SYNOPSIS

Name of Sponsor:
Abbott

Individual Study Table:

(For National Authority Use only)

Name of Finished Product:
Creon IR

Name of Active Ingredient:
Pancreatin

Study Title:
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

Investigator(s):
Multicenter, 16 investigators

Study Center(s):
Two centers in the Czech Republic, 3 centers in Hungary, 5 centers in Poland and 6 centers in Spain

Publication (Reference):
Not applicable

Study Period:
05 MAR 2015 (first subject first visit) to
04 JUL 2015 (last subject last visit)

Phase of Development:
II

Objectives:
Primary objective: to compare and model the efficacy of four different doses of Creon immediate release (IR) and the active control (Creon® Delayed Release / Gastro Resistant (DR/GR)). The primary efficacy objective was based on the evaluation of fat digestion as measured by coefficient of fat absorption (CFA (%)).

Secondary objective: to compare the effect on protein digestion (measured by coefficient of nitrogen absorption (CNA)), stool fat content and stool weight, of four different doses of Creon IR and Creon® (DR/GR).

Safety objective: to determine the clinical safety of Creon IR based on the evaluation of clinical symptomatology (stool frequency, stool consistency, abdominal pain, flatulence) associated with pancreatic exocrine insufficiency (PEI), vital signs, physical examination findings, safety laboratory values and adverse events (AEs) .

Methodology:
The study was a double-blind, randomized, multicenter, parallel-group study, using four different doses of Creon IR (300, 1,200, 2,400 and 4,000 Ph. Eur U lipase/gram (g) fat intake) and Creon® (DR/GR) as active comparator at a dose of 4,000 Ph. Eur. U lipase/g fat intake. The

study consisted of three periods: a screening period, a double-blind treatment period, and a safety follow-up period. Fat and protein intake was recorded on Days 3 to 5, blue dye stool markers were taken on the evening of Days 2 and 5, and stool collection was performed after the first blue stool following the first dye marker intake until (including) the first blue stool following the second dye marker intake. Study medication was to be administered on Days 1 to 5 (i.e., until the appearance of the second dyed stool, which may have been on Day 6 or 7) of the double-blind treatment period.

Visits were performed at screening, baseline (before start of double-blind treatment), and the end of the double-blind treatment period. A safety follow-up call was conducted 5 to 7 days after discharge from the clinical site.

Number of Subjects (Planned, Consented, Randomized and Analyzed):
Planned: 65 subjects to complete the double blind period, 13 per treatment group.
Actually randomized: 70 subjects, 14 per treatment group; completed study: 68 subjects; safety subject sample: 70 subjects; full analysis (FA) subject sample: 66 subjects (14 subjects in Creon IR 2,400 group, 13 subjects in all other groups); Per protocol (PP) analysis sample: 65 subjects (12 in Creon IR 1,200 group, 14 in Creon IR 2,400 group, 13 in the other treatment groups).

Diagnosis and Main Criteria for Inclusion:
Subjects 12 years of age or older with confirmed diagnosis of PEI and cystic fibrosis (CF) with PEI currently controlled under treatment with a commercially available pancreatic enzyme replacement therapy and a human fecal elastase < 100µg/g stool at screening.

Test Product, Dose and Mode of Administration, Batch Number:

Test product: Capsules with Creon IR; small capsules: 4,000 Ph. Eur U lipase/capsule, large capsules: 30,000 Ph. Eur U lipase/capsule.

Route: Oral during each meal and snack, without chewing or crushing. The capsules were taken at the start of the meal with sufficient fluid.

Daily Dose: 4 dose levels: low (300 Ph. Eur U lipase/g fat), medium (1,200 Ph. Eur U lipase/g fat), high (2,400 Ph. Eur U lipase/g fat), maximum (4,000 Ph. Eur U lipase/g fat) proportionally distributed across 3 meals and 2 snacks.

Batch Numbers: 811332 (small size capsules), 811333 (large size capsules)

Corresponding Placebo Batch Numbers: 811369, 811368.

Duration of Treatment:

Six to seven days.

Reference Therapy, Dose and Mode of Administration, Batch Number:

Reference product: Capsules with Creon® (DR/GR) containing 25,000 Ph. Eur U lipase.

Route: Oral during each meal and snack, without chewing or crushing. The capsules were taken at the start of the meal with sufficient fluid.

Daily Dose: 4,000 Ph. Eur U lipase/g fat intake, proportionally distributed across 3 meals and 2 snacks.

Batch Number: 811367

Corresponding Placebo Batch Number: 811370

Criteria for Evaluation

Efficacy:

Primary: Comparison of treatments with regard to CFA. CFA = 100*(total fat intake - total fat excretion)/total fat intake. Fat intake was controlled via diet. 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.

Secondary: Comparison of treatments with regard to CNA, stool fat (total fat excretion), stool nitrogen (total nitrogen excretion) and stool weight.

CNA was calculated in the same way as CFA but with fat replaced by nitrogen. Nitrogen intake was derived from protein intake (nitrogen intake = 0.16*protein intake).

Safety:

Adverse events, safety laboratory tests, vital signs, physical examination and clinical symptomatology associated with PEI.

Statistical Methods:

Treatments were compared using analysis of variance (ANOVA) for CFA. The model included country and treatment as fixed effects. From this model, an estimate of all pairwise treatment differences along with a 95% confidence interval (CI) was derived. The analyses were performed for the FA subject sample and the PP subject sample. Multiple Comparison Procedure (MCP) modeling was used to estimate target doses of Creon IR for the FA subject sample.

The same analyses were performed for CNA.

Descriptive statistics for continuous variables were calculated for all efficacy variables. CFA and CNA were summarized by subgroups of subjects using / not using concomitant proton pump inhibitors (PPIs) and by country.

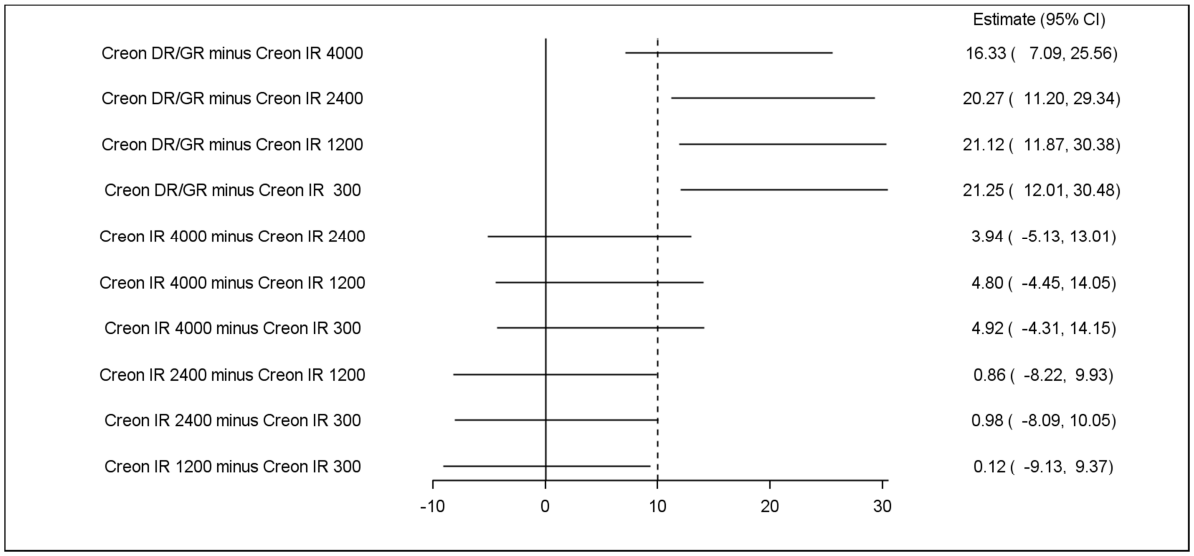
Safety variables were summarized using frequency tables and other descriptive statistics for the Safety subject sample.

Summary - Conclusions

Efficacy Results:

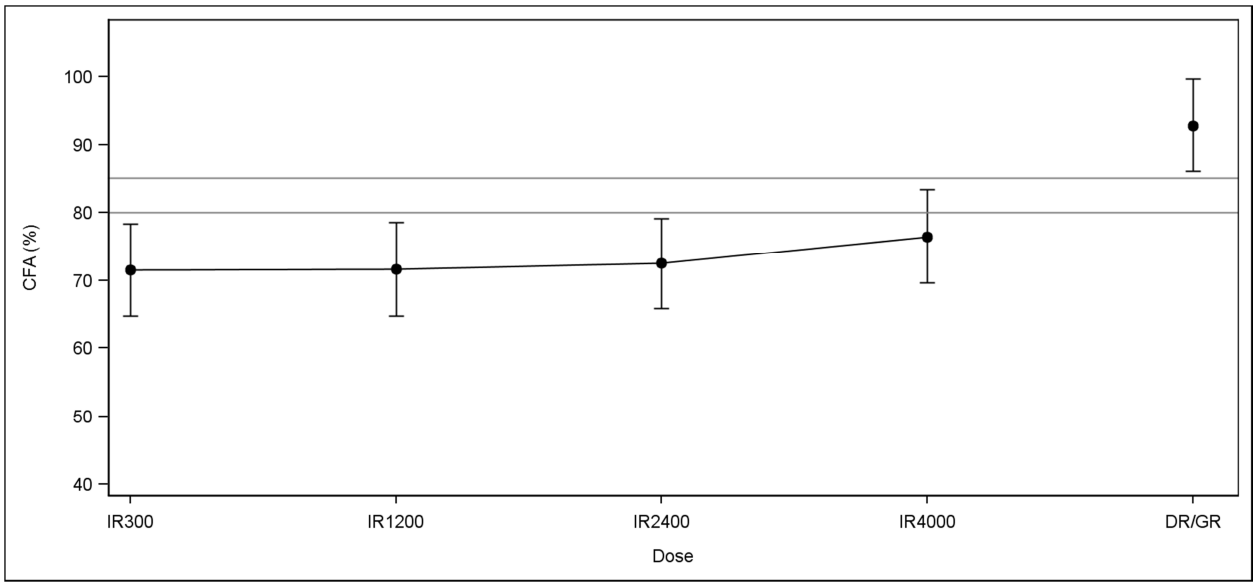
CFA

For the FA subject sample, least square (LS) mean CFA values estimated from the ANOVA model were 71.5% for Creon IR 300; 71.7% for Creon IR 1,200, 72.5% for Creon IR 2,400, 76.5% for Creon IR 4,000 and 92.8% for Creon® (DR/GR), respectively. The figure below shows the estimates and 95% CIs for CFA for all pairwise treatment difference for the FA subject sample. The active comparator Creon® (DR/GR) is statistically significantly better than all Creon IR doses since none of the corresponding 95% CIs includes 0. Differences between each two Creon IR doses only show a small tendency towards higher average CFA values with the higher doses.



The dotted line represents the reference limit for the comparison between Creon IR doses and Creon® (DR/GR)

LS mean CFA values for all treatment groups together with their 95% CIs are shown in the following figure.



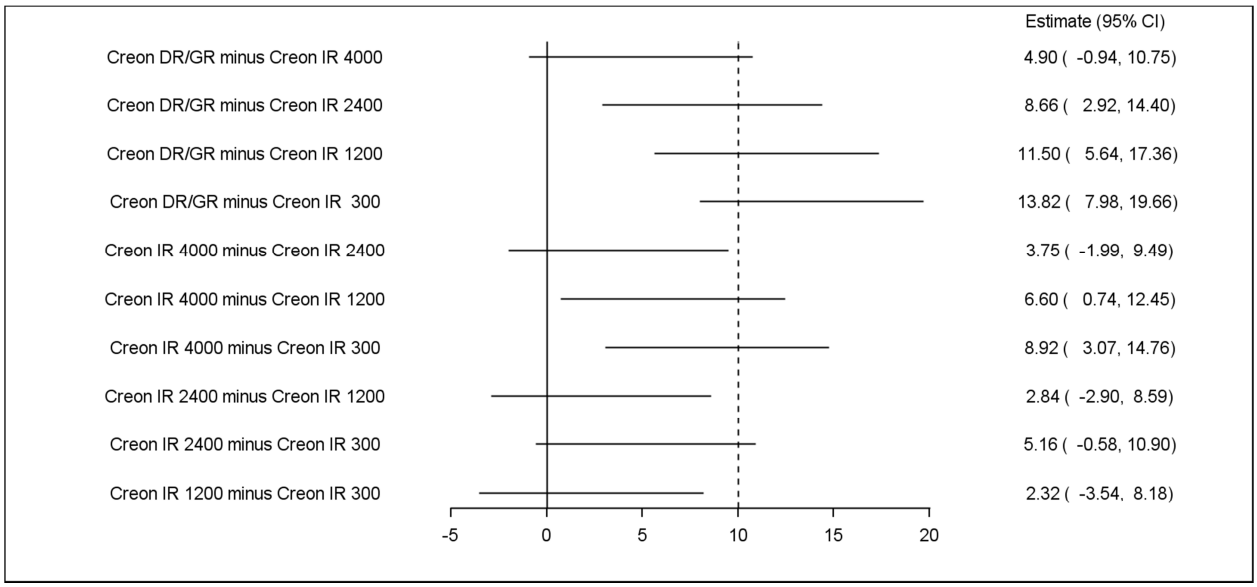
From the list of four models to potentially describe the dose-response relationship of Creon IR (linear, Emax, logistic, beta) including the observed data of the four Creon IR groups and historical placebo data, the Emax model was chosen by the MCP modeling procedure since it had the highest value for the test statistic. When applying the Emax model to estimate the Creon IR target doses (target dose to have a CFA equal to the mean CFA of active control, target dose to have a CFA equal to the mean CFA of active control minus 10%, target dose to reach a CFA of 80%, target dose to reach a CFA of 85%), these were, however, not estimable, since none of the Creon IR doses had an appropriate response (all Creon IR doses had a mean CFA < 80 %).

CFA results in subjects using concomitant PPI were higher than in subjects not using PPIs in all Creon IR groups (except Creon IR 4,000 where this could not be analyzed since none of the

subjects used a PPI). In subjects using PPI, a dose response relationship was apparent with respect to CFA (average of 73.8% for Creon IR 300, 84.1% for Creon IR 1,200 and 90.0% for Creon IR 2,400). In the active comparator Creon® (DR/GR) group, results for subjects using PPI/not using PPI were similar (mean of 93.5% and 91.9%, respectively) and higher than in all Creon IR groups.

CNA

For the FA subject sample, LS mean CNA values estimated from the ANOVA model were 71.6% for Creon IR 300; 73.9% for Creon IR 1,200, 76.7% for Creon IR 2,400, 80.5% for Creon IR 4,000 and 85.4% for Creon® (DR/GR), respectively. The figure below shows the estimates and 95% CIs for CNA for all pairwise treatment difference for the FA subject sample. As for CFA, results were better for the active comparator Creon® (DR/GR) compared to all Creon IR groups.



The dotted line represents the reference limit for the comparison between Creon IR doses and Creon® (DR/GR)

From the list of four models to potentially describe the dose-response relationship of Creon IR (linear, Emax, logistic, beta) including the observed data of the four Creon IR groups and historical placebo data, the Emax model was chosen since it had the highest value for the test statistic. When applying this model to estimate the Creon IR target doses as above for CFA only the daily target dose to have an effect as active control minus 10% was estimable and was estimated as 2,285 lipase units per gram fat.

Fat Excretion, Nitrogen Excretion, Stool Weight

On average, the total fat excretion was considerably lower in the Creon® (DR/GR) group (23.5 g/72h) than in all Creon IR groups (between 73.0 g/72h in Creon IR 4,000 group and 87.5 g/72h in Creon IR 300 group) in the FA subject sample. On average, the total nitrogen excretion was considerably lower in the Creon® (DR/GR) group (5.56 g/72 h) than in all Creon IR groups (between 7.26 g/72 h in Creon IR 4,000 group and 10.47 g/72 h in Creon IR 300 group) in the FA subject sample. Average total stool weight was on average highest in the

Creon IR 1,200 group and lowest in the Creon® (DR/GR) group.

Safety Results:

No subject died during the study. One subject randomized to Creon IR 2,400 experienced a treatment emergent SAE, an infective pulmonary exacerbation of CF on Day 8, one day after the last dose of study medication. One subject randomized to Creon IR 1,200 discontinued the study due to severe abdominal pain. The percentage of subjects with at least one treatment emergent AE (TEAE) was lower with Creon® (DR/GR) (50.0%) than with Creon IR (62.5%). Three subjects treated with Creon IR 1,200 and one subject treated with Creon IR 4,000 experienced a TEAE of severe intensity, all of them were considered possibly or probably related to study drug by the Investigators. The percentage of subjects with TEAEs considered as possibly related to study drug was lower in the Creon® (DR/GR) group (28.6%) compared to Creon IR (46.4%).

The majority of subjects with TEAEs reported gastrointestinal disorders (55.4% with Creon IR and 35.7% with Creon® (DR/GR)), in particular abdominal pain (42.9% with Creon IR, 14.3% with Creon® (DR/GR)) and flatulence (23.2% and 14.3% with Creon IR and Creon® (DR/GR), respectively).

TEAEs regarded as possibly or probably related to study drug were more frequently reported for subjects treated with any Creon IR dose (46.4%) compared to Creon® (DR/GR) (28.6%). Most frequently reported TEAEs considered possibly or probably related to study drug were gastrointestinal system disorders (46.4% with any dose of Creon IR, 28.6% with Creon® (DR/GR)), in particular abdominal pain (35.7% with any dose of Creon IR, 7.1% with Creon® (DR/GR)) and flatulence (19.6% with any dose of Creon IR, 14.3% with Creon® (DR/GR)).

Blood samples for laboratory tests were taken at Visit 1 and at the end of the double-blind treatment period. The median change from baseline to end of treatment was generally small and no clinically relevant difference was observed between treatments for any laboratory test.

Hematology and biochemistry parameters were screened for markedly abnormally low and high values. The percentage of subjects with markedly abnormal laboratory values was small and similar between treatment groups. Overall, nine subjects had at least one markedly abnormal value during treatment. The incidence per treatment group never exceeded one subject.

No clinically relevant mean changes from baseline were observed in vital signs, body weight and body mass index (BMI) for any treatment group. There were also no clinically relevant differences between treatments. No markedly abnormal values were observed.

Conclusion:

In this study, the tested immediate release formulation of Creon (Creon IR) was inferior to the marketed delayed release / gastro resistant formulation (Creon® (DR/GR)) both in terms of efficacy and clinical safety/tolerability.