



Clinical trial results:

A Phase II, Multicenter, Parallel-Group, Active-Controlled, Randomized, Double-blind, Dose-Ranging Study to Evaluate the Efficacy and Safety of Different Doses of Creon IR in Subjects with Pancreatic Exocrine Insufficiency due to Cystic Fibrosis

Summary

EudraCT number	2014-004519-35
Trial protocol	HU CZ ES GB
Global end of trial date	07 July 2015

Results information

Result version number	v1 (current)
This version publication date	04 June 2016
First version publication date	04 June 2016
Summary attachment (see zip file)	Synopsis of the CSR (PANC2002- synopsis- SOLID (panc2002-synopsis-SOLID 1000606800.pdf)

Trial information

Trial identification

Sponsor protocol code	PANC2002
-----------------------	----------

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02415959
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Abbott Laboratories GmbH
Sponsor organisation address	Freundallee 9A, Hannover, Germany, 30173
Public contact	Gregor Eibes, Abbott Laboratories GmbH, +31 29447 7367, gregor.eibes@abbott.com
Scientific contact	Gregor Eibes, Abbott Laboratories GmbH, +31 29447 7367, gregor.eibes@abbott.com
Sponsor organisation name	Abbott Laboratories GmbH
Sponsor organisation address	Freundallee 9A, Hannover, Germany, 30173
Public contact	Suntje Sander-Struckmeier, Abbott Laboratories GmbH, 0049 1167503254, suntje.sander@abbott.com
Scientific contact	Suntje Sander-Struckmeier, Abbott Laboratories GmbH, 0049 1167503254, suntje.sander@abbott.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 1901/2006 apply to this trial?	No
--	----

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	17 December 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	07 July 2015
Global end of trial reached?	Yes
Global end of trial date	07 July 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare and model the efficacy of four different doses of Creon Immediate Release (IR) capsule formulation and the currently registered active control (Creon® (Delayed Release/Gastro-Resistant) [Creon® DR/GR] capsules) in subjects with pancreatic exocrine insufficiency (PEI) due to cystic fibrosis (CF). The primary efficacy objective is based on the evaluation of fat digestion as measured by coefficient of fat absorption (CFA) (%).

Protection of trial subjects:

All study investigators expressly agreed not to disclose the identity of the patients treated and to abide by the confidentiality rules as regards data and information to which they had access by participating in the study.

All the data related to the participating patients were recorded and treated according to the regulatory law of data protection.

All information obtained as a result of this study was considered confidential until the sponsor deemed it appropriate. The investigator could only inform on the study conduct and results to the sponsor, ethics committee, and regulatory authorities.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 March 2015
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	Poland: 30
Country: Number of subjects enrolled	Spain: 20
Country: Number of subjects enrolled	Czech Republic: 5
Country: Number of subjects enrolled	Hungary: 15
Worldwide total number of subjects	70
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)	0
Adolescents (12-17 years)	22
Adults (18-64 years)	48
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients were recruited at 16 sites: 2 in the Czech Republic, 3 in Hungary, 5 in Poland, and 6 in Spain from 05 March 2015 to 03 June 2015.

Pre-assignment

Screening details:

Patients 12 years of age or older with confirmed diagnosis of PEI and cystic fibrosis (CF) whose PEI was controlled under treatment with a commercially available pancreatic enzyme replacement therapy and with a human fecal elastase <100µg/g stool at screening.

Period 1

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

Blinding implementation details:

Blinded and packaged study drug was provided to the clinical site and administered in a double-blind manner. Study drug for all study arms had identical appearance (same number of capsules, appearance, shapes, smells, and tastes) and were packaged to maintain proper dosage proportions. If emergency unblinding occurred, IWRS was to be used.

Arms

Are arms mutually exclusive?	Yes
Arm title	Creon IR 300

Arm description:

Creon IR low dose, 300 Ph. Eur. U lipase/g fat, proportionally administered five times daily (during 3 meals and 2 snacks) for 6 to 7 days (target total daily dose of 30,000 lipase units)

Arm type	Experimental
Investigational medicinal product name	Pancreatin
Investigational medicinal product code	Creon IR 300
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

The study drug capsules were swallowed intact (capsules were not to be crushed, chewed, or opened), and were taken at the start of a meal or taken with a snack; sufficient fluids were taken at administration. Treatment was administered to each subject by the clinical site personnel.

Arm title	Creon IR 1,200
------------------	----------------

Arm description:

Creon IR medium dose, 1,200 Ph. Eur. U lipase/g fat, proportionally administered five times daily (during 3 meals and 2 snacks) for 6 to 7 days (target total daily dose of 120,000 lipase units).

Arm type	Experimental
Investigational medicinal product name	Pancreatin
Investigational medicinal product code	Creon IR 1,200
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

The study drug capsules were swallowed intact (capsules were not to be crushed, chewed, or opened), and were taken at the start of a meal or taken with a snack; sufficient fluids were taken at administration. Treatment was administered to each subject by the clinical site personnel.

Arm title	Creon IR 2,400
Arm description: Creon IR high dose, 2,400 Ph. Eur. U lipase/g fat, proportionally administered five times daily (during 3 meals and 2 snacks) for 6 to 7 days (target total daily dose of 240,000 lipase units)	
Arm type	Experimental
Investigational medicinal product name	Pancreatin
Investigational medicinal product code	Creon IR 2,400
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

The study drug capsules were swallowed intact (capsules were not to be crushed, chewed, or opened), and were taken at the start of a meal or taken with a snack; sufficient fluids were taken at administration. Treatment was administered to each subject by the clinical site personnel.

Arm title	Creon IR 4,000
Arm description: Creon IR maximum dose, 4,000 Ph. Eur. U lipase/g fat, proportionally administered five times daily (during 3 meals and 2 snacks) for 6 to 7 days (target total daily dose of 400,000 lipase units)	
Arm type	Experimental
Investigational medicinal product name	Pancreatin
Investigational medicinal product code	Creon IR 4,000
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

The study drug capsules were swallowed intact (capsules were not to be crushed, chewed, or opened), and were taken at the start of a meal or taken with a snack; sufficient fluids were taken at administration. Treatment was administered to each subject by the clinical site personnel.

Arm title	Creon (DR/GR)
Arm description: Creon® 25,000 (DR/GR), 4,000 Ph. Eur. U lipase/g fat, proportionally administered five times daily (during 3 meals and 2 snacks) for 6 to 7 days (target total daily dose of 400,000 lipase units)	
Arm type	Active comparator
Investigational medicinal product name	Pancreatin
Investigational medicinal product code	Creon (DR/GR)
Other name	Creon 25,000 DR/GR
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

The study drug capsules were swallowed intact (capsules were not to be crushed, chewed, or opened), and were taken at the start of a meal or taken with a snack; sufficient fluids were taken at administration. Treatment was administered to each subject by the clinical site personnel.

Number of subjects in period 1	Creon IR 300	Creon IR 1,200	Creon IR 2,400
Started	14	14	14
Completed	14	13	14
Not completed	0	1	0
Adverse event, non-fatal	-	1	-
Protocol deviation	-	-	-

Number of subjects in period 1	Creon IR 4,000	Creon (DR/GR)
Started	14	14
Completed	13	14
Not completed	1	0
Adverse event, non-fatal	-	-
Protocol deviation	1	-

Baseline characteristics

Reporting groups

Reporting group title	Creon IR 300
Reporting group description: Creon IR low dose, 300 Ph. Eur. U lipase/g fat, proportionally administered five times daily (during 3 meals and 2 snacks) for 6 to 7 days (target total daily dose of 30,000 lipase units)	
Reporting group title	Creon IR 1,200
Reporting group description: Creon IR medium dose, 1,200 Ph. Eur. U lipase/g fat, proportionally administered five times daily (during 3 meals and 2 snacks) for 6 to 7 days (target total daily dose of 120,000 lipase units).	
Reporting group title	Creon IR 2,400
Reporting group description: Creon IR high dose, 2,400 Ph. Eur. U lipase/g fat, proportionally administered five times daily (during 3 meals and 2 snacks) for 6 to 7 days (target total daily dose of 240,000 lipase units)	
Reporting group title	Creon IR 4,000
Reporting group description: Creon IR maximum dose, 4,000 Ph. Eur. U lipase/g fat, proportionally administered five times daily (during 3 meals and 2 snacks) for 6 to 7 days (target total daily dose of 400,000 lipase units)	
Reporting group title	Creon (DR/GR)
Reporting group description: Creon® 25,000 (DR/GR), 4,000 Ph. Eur. U lipase/g fat, proportionally administered five times daily (during 3 meals and 2 snacks) for 6 to 7 days (target total daily dose of 400,000 lipase units)	

Reporting group values	Creon IR 300	Creon IR 1,200	Creon IR 2,400
Number of subjects	14	14	14
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			
Age continuous Units: years			
arithmetic mean	24.7	22.9	22
standard deviation	± 7.6	± 8.5	± 7.3
Gender categorical Units: Subjects			
Female	6	9	7
Male	8	5	7
Race Units: Subjects			
Asian	0	0	0
Black	0	0	0

White	14	14	14
Other	0	0	0
Country			
Number of patients of each treatment group in each country.			
Units: Subjects			
Czech Republic	1	1	1
Hungary	3	3	3
Poland	6	6	6
Spain	4	4	4
Height			
Height of each subject.			
Units: meters			
arithmetic mean	1.675	1.626	1.646
standard deviation	± 0.108	± 0.12	± 0.128
Weight			
Units: kilograms			
arithmetic mean	58.48	54.11	59.44
standard deviation	± 9.53	± 10.27	± 11.82
BMI			
Body mass index of each patient, calculated as weight (kg) / body surface area (m ²).			
Units: kg/m ²			
arithmetic mean	20.79	20.29	21.73
standard deviation	± 2.42	± 2.06	± 2.43
Sitting Systolic Blood Pressure			
Units: mmHg			
arithmetic mean	116.4	112.3	118.8
standard deviation	± 12.2	± 14.4	± 14.9
Sitting Diastolic Blood Pressure			
Units: mmHg			
arithmetic mean	69.6	70.9	72
standard deviation	± 8.9	± 8.8	± 10.1
Sitting Pulse			
Units: Beats per minute (bpm)			
arithmetic mean	78.4	83.7	75.9
standard deviation	± 13.2	± 10.8	± 19.2

Reporting group values	Creon IR 4,000	Creon (DR/GR)	Total
Number of subjects	14	14	70
Age categorical			
Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			0
Newborns (0-27 days)			0
Infants and toddlers (28 days-23 months)			0
Children (2-11 years)			0
Adolescents (12-17 years)			0
Adults (18-64 years)			0
From 65-84 years			0
85 years and over			0

Age continuous Units: years arithmetic mean standard deviation	19.7 ± 8.4	22.6 ± 7.1	-
Gender categorical Units: Subjects			
Female	5	6	33
Male	9	8	37
Race Units: Subjects			
Asian	0	0	0
Black	0	0	0
White	14	14	70
Other	0	0	0
Country			
Number of patients of each treatment group in each country.			
Units: Subjects			
Czech Republic	1	1	5
Hungary	3	3	15
Poland	6	6	30
Spain	4	4	20
Height Units: meters arithmetic mean standard deviation	1.666 ± 0.12	1.671 ± 0.067	-
Weight Units: kilograms arithmetic mean standard deviation	57.31 ± 13.4	55.98 ± 8.31	-
BMI Units: kg/m ² arithmetic mean standard deviation	20.38 ± 2.59	19.96 ± 1.97	-
Sitting Systolic Blood Pressure Units: mmHg arithmetic mean standard deviation	115.7 ± 13.4	112 ± 14.3	-
Sitting Diastolic Blood Pressure Units: mmHg arithmetic mean standard deviation	71.1 ± 6.9	68.4 ± 7.5	-
Sitting Pulse Units: Beats per minute (bpm) arithmetic mean standard deviation	81.9 ± 11.2	76.4 ± 10.7	-

End points

End points reporting groups

Reporting group title	Creon IR 300
Reporting group description: Creon IR low dose, 300 Ph. Eur. U lipase/g fat, proportionally administered five times daily (during 3 meals and 2 snacks) for 6 to 7 days (target total daily dose of 30,000 lipase units)	
Reporting group title	Creon IR 1,200
Reporting group description: Creon IR medium dose, 1,200 Ph. Eur. U lipase/g fat, proportionally administered five times daily (during 3 meals and 2 snacks) for 6 to 7 days (target total daily dose of 120,000 lipase units).	
Reporting group title	Creon IR 2,400
Reporting group description: Creon IR high dose, 2,400 Ph. Eur. U lipase/g fat, proportionally administered five times daily (during 3 meals and 2 snacks) for 6 to 7 days (target total daily dose of 240,000 lipase units)	
Reporting group title	Creon IR 4,000
Reporting group description: Creon IR maximum dose, 4,000 Ph. Eur. U lipase/g fat, proportionally administered five times daily (during 3 meals and 2 snacks) for 6 to 7 days (target total daily dose of 400,000 lipase units)	
Reporting group title	Creon (DR/GR)
Reporting group description: Creon® 25,000 (DR/GR), 4,000 Ph. Eur. U lipase/g fat, proportionally administered five times daily (during 3 meals and 2 snacks) for 6 to 7 days (target total daily dose of 400,000 lipase units)	

Primary: Coefficient of Fat Absorption (CFA)

End point title	Coefficient of Fat Absorption (CFA)
End point description:	
End point type	Primary
End point timeframe: 7 days	

End point values	Creon IR 300	Creon IR 1,200	Creon IR 2,400	Creon IR 4,000
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	13	13	14	13
Units: Percentage				
arithmetic mean (confidence interval 95%)	71.5 (64.7 to 78.4)	71.7 (64.8 to 78.5)	72.5 (65.9 to 79.1)	76.5 (69.7 to 83.3)

End point values	Creon (DR/GR)			
Subject group type	Reporting group			
Number of subjects analysed	13			
Units: Percentage				
arithmetic mean (confidence interval	92.8 (86 to			

95%)	99.6)
------	-------

Statistical analyses

Statistical analysis title	Pairwise differences
Statistical analysis description: The model included country and treatment as fixed effects	
Comparison groups	Creon IR 300 v Creon IR 1,200 v Creon IR 2,400 v Creon IR 4,000 v Creon (DR/GR)
Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	other ^[1]
P-value	< 0.05
Method	ANOVA
Parameter estimate	Least Squares Mean (LSM)

Notes:

[1] - No formal statistical analysis provided for the CFA, only pairwise differences derived between the treatment groups

Secondary: Coefficient of Nitrogen Absorption (CNA)

End point title	Coefficient of Nitrogen Absorption (CNA)
End point description:	
End point type	Secondary
End point timeframe:	
7 days	

End point values	Creon IR 300	Creon IR 1,200	Creon IR 2,400	Creon IR 4,000
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	13	13	14	13
Units: Percentage				
arithmetic mean (confidence interval 95%)	71.6 (67.2 to 75.9)	73.9 (69.5 to 78.2)	76.7 (72.5 to 80.9)	80.5 (76.2 to 84.8)

End point values	Creon (DR/GR)			
Subject group type	Reporting group			
Number of subjects analysed	13			
Units: Percentage				
arithmetic mean (confidence interval 95%)	85.4 (81.1 to 89.7)			

Statistical analyses

Statistical analysis title	Pairwise differences
Statistical analysis description: The model included country and treatment as fixed effects	
Comparison groups	Creon IR 300 v Creon IR 1,200 v Creon IR 2,400 v Creon IR 4,000 v Creon (DR/GR)
Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.05
Method	ANOVA
Parameter estimate	Least Squares Mean (LSM)

Secondary: Total Fat Excretion (Stool Fat)

End point title	Total Fat Excretion (Stool Fat)
End point description:	
End point type	Secondary
End point timeframe:	
72 hours	

End point values	Creon IR 300	Creon IR 1,200	Creon IR 2,400	Creon IR 4,000
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	13	13	14	13
Units: gram/72 hours				
arithmetic mean (standard deviation)	301.8 (± 4.43)	299.7 (± 5.23)	300 (± 6.41)	303 (± 5.18)

End point values	Creon (DR/GR)			
Subject group type	Reporting group			
Number of subjects analysed	13			
Units: gram/72 hours				
arithmetic mean (standard deviation)	302.9 (± 3.13)			

Statistical analyses

No statistical analyses for this end point

Secondary: Total Fat Excretion

End point title	Total Fat Excretion
-----------------	---------------------

End point description:

End point type	Secondary
----------------	-----------

End point timeframe:

72 hours

End point values	Creon IR 300	Creon IR 1,200	Creon IR 2,400	Creon IR 4,000
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	13	13	14	13
Units: grams / 72 hours				
arithmetic mean (standard deviation)	87.5 (± 37.5)	87.1 (± 40.95)	84.1 (± 44.86)	73 (± 28.2)

End point values	Creon (DR/GR)			
Subject group type	Reporting group			
Number of subjects analysed	13			
Units: grams / 72 hours				
arithmetic mean (standard deviation)	23.5 (± 11.27)			

Statistical analyses

No statistical analyses for this end point

Secondary: Total Nitrogen Intake

End point title	Total Nitrogen Intake
-----------------	-----------------------

End point description:

End point type	Secondary
----------------	-----------

End point timeframe:

72 hours

End point values	Creon IR 300	Creon IR 1,200	Creon IR 2,400	Creon IR 4,000
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	13	13	14	13
Units: grams / 72 hours				
arithmetic mean (standard deviation)	36.4 (± 5.3)	35.1 (± 5.76)	37.3 (± 5)	36 (± 4.93)

End point values	Creon (DR/GR)			
Subject group type	Reporting group			
Number of subjects analysed	13			
Units: grams / 72 hours				
arithmetic mean (standard deviation)	36.3 (± 5.86)			

Statistical analyses

No statistical analyses for this end point

Secondary: Total Nitrogen Excretion

End point title	Total Nitrogen Excretion
End point description:	
End point type	Secondary
End point timeframe:	
72 hours	

End point values	Creon IR 300	Creon IR 1,200	Creon IR 2,400	Creon IR 4,000
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	13	13	14	13
Units: grams / 72 hours				
arithmetic mean (standard deviation)	10.47 (± 3.884)	9.21 (± 1.886)	8.81 (± 3.062)	7.26 (± 2.951)

End point values	Creon (DR/GR)			
Subject group type	Reporting group			
Number of subjects analysed	13			
Units: grams / 72 hours				
arithmetic mean (standard deviation)	5.56 (± 1.97)			

Statistical analyses

No statistical analyses for this end point

Secondary: Total Stool Weight

End point title	Total Stool Weight
-----------------	--------------------

End point description:

End point type	Secondary
----------------	-----------

End point timeframe:

Dye marker period (48 hours)

End point values	Creon IR 300	Creon IR 1,200	Creon IR 2,400	Creon IR 4,000
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	13	13	14	13
Units: grams				
arithmetic mean (standard deviation)	889 (± 294.2)	905.3 (± 225.7)	793.8 (± 279.8)	755.7 (± 383.2)

End point values	Creon (DR/GR)			
Subject group type	Reporting group			
Number of subjects analysed	13			
Units: grams				
arithmetic mean (standard deviation)	545.7 (± 256.3)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

14 days including a 7 day safety follow up.

Adverse event reporting additional description:

AEs were reported per-subject, counting events in subjects rather than separate events. If a subject suffered the same AE(s) repeatedly, events were counted only once for any given period. Repeated events per subject were classified the worst severity, according to the closest relationship to the study drug and the earliest starting date.

Assessment type	Systematic
-----------------	------------

Dictionary used

Dictionary name	MedDRA
-----------------	--------

Dictionary version	18.0
--------------------	------

Reporting groups

Reporting group title	Creon IR 300
-----------------------	--------------

Reporting group description:

Creon IR low dose, 300 Ph. Eur. U lipase/g fat, proportionally administered five times daily (during 3 meals and 2 snacks) for 6 to 7 days (target total daily dose of 30,000 lipase units)

Reporting group title	Creon IR 1,200
-----------------------	----------------

Reporting group description:

Creon IR medium dose, 1,200 Ph. Eur. U lipase/g fat, proportionally administered five times daily (during 3 meals and 2 snacks) for 6 to 7 days (target total daily dose of 120,000 lipase units).

Reporting group title	Creon IR 2,400
-----------------------	----------------

Reporting group description:

Creon IR high dose, 2,400 Ph. Eur. U lipase/g fat, proportionally administered five times daily (during 3 meals and 2 snacks) for 6 to 7 days (target total daily dose of 240,000 lipase units)

Reporting group title	Creon IR 4,000
-----------------------	----------------

Reporting group description:

Creon IR maximum dose, 4,000 Ph. Eur. U lipase/g fat, proportionally administered five times daily (during 3 meals and 2 snacks) for 6 to 7 days (target total daily dose of 400,000 lipase units)

Reporting group title	Creon (DR/GR)
-----------------------	---------------

Reporting group description:

Creon® 25,000 (DR/GR), 4,000 Ph. Eur. U lipase/g fat, proportionally administered five times daily (during 3 meals and 2 snacks) for 6 to 7 days (target total daily dose of 400,000 lipase units)

Serious adverse events	Creon IR 300	Creon IR 1,200	Creon IR 2,400
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	1 / 14 (7.14%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Infections and infestations			
Infective pulmonary exacerbation of cystic fibrosis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Creon IR 4,000	Creon (DR/GR)	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Infections and infestations			
Infective pulmonary exacerbation of cystic fibrosis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	
occurrences causally related to treatment / all	0 / 0	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	Creon IR 300	Creon IR 1,200	Creon IR 2,400
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 14 (71.43%)	9 / 14 (64.29%)	7 / 14 (50.00%)
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 14 (7.14%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 14 (7.14%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 14 (7.14%)	0 / 14 (0.00%)	1 / 14 (7.14%)
occurrences (all)	1	0	1
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 14 (0.00%)	1 / 14 (7.14%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	6 / 14 (42.86%)	8 / 14 (57.14%)	6 / 14 (42.86%)
occurrences (all)	6	8	6
Flatulence			

subjects affected / exposed	2 / 14 (14.29%)	2 / 14 (14.29%)	6 / 14 (42.86%)
occurrences (all)	2	2	6
Abdominal distension			
subjects affected / exposed	3 / 14 (21.43%)	3 / 14 (21.43%)	0 / 14 (0.00%)
occurrences (all)	3	3	0
Diarrhoea			
subjects affected / exposed	4 / 14 (28.57%)	4 / 14 (28.57%)	2 / 14 (14.29%)
occurrences (all)	4	4	2
Faeces soft			
subjects affected / exposed	2 / 14 (14.29%)	1 / 14 (7.14%)	1 / 14 (7.14%)
occurrences (all)	2	1	1
Toothache			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Steatorrhoea			
subjects affected / exposed	1 / 14 (7.14%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Constipation			
subjects affected / exposed	0 / 14 (0.00%)	1 / 14 (7.14%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 14 (0.00%)	1 / 14 (7.14%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
Haemoptysis			
subjects affected / exposed	1 / 14 (7.14%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Epistaxis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Musculoskeletal chest pain			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			

Upper respiratory tract infection subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1	0 / 14 (0.00%) 0	0 / 14 (0.00%) 0
Metabolism and nutrition disorders Hyperglycaemia subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1	0 / 14 (0.00%) 0	0 / 14 (0.00%) 0

Non-serious adverse events	Creon IR 4,000	Creon (DR/GR)	
Total subjects affected by non-serious adverse events subjects affected / exposed	9 / 14 (64.29%)	7 / 14 (50.00%)	
Investigations Alanine aminotransferase increased subjects affected / exposed occurrences (all) Aspartate aminotransferase increased subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0 0 / 14 (0.00%) 0	0 / 14 (0.00%) 0 0 / 14 (0.00%) 0	
Nervous system disorders Headache subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1	0 / 14 (0.00%) 0	
General disorders and administration site conditions Pyrexia subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	0 / 14 (0.00%) 0	
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all) Flatulence subjects affected / exposed occurrences (all) Abdominal distension subjects affected / exposed occurrences (all) Diarrhoea	4 / 14 (28.57%) 4 3 / 14 (21.43%) 3 2 / 14 (14.29%) 2	2 / 14 (14.29%) 2 2 / 14 (14.29%) 2 1 / 14 (7.14%) 1	

subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1	1 / 14 (7.14%) 1	
Faeces soft subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1	2 / 14 (14.29%) 2	
Toothache subjects affected / exposed occurrences (all)	2 / 14 (14.29%) 2	0 / 14 (0.00%) 0	
Steatorrhoea subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1	0 / 14 (0.00%) 0	
Constipation subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	0 / 14 (0.00%) 0	
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	1 / 14 (7.14%) 1	
Haemoptysis subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	0 / 14 (0.00%) 0	
Epistaxis subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1	0 / 14 (0.00%) 0	
Musculoskeletal and connective tissue disorders Musculoskeletal chest pain subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	1 / 14 (7.14%) 1	
Infections and infestations Upper respiratory tract infection subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	0 / 14 (0.00%) 0	
Metabolism and nutrition disorders Hyperglycaemia subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	0 / 14 (0.00%) 0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 March 2015	Protocol Amendment 1 became effective on 03 MAR 2015, prior to inclusion of the first subject into the study, and introduced several clarifications regarding study schedule and stool collection, physical examination, body weight measurement, and diary data. Protein range intake was adapted from 50-60 g to 50-90 g since this was considered more appropriate for adult subjects. Several concomitant medication criteria were changed: Steroids, as well as prebiotic or probiotic drugs, were allowed; however, such drugs should have been taken by the subject for more than 4 weeks before start of the study at the prescribed dose, and the dose should not have been changed during the course of the study. Fat- or protein-containing nutritional supplements were prohibited because the determination of the coefficient of fat absorption and the coefficient of nitrogen absorption must be based on diet and not on content of nutritional supplements. Additionally, the amendment prohibited subjects from being treated with intravenous antibiotics during the study because of possible effects on gastrointestinal motility. Since Protocol Amendment 1 became effective prior to first subject first visit, no impact on the study was expected to occur.
24 April 2015	Protocol Amendment 2 became effective on 24 APR 2015 and allowed a prolonged screening period of an extra 14 days inclusive, introduced the possibility of re-screening, and clarified that the daily fat intake could be 100 to 105 g to account for an acceptable variation in meals of 5 g of dietary fat. No impact on the study results was expected to occur by adoption of Protocol Amendment 2.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

None reported.

Notes: