Clinical trial results:
A randomised, double blind, active-controlled, two-treatment, crossover multinational, multicentre trial to compare two pancreatic enzyme products in the treatment of exocrine pancreatic insufficiency in subjects with cystic fibrosis

Summary

EudraCT number	2009-012842-21
Trial protocol	GB DE IT BG BE HU
Global end of trial date	03 January 2014

Results information

Result version number	v1 (current)
This version publication date	06 July 2019
First version publication date	06 July 2019

Trial information

Trial identification

Sponsor protocol code	PR-005

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Allergan plc
Sponsor organisation address	Harborside Financial Center Plaza V, Suite 1900, Jersey City, United States, 07302
Public contact	Steven Shiff, MD, Allergan plc, steven.shiff@allergan.com
Scientific contact	Steven Shiff, MD, Allergan plc, steven.shiff@allergan.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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	03 January 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	03 January 2014
Global end of trial reached?	Yes
Global end of trial date	03 January 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study is to evaluate the safety and efficacy of EUR-1008 as compared to Creon in the treatment of EPI associated with CF in subjects 12 years of age and older, and able to swallow the capsules whole.

Protection of trial subjects:

This study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with good clinical practices and applicable regulatory requirements. Written informed consent and assent from minors (according to national legal requirements) were obtained before initiating study-related assessments or procedures.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	03 September 2012
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	Poland: 32
Country: Number of subjects enrolled	United Kingdom: 3
Country: Number of subjects enrolled	Belgium: 3
Country: Number of subjects enrolled	Bulgaria: 18
Country: Number of subjects enrolled	Germany: 3
Country: Number of subjects enrolled	Hungary: 13
Country: Number of subjects enrolled	Italy: 24
Worldwide total number of subjects	96
EEA total number of subjects	96

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	51
Adults (18-64 years)	45
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 96 subjects aged 12 years or older, with a definite diagnosis of Cystic Fibrosis (CF) were enrolled in the study.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Sequence 1: EUR-1008/Kreon

Arm description:

Subjects received EUR-1008 or Kreon in Treatment Periods 1 and 2, respectively. EUR-1008 and Kreon were administered at a dose as close as possible to their stabilised, existing PEP treatment for 28 days (± 2 days), to a maximum dose of 10,000 lipase units/kg of body weight per day.

Arm type	Experimental
Investigational medicinal product name	EUR-1008
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

EUR-1008 was administered orally, during meals, at a dose as close as possible to the stabilised, existing PEP treatment but not exceeding 10,000 lipase units/kg of body weight per day or 4000 lipase units/g of fat ingested per day.

Investigational medicinal product name	Kreon
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Kreon was administered orally, during meals, at a dose as close as possible to the stabilised, existing PEP treatment but not exceeding 10,000 lipase units/kg of body weight per day or 4000 lipase units/g of fat ingested per day.

Arm title	Sequence 2: Kreon/EUR-1008

Arm description:

Subjects received Kreon or EUR-1008 in Treatment Periods 1 and 2, respectively. Kreon and EUR-1008 were administered at a dose as close as possible to their stabilised, existing PEP treatment for 28 days (± 2 days), to a maximum dose of 10,000 lipase units/kg of body weight per 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:

Kreon was administered orally, during meals, at a dose as close as possible to the stabilised, existing PEP treatment but not exceeding 10,000 lipase units/kg of body weight per day or 4000 lipase units/g of fat ingested per day.

Investigational medicinal product name	EUR-1008
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

EUR-1008 was administered orally, during meals, at a dose as close as possible to the stabilised, existing PEP treatment but not exceeding 10,000 lipase units/kg of body weight per day or 4000 lipase units/g of fat ingested per day.

Number of subjects in period 1	Sequence 1: EUR-1008/Kreon	Sequence 2: Kreon/EUR-1008
Started	48	48
Completed	42	44
Not completed	6	4
Consent withdrawn by subject	2	-
Adverse event, non-fatal	2	1
Protocol deviation	2	3

Baseline characteristics

Reporting groups

Reporting group title	Sequence 1: EUR-1008/Kreon

Reporting group description:

Subjects received EUR-1008 or Kreon in Treatment Periods 1 and 2, respectively. EUR-1008 and Kreon were administered at a dose as close as possible to their stabilised, existing PEP treatment for 28 days (± 2 days), to a maximum dose of 10,000 lipase units/kg of body weight per day.

Reporting group title	Sequence 2: Kreon/EUR-1008

Reporting group description:

Subjects received Kreon or EUR-1008 in Treatment Periods 1 and 2, respectively. Kreon and EUR-1008 were administered at a dose as close as possible to their stabilised, existing PEP treatment for 28 days (± 2 days), to a maximum dose of 10,000 lipase units/kg of body weight per day.

Reporting group values	Sequence 1: EUR-1008/Kreon	Sequence 2: Kreon/EUR-1008	Total
Number of subjects	48	48	96
Age categorical Units: Subjects			
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
Adolescents (12-17 years)	21	30	51
Adults (18-64 years)	27	18	45
From 65-84 years	0	0	0
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	19	19	38
Male	29	29	58

Subject analysis sets

Subject analysis set title	Sequence 1 - ITT
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The Intent-to-Treat (ITT) Population consists of randomised subjects who received at least 1 dose of study drug (EUR-1008 or Kreon).

Subject analysis set title	Sequence 2 - ITT
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The Intent-to-Treat (ITT) Population consists of all randomised subjects who received at least 1 dose of study drug (EUR-1008 or Kreon).

Subject analysis set title	Sequence 1 - Safety Population
Subject analysis set type	Safety analysis

Subject analysis set description:

The Safety Population consists of all randomised subjects who received at least 1 dose of study drug (EUR-1008 or Kreon)

Subject analysis set title	Sequence 2 - Safety Population
Subject analysis set type	Safety analysis

Subject analysis set description:

The Safety Population consists of all randomised subjects who received at least 1 dose of study drug (EUR-1008 or Kreon).

Subject analysis set title	Sequence 1 - Completers Population
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

The Completers Population consists of all subjects from the ITT Population who completed both treatment periods and had non-missing CFA-72h in both periods.

Subject analysis set title	Sequence 2 - Completers Population
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

The Completers Population consists of all subjects from the ITT Population who completed both treatment periods and had non-missing CFA-72h in both periods.

Subject analysis set title	Sequence 1 - PP
Subject analysis set type	Per protocol

Subject analysis set description:

The Per Protocol (PP) Population consists of all subjects from the Completers Population with no significant protocol deviations.

Subject analysis set title	Sequence 2 - PP
Subject analysis set type	Per protocol

Subject analysis set description:

The Per Protocol (PP) Population consists of all subjects from the Completers Population with no significant protocol deviations.

Reporting group values	Sequence 1 - ITT	Sequence 2 - ITT	Sequence 1 - Safety Population
Number of subjects	48	48	48
Age categorical Units: Subjects			
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
Adolescents (12-17 years)	21	30	21
Adults (18-64 years)	27	18	27
From 65-84 years	0	0	0
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female			
Male			

Reporting group values	Sequence 2 - Safety Population	Sequence 1 - Completers Population	Sequence 2 - Completers Population
Number of subjects	48	41	42
Age categorical Units: Subjects			
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)	30	0	0
Adolescents (12-17 years)	18	18	27
Adults (18-64 years)	0	23	15
From 65-84 years	0	0	0
85 years and over	0	0	0
Gender categorical			
Units: Subjects			
Female			
Male			

Reporting group values	Sequence 1 - PP	Sequence 2 - PP	
Number of subjects	35	32	
Age categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	17	21	
Adults (18-64 years)	18	11	
From 65-84 years	0	0	
85 years and over	0	0	
Gender categorical			
Units: Subjects			
Female			
Male			

End points

End points reporting groups

Reporting group title	Sequence 1: EUR-1008/Kreon
Reporting group description:	
Subjects received EUR-1008 or Kreon in Treatment Periods 1 and 2, respectively. EUR-1008 and Kreon were administered at a dose as close as possible to their stabilised, existing PEP treatment for 28 days (± 2 days), to a maximum dose of 10,000 lipase units/kg of body weight per day.	
Reporting group title	Sequence 2: Kreon/EUR-1008
Reporting group description:	
Subjects received Kreon or EUR-1008 in Treatment Periods 1 and 2, respectively. Kreon and EUR-1008 were administered at a dose as close as possible to their stabilised, existing PEP treatment for 28 days (± 2 days), to a maximum dose of 10,000 lipase units/kg of body weight per day.	
Subject analysis set title	Sequence 1 - ITT
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
The Intent-to-Treat (ITT) Population consists of randomised subjects who received at least 1 dose of study drug (EUR-1008 or Kreon).	
Subject analysis set title	Sequence 2 - ITT
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
The Intent-to-Treat (ITT) Population consists of all randomised subjects who received at least 1 dose of study drug (EUR-1008 or Kreon).	
Subject analysis set title	Sequence 1 - Safety Population
Subject analysis set type	Safety analysis
Subject analysis set description:	
The Safety Population consists of all randomised subjects who received at least 1 dose of study drug (EUR-1008 or Kreon)	
Subject analysis set title	Sequence 2 - Safety Population
Subject analysis set type	Safety analysis
Subject analysis set description:	
The Safety Population consists of all randomised subjects who received at least 1 dose of study drug (EUR-1008 or Kreon).	
Subject analysis set title	Sequence 1 - Completers Population
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
The Completers Population consists of all subjects from the ITT Population who completed both treatment periods and had non-missing CFA-72h in both periods.	
Subject analysis set title	Sequence 2 - Completers Population
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
The Completers Population consists of all subjects from the ITT Population who completed both treatment periods and had non-missing CFA-72h in both periods.	
Subject analysis set title	Sequence 1 - PP
Subject analysis set type	Per protocol
Subject analysis set description:	
The Per Protocol (PP) Population consists of all subjects from the Completers Population with no significant protocol deviations.	
Subject analysis set title	Sequence 2 - PP
Subject analysis set type	Per protocol
Subject analysis set description:	
The Per Protocol (PP) Population consists of all subjects from the Completers Population with no significant protocol deviations.	

Primary: Coefficient of fat absorption over 72 hours

End point title	Coefficient of fat absorption over 72 hours

End point description:

The coefficient of fat absorption (CFA) was determined by measurement of fat and protein dietary intake and fat and protein excretion in the stools. CFA-72h was assessed during the two 72-hour stool collection periods at the end of each of the treatment periods using dietary fat intake and stool fat excretion data.

End point type	Primary

End point timeframe:

The coefficient of fat absorption over 72 hours (CFA-72h) is calculated from stools collected during the last 3 days (72 consecutive hours) of each treatment period.

End point values	Sequence 1 - ITT	Sequence 2 - ITT	Sequence 1 - Completers Population	Sequence 2 - Completers Population
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	48	48	41	42
Units: percent				
arithmetic mean (standard deviation)				
Period 1	82.28 (± 10.792)	85.85 (± 8.72)	82.16 (± 10.894)	85.61 (± 8.671)
Period 2	85.06 (± 9.618)	85.63 (± 11.182)	85.06 (± 9.618)	86.01 (± 11.041)

End point values	Sequence 1 - PP	Sequence 2 - PP		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	35	32		
Units: percent				
arithmetic mean (standard deviation)				
Period 1	81.04 (± 11.189)	85.59 (± 9.376)		
Period 2	83.85 (± 9.788)	86.76 (± 9.736)		

Statistical analyses

Statistical analysis title	Non-inferiority Analysis
Comparison groups	Sequence 1 - Completers Population v Sequence 2 - Completers Population
Number of subjects included in analysis	83
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.2428
Method	Mixed models analysis

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

Adverse events were collected from the time the ICF was signed through the end of the 7-day Follow-up Period, except for serious adverse events (SAEs), which were to be reported through 30 days after the last dose of treatment.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15.0

Reporting groups

Reporting group title	EUR-1008 - Safety Population
Reporting group description: -	
Reporting group title	Kreon - Safety Population
Reporting group description: -	

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: No adverse events occurred at frequency of occurrence of 5% or greater in any study arm.

Serious adverse events	EUR-1008 - Safety Population	Kreon - Safety Population	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 48 (0.00%)	2 / 48 (4.17%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Surgical and medical procedures			
Urethral repair			
subjects affected / exposed	0 / 48 (0.00%)	1 / 48 (2.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Portal vein thrombosis			
subjects affected / exposed	0 / 48 (0.00%)	1 / 48 (2.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	EUR-1008 - Safety Population	Kreon - Safety Population	
Total subjects affected by non-serious adverse events subjects affected / exposed	0 / 48 (0.00%)	0 / 48 (0.00%)	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 February 2012	The following changes were implemented with Amendment 1: change in the comparator drug formulation, inclusion of a two-sided confidence interval in relation to the relative efficacy of EUR-1008 and Kreon, changes in exclusion criteria and other clarifications.
14 December 2012	The following changes were implemented with Amendment 2: updated number of countries and regions participating in the study, changes to inclusion/exclusion criteria and other clarifications.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported