SYNOPSIS

Name of Sponsor:
Abbott Laboratories GmbH

Individual Study Table:

(For National Authority Use only)

Name of Finished Product:
Creon N

Name of Active Ingredient:
Pancreatin

Study Title:
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

Investigator(s):
Eight investigators

Study Center(s):
Eight centers, four in Hungary and four in Spain

Publication (Reference):
Not applicable

Study Period:
15 JAN 2014 (first subject first visit) to
25 AUG 2014 (last subject last visit)

Phase of Development:
IIIb

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

Secondary objectives: To investigate the effect of Creon N 25000 and Creon® 25000 on coefficient of nitrogen absorption (CNA), on stool fat and on clinical symptomatology (stool frequency, stool consistency, abdominal pain, flatulence).

Safety objectives: To evaluate the short-term safety of Creon N 25000 and Creon® 25000 including vital signs, body weight, physical examination, safety laboratory values, and adverse events (AEs).

Methodology:
The study was a double-blind, randomized, multicenter, cross-over (CO) study performed to show therapeutic equivalence of Creon N 25000 (Creon N) with the currently registered Creon® 25000 (Creon R). Creon N and Creon R are essentially the same products but differ with regard to the manufacturing process. Pancreatic enzyme supplementations are not systemically available. Therefore a bioequivalence study was not possible.

The study consisted of five periods: screening period, first cross-over period, wash-out period, second cross-over period, and a safety follow-up period. Study medication was administered on Day 1 to 5 of each CO period and pre-study pancreatic enzyme replacement therapy (PERT) on all other days including the wash-out period. Fat and protein intake was recorded on Day 3 to 5 of each CO period, blue dye stool markers taken on the evening of Day 2 and 5, and stool collection performed between the first and second blue dyed stools.

Visits were performed at screening, baseline (before start of first CO period), end of first CO period (after end of first stool collection on Day 6 or 7), end of 3 to 14 days wash-out period, and end of second CO period (after end of second stool collection on Day 6 or 7 of period). A safety follow-up call was conducted 3 to 5 days after last visit.

Number of Subjects (Planned, Consented, Randomized and Analyzed):
Number of subjects planned to be randomized: 40 subjects, 20 per treatment sequence.

Consented: 50 subjects. Randomized: 41 subjects, 20 to treatment sequence Creon N - Creon R, 21 to sequence Creon R - Creon N. Treated: 41 subjects. Prematurely withdrawn: 2 subjects, both withdrew their consent during the first CO period under treatment with Creon N.

Included in analysis samples:

	By Treatment Sequence		By Treatment Started	
	Creon N - Creon R	Creon R - Creon N	Creon N	Creon R
Randomized and treated	20	21	41	39
Safety subject sample	20	21	41	39
Full analysis (FA) sample	19	21	40	39
Per protocol (PP) subject sample	18	20	38	38

The Safety subject sample included randomized subjects who received at least one dose of study drug.

The FA subject sample included all subjects of the Safety subject sample who had data for at least one post-baseline assessment of any efficacy measurement. One of the two subjects who discontinued prematurely had no post-baseline efficacy measurement and was therefore excluded.

The PP subject sample included all subjects of the FA subject sample who had no major protocol deviations. Two subjects were excluded because they did not perform the stool collection as planned. This included the second subject who discontinued prematurely.

Diagnosis and Main Criteria for Inclusion:
The study was performed in adolescent and adult subjects (age ≥ 12 years) with proven PEI and CF who were clinically stable (no acute respiratory disease within 1 month of enrollment, no decrease of body weight ≥ 5% within 3 months of enrollment), were on continuous and stable treatment with a commercially available pancreatic enzyme product, and were able to swallow capsules with each meal and snack.

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

Test product: Capsules with Creon N 25000 containing 25000 lipase units per capsule

Route: Oral during each meal and snack, without chewing or crushing

Dose: Subjects had to receive 8000 to <10000 lipase units per kg body weight and day, equally distributed across 3 meals and 2 snacks with 2 snacks counted as about one meal.

Batch Number(s): 811043, 811216

Duration of Treatment:

Five days during each CO period in accordance with the randomized treatment sequence

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

Reference product: Capsules with currently registered Creon R 25000 containing 25000 lipase units per capsule

Route: Oral during each meal and snack, without chewing or crushing

Dose: as for Creon N

Batch Number(s): 810888

Criteria for Evaluation

Efficacy:

Primary: Comparison of treatments with regard to CFA. Equivalence of treatments was to be shown. 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 (=first 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) and clinical symptomatology (stool frequency, stool consistency, abdominal pain, flatulence).

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).

Stool frequency, stool consistency (hard, formed/normal, soft, watery), abdominal pain and flatulence (none, mild, moderate, severe) were recorded in a diary on each day of a CO period. The mean stool frequency and the percentage of days at a specified level of a symptom were determined were determined for each subject and CO period. In the analysis of symptoms, only days with study medication within Day 1 to 5 of a CO period were taken into account.

Other: The investigator assessed the clinical global impression (CGI) of disease symptoms at baseline and at the end of each CO period. Total stool weight was recorded for each CO period.

Safety:

Adverse events, safety laboratory tests, and vital signs.

Statistical Methods:

Treatments were compared using analysis of variance (ANOVA) for CFA. The model included sequence, period and treatment as fixed effects and subject within sequence as random effect. From this model, an estimate of the treatment difference along with a 95% confidence interval (CI) was derived. To show equivalence the two-sided 95% CI for the treatment difference had to lie entirely in the equivalence range (-8% , 8%). The analyses were performed for the FA subject sample and the PP subject sample.

The same analysis was performed for CNA, also using the same equivalence range.

Descriptive statistics for continuous variables were calculated for all efficacy variables except CGI, by treatment and by CO period and treatment sequence. The summary by treatment also included a summary of the intra-individual treatment difference. The CGI and intra-individual treatment differences in CGI were tabulated in frequency tables.

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

Summary - Conclusions

Efficacy Results:

Creon N and Creon R were shown to be equivalent with regard to their effect on the primary analysis variable, the CFA. The CFA was slightly higher under Creon N than under Creon R. These results were obtained for both the PP and FA subject sample. The 95% CI for the treatment difference was [-1.0%, 3.6%] for the PP subject sample and [-0.9%, 3.6%] for the FA subject sample (ANOVA estimates) and therefore clearly within the equivalence range [-8%, 8%].

Creon N and Creon R were also shown to be equivalent with regard to their effect on CNA. The difference between Creon N and Creon R was 0.0 for both the PP and FA subject sample, the 95% CIs were [-1.8%, 1.9%] and [-1.8%, 1.7%] for the PP and FA subject sample, respectively.

The mean total fat excretion was slightly lower under Creon N (42.3 g) than under Creon R (48.1 g) while the mean total fat intake was slightly higher (415.5 g for Creon N, 403.7 g for Creon R). Results were similar for the FA subject sample.

No relevant difference was observed between treatments with regard to the clinical symptoms recorded in the subject's diary:

On average, the mean number of stools per day was nearly identical under Creon N and under Creon R (1.46 and 1.54, respectively).

The mean percent of days with formed/normal stool was 6.2% lower under Creon N (73.6%) than under Creon R (79.8%) while days with hard and soft stools were slightly more frequent. Watery stools did not occur under Creon N and only once under Creon R.

No subject experienced severe abdominal pain while treated with study medication. Days with moderate pain were infrequent under both treatments (between 2 and 3%). The mean percent of days with mild pain was slightly lower under Creon N (8.0%) than under Creon R (11.1%). On most of the days, subjects had no pain (89.3% and 86.8%, respectively).

The mean percent of days with no flatulence was 5.9% higher under Creon N (57.5%) than under Creon R (51.6%), and the mean percent of days with mild flatulence was 9.2% lower (33.9% and 43.2%, respectively). Days with moderate flatulence were 3.3% more frequent under Creon N (8.6%) than under Creon R (5.3%) on average. No subject reported severe flatulence during Day 1 to 5 of each treatment.

In one subject, the CGI was "1 point better" under Creon N compared to Creon R. In all other subjects, the CGI was the same under both treatments. In more than 80% of subjects, symptoms were not present or mild.

Hardly any difference was seen between treatments for mean total nitrogen intake and mean

total nitrogen excretion.

Safety Results:

No subject died during the study. One SAE (spontaneous right apical pneumothorax) occurred prior to start of study medication.

The overall incidence of treatment emergent adverse events (TEAEs) was lower under Creon N (14.6%) than under Creon R (23.1%). Under both treatments, there was no TESAE, no TEAE leading to study termination, and no severe TEAE.

The majority of subjects with TEAEs reported gastrointestinal disorders (7.3% under Creon N, 15.4% under Creon R), in particular flatulence (none under Creon N, 7.7% under Creon R) and abdominal pain (4.9% and 5.1% under Creon N and Creon R, respectively).

The severity of all TEAEs was rated as mild except one which was rated as moderate.

Six TEAEs were regarded as possibly or probably related to study drug intake. Four of them occurred or worsened in three subjects under Creon N, and two events occurred or worsened in two subjects under Creon R.

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

Laboratory values were classified as being below, within, or above the laboratory's reference range. For most laboratory tests, the number of subjects with a different classification for Creon N and Creon R was low or the number of subjects who had a worse value under one treatment was similar to the number of subjects who had a worse value under the other treatment. Small imbalances were seen for monocytes (high values more frequent under Creon R) and glucose (high values more frequent under Creon N).

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 under both treatments. Overall five subjects had at least one markedly abnormal value, none of them was considered clinically significant by the investigator.

On average, no relevant change from baseline was observed in vital signs, body weight and body mass index (BMI). Treatments were comparable. No markedly abnormal values were observed.

Conclusion:

Based on the results of this study, it can be concluded that the two tested Creon 25000 formulations (Creon N and Creon R) are therapeutically equivalent and interchangeable. Specifically:

- The 95% CI for the treatment difference in CFA (primary efficacy variable) was within the predefined equivalence range.
- The 95% CI for the treatment difference in CNA (main secondary efficacy variable) was also within the predefined equivalence range.
- All other secondary parameters related to stool and clinical symptomatology showed no clinically relevant differences between Creon N and Creon R treatment groups.
- AE data as well as laboratory data and vital signs showed that both Creon N and Creon

R are generally well tolerated in subjects with PEI due to CF, without apparent formulation differences.