



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 | Subject, Investigator, Monitor, Data analyst |

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