# Efficacy and safety of Creon® 24,000 in subjects with exocrine pancreatic insufficiency due to cystic fibrosis ☆

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## Abstract

*Background:* Pancreatic enzyme replacement therapy is critical for adequate nutrition in cystic fibrosis (CF) patients with exocrine pancreatic insufficiency (EPI).
*Methods:* This was a double-blind, randomised, placebo-controlled, two-period crossover study assessing efficacy and safety of Creon 24,000-unit capsules in CF subjects ≥ 12 years with EPI. Patients were randomised to one of two 5-day sequences, Creon/placebo or placebo/Creon (target dose, 4000 lipase units/g fat). Primary outcome was the coefficient of fat absorption (CFA); secondary outcomes were coefficient of nitrogen absorption (CNA), symptoms, and safety.
*Results:* Thirty-two subjects were randomised. Mean CFA and CNA were significantly greater with Creon than placebo (CFA, 88.6% vs. 49.6%; CNA, 85.1% vs. 49.9%; $p < 0.001$ for both). Symptoms were improved and fewer treatment-emergent adverse events were reported with Creon than placebo. One patient discontinued for weight loss unrelated to study drug.
*Conclusions:* This study demonstrated Creon was effective in treating EPI due to CF and was safe and well tolerated.
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*Keywords:* Coefficient of fat absorption; Coefficient of nitrogen absorption; Pancreatic enzyme replacement therapy; Pancrelipase; Pancreatin; Randomised, controlled trial

## 1. Introduction

Exocrine pancreatic insufficiency (EPI) occurs in as many as 85% to 90% of individuals with cystic fibrosis (CF) [1]. The resulting lack of digestive enzymes leads to intestinal maldigestion with resultant malabsorption [2]. If left untreated, EPI can cause steatorrhoea, abdominal cramping, severe discomfort, frequent stools, and other adverse gastrointestinal symptoms and leads to failure to thrive in infants, poor growth in children, and weight loss in adults [3,4].

Typically, EPI is treated with pancreatic enzyme replacement therapy, with the goal of restoring normal digestion and achieving and maintaining adequate nutritional status [2]. Enzyme replacement therapy is generally considered safe, effective, and well tolerated based on a limited number of clinical trials and extensive clinical experience. For example, pancrelipase (pancreatin) delayed-release capsules, USP (Creon®, Solvay Pharmaceuticals, Inc., Marietta, GA, USA) have been available in the United States

for more than 20 years and have been demonstrated to be safe and effective in randomised clinical trials [5–7]. Pancreatic enzyme supplements were developed prior to enactment of the US Food and Drug Administration (FDA) drug approval requirements. However, in response to reports of adverse events (AEs) associated with high doses of some enzyme supplements [8] and a lack of therapeutic effect of some preparations [9], the FDA ruled in 2004 that manufacturers of pancreatic enzyme supplements must file new drug applications to ensure consistent efficacy, safety, and quality of these agents [10].

A new formulation of Creon capsules has been developed to comply with the new 2004 FDA mandate. Part of this mandate requires manufacturers to target actual lipase activity at 100% of the label claim [11]. Historically, these products have been manufactured to meet USP standards of 90% to 165% lipase activity of label claims. This reformulation containing 6000, 12,000, or 24,000 units of lipase is comparable in terms of lipase activity to currently marketed Creon capsules labelled as 5000, 10,000, and 20,000 lipase units. In addition, light mineral oil has been removed from the pellets and dibutyl phthalate has been removed from the enteric coating in response to general FDA and EU directives, respectively.

The current study was designed to assess the efficacy of the reformulated Creon 24,000-unit capsule (at a target dose of 4000 lipase units/g fat) in improving fat absorption, protein absorption, and the effects on clinical symptoms of malabsorption in individuals with CF. Safety and tolerability also were evaluated. A preliminary account of this study has been presented in abstract form [12].

## 2. Methods

This study used a double-blind, randomised, placebo-controlled two-arm, crossover design and was conducted at 10 centres in the United States between November 15, 2007 and March 6, 2008 (NCT00510484). The protocol was approved by the Institutional Review Board/Independent Ethics Committee at each site, and all subjects provided written informed consent.

### 2.1. Inclusion/exclusion criteria

Males and females ≥ 12 years of age were eligible if they had a diagnosis of CF (confirmed by two positive chloride sweat tests and/or *CFTR* gene analysis) and EPI (confirmed by either a coefficient of fat absorption [CFA] <70% without supplementation or faecal elastase <50 µg/g stool within the past 12 months). Subjects were required to be currently receiving treatment with a commercially available pancreatic enzyme product at a stable dose for ≥ 3 months and to be clinically stable without evidence of acute respiratory disease or other acute, major medical illness. They were required to have a stable body weight, defined as no more than a 5% decline within the previous 3 months. Females of child-bearing potential had to agree to continue using a medically acceptable method of birth control.

Subjects were excluded if they had ileus or acute abdomen; distal ileal obstruction syndrome within 6 months of enrolment; gastrointestinal malignancy within 5 years of enrolment; a history of pancreatitis or fibrosing colonopathy; or known infection with human immunodeficiency virus. Subjects aged <18 years also were excluded if their body mass index (BMI) percentile for their age was <10%. Prohibited treatments included narcotic analgesics, antidiarrhoeals, antispasmodics, laxatives, and nutritional supplements containing medium-chain triglycerides. Stable doses of commercially available medications influencing duodenal pH or gastric emptying were allowed if prescribed according to the recommended dose range and if taken for more than 4 weeks prior to the start of the study.

### 2.2. Study design and treatments

Following initial screening, eligible subjects continued for up to 14 days on their usual pancreatic enzyme supplementation before randomisation to a treatment sequence using an interactive voice response system.

Prior to study initiation, an individualised diet to be provided during days 1 to 5 of each crossover period was designed by a registered dietitian at each study site. The diet was developed in consultation with each subject and provided at least 100 g/day of fat and included 40% of total calories from fat, as recommended in CF Foundation nutrition guidelines [13]. Study drug intake and dietary consumption were monitored by site personnel. Subjects were considered noncompliant if they took less than 95% of scheduled doses of Creon, if they consumed less than 80% of the planned fat consumption or if the difference in fat consumption in the two treatment periods was more than 10% based on the lower amount consumed. Subjects were randomised 1:1 to one of two crossover treatment sequences: Creon then placebo or placebo then Creon. Creon 24,000 capsules were administered to achieve a dose of 4000 lipase units/g fat based on the prescribed fat intake per meal/snack according to the upper limit of the recommendation of CF consensus statements [13–15]. This dose was selected to maximise fat absorption.

Subjects were either hospitalised or studied in a General Clinical Research Center unit for both crossover treatment periods. Study medication was provided for 5 days in each crossover period, and these periods were separated by a washout period of 3 to 14 days during which the subjects consumed their usual diet and used their usual pancreatic enzyme replacement product. Blinding was maintained by provision of identical capsules and packaging for placebo and Creon.

### 2.3. Efficacy assessments

The primary objective of the study was to demonstrate superior efficacy of Creon over placebo in improving fat absorption as measured by the CFA. To ensure accurate recording of stool samples, subjects were given a stool marker (FD&C Blue #2, 500 mg) on the evenings of day 2 and day 5 of each crossover period. Dietary recording was performed between administrations of the stool markers. The stool collection was performed from the first appearance of the dyed stool to the next appearance of the dyed stool (Day 6 or 7 of each crossover period, depending on the subject's intestinal motility). Stool fat was determined by the gravimetric method.

The CFA is currently the standard measure for evaluating fat absorption, [16] and the treatment difference in the CFA was the primary efficacy outcome. The CFA was calculated from the fat intake and excretion according to the following equation:

$$CFA(\%) = 100 \times [(\text{grams fat intake} - \text{grams fat excretion})/\text{grams fat intake}]$$

Secondary efficacy outcomes included the coefficient of nitrogen absorption (CNA), stool fat, stool weight, clinical symptomatology, and assessments using the Clinical Global Impression of Disease Symptoms (CGI) scale. Nitrogen intake was determined from protein dietary intake, and nitrogen excretion was measured in stools using standard methodology (Kjeldahl [17]). The CNA was calculated according to the following equation:

$$CNA(\%) = 100 \times [(\text{grams nitrogen intake} - \text{grams nitrogen excretion})/\text{grams nitrogen intake}]$$

Clinical symptomatology was determined from data recorded daily by subjects regarding the stool frequency (number per day), stool consistency (0 = hard, 1 = formed/normal, 2 = soft, 3 = watery), flatulence (0 = none, 1 = mild, 2 = moderate, 3 = severe), and abdominal pain (0 = none, 1 = mild, 2 = moderate, 3 = severe). The CGI was rated independently by both the site investigators and the subjects at the beginning and end of each study period according to the following scale: 0 = none (symptoms not present), 1 = mild (symptoms present but not bothersome), 2 = moderate (symptoms bothersome), 3 = severe (symptoms interfered with normal activities), 4 = incapacitating (symptoms prevented continuation of normal activities). Subjects also answered questions regarding stool consistency, flatulence, and abdominal pain to determine their eligibility to enter the second crossover period. Subjects were permitted to enter the second period only if the scores on those parameters were no more than one level above the baseline score.

### 2.4. Safety evaluation

All randomised subjects who received at least one dose of study medication were included in the safety analysis. The safety and tolerability data collected included vital signs, physical examination, weight, BMI, safety laboratory values (including haematology and biochemistry), and AEs. Physical examinations were performed during screening and at the end of each crossover period. Laboratory safety tests were performed during screening, at the end of the first crossover period, and at the beginning and end of the second crossover period. AEs were monitored beginning during the specified pre-treatment through to the follow-up period. Laboratory samples were analysed by Mayo Clinic Clinical Trial Services (Rochester, MN, USA). Any AE that started or worsened during a treatment period (plus one day) was considered treatment emergent for that treatment arm.

### 2.5. Statistics

Since there is no general agreement on what a clinically meaningful change in CFA is considered, we chose the following method to establish the correct sample size to appropriately power the study. A 7% change in body weight is considered clinically significant in other patient populations [18,19]. A weight gain of 7% over 1 year in a 70-kg subject would require an increase in the CFA of 11% to 14% based on a diet that includes 80 to 100 g/day of fat. Thus, the minimum clinically relevant difference in CFA between Creon and placebo of 14% was selected for this study. Assuming a difference of 14% and a standard deviation of 20%, the effect size would be 0.7. A sample size of 24 had 90% power to detect an effect size of 0.7 using a paired *t*-test with a 0.05 two-sided level of significance. Thus, at least 24 subjects who completed both crossover periods were required. To account for dropouts, a minimum of 26 subjects (13 per treatment sequence) were planned to be randomised.

The primary analysis was performed on the full analysis sample, which included all randomised subjects who took at least one dose of double-blind study medication and for whom at least one post-baseline assessment of any efficacy parameter was available. One patient dropped out during the first period (on placebo) due to a medication error and was allowed a second entry which was completed according to protocol (only data from the second entry was used in the analysis). All efficacy and safety variables were summarised by standard descriptive methods.

The CFA data were analysed using analysis of variance. The model included sequence, period, and treatment as fixed effects and subject within sequence as a random effect. This was used to derive an estimate of the treatment difference, 95% confidence interval, and *p* value for comparison of Creon and placebo. A test for carryover was not performed. Data were assessed graphically (box plots, normal probability plots, residual-by-predicted plots) to confirm normality.

Prospectively planned exploratory subanalyses also were performed for CFA, CNA, and clinical symptomatology with respect to subject age (ages 12–18 years vs. >18 years) and severity of off-treatment EPI (placebo CFA ≤50% vs. >50%).

All analysis data sets and statistical output were produced using the SAS® system Version 8.2 or higher.

## 3. Results

Thirty-four patients provided consent; 32 were randomised (16 to each crossover group) and 31 subjects completed period 2 (Fig. 1). The Creon/placebo treatment sequence group had a larger proportion of females (Table 1). Eighteen patients took acid suppression medications during the study (9 in each treatment sequence group).

### 3.1. Efficacy

CFA (least squares [LS] mean) was significantly (*p* < 0.001) greater with Creon compared with placebo (Table 2). All subjects
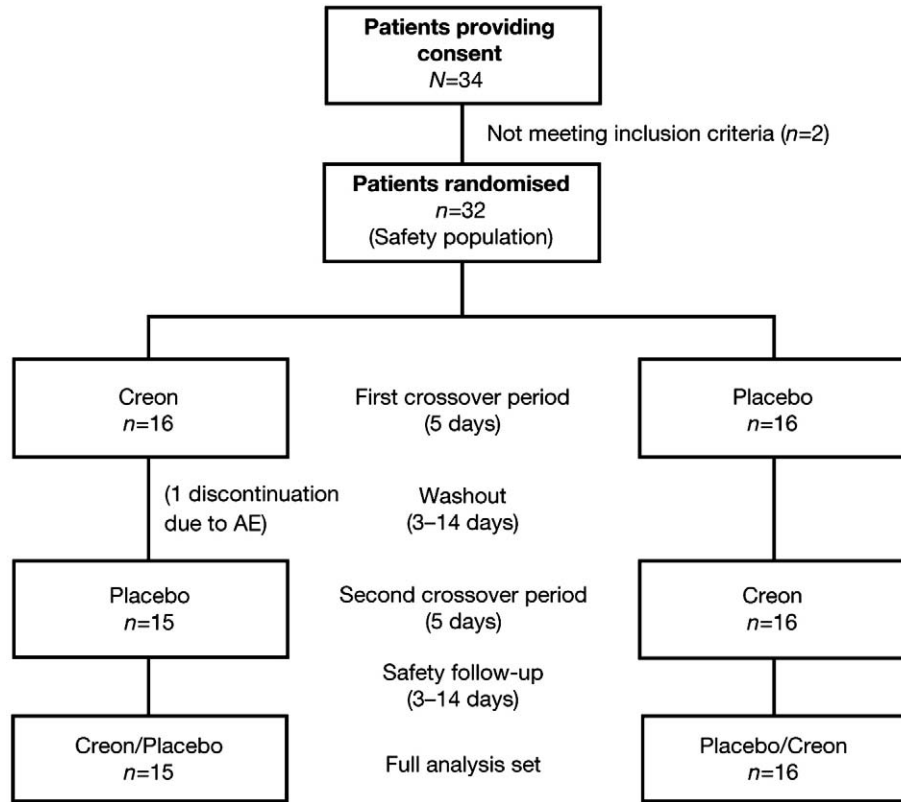
Fig. 1. Study design and patient disposition. AE: adverse event.

achieved a CFA of ≥70% and 68% (21/31) achieved a CFA of ≥85% with Creon irrespective of their CFA during placebo (Fig. 2A). The mean total fat intake for days 3 to 5 of each crossover period was similar for both treatments (mean±standard deviation [SD]: Creon, 476.6±136.9 g; placebo, 490.6±156.6 g; statistical significance not tested) and the mean±SD lipase dose was 4189±732 units/g fat intake during Creon treatment. This exceeded the target dose of 4000 units/g fat due to incomplete consumption of dietary fat provided. Expressed as a function of body weight, subjects received a mean daily dose of 10,942.7 lipase units/kg.

No clinically meaningful difference in Creon treatment effect on the CFA was observed between subjects aged 12 to 18 years and those aged >18 years. Both groups achieved significant increases in CFA with Creon compared with placebo (LS mean±standard

error [SE] for treatment difference, 43.4±5.7% vs. 37.3±4.2%, respectively; $p < 0.001$ for both). Subjects with more severe EPI, as determined by a placebo CFA of ≤50%, demonstrated a greater effect of Creon treatment compared with subjects whose placebo CFA was >50% (LS mean±SE for treatment difference, 52.4± 2.5% vs. 23.3±2.9%, respectively), but treatment differences were significant in both of these subgroups ($p < 0.001$ for both) and LS mean CFA values during Creon treatment were similar (LS mean± SE, 88.7±1.8% vs. 88.7±2.0%, respectively).

The CNA (LS mean) was also significantly $(p < 0.001)$ greater with Creon treatment compared with placebo (Table 2, Fig. 2B). The mean±SD total nitrogen intake for days 3 to 5 of each crossover period was similar for both treatments (Creon, 58.5±21.0 g; placebo, 60.2±21.8 g; statistical significance not tested). No clinically meaningful differences in CNA were observed by age group (LS mean±SE for treatment difference,

Table 1
Subject characteristics at baseline.

|  | Placebo/Creon (n=16) | Creon/placebo (n=16) | Total (N=32) |
|---|---|---|---|
| Median age (range), y | 21.5 (12–43) | 22.5 (13–38) | 22.0 (12–43) |
| Female, n (%) | 4 (25.0) | 7 (43.8) | 11 (34.4) |
| Race, n (%) |  |  |  |
| White | 16 (100) | 16 (100) | 32 (100) |
| CFA category during placebo, n (%) |  |  |  |
| ≤50 | 8 (50.0) | 9 (60.0) | 17 (54.8) |
| >50 | 8 (50.0) | 6 (40.0) | 14 (45.2) |
| Mean BMI (SD) | 21.6 (3.3) | 21.0 (2.0) | 21.3 (2.7) |

BMI: Body mass index; SD: standard deviation; CFA: coefficient of fat absorption.

Table 2
Coefficient of fat and nitrogen absorption.

|  | On Creon (n=32 [a]) | On placebo (n=31) | Treatment difference | p value for difference |
|---|---|---|---|---|
| n | 31 | 31 |  |  |
| LS mean CFA (SE) | 88.6 (2.3) | 49.6 (2.3) | 39.0 (3.1) | <0.001 |
| LS mean CNA (SE) | 85.1 (1.9) | 49.9 (1.9) | 35.2 (2.7) | <0.001 |

CFA, coefficient of fat absorption; CNA, coefficient of nitrogen absorption; LS, least squares.
[a] One subject was discontinued one day after the last dose of Creon treatment.
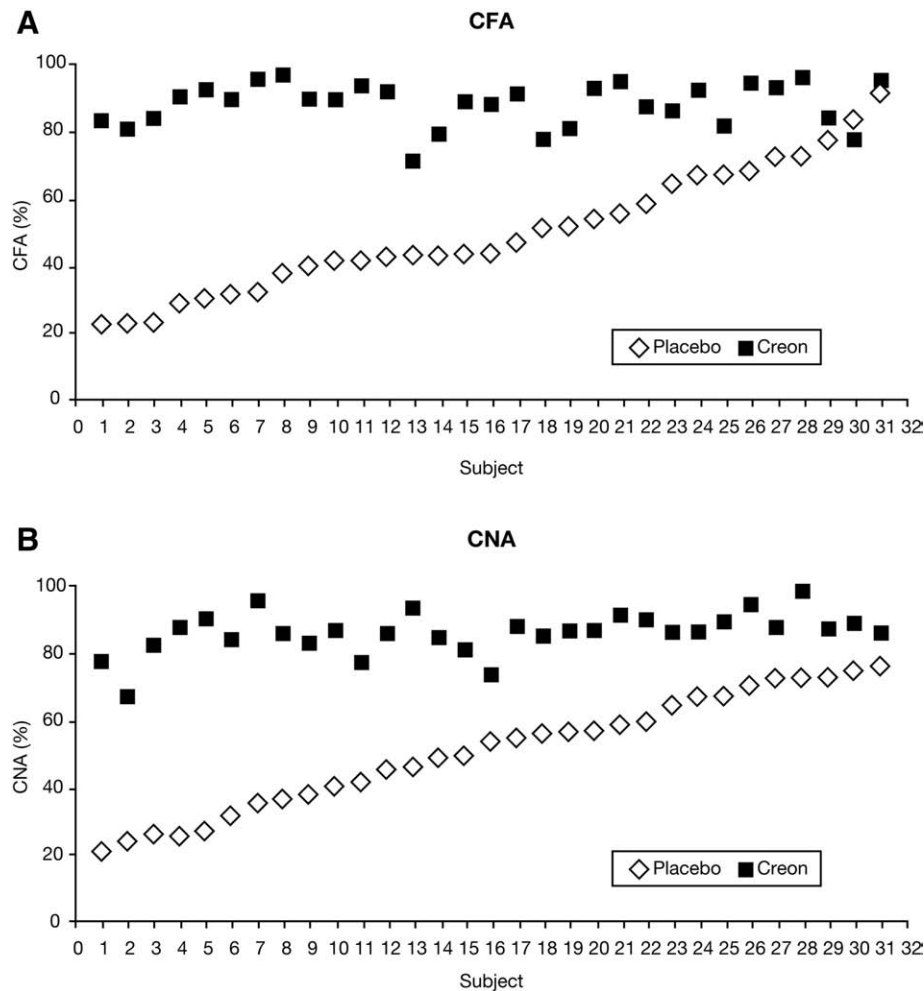
Fig. 2. Individual subject data for (A) coefficient of fat absorption (CFA) and (B) coefficient of nitrogen absorption (CNA) during treatment with Creon or placebo.

$39.0\pm5.2\%$ in the 12–18 years subgroup and $33.6\pm3.3\%$ in the >18 years subgroup; $p<0.001$ for both). As observed in the analysis of CFA by severity of EPI, subjects whose placebo CFA was $\leq50\%$ demonstrated a greater treatment effect of Creon treatment on their CNA compared with subjects whose placebo CFA was >50% (LS mean$\pm$SE for treatment difference, $42.3\pm3.0\%$ and $26.6\pm3.9\%$, respectively), but treatment differences were significant in both subgroups ($p<0.001$ for both) and LS mean$\pm$SE CFA values reached similar levels with treatment ($83.7\pm2.1\%$ and $86.3\pm2.7\%$, respectively; statistical significance not tested).

Stool fat, stool nitrogen, and stool weight were all significantly lower with Creon treatment compared with placebo (LS mean$\pm$SE stool fat, $57.9\pm12.2$ g vs. $244.5\pm12.2$ g; LS mean$\pm$SE stool nitrogen, $9.0\pm1.1$ g vs. $29.4\pm1.1$ g; LS mean$\pm$SE stool weight, $631.1\pm66.5$ g vs. $1587.3\pm66.5$ g; $p<0.001$ for all comparisons).

Adverse clinical symptoms (stool frequency, abdominal pain, stool consistency, and flatulence) occurred less frequently in the Creon group compared with the placebo group. The daily stool frequency was reduced with Creon compared with placebo (LS mean$\pm$SE, $1.8\pm0.1$ vs. $2.8\pm1.1$, respectively; $p<0.001$). Abdominal pain and flatulence were less severe and stool consistency was less watery with Creon compared with placebo.

These differences were apparent on the first day of treatment and maintained throughout the 5-day treatment period (Fig. 3). Compared with placebo, subjects on Creon reported significantly more total days without abdominal pain (LS mean$\pm$SE percent of diary days, $90.3\pm5.9$ vs. $58.4\pm6.1$, respectively; $p<0.001$), without flatulence (LS mean$\pm$SE percent of diary days, $41.6\pm4.4$ vs. $25.1\pm4.5$, respectively; $p=0.013$), and with formed/normal stools (LS mean$\pm$SE percent of diary days, $75.0\pm4.5$ vs. $24.4\pm4.7$, respectively; $p<0.001$).

No clinically meaningful differences were observed by age regarding the effects of Creon on abdominal pain, stool consistency, and flatulence (data not shown). As observed for the CFA and CNA, the differences between Creon and placebo for these symptoms were greater in subjects whose placebo CFA was $\leq50\%$ compared with subjects whose placebo CFA was >50%; however, the sample size was too small to reach meaningful conclusions (data not shown).

During Creon treatment, both the investigators' and the subjects' CGI assessments reflected a stable condition with no meaningful changes from the beginning to the end of the treatment period (Fig. 3). In contrast, the investigators and the subjects assessed the symptoms as worsening during treatment with placebo (Fig. 3).

**Abdominal Pain**



**Stool Consistency**
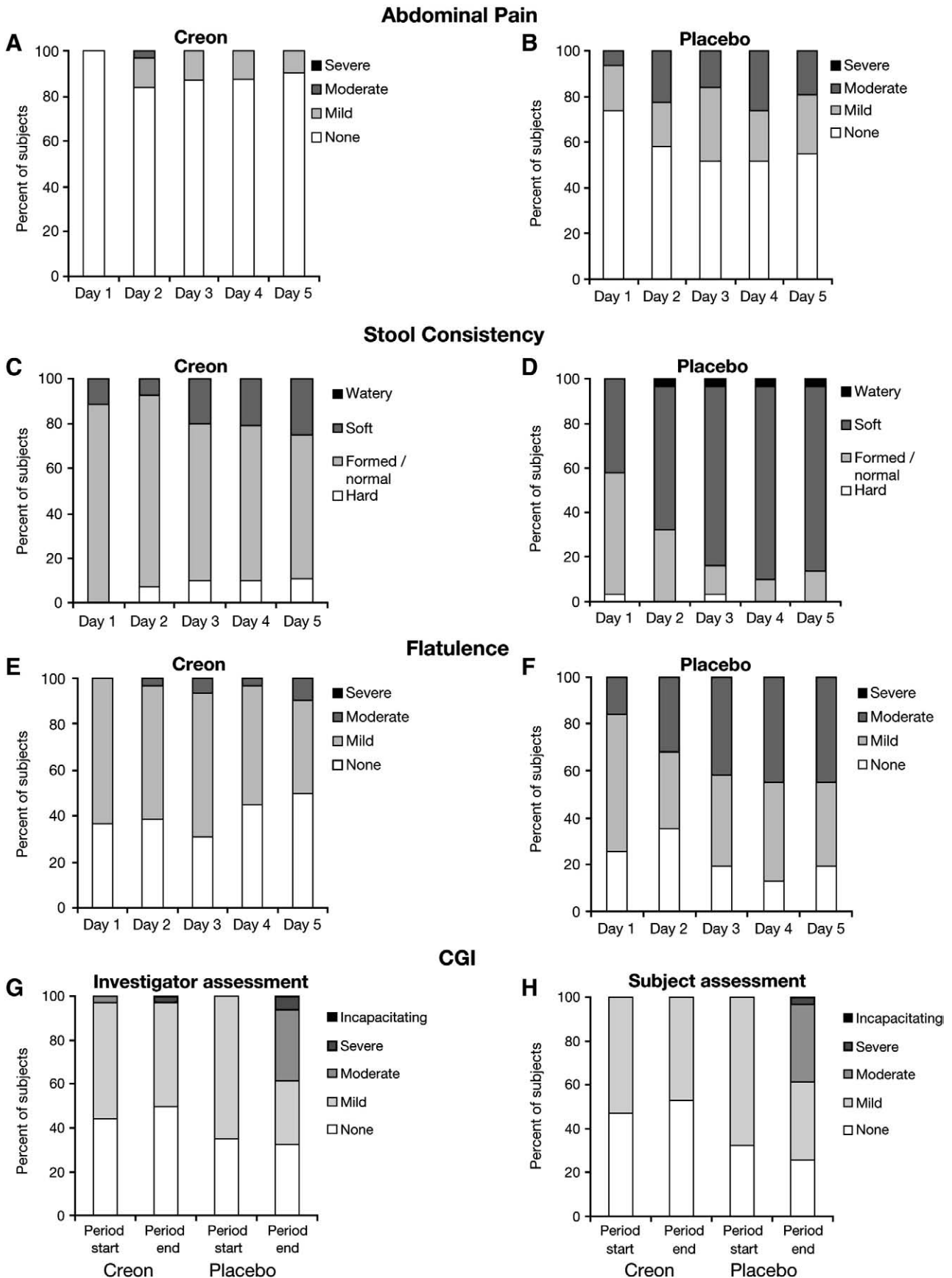


**Flatulence**



**CGI**



Fig. 3. Effect of Creon on abdominal pain (A, B), stool consistency (C, D), and flatulence (E, F), and Clinical Global Impression of Disease Severity (CGI) assessed by investigators (G) and by subjects (H).

Table 3
Treatment-emergent adverse events (TEAEs).

|  | On Creon $n=32$ (100%) | On placebo $n=31$(100%) |
|---|---|---|
| Any TEAE | 14 (43.8) | 20 (64.5) |
| Serious TEAE | 0 | 0 |
| Discontinuation due to TEAE | 1 (3.1) | 0 |
| Severe TEAE | 1 (3.1) | 1 (3.2) |
| Treatment-related TEAE | 6 (18.8) | 12 (38.7) |
| Most common TEAE [a] |  |  |
|   Gastrointestinal disorder | 6 (18.8) | 12 (38.7) |
|     Abnormal faeces | 1 (3.1) | 6 (19.4) |
|     Flatulence | 3 (9.4) | 8 (25.8) |
|     Abdominal pain | 3 (9.4) | 8 (25.8) |
|     Abdominal pain, upper | 0 | 2 (6.5) |
|   Investigations | 1 (3.1) | 2 (6.5) |
|     Weight decreased | 1 (3.1) | 2 (6.5) |
|   Nervous system disorders | 4 (12.5) | 7 (22.6) |
|     Headache | 2 (6.3) | 7 (22.6) |
|     Dizziness | 2 (6.3) | 0 |
|   Respiratory/thoracic/mediastinal disorders | 4 (12.5) | 1 (3.2) |
|     Cough | 2 (6.3) | 0 |

[a] Occurring in $\geq 5\%$ of subjects in either treatment group.

## 3.2. Safety

Treatment-emergent AEs (TEAEs) and treatment-related TEAEs had a lower overall incidence during Creon treatment than during placebo treatment (Table 3). Two severe TEAEs were reported for one subject: one TEAE occurred during Creon treatment (dizziness) and one TEAE during placebo treatment (severe upper abdominal pain).

During the washout period, one subject in the Creon/placebo treatment sequence was discontinued per protocol one day after the last dose of Creon due to a TEAE (weight decrease) that was considered unlikely related to study drug (Table 3). One subject in the Creon/placebo treatment sequence experienced serious AEs (duodenitis and gastritis) more than 2 weeks after the last dose of Creon. These AEs were considered unrelated to study participation. Analysis of AEs did not reveal any TEAEs with a clinically meaningfully greater incidence in the Creon group compared with the placebo group, and no cases of hypersensitivity were reported. No meaningful treatment group differences were observed for any of the laboratory parameters or vital signs. No deaths occurred in this study.

## 4. Discussion

These data demonstrate that Creon 24,000 capsules are an effective treatment for maldigestion with resultant malabsorption associated with EPI due to CF. Compared with placebo, fat absorption was significantly improved, as was nitrogen absorption (a marker for protein absorption) and overall symptoms of maldigestion. Creon was safe and well tolerated within the limited duration of the study; fewer TEAEs were observed with Creon treatment compared with placebo.

The CFA values achieved on Creon treatment, as well as differences in CFA values observed between Creon and placebo,

were consistent with those observed in a double-blind study of Creon 20 published by Stern et al. [7]. Similar CFA values were achieved with Creon 10 in two crossover studies that included subjects <7 years of age (78.0% and 90.5%) and subjects ≥7 years of age (CFA 83.1% and 91.8%) [6]. The average CFA achieved with Creon by subjects with CF in this study was also within the range previously observed in healthy adult subjects (86.6%–98.2%), albeit slightly lower than the mean CFA observed in those subjects (93.5%) [20].

The use of CNA to measure protein absorption is not as well characterised, although increases in CNA have been observed with pancreatic enzyme supplements in previous studies [21,22]. The significant treatment-associated differences in the CNA in the current study suggest that Creon was effective in improving protein digestion and absorption. As observed for CFA, the average CNA achieved with Creon by subjects in this study was within the range previously observed in healthy adult subjects (78.0%–94.7%) and slightly lower than the mean CNA observed in those subjects (88.1%) [20]. Ultimately, this improved nitrogen/protein absorption suggests nutritional benefits of treatment in persons with CF.

The upper limit of the lipase dose range recommended by CF Foundation consensus reports for this age group was selected for this study in order to maximise fat absorption. The mean dose in the current study slightly exceeded the upper limit of 4000 lipase units/g fat/day [13] as a result of incomplete consumption of the meals provided. The upper limit of dosing recommendations for pancreatic enzyme replacement are based on preventing the occurrence of fibrosing colonopathy, which may be associated with extremely high doses of high-strength pancreatic enzyme products [8]. Given the evidence that enzyme preparations were previously overfilled [23], dosing guidelines for pancreatic enzyme replacement therapy in patients with CF may require revisiting.

Although this study was of limited duration, no issues relating to either safety or tolerability were noted and no unexpected TEAEs were observed. In fact, the apparent treatment-associated improvement in symptomatology and in the CGI were consistent with the fewer TEAEs observed with Creon compared with placebo.

One limitation of this study is the relatively high dose chosen, coupled with dosing per gram of fat rather than per kilogram of body weight, may not be easily compared with dosing practices commonly used in the clinical setting. There are a lack of dose-response data for pancreatic enzyme replacement therapies because of the complexity of designing a study that balances the variability introduced by patient-level factors, dietary factors, and dose. In addition, CFA is not routinely determined in the course of clinical practice so the results from any short-term study with a CFA primary endpoint is of limited value in the management of individual patients. Finally, the short duration of the study does not allow conclusions to be drawn regarding long-term tolerability or symptomatology.

Taken together, the data in this study provide strong evidence for the effectiveness of Creon 24,000 capsules at a dose of approximately 4000 lipase units/g fat in the treatment of EPI in subjects with CF. In addition, these data tend to support the consistency of efficacy of these capsules with Creon 20.

## Role of the funding source

## Conflict of interest statement

Bruce Trapnell and Gavin Graff have no conflicts to report. Karen Maguiness is a consultant to both Solvay Pharmaceuticals and Altus Pharmaceuticals. David Boyd and Steven Caras are employees of Solvay Pharmaceuticals, Inc., Marietta, GA, USA. Katrin Beckmann is an employee of Solvay Pharmaceuticals GmbH, Hannover, Germany.

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