Clinical trial results:
A Double-blind, Randomized, Multicenter, Cross-over Study to Compare the Effect of Creon N and Creon® on Fat Digestion in Subjects 12 years of Age with Pancreatic Exocrine Insufficiency Due to Cystic Fibrosis

Summary

EudraCT number	2013-002819-10
Trial protocol	HU ES
Global end of trial date	25 August 2014

Results information

Result version number	v1 (current)
This version publication date	02 March 2016
First version publication date	02 March 2016
Summary attachment (see zip file)	Synopsis of the CSR (M13-621--synopsis-SOLID 1000594907.pdf)

Trial information

Trial identification

Sponsor protocol code	M13-621

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Abbott Laboratories GmbH
Sponsor organisation address	Freundallee 9A, Hannover, Germany, 30173
Public contact	Senior Clinical Trial Manager, Abbott Laboratories GmbH, +49 511 6750 2733, gregor.eibes@abbott.com
Scientific contact	Senior Clinical Trial Manager, Abbott Laboratories GmbH, +49 511 6750 2733, gregor.eibes@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	23 January 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	25 August 2014
Global end of trial reached?	Yes
Global end of trial date	25 August 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the therapeutic equivalence of Creon N 25000 with Creon® 25000 on coefficient of fat absorption (CFA) in adolescent and adult subjects with pancreatic exocrine insufficiency (PEI) due to cystic fibrosis (CF).

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, EC, and regulatory authorities.

Background therapy:

None

Evidence for comparator:

Creon capsules contain pancreatin which is released in the stomach. The particles mix with the chyme in the stomach and do not dissolve due to the pH-resistant enteric coating. Upon entering the duodenum the coating dissolves to release the enzymes for food digestion, dependent on the pH of the duodenum. The pH-sensitive enteric-coated minimicrospheres have been developed to improve the delivery of active enzymes to the small intestine.

Actual start date of recruitment	02 December 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	Spain: 15
Country: Number of subjects enrolled	Hungary: 26
Worldwide total number of subjects	41
EEA total number of subjects	41

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)	12
Adults (18-64 years)	29
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients were recruited in 8 sites in Spain (4 sites) and Hungary (4 sites) from 31 January to 14 July 2014

Pre-assignment

Screening details:

Patients had to have a diagnosis of cystic fibrosis confirmed by two positive chloride sweat tests or gene analysis and a diagnosis of pancreatic exocrine insufficience proven by coefficient of fat absorption < 70% without supplementation or human fecal elastase <50 mcg/g stool

Pre-assignment period milestones

Number of subjects started	41
Number of subjects completed	41

Period 1

Period 1 title	Baseline period (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 medication was provided to the investigational site and dispensed to the subjects. All the capsules were identical in appearance, shape, smell and taste, and packaged in the proper proportion to assure desired dosages and maintenance of the blinding

Arms

Are arms mutually exclusive?	Yes
Arm title	Creon N - Creon R

Arm description:

Creon N during the first cross-over period followed by Creon R during the second cross-over period

Arm type	Experimental
Investigational medicinal product name	Creon N
Investigational medicinal product code	Creon N 25000
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Creon N 2500 was administered during the course of the meals and snacks. The capsules should be swallowed intact, without crushing or chewing, with enough fluid during or after each meal or snack. In-between the two-treatment periods, there was a wash-out period of 3 to 14 days where the subjects were treated with their usual pancreatic enzyme supplementation in the usual dose.

Arm title	Creon R - Creon N

Arm description:

Creon R during the first cross-over period followed by Creon N

Arm type	Active comparator

Investigational medicinal product name	Creon R
Investigational medicinal product code	Creon R 25000
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Creon R was taken during the course of the meals and snacks. The capsules were swallowed intact, without crushing or chewing, with enough fluid during or after each meal or snack. In-between the two-treatment periods, there was a wash-out period of 3 to 14 days where the subjects were treated with their usual pancreatic enzyme supplementation in the usual dose

Number of subjects in period 1	Creon N - Creon R	Creon R - Creon N
Started	20	21
Completed	18	21
Not completed	2	0
Consent withdrawn by subject	2	-

Baseline characteristics

Reporting groups	
Reporting group title	Creon N - Creon R
Reporting group description:	
Creon N during the first cross-over period followed by Creon R during the second cross-over period	
Reporting group title	Creon R - Creon N
Reporting group description:	
Creon R during the first cross-over period followed by Creon N	

Reporting group values	Creon N - Creon R	Creon R - Creon N	Total
Number of subjects	20	21	41
Age categorical			
Units: Subjects			
Adolescents (12-17 years)	8	4	12
Adults (18-64 years)	12	17	29
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous			
Units: years			
arithmetic mean	21	25.9	
standard deviation	± 6.6	± 8.6	-
Gender categorical			
Units: Subjects			
Female	14	13	27
Male	6	8	14
Race			
Units: Subjects			
Asian	0	0	0
Black	0	0	0
White	20	21	41
Height			
Units: metres			
arithmetic mean	1.624	1.665	
standard deviation	± 0.101	± 0.129	-
Weight			
Units: Kilograms			
arithmetic mean	51.68	56.8	
standard deviation	± 9.59	± 14.98	-
Body mass index			
Units: Kg/m2			
arithmetic mean	19.46	20.2	

standard deviation	± 2.43	± 3.61	-
Sitting Systolic Blood Pressure Units: mmHg			
arithmetic mean	113.9	114	
standard deviation	± 10.93	± 10.84	-
Sitting Diastolic Blood Pressure Units: mmHg			
arithmetic mean	70.4	71.38	
standard deviation	± 7.29	± 6.14	-
Sitting pulse Units: beats per minute			
arithmetic mean	78.55	81.14	
standard deviation	± 10.17	± 9.32	-

End points

End points reporting groups

Reporting group title	Creon N - Creon R
Reporting group description:	
Creon N during the first cross-over period followed by Creon R during the second cross-over period	
Reporting group title	Creon R - Creon N
Reporting group description:	
Creon R during the first cross-over period followed by Creon N	

Primary: Equivalence of Creon N and Creon R

End point title	Equivalence of Creon N and Creon R
End point description:	
The primary objective was to show that Creon N and Creon R were equivalent with regard to the coefficient of fat absorption (CFA). To prove equivalence, the 95% confidence interval for the treatment difference had to lie entirely within the equivalence range (-8%, 8%)	
End point type	Primary
End point timeframe:	
Full cross-over period	

End point values	Creon N - Creon R	Creon R - Creon N		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	21		
Units: Percentage				
least squares mean (standard error)	89.1 (± 1.26)	87.8 (± 1.26)		

Statistical analyses

Statistical analysis title	ANOVA
Statistical analysis description:	
The model included sequence, period and treatment as fixed effects and subject within sequence as random effect	
Comparison groups	Creon N - Creon R v Creon R - Creon N
Number of subjects included in analysis	41
Analysis specification	Pre-specified
Analysis type	equivalence[1]
P-value	< 0.05
Method	ANCOVA

Notes:

[1] - The primary objective was to show that Creon N and Creon R were requivalent with regard to the CFA

Secondary: Coefficient of Nitrogen Absorption

End point title	Coefficient of Nitrogen Absorption

End point description:

The coefficient of nitrogen absorption was analyzed in the same way as the coefficient of fat absorption (primary variable)

End point type	Secondary

End point timeframe:

The full cross-over period

End point values	Creon N - Creon R	Creon R - Creon N		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	21		
Units: Percentage				
least squares mean (standard error)	87.5 (± 0.84)	87.6 (± 0.84)		

Statistical analyses

Statistical analysis title	ANOVA

Statistical analysis description:

The model included sequence, period and treatment as fixed effects and subject within sequence as random effect

Comparison groups	Creon N - Creon R v Creon R - Creon N
Number of subjects included in analysis	41
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.05
Method	ANCOVA

Secondary: Clinical symptomatology (number of stools)

End point title	Clinical symptomatology (number of stools)

End point description:

End point type	Secondary

End point timeframe:

The full cross-over periods

End point values	Creon N - Creon R	Creon R - Creon N		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	21		
Units: number of stools				
arithmetic mean (standard deviation)	1.49 (± 0.547)	1.57 (± 0.576)		

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical symptomatology (stool consistency)

End point title	Clinical symptomatology (stool consistency)

End point description:

End point type	Secondary

End point timeframe:

The full cross-over periods

End point values	Creon N - Creon R	Creon R - Creon N		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	21		
Units: percentage				
arithmetic mean (standard deviation)				
hard	14.1 (± 23.9)	11.8 (± 17.78)		
formed/normal	73.6 (± 29.5)	79.8 (± 21.21)		
soft	12.4 (± 22.47)	7.9 (± 15.1)		
watery	0 (± 0)	0.5 (± 3.24)		

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical symptomatology (abdominal pain)

End point title	Clinical symptomatology (abdominal pain)

End point description:

End point type	Secondary

End point timeframe:

The full cross-over periods

End point values	Creon N - Creon R	Creon R - Creon N		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	21		
Units: percentage of days				
arithmetic mean (standard deviation)				
None	89.3 (± 19.67)	86.8 (± 22.91)		
Mild	8 (± 12.06)	11.1 (± 18.42)		
Moderate	2.6 (± 13.29)	2.1 (± 7.77)		
Severe	0 (± 0)	0 (± 0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical symptomatology (flatulence)

End point title	Clinical symptomatology (flatulence)

End point description:

End point type	Secondary

End point timeframe:

The fulll cross-over periods

End point values	Creon N - Creon R	Creon R - Creon N		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	21		
Units: percentage of days				
arithmetic mean (standard deviation)				
None	57.5 (± 43.31)	51.6 (± 46.65)		
Mild	33.9 (± 38.45)	43.2 (± 42.24)		
Moderate	8.6 (± 24.07)	5.3 (± 11.09)		
Severe	0 (± 0)	0 (± 0)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Clinical Global Impression of Disease Symptoms

End point title	Clinical Global Impression of Disease Symptoms

End point description:

End point type	Other pre-specified

End point timeframe:
The full cross-over periods

End point values	Creon N - Creon R	Creon R - Creon N		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	21		
Units: number				
number (not applicable)				
None (Symptoms not present)	11	11		
Mild (symptoms present but not bothersome)	21	20		
Moderate (symptoms bothersome)	6	7		
Severe (symptoms interfere with normal activities)	0	0		
Incapacitating	0	0		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Total fat intake, total nitrogen excretion, total nitrogen intake

End point title	Total fat intake, total nitrogen excretion, total nitrogen intake

End point description:

End point type	Other pre-specified

End point timeframe:
The full cross-over periods

End point values	Creon N - Creon R	Creon R - Creon N		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	21		
Units: grams				
arithmetic mean (standard deviation)				
total fat intake (g)	415.5 (± 124.61)	403.7 (± 117.61)		
total fat excretion (g/72h)	42.3 (± 27.05)	48.1 (± 43.28)		
Total nitrogen intake (g)	58 (± 13.2)	57.3 (± 12.85)		
Total nitrogen excretion (g/72h)	7.08 (± 3.088)	7.05 (± 3.633)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Total stool weight

End point title	Total stool weight

End point description:

End point type	Other pre-specified

End point timeframe:

The full cross-over periods

End point values	Creon N - Creon R	Creon R - Creon N		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	21		
Units: grams				
arithmetic mean (standard deviation)	552.8 (± 281.41)	555.4 (± 341.59)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Treatment-emergent adverse events that started during a unique treatment or that already existed before the start of that unique treatment but worsened during the treatment, including any subsequent wash-out or post-treatment period	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups	
Reporting group title	Creon N
Reporting group description:	
Subjects treated with Creon N	
Reporting group title	Creon R
Reporting group description:	
Subjects treated with Creon R	

Serious adverse events	Creon N	Creon R	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 41 (0.00%)	0 / 39 (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: 2 %

Non-serious adverse events	Creon N	Creon R	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	9 / 41 (21.95%)	9 / 39 (23.08%)	
Investigations			
gastric pH decreased			
subjects affected / exposed	1 / 41 (2.44%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
Injury, poisoning and procedural complications			
arthropod bite			
subjects affected / exposed	0 / 41 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
Nervous system disorders			

headache			
subjects affected / exposed	0 / 41 (0.00%)	2 / 39 (5.13%)	
occurrences (all)	0	2	
Gastrointestinal disorders			
Flatulence			
subjects affected / exposed	0 / 41 (0.00%)	3 / 39 (7.69%)	
occurrences (all)	0	3	
abdominal pain upper			
subjects affected / exposed	1 / 41 (2.44%)	1 / 39 (2.56%)	
occurrences (all)	1	1	
abdominal pain			
subjects affected / exposed	0 / 41 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
abdominal pain lower			
subjects affected / exposed	1 / 41 (2.44%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
constipation			
subjects affected / exposed	1 / 41 (2.44%)	1 / 39 (2.56%)	
occurrences (all)	1	1	
diarrhoea			
subjects affected / exposed	1 / 41 (2.44%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal hypermotility			
subjects affected / exposed	0 / 41 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
Steatorrhoea			
subjects affected / exposed	0 / 41 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
Reproductive system and breast disorders			
Dysmenorrhoea			
subjects affected / exposed	1 / 41 (2.44%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
cough			
subjects affected / exposed	1 / 41 (2.44%)	0 / 39 (0.00%)	
occurrences (all)	1	0	

Infections and infestations viral rhinitis subjects affected / exposed occurrences (all)	 0 / 41 (0.00%) 0	 1 / 39 (2.56%) 1	
Metabolism and nutrition disorders decreased appetite subjects affected / exposed occurrences (all) Hypoglycaemia subjects affected / exposed occurrences (all)	 1 / 41 (2.44%) 1 1 / 41 (2.44%) 1	 0 / 39 (0.00%) 0 0 / 39 (0.00%) 0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 April 2014	Change in the specified food subjects receive (2 snacks instead of 3) Addition of vital signs and clinical global impression at day 1 of second cross-over period (Visit 4) Addition of a GI diary at Day 6 or 7 only in case blue dye is passed on Day 6 Change in the reporting serious adverse events that would be done by email instead of fax

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported