Clinical trial results:
An Open-Label, Multicenter, Randomized, Cross-over Study to Compare the Safety and Efficacy of Panzytrat® 25,000 to Kreon® 25,000 in the Control of Steatorrhea in Subjects Aged 7 Years and Older with Cystic Fibrosis (CF) and Exocrine Pancreatic Insufficiency (EPI)

Summary

EudraCT number	2010-019267-11
Trial protocol	DE
Global end of trial date	14 May 2012

Results information

Result version number	v1 (current)
This version publication date	22 August 2018
First version publication date	22 August 2018

Trial information

Trial identification

Sponsor protocol code	MA-PA25CF10-01

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01327703
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Forest Laboratories, LLC, an Allergan Affiliate
Sponsor organisation address	5 Giralda Farms, Madison, United States, 07940
Public contact	Clinical Trials Registry Team, Allergan plc, 001 8772778566, IR-CTRegistration@allergan.com
Scientific contact	Therapeutic Area Head, Allergan plc, 001 862-261-7000, IR-CTRegistration@Allergan.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	
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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	14 May 2012
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	14 May 2012
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This study assessed the efficacy and safety of Panzytrat® 25,000 compared to Kreon® 25,000 in the control of steatorrhea in participants with cystic fibrosis (CF) and exocrine pancreatic insufficiency (EPI).

Protection of trial subjects:

All study participants were required to read and sign an Informed Consent Form.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	07 April 2011
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	Germany: 60
Country: Number of subjects enrolled	Poland: 27
Worldwide total number of subjects	87
EEA total number of subjects	87

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)	37
Adolescents (12-17 years)	35
Adults (18-64 years)	15
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants took part in the study at 14 investigative sites in Germany and Poland from 7 April 2011 to 14 May 2012.

Pre-assignment

Screening details:

Participants with a diagnosis of with Cystic Fibrosis and Exocrine Pancreatic Insufficiency where enrolled in this crossover study and received Panzytrat® 25,000 and Kreon® 25,000.

Period 1

Period 1 title	First Treatment Period
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Panzytrat® First, Then Kreon®

Arm description:

Panzytrat® 25,000 capsule orally daily at a stabilized dose, as per investigator's discretion, for 14 days in first treatment period followed by Kreon® 25,000 capsule orally daily at a stabilized dose, as per investigator's discretion, for 14 days in second treatment period. Stabilized dose for a participant was the optimal dose determined during a qualification phase that preceded the first treatment period and was based upon the participant's usual lipase and lipid intake and total dose was not to exceed 10,000 European Pharmacopoeia (Ph.Eur.) units lipase/kilogram (kg) body weight/day.

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

Dosage and administration details:

≤10,000 Ph.Eur.-E. units lipase/kilogram(kg) body weight/day.

Arm title	Kreon® First, Then Panzytrat®

Arm description:

Kreon® 25,000 capsule orally daily at a stabilized dose, as per investigator's discretion, for 14 days in first treatment period followed by Panzytrat® 25,000 capsule orally daily at a stabilized dose, as per investigator's discretion, for 14 days in second treatment period. Stabilized dose for a participant was the optimal dose determined during a qualification phase that preceded the first treatment period and was based upon the participant's usual lipase and lipid intake and total dose was not to exceed 10,000 Ph.Eur. units lipase/kg body weight/day.

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

Dosage and administration details:

≤10,000 Ph.Eur.-E. units lipase/kilogram(kg) body weight/day.

Number of subjects in period 1	Panzytrat® First, Then Kreon®	Kreon® First, Then Panzytrat®
Started	42	45
Completed	42	45

Period 2

Period 2 title	Second Treatment Period
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Panzytrat® First, Then Kreon®

Arm description:

Panzytrat® 25,000 capsule orally daily at a stabilized dose, as per investigator's discretion, for 14 days in first treatment period followed by Kreon® 25,000 capsule orally daily at a stabilized dose, as per investigator's discretion, for 14 days in second treatment period. Stabilized dose for a participant was the optimal dose determined during a qualification phase that preceded the first treatment period and was based upon the participant's usual lipase and lipid intake and total dose was not to exceed 10,000 European Pharmacopoeia (Ph.Eur.) units lipase/kilogram (kg) body weight/day.

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

Dosage and administration details:

≤10,000 Ph.Eur.-E. units lipase/kilogram(kg) body weight/day.

Arm title	Kreon® First, Then Panzytrat®

Arm description:

Kreon® 25,000 capsule orally daily at a stabilized dose, as per investigator's discretion, for 14 days in first treatment period followed by Panzytrat® 25,000 capsule orally daily at a stabilized dose, as per investigator's discretion, for 14 days in second treatment period. Stabilized dose for a participant was the optimal dose determined during a qualification phase that preceded the first treatment period and was based upon the participant's usual lipase and lipid intake and total dose was not to exceed 10,000 Ph.Eur. units lipase/kg body weight/day.

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

Dosage and administration details:

≤10,000 Ph.Eur.-E. units lipase/kilogram(kg) body weight/day.

Number of subjects in period 2[1]	Panzytrat® First, Then Kreon®	Kreon® First, Then Panzytrat®
Started	40	44
Completed	39	42
Not completed	1	2
Adverse event, non-fatal	1	1
Protocol deviation	-	1

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: 3 participants who completed Period 1 did not participate in Period 2.

Baseline characteristics

Reporting groups

Reporting group title	First Treatment Period

Reporting group description: -

Reporting group values	First Treatment Period	Total	
Number of subjects	87	87	
Age categorical Units: Subjects			
7 to 12 Years	47	47	
13 to 18 Years	27	27	
19 to 30 Years	10	10	
>30 Years	3	3	
Age Continuous Units: years			
arithmetic mean	13.6		
standard deviation	± 6.14	-	
Gender, Male/Female Units: Subjects			
Female	34	34	
Male	53	53	
Nutritional Status as assessed by Vitamin A Level			
Nutritional status was assessed by determining Vitamin A level.			
Units: micromole/liter (mcmol/L)			
arithmetic mean	1.403		
standard deviation	± 0.5329	-	
Nutritional status as assessed by Vitamin E (Alpha-Tocopherol) Level			
Nutritional status was assessed by determining Vitamin E (Alpha-Tocopherol) level.			
Units: micromole/liter (mcmol/L)			
arithmetic mean	18.554		
standard deviation	± 8.9713	-	
Nutritional status as assessed by Vitamin D Level			
Nutritional status was assessed by determining Vitamin D level. Number of participants who were evaluable for Vitamin D level was 86.			
Units: nanomole/L (nmol/L)			
arithmetic mean	55.4		
standard deviation	± 33.24	-	
Nutritional Status as assessed by Vitamin E (Beta-Gamma-Tocopherol) Level (n=83)|			
Nutritional status was assessed by determining Vitamin E (Beta-Gamma-Tocopherol) level. Here, 'n' signifies number of participants who were evaluable for Vitamin E (Beta-Gamma-Tocopherol) level.			
Units: micromole/liter (mcmol/L)			
arithmetic mean	1.231		
standard deviation	± 2.0781	-	

End points

End points reporting groups

Reporting group title	Panzytrat® First, Then Kreon®

Reporting group description:

Panzytrat® 25,000 capsule orally daily at a stabilized dose, as per investigator's discretion, for 14 days in first treatment period followed by Kreon® 25,000 capsule orally daily at a stabilized dose, as per investigator's discretion, for 14 days in second treatment period. Stabilized dose for a participant was the optimal dose determined during a qualification phase that preceded the first treatment period and was based upon the participant's usual lipase and lipid intake and total dose was not to exceed 10,000 European Pharmacopoeia (Ph.Eur.) units lipase/kilogram (kg) body weight/day.

Reporting group title	Kreon® First, Then Panzytrat®

Reporting group description:

Kreon® 25,000 capsule orally daily at a stabilized dose, as per investigator's discretion, for 14 days in first treatment period followed by Panzytrat® 25,000 capsule orally daily at a stabilized dose, as per investigator's discretion, for 14 days in second treatment period. Stabilized dose for a participant was the optimal dose determined during a qualification phase that preceded the first treatment period and was based upon the participant's usual lipase and lipid intake and total dose was not to exceed 10,000 Ph.Eur. units lipase/kg body weight/day.

Reporting group title	Panzytrat® First, Then Kreon®

Reporting group description:

Panzytrat® 25,000 capsule orally daily at a stabilized dose, as per investigator's discretion, for 14 days in first treatment period followed by Kreon® 25,000 capsule orally daily at a stabilized dose, as per investigator's discretion, for 14 days in second treatment period. Stabilized dose for a participant was the optimal dose determined during a qualification phase that preceded the first treatment period and was based upon the participant's usual lipase and lipid intake and total dose was not to exceed 10,000 European Pharmacopoeia (Ph.Eur.) units lipase/kilogram (kg) body weight/day.

Reporting group title	Kreon® First, Then Panzytrat®

Reporting group description:

Kreon® 25,000 capsule orally daily at a stabilized dose, as per investigator's discretion, for 14 days in first treatment period followed by Panzytrat® 25,000 capsule orally daily at a stabilized dose, as per investigator's discretion, for 14 days in second treatment period. Stabilized dose for a participant was the optimal dose determined during a qualification phase that preceded the first treatment period and was based upon the participant's usual lipase and lipid intake and total dose was not to exceed 10,000 Ph.Eur. units lipase/kg body weight/day.

Subject analysis set title	Panzytrat®
Subject analysis set type	Per protocol

Subject analysis set description:

Panzytrat® 25,000 capsule orally daily at a stabilized dose, as per investigator's discretion, for 14 days in either first treatment period or second treatment period.

Subject analysis set title	Kreon®
Subject analysis set type	Per protocol

Subject analysis set description:

Kreon® 25,000 capsule orally daily at a stabilized dose, as per investigator's discretion, for 14 days in either first treatment period or second treatment period.

Subject analysis set title	Panzytrat®
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Panzytrat® 25,000 capsule orally daily at a stabilized dose, as per investigator's discretion, for 14 days in either first treatment period or second treatment period.

Subject analysis set title	Kreon®
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Kreon® 25,000 capsule orally daily at a stabilized dose, as per investigator's discretion, for 14 days in either first treatment period or second treatment period.

Subject analysis set title	Panzytrat®
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Panzytrat® 25,000 capsule orally daily at a stabilized dose, as per investigator's discretion, for 14 days in either first treatment period or second treatment period.

Subject analysis set title	Kreon®
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Kreon® 25,000 capsule orally daily at a stabilized dose, as per investigator's discretion, for 14 days in either first treatment period or second treatment period.

Subject analysis set title	Kreon®
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Kreon® 25,000 capsule orally daily at a stabilized dose, as per investigator's discretion, for 14 days in either first treatment period or second treatment period.

Subject analysis set title	Panzytrat®
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Panzytrat® 25,000 capsule orally daily at a stabilized dose, as per investigator's discretion, for 14 days in either first treatment period or second treatment period.

Subject analysis set title	Kreon®
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Kreon® 25,000 capsule orally daily at a stabilized dose, as per investigator's discretion, for 14 days in either first treatment period or second treatment period.

Subject analysis set title	Kreon®, First, Then Panzytrat®
Subject analysis set type	Safety analysis

Subject analysis set description:

Kreon® 25,000 capsule orally daily at a stabilized dose, as per investigator's discretion, for 14 days in first treatment period followed by Panzytrat® 25,000 capsule orally daily at a stabilized dose, as per investigator's discretion, for 14 days in second treatment period. Stabilized dose for a participant was the optimal dose determined during a qualification phase that preceded the first treatment period and was based upon the participant's usual lipase and lipid intake and total dose was not to exceed 10,000 Ph.Eur. units lipase/kg body weight/day.

Primary: Percent Coefficient of Fat Absorption (CFA)

End point title	Percent Coefficient of Fat Absorption (CFA)

End point description:

Percent CFA was calculated as ([fat intake - fat excretion]/fat intake)*100, determined in the stools which were collected over a 3-day period (Day 12 to morning of Day 15) during each treatment period. Least squares mean percent (%) CFA was calculated for Day 12 to Day 15 in first and second treatment periods. Percent CFA was based on log transformed data.

End point type	Primary

End point timeframe:

Day 12 up to Day 15 in first and second treatment periods

End point values	Panzytrat®	Kreon®		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	38	38		
Units: percent CFA				
least squares mean (standard error)	78.27 (± 1.033)	80.35 (± 1.033)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Mixed model analysis method was used for comparison using log-transformed percent CFA as the response variable, fixed effect factors for treatment, period, treatment sequence and pooled site and participant within treatment sequence as a random effect.

Comparison groups	Panzytrat® v Kreon®
Number of subjects included in analysis	76
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.459 [1]
Method	Mixed models analysis
Parameter estimate	Treatment difference
Point estimate	-2.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.23
upper limit	4.02

Notes:

[1] - As there was only a single pre-specified primary analysis, there was no adjustment for multiplicity.

Secondary: Mean Daily Number of Stools

End point title	Mean Daily Number of Stools

End point description:

Mean daily number of stools of each participant was calculated from frequency of stools by the participant per day. Mean daily number of stools during the collection period (Day 12 to Day 15 in first and second treatment periods) for total participants was summarized.

End point type	Secondary

End point timeframe:

Day 12 up to Day 15 in first and second treatment periods

End point values	Panzytrat®	Kreon®		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	85	84		
Units: stools per day				
arithmetic mean (standard deviation)	4.5 (± 2.43)	4.2 (± 2.14)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Stools With Normal Consistency

End point title	Percentage of Stools With Normal Consistency

End point description:

Normal consistency of stool was defined as formed hard, normal or soft stool and abnormal consistency was defined as loose and unformed, liquid stool and diarrhea. Percentage of stools with normal consistency of each participant was calculated as the number of stools with normal consistency relative to the total number of stools during the collection period. Mean percentage of stool with normal consistency during the collection period (Day 12 to Day 15 in first and second treatment periods) for total participants was summarized.

End point type	Secondary

End point timeframe:

Day 12 up to Day 15 in first and second treatment periods

End point values	Panzytrat®	Kreon®		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	83	83		
Units: percentage of stools				
arithmetic mean (standard deviation)	0.644 (± 0.3442)	0.635 (± 0.3517)		

Statistical analyses

No statistical analyses for this end point

Secondary: Total Weight of Stools

End point title	Total Weight of Stools

End point description:

Mean total weight of stools was calculated for Day 12 to Day 15 in first and second treatment periods.

End point type	Secondary

End point timeframe:

Day 12 up to Day 15 in first and second treatment periods

End point values	Panzytrat®	Kreon®		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	85	84		
Units: gram				
arithmetic mean (standard deviation)	521.6 (± 301.95)	484.0 (± 326.81)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Weight per Stool Sample

End point title	Mean Weight per Stool Sample

End point description:

Mean weight per stool sample was calculated for Day 12 to Day 15 in first and second treatment periods.

End point type	Secondary

End point timeframe:

Day 12 up to Day 15 in first and second treatment periods

End point values	Panzytrat®	Kreon®		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	83	82		
Units: gram				
arithmetic mean (standard deviation)	131.7 (± 79.67)	124.0 (± 81.71)		

Statistical analyses

No statistical analyses for this end point

Secondary: Relative Frequency of Days With Abdominal Symptoms

End point title	Relative Frequency of Days With Abdominal Symptoms

End point description:

Abdominal symptoms included abdominal pain and flatulence. Symptoms were classified by severity as mild (no impairment of daily activities), moderate (slight impairment of daily activities), or severe (unable to perform daily activities). For each type of abdominal symptom, the relative frequency of days with the symptom for each participant in a treatment period was calculated as the number of days in which the symptom was reported divided by the total number of days in which the abdominal symptom case report form (CRF) was completed. Mean relative frequency of days with abdominal symptoms was calculated during each treatment period (Day 1 to Day 15).

End point type	Secondary

End point timeframe:

Day 1 up to Day 15 in first and second treatment periods

End point values	Panzytrat®	Kreon®		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	86	85		
Units: days				
arithmetic mean (standard deviation)				
Abdominal pain (n=86, 85)|	0.227 (± 0.2500)	0.216 (± 0.2251)		

Mild abdominal pain (n=58, 57)|	0.302 (± 0.2440)	0.308 (± 0.2199)		
Moderate abdominal pain (n=37, 39)|	0.434 (± 0.2496)	0.374 (± 0.2269)		
Severe abdominal pain (n=14, 12)|	0.429 (± 0.2646)	0.400 (± 0.2741)		
Flatulence (n=86, 85)|	0.365 (± 0.3215)	0.329 (± 0.3290)		
Mild flatulence (n=67, 61)|	0.467 (± 0.2912)	0.459 (± 0.3018)		
Moderate flatulence (n=35, 40)|	0.351 (± 0.2649)	0.577 (± 0.2806)		
Severe flatulence (n=20, 13)|	0.616 (± 0.2959)	0.554 (± 0.1968)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Abdominal Distension

End point title	Percentage of Participants With Abdominal Distension

End point description:

Abdominal distension is a sense of increased abdominal pressure by the participant that involves an actual measurable change in the circumference of a participant's abdomen on physical examination. Percentage of participants with abdominal distension was calculated for each treatment period (Day 1 to Day 15).

End point type	Secondary

End point timeframe:

Day 1 up to Day 15 in first and second treatment periods

End point values	Panzytrat®	Kreon®		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	86	85		
Units: percentage of participants				
number (not applicable)	12.8	11.8		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Coefficient of Fat Absorption (CFA) Based on Concomitant use of Proton Pump Inhibitors (PPIs)

End point title	Percent Coefficient of Fat Absorption (CFA) Based on Concomitant use of Proton Pump Inhibitors (PPIs)

End point description:

Percent CFA was calculated as ([fat intake - fat excretion]/fat intake)*100, determined in the stools which were collected over a 3-day period (Day 12 to morning of Day 15) during each treatment period. Least squares mean percent (%) CFA was calculated for Day 12 to Day 15 in first and second treatment

periods. Percent CFA was based on log transformed data. Percent CFA was calculated separately for participants who used and did not use acid suppressing therapy (PPIs) during the study.

End point type	Secondary

End point timeframe:

Day 12 up to Day 15 in first and second treatment periods

End point values	Panzytrat®	Kreon®		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	38	38		
Units: percent CFA				
least squares mean (standard error)				
PPIs used (n=7, 7)|	79.66 (± 1.071)	94.29 (± 1.071)		
PPIs not used (n=31, 31)|	80.89 (± 1.037)	79.24 (± 1.037)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Treatment-Emergent Adverse Events (TEAEs) or Serious Adverse Events (SAEs)

End point title	Number of Participants With Treatment-Emergent Adverse Events (TEAEs) or Serious Adverse Events (SAEs)

End point description:

An AE was defined as any untoward medical occurrence regardless of its causal relationship to study drug. A TEAE was defined as any event not present prior to exposure to study drug or any event already present that worsens in either intensity or frequency following exposure to test drug. A SAE was defined as any event that results in death, is immediately life threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect or is assessed as medically important.

End point type	Secondary

End point timeframe:

Baseline up to 30 days after last dose

End point values	Panzytrat®	Kreon®		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	86	85		
Units: participants				
AEs|	32	20		
SAEs|	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Nutritional Status as Assessed by Body Weight

End point title	Nutritional Status as Assessed by Body Weight

End point description:

Mean body weight was calculated at end of treatment (within 3 days after Day 15 of first and second treatment periods).

End point type	Secondary

End point timeframe:

Baseline, end of treatment (within 3 days after Day 15 of first and second treatment periods) or early discontinuation

End point values	Panzytrat®	Kreon®		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	86	85		
Units: kg				
arithmetic mean (standard deviation)				
Baseline|	40.82 (± 16.001)	41.43 (± 15.861)		
End of treatment|	41.22 (± 15.999)	41.88 (± 15.886)		

Statistical analyses

No statistical analyses for this end point

Secondary: Nutritional Status as Assessed by Body Mass Index (BMI)

End point title	Nutritional Status as Assessed by Body Mass Index (BMI)

End point description:

Nutritional status of participants was assessed by determining their BMI. BMI was calculated by dividing body weight (kg) by square of height in meter (m). Mean BMI was calculated at end of treatment (within 3 days after Day 15 of first and second treatment periods).

End point type	Secondary

End point timeframe:

Baseline, end of treatment (within 3 days after Day 15 of first and second treatment periods) or early discontinuation

End point values	Panzytrat®	Kreon®		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	85	85		
Units: kg/m^2				
arithmetic mean (standard deviation)				
Baseline|	17.84 (± 3.296)	17.90 (± 3.264)		

End of treatment|	17.94 (± 3.244)	18.01 (± 3.240)		

Statistical analyses

No statistical analyses for this end point

Secondary: Nutritional Status as Assessed by Electrolytes Level

End point title	Nutritional Status as Assessed by Electrolytes Level[2]

End point description:

Nutritional status of participants was assessed by determining their electrolytes (sodium, potassium and chloride) level. Mean electrolytes level was calculated at end of treatment (within 3 days after Day 15 of first and second treatment periods).

End point type	Secondary

End point timeframe:

Baseline, end of treatment (within 3 days after Day 15 of first and second treatment periods) or early discontinuation

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: A Subject Analysis Set was used for the Kreon® First, Then Panzytrat® arm of the Baseline Period.

End point values	Panzytrat® First, Then Kreon®	Kreon®, First, Then Panzytrat®		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	42	43		
Units: millimole/L (mmol/L)				
arithmetic mean (standard deviation)				
Sodium: Baseline (n=42, 43)|	138.41 (± 3.026)	138.54 (± 3.356)		
Sodium: End of treatment (n=42, 43)|	139.11 (± 2.350)	139.07 (± 2.466)		
Potassium: Baseline (n=42, 42)|	4.441 (± 0.4799)	4.371 (± 0.3721)		
Potassium: End of treatment (n=42, 42)|	4.322 (± 0.4113)	4.344 (± 0.3506)		
Chloride: Baseline (n=38, 40)|	102.08 (± 3.436)	101.40 (± 3.193)		
Chloride: End of treatment (n=38, 40)|	102.13 (± 2.796)	102.18 (± 2.541)		

Statistical analyses

No statistical analyses for this end point

Secondary: Nutritional Status as Assessed by Albumin, Serum Transferrin and Hemoglobin Level

End point title	Nutritional Status as Assessed by Albumin, Serum Transferrin

	and Hemoglobin Level

End point description:

Nutritional status of participants was assessed by determining their albumin, serum transferrin and hemoglobin level. Mean albumin, serum transferrin and hemoglobin level was calculated at end of treatment (within 3 days after Day 15 of first and second treatment periods).

End point type	Secondary

End point timeframe:

Baseline, end of treatment (within 3 days after Day 15 of first and second treatment periods) or early discontinuation

End point values	Panzytrat® First, Then Kreon®	Kreon® First, Then Panzytrat®		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	42		
Units: gram/L (g/L)				
arithmetic mean (standard deviation)				
Albumin: Baseline (n=41, 42)|	40.553 (± 11.3568)	37.995 (± 14.8405)		
Albumin: End of treatment (n=41, 42)|	40.785 (± 11.1893)	37.991 (± 14.9636)		
Serum transferrin: Baseline (n=40, 41)|	2.877 (± 0.9769)	2.618 (± 1.1857)		
Serum transferrin: End of treatment (n=40, 41)|	2.916 (± 0.9416)	2.626 (± 1.1618)		
Hemoglobin: Baseline (n=42, 42)|	137.337 (± 11.7570)	141.118 (± 11.4577)		
Hemoglobin: End of treatment (n=42, 42)|	137.935 (± 11.4543)	141.263 (± 11.4412)		

Statistical analyses

No statistical analyses for this end point

Secondary: Nutritional Status as Assessed by Hematocrit Level

End point title	Nutritional Status as Assessed by Hematocrit Level

End point description:

Nutritional status of participants was assessed by determining their hematocrit level. Mean hematocrit level was calculated at end of treatment (within 3 days after Day 15 of first and second treatment periods).

End point type	Secondary

End point timeframe:

Baseline, end of treatment (within 3 days after Day 15 of first and second treatment periods) or early discontinuation

End point values	Panzytrat® First, Then Kreon®	Kreon® First, Then Panzytrat®		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	42		
Units: proportion of hematocrit				
arithmetic mean (standard deviation)				
Baseline|	0.408 (± 0.0324)	0.417 (± 0.0333)		
End of treatment|	0.409 (± 0.0311)	0.416 (± 0.0328)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline up to 30 days after last dose

Adverse event reporting additional description:

Adverse event (AE) was any untoward medical occurrence regardless of causal relationship to study drug. Serious AE was any event that resulted in death, life threatening, required or prolonged in-patient hospitalization, significant disability/incapacity, or was a congenital anomaly/birth defect. Participants at risk: Panzytrat®=86 and Kreon®=85.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	13.1

Reporting groups

Reporting group title	Kreon®

Reporting group description:

Kreon® 25,000 capsule orally daily at a stabilized dose, as per investigator's discretion, for 14 days in either first treatment period or second treatment period.

Reporting group title	Panzytrat®

Reporting group description:

Panzytrat® 25,000 capsule orally daily at a stabilized dose, as per investigator's discretion, for 14 days in either first treatment period or second treatment period.

Serious adverse events	Kreon®	Panzytrat®	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 85 (0.00%)	0 / 86 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

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

Non-serious adverse events	Kreon®	Panzytrat®	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	20 / 85 (23.53%)	32 / 86 (37.21%)	
Investigations			
Pseudomonas test positive			
subjects affected / exposed	1 / 85 (1.18%)	0 / 86 (0.00%)	
occurrences (all)	1	0	
Vitamin A decreased			

subjects affected / exposed	0 / 85 (0.00%)	1 / 86 (1.16%)	
occurrences (all)	0	1	
Vascular disorders			
Haematoma			
subjects affected / exposed	1 / 85 (1.18%)	0 / 86 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 85 (1.18%)	2 / 86 (2.33%)	
occurrences (all)	1	2	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	2 / 85 (2.35%)	2 / 86 (2.33%)	
occurrences (all)	2	2	
Eye disorders			
Conjunctivitis			
subjects affected / exposed	0 / 85 (0.00%)	1 / 86 (1.16%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Flatulence			
subjects affected / exposed	6 / 85 (7.06%)	15 / 86 (17.44%)	
occurrences (all)	6	20	
Abdominal pain			
subjects affected / exposed	9 / 85 (10.59%)	11 / 86 (12.79%)	
occurrences (all)	14	20	
Diarrhoea			
subjects affected / exposed	0 / 85 (0.00%)	2 / 86 (2.33%)	
occurrences (all)	0	2	
Vomiting			
subjects affected / exposed	0 / 85 (0.00%)	2 / 86 (2.33%)	
occurrences (all)	0	2	
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	1 / 85 (1.18%)	2 / 86 (2.33%)	
occurrences (all)	1	2	
Cough			

subjects affected / exposed	0 / 85 (0.00%)	1 / 86 (1.16%)	
occurrences (all)	0	1	
Epistaxis			
subjects affected / exposed	0 / 85 (0.00%)	1 / 86 (1.16%)	
occurrences (all)	0	1	
Sputum increased			
subjects affected / exposed	0 / 85 (0.00%)	1 / 86 (1.16%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Neck pain			
subjects affected / exposed	0 / 85 (0.00%)	1 / 86 (1.16%)	
occurrences (all)	0	1	
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	0 / 85 (0.00%)	3 / 86 (3.49%)	
occurrences (all)	0	3	
Nasopharyngitis			
subjects affected / exposed	1 / 85 (1.18%)	1 / 86 (1.16%)	
occurrences (all)	1	1	
Rhinitis			
subjects affected / exposed	1 / 85 (1.18%)	1 / 86 (1.16%)	
occurrences (all)	1	1	
Gastrointestinal infection			
subjects affected / exposed	0 / 85 (0.00%)	1 / 86 (1.16%)	
occurrences (all)	0	1	
Infective pulmonary exacerbation of cystic fibrosis			
subjects affected / exposed	0 / 85 (0.00%)	1 / 86 (1.16%)	
occurrences (all)	0	1	
Pharyngitis			
subjects affected / exposed	1 / 85 (1.18%)	0 / 86 (0.00%)	
occurrences (all)	1	0	
Varicella			
subjects affected / exposed	0 / 85 (0.00%)	1 / 86 (1.16%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 August 2010	Amendment 1: -Added "proposal of a new example of compliance calculation with a lower daily fixed dose of capsules (18 capsules per day was changed for 12 capsules per day)"; -Inclusion criteria: added subject has a diagnosis of severe EPI confirmed by ELISA measurement of fecal elastase (FE-I) (test could have been performed in the past and result available); -Inclusion criteria: added women of childbearing potential must have a negative pregnancy test at study entry and must use a medically acceptable contraceptive method for the duration of the study (i.e. from the qualification visit up to 30 days after the last study visit); -Exclusion criteria: added recent treatment of an emergent acute infection with oral or intravenous (IV) antibiotics that was not stopped at least 14 days prior to randomization; -Exclusion criteria: added use of enteral tube feeding over day and night; -Qualification phase: added this phase will last 5 to 15 days in order to obtain FE-I result (if necessary) ... standardized Cystic Fibrosis (CF) diet and standardized dose of lipase; -Prohibited medications: added chronic use of inhaled or oral antibiotics for infection prophylaxis is allowed provided that the drugs and the doses remain the same during the study; -Added "females who do not use an acceptable contraceptive regimen will be allowed to participate in this study only if they are not of childbearing potential"; -Added "subjects will only be identified with a subject identifier";
06 August 2010	-Added the "study personnel will contact the subject by phone on Day 10 to remind him/her to start the accurate food recording on Day 11"; -Added to Period 1: The subject will continue the same standardized diet and will continue the food recording very accurately from Day 12 to Day 15 AM. During this period, the subject will continue to record the number of capsules of study drug taken at each meal and snack and the presence of abdominal symptoms (abdominal pain and flatulence) as well; -Added "stools will be kept refrigerated or frozen"; -added "The physical exam will collect body weight in kilograms (kg), height in centimeters (cm) and vital signs after the subject has been seated for at least 5 minutes"; -Added "study procedures will not resume before 14 days after the end of antibiotic administration and the maximal time frame for the PAUSE period will be 45 days"; -Added "all samples of urine and blood will be sent to a local laboratory for analysis and all samples of stools will be sent to a central laboratory according to their shipment requirements. For sites that cannot have vitamins A, D and E analysis at their local laboratory, frozen serum will be sent to the central laboratory for analysis"; -Added "The investigator has the responsibility to notify the local Ethics Committee about serious adverse events (SAEs) according to local regulatory requirements".
24 September 2010	Amendment 2: -Removed "Study Phase: IIIb" and replaced with "Study Phase: IV", in all applicable areas.

05 October 2011	Amendment 3: -Added "Axcan Pharma Inc. was replaced by Aptalis Pharma Canada, Inc, because on September 8, 2011, Axcon Pharma Inc., a subsidiary of Aptalis Pharma Inc., changed its name to Aptalis Pharma Canada. Inc."; -Added "Axcon Pharma SAS was replaced by Apatalis Pharma SAS, because on June 8, 2011, Axcan Pharma SAS, a subsidiary of Aptalis Pharma Inc., changed its name to Aptalis SAS."; -Added "capsules of lower dosage will not be allowed for snacks and small meals. The usual enzyme treatment capsules (Panzytrat® 25,000 or Kreon® 25,000) will need to be opened to provide a smaller amount of lipase", to the study description; -Updated the list and contact information of the sponsor's personnel involved in the study; -Removed the Netherlands from the list of countries with study sites involved in this study; -Exclusion criteria: Use of enteral tube feeding or gastric tube feeding (G-tube) for continuous feeding over day or night; -Clarified the dose will be limited to a maximum of 4000 lipase units per gram of fat ingested and will not exceed 10,000 The European Pharmacopoeia (Ph.Eur.-E) units of lipase per kilogram of body weight per day; -Clarified the primary efficacy endpoint – only fat intakes cumulated over Day 12, Day 13 and Day 14 will be used to calculate the CFA%%.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported