

Rapporteur's Public Assessment Report for paediatric studies submitted in accordance with article 46 of regulation (EC) No 1901/2006, as amended

Kreon 25 000

International non-proprietary name: Pancreatin

Procedure no.: DE/W/105/pdWS/001

Marketing authorisation holder (MAH): Abbot Laboratories GmbH, Hannover, Germany

Rapporteur:	Germany (DE)
Finalisation of procedure	2016-09-19
Date of finalisation of PAR	2016-11-17

Administrative information

Invented name of the medicinal product:	Kreon 25 000
INN (or common name) of the active substance(s):	Pancreatin
MAH:	Abbott GmbH, Hannover, Germany
Currently approved Indication(s)	Impaired exocrine pancreatic function associated with maldigestion. For the support of impaired function of the pancreas in cystic fibrosis.
Pharmaco-therapeutic group (ATC Code):	ATC-Code: A09AA02
Pharmaceutical form(s) and strength(s):	Capsules, hard with gastro-resistant pellets

Introduction

In April 2016 the MAH submitted a completed paediatric study for Kreon 25 000 (Creon®), in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

Scientific discussion

Information on the development program

The MAH stated that the study conducted (PANC2002) does not relate to the development programme of the currently registered Kreon 25 000 (Creon®) product. The purpose of the phase II clinical study, PANC2002 was to evaluate the efficacy and safety of various doses of a new Creon (pancreatin) formulation compared to the currently registered and marketed Creon® product in subjects with pancreatic exocrine insufficiency (PEI) due to Cystic Fibrosis.

Clinical aspects

1. Introduction

The MAH submitted one final report(s) for:

- Study PANC2002
- A Phase II, Multicenter, Parallel-Group, Active- Controlled, Randomized, Double-blind, Dose-Ranging Study to Evaluate the Efficacy and Safety of Different Doses of a new Creon formulation in Subjects with Pancreatic Exocrine Insufficiency due to Cystic Fibrosis.

2. Clinical study(ies)

Study PANC2002:

Description

As indicated in the title, the study was a phase II, pharmacodynamics study of a new Creon formulation containing pancreatin. Based on animal experiments, the expectation was that the new Creon formulation would possess improved stability of the contained enzymes towards gastric acid and increased potency compared to currently available PERT products. It was therefore expected that a similar coefficient of fat absorption (CFA) could be achieved with lower doses of the new formulation as compared to the currently registered Creon® product.

Methods

- Objective(s)

The objective of this study was to assess the efficacy and safety of different doses of a new Creon formulation in comparison to currently registered Creon® product in subjects with PEI due to CF. The determination of efficacy based on coefficient of fat absorption (CFA) of four different doses of the new Creon formulation was declared the primary objective, the coefficient of nitrogen absorption (CAN), stool fat content, and stool weight of the four doses were declared secondary objectives. Safety documentation was also declared an objective.

- Study design

This study was a Phase II, randomized, parallel-group, active-controlled, double-blind, multicenter study with four different doses of a new Creon formulation and one dose of the active control of the currently registered Creon® product, administered in subjects of 12 years or older with PEI due to CF.

The study was divided into two periods: a screening period of 14 days (plus an extra 14 days, upon specific approval by the sponsor) and a double-blind treatment period of 6 to 7 days.

During the screening period, the subjects continued to take their usual PERT on their individual dose until they were randomized into one of the double-blind treatment arms.

Subjects stopped their usual PERT treatment and were randomized in a 1:1:1:1:1 ratio in each country to one of the five treatment arms: Creon new formulation low dose, medium dose, high dose or maximum dose and the currently registered Creon® product (with 300/1,200/2,400/4,000/4,000 Ph. Eur. U lipase/g fat intake, respectively).

A safety follow-up telephone contact was performed 5 to 7 days after discharge from the clinical site to verify the subject's well-being and to check for AEs and use of concomitant medication.

The total study duration for each subject was approximately 25 to 28 days.

The study design was considered appropriate for the objective of the study.

- Study population /Sample size

Each subject had to be over 12 years of age and meet an appropriate inclusion criteria to be eligible for the study.

Patients with a history of relevant GI disorders, too low BMI or Z-score, relevant GI surgery, diabetes, or other relevant disease were excluded from the study.

The patient population was considered suitable for this kind of study.

- Treatments

The study consisted of five arms, four arms with varying doses of the new Creon formulation and a fifth active control arm using the currently registered Creon® product. Each Creon formulation was proportionally administered five times daily (during 3 meals and 2 snacks) for 6 to 7 days to achieve a target total daily dose.

Study drug was administered in a double-blind manner. Neither the subject nor the Investigator nor any other person involved in the conduct of the study knew which medication the subject received.

- Outcomes/endpoints

The primary endpoint was the comparison of the treatment with regard to the coefficient of fat absorption (CFA). $CFA = 100 \times (\text{total fat intake} - \text{total fat excretion}) / \text{total fat intake}$. All fat consumed between first and second intake of blue dye stool marker (taken in the evening of Day 2 and 5) was recorded. All stools after first blue stool (after intake of first marker) and not later than second blue stool (blue stool after intake of second marker) were collected and the total fat content determined.

The secondary efficacy evaluations were the comparison of treatments with regard to coefficient of nitrogen absorption (CAN), stool fat (total fat excretion), stool nitrogen (total nitrogen excretion) and stool weight. CNS was calculated in the same way as CFA. Nitrogen intake was derived from protein intake (nitrogen intake = $0.16 \times \text{protein intake}$).

The chosen parameters are considered fully acceptable and represent standard parameters for this type of study.

- Statistical Methods

These included the comparisons of the four new Creon formulation doses among themselves and the use of a reference limit of 10% for the CFA at the end of the double-blind treatment period to compare new Creon formulation (4 different doses) with the active control of currently registered Creon® product. An analysis of variance (ANOVA) was performed. The model included country and treatment as fixed effects. In case of a single incomplete block within countries, pooling of countries was considered. From this model, two-sided 95% CIs based on least squares (LS) means were derived for the difference between any two groups.

Any new Creon formulation doses with the upper bound of the 95% CI of the difference Creon® minus the new Creon formulation below the reference limit of 10% were deemed non-inferior to the active control of the currently registered Creon® product. This was considered appropriate.

This was a phase II study for which the exploration of the dose-response relationship was the primary objective. The chosen methods are considered appropriate to achieve this.

Results

- Recruitment/ Number analysed

76 subjects were screened, of which 3 withdrew their consent and two discontinued due to a protocol violation, and one due to an adverse event. Thus, 70 subjects were randomised.

All subjects who were allocated to treatment received at least one dose of the study drug and were therefore included in the Safety subject sample.

The exclusion of subjects without post-baseline data is acceptable due to the nature of the study.

- Baseline data

There were no major differences between the treatment groups with regard to weight, height, BMI, blood pressure, and pulse as well as faecal elastase content at baseline.

The populations were also comparable with regard to medical history, which comprised the “usual” CF related diseases/complications, such as bronchiectasis, chronic bronchitis, GORD, pseudomonas infection, sinusitis, hypovitaminosis. The underlying disease was also well reflected without any relevant imbalance between groups in the concomitant medications taken – such as expectorants, inhalants (adrenergics), digestive enzyme preparations, antibiotics, acid suppressives, and vitamins.

- Efficacy results

The primary efficacy evaluation estimated the least square /LS) mean CFA from the ANOVA model as follows:

- 71.5% for Creon new formulation low dose (300 U)
- 71.7% for Creon new formulation medium dose (1,200 U)
- 72.5% for Creon new formulation high dose (2,400 U)
- 76.5% for Creon new formulation maximum dose (4,000 U)
- 92.8% for currently registered Creon® product (4,000 U)

The following conclusions are based on the results of an efficacy analyses:

All four doses of the new Creon formulation in this study were inferior to the active control of the currently registered Creon® product with respect to CFA.

An average CFA of 80% could not be reached with any of the new Creon formulation doses.

No dose response relationship was apparent for the new Creon formulation doses for CFA.

CFA results in subjects using concomitant PPI are better than in subjects not using concomitant PPI for all new Creon formulations, except the lowest strength new Creon formulation since this could not be analysed because none of the subjects used a PPI. In subjects using a PPI, a dose response relationship of the new Creon formulation was apparent for CFA.

The new Creon formulation doses also showed considerably lower CNA values than the active control of currently registered Creon® product.

The mean total fat excretion and the mean total nitrogen excretion were lower under the active control of currently registered Creon® product than under all the new Creon formulation doses in both subject samples as was the mean total stool weight.

This is essentially a failed study, showing inconclusive results for all comparisons. Obviously none of the hypotheses based on the mini-pig data could be verified in this trial. It appears that the whole assumption of higher stability of the new drug substance did not hold. Apparently – based on the data for the PPI intake (not reported in detail above) – gastric acid resistance of the new compound is similarly low as for the “non-virus-inactivated” drug substance. For the currently registered Kreon 25 000 (Creon®) product on the market in Germany, the conclusion can be drawn that the results achieved are considered to be as expected, and compliant with the established pharmacodynamics effects. The study is suitable to confirm the known beneficial effects of the compound in patients with CF.

- Safety results

The study reports the following on safety:

- The overall incidence of TEAEs was higher with the new Creon formulation compared to the active control of currently registered Creon® product.
- GI-related symptoms associated with malabsorption such as abdominal pain, abdominal distension, diarrhoea and flatulence were reported more often by subjects taking the new Creon formulation compared to the active control of the currently registered Creon® product.
- Laboratory parameters, vital signs, and body weight did not show any clinically relevant difference between treatments.
- No safety concerns arose from the results of this study with respect to the severity or seriousness of AEs during the treatment periods, laboratory parameters, and vital signs.
- The reported TEAEs for the currently registered Creon® product assessed by the Investigator as possibly or probably related to study drug are consistent with the known safety profile of the registered product and/or symptoms of the underlying disease.

The conclusions of the study report are agreed with.

It appears that the lower efficacy is fully reflected in the adverse event profile with the higher occurrence of AEs being clearly located in the GI SOC.

The data do confirm the safety profile of the currently registered Kreon 25 000 (Creon®) product as known from clinical trials and post-licensing data and do not add new findings.

Rapporteur's overall conclusion and recommendation

Based on the efficacy and safety data submitted, it is concluded that the benefit-risk profile of currently registered Kreon 25000 (Creon®) product is not altered by the new data available.

The applicant has justified appropriately that a need to change the prescriber's information (SmPC, PL) has not been identified. This is agreed with.

Overall conclusion

Recommendation

No regulatory action required

Additional clarifications requested

N/A