment was to update all references of MT 4, 10, 16, and 20 to MT 4.2, 10.5, 16.8, and 21, respectively. The age range was clarified for children/adolescents, and screening phase information was streamlined. The units for percent COA protein/protease were added to the exploratory analyses.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported