Journal of Cystic Fibrosis 15 (2016) 675–680

www.elsevier.com/locate/jcf

Original Article

Comparison of two pancreatic enzyme products for exocrine insufficiency in patients with cystic fibrosis☆

C.J. Taylor [a,*], R. Thieroff-Ekerdt [b], S. Shiff [c], L. Magnus [c], R. Fleming [b], C. Gommoll [c]

[a] University of Sheffield, Sheffield, UK
[b] Former employee of Forest Research Institute, Inc., an affiliate of Actavis, Inc., Jersey City, NJ, USA
[c] Forest Research Institute, Inc., an affiliate of Actavis, Inc., Jersey City, NJ, USA

Received 21 July 2015; revised 22 February 2016; accepted 23 February 2016
Available online 21 March 2016

Abstract

Background: Zenpep (APT-1008) is a pancreatic enzyme product for the treatment of exocrine pancreatic insufficiency (EPI) associated with cystic fibrosis (CF).
Methods: Zenpep and Kreon, both containing 25,000 lipase units, were compared in a randomised, double-blind, crossover, non-inferiority study for CF-associated EPI in patients aged ≥12 years. Patients on a standardised diet and stabilised treatment were randomised to two treatment sequences: Zenpep/Kreon or Kreon/Zenpep. The primary efficacy endpoint was the coefficient of fat absorption over 72 h (CFA-72 h).
Results: 96 patients (mean age 19.2 years, 60.4% males) were randomised with 83 completers of both sequences comprising the efficacy population. Zenpep demonstrated non-inferiority and equivalence to Kreon in fat absorption (LS mean CFA-72 h: Zenpep, 84.1% [SE 1.1] vs. Kreon, 85.3% [SE 1.1]; $p = 0.297$). Safety and tolerability were similar.
Conclusions: Zenpep is comparable with Kreon in efficacy and safety for the treatment of adolescents and adults with CF-associated EPI.
NCT01641393

Keywords: Cystic fibrosis; Clinical trial; Pancreatic enzyme product (PEP); Exocrine pancreatic insufficiency (EPI); Zenpep; Enzepi

1. Introduction

Approximately 85% of patients with cystic fibrosis (CF) exhibit signs of exocrine pancreatic insufficiency (EPI) in addition to respiratory signs and symptoms [1]. EPI is characterised by severely decreased secretion of pancreatic digestive enzymes (i.e., amylase, lipase, colipase, proteases, and phospholipases), and bicarbonate due to impaired fluid secretion and obstruction of pancreatic ducts by dehydrated aggregates of pro-enzymes [2,3]. Pancreatic dysfunction is thought to be the main cause of severe malabsorption and poor nutrition in CF. Clinical manifestations of EPI include poor fat and protein absorption and hence high faecal excretion of fat and nitrogen, high faecal weight, increased stool frequency and poor weight gain. Malnourishment and pancreatic insufficiency have been associated with reduced lung function and poor clinical course [4,5].

Pancreatic enzymes products (PEPs) have been used for several decades in the treatment of patients with EPI associated with CF or other conditions [6]. These preparations contain mixtures of pancreatic lipase, amylase, protease, and other pancreas-derived proteins and nucleic acids [7]. Conventional

Abbreviations: AE, Adverse event; BMI, Body mass index; CF, Cystic fibrosis; CFA, Coefficient of fat absorption; CFA-72 h, CFA over 72 h; CFN, Coefficient of nitrogen absorption; CNA-72 h, CNA over 72 h; CFQ-R, Cystic Fibrosis Questionnaire-Revised; EPI, Exocrine pancreatic insufficiency; LS, Least-squares; PEP, Pancreatic enzymes product; TEAE, Treatment-emergent adverse event.

☆ Previously presented at the 38th European Cystic Fibrosis Conference, 10–13 June, 2015; Brussels, Belgium.

* Corresponding author at: Sheffield Children's NHS Trust Hospital, Academic Unit of Child Health, Western Bank, Sheffield S10 2TH, UK. Tel.: +44 114 271 7304.
E-mail addresses: c.j.taylor1@sheffield.ac.uk (C.J. Taylor), rekerdt@cortendo.com (R. Thieroff-Ekerdt), steven.shiff@frx.com (S. Shiff), leslie.magnus@frx.com (L. Magnus), rosabfleming@yahoo.com (R. Fleming), carl.gommoll@frx.com (C. Gommoll).

http://dx.doi.org/10.1016/j.jcf.2016.02.010

powder or tablet formulations (not enteric-coated) were only partially effective in relieving EPI symptoms as pancreatic enzymes were inactivated by pepsin and gastric acidity [8]. These observations prompted development of enteric-coated tablets and later, enteric-coated microspheres. These products dissolve at a pH >5.5, allowing intact passage through the stomach with dissolution and activation in the higher pH of the duodenum.

This study compared two enteric-coated PEPs, Zenpep 25,000 lipase units (APT-1008, awaiting approval in the European Union, to be marketed as Enzepi®), and the comparator, Kreon® 25,000 lipase units. Both Zenpep and Kreon are porcine-derived pancreatic enzyme products containing various enzymes with proteolytic, lipolytic, and amylolytic activity [9]. PEPs are dosed based on lipase activity (in terms of lipase units). Lipase is, however, unstable in the presence of moisture and degrades over time, meaning that an overage as high as 160% (as overfill) has historically been included in PEPs, including Kreon. Zenpep, aligned with the Committee for Medicinal Products for Human Use guideline on the clinical development of medicinal products for the treatment of CF [10], is a novel moisture-resistant PEP formulated to reliably contain between 90% to 110% labelled lipase content over the shelf life of the product, without overfill. This distinctive feature enables more accurate dosing, both providing more predictable therapeutic effects and reducing the risk of overdose, which is discussed as a potential risk factor for fibrosing colonopathy, a rare and serious condition [11]. The primary objective of this study was to evaluate the safety and efficacy of Zenpep compared with Kreon in the treatment of CF-associated EPI in patients aged 12 years and older who were able to swallow the capsules whole.

2. Patients and methods

This was a randomised, double-blind, active-controlled, crossover, multinational, non-inferiority study comparing Zenpep and Kreon (each capsule containing approximately 25,000 Ph. Eur. lipase units) in the treatment of CF-associated EPI with CF in patients aged 12 years and older (NCT01641393). The study was conducted at 34 sites in seven European countries including Belgium, Bulgaria, Germany, Hungary, Italy, Poland, and the UK. The study was conducted in compliance with the clinical study protocol and in accordance with the International Conference on Harmonisation (ICH) guidelines for Good Clinical Practice (GCP), the ICH Tripartite Guideline for GCP, and the Declaration of Helsinki. Informed consent was obtained from each patient (or parent/legal guardian for minors) before study entry.

Inclusion criteria included definitive diagnosis of CF based on one clinical feature consistent with CF and either a genotype with two identifiable disease-causing CF mutations or a sweat chloride concentration >60 mmol/L. Other inclusion criteria were pancreatic insufficiency documented by a monoclonal faecal elastase ≤100 μg/g stool at screening, current treatment with pancreatic enzyme replacement therapy, and adequate nutritional status based on a body mass index (BMI) >19 kg/m^2 in adult patients or a BMI ≥10th percentile for age in adolescents aged 12–17 years. Exclusion criteria included patients with clinically significant cardiac, renal, neurological, gastrointestinal (e.g., fibrosing colonopathy), hepatic, or endocrine disease.

The primary efficacy variable was the coefficient of fat absorption over 72 h (CFA-72 h) calculated from dietary fat intake and stools collected during the last 3 days (72 consecutive hours) of each treatment period. The secondary efficacy variables were: change in body weight, coefficient of nitrogen absorption over 72 h (CNA-72 h), signs and symptoms of EPI as recorded in patient diaries, and impact on overall health, daily life, perceived well-being, and CF symptoms as evaluated by the Cystic Fibrosis Questionnaire-Revised (CFQ-R).

Patients entered the study with an established PEP regimen. In consultation with a dietician, a daily 100 g (±15 g) fat diet was assigned and maintained throughout the study. The 96 eligible patients (mean age 19.2 years, 60.4% males) were randomised to one of two treatment sequences of 28 days (±2 days), group A or B. Patients in group A received Zenpep in treatment period 1 and crossed over to Kreon in treatment period 2; patients in group B received the two study drugs in reverse order. In treatment period 1, patients began the assigned treatment (Kreon or Zenpep, depending on treatment sequence) at a dose as close as possible to their established PEP treatment (Fig. 1). No washout periods were included in this study as any residual lipase from the prior treatment period was considered to have had a negligible influence on the subsequent CFA-72 h determination. Daily dose could be rounded up from the initial dose to the nearest number of capsules to a maximum of 10,000 lipase units/kg of body weight per day or 4000 lipase units/g of fat ingested per day, not to exceed a dose of 10,000 lipase units/kg of body weight per day, in which case the dose was rounded down to the nearest number of whole capsules. Dosage adjustment to relieve clinical symptoms was permitted during the first 2 weeks of each treatment period. In treatment period 2, patients began the assigned treatment at the same starting dose used for treatment period 1. Throughout the study, patients were required to abstain from nutritional supplements containing high concentrations of (≥30%) medium-chain triglycerides [12,13].

Stool samples were collected in a hospital/clinic or other controlled environment to ensure adherence to the prescribed diet and quantitative stool collection. Stools were collected for 72 consecutive hours starting on the morning of day 26 (±2 days) of each of the 28-day (±2 days) treatment periods. Stool fat and nitrogen were measured, and the coefficient of fat absorption (CFA) and coefficient of nitrogen absorption (CNA) were calculated. Percent CFA was calculated as: percent CFA = {[dietary fat intake (grams) − stool fat excretion (grams)] / dietary fat intake (grams)} × 100 [13].

CNA-72 h was calculated, similarly to CFA, at the end of each treatment period, based on dietary protein intake and protein excretion data from the stools collected during the last 72 h of each treatment period. Protein content in the stool was assessed by a specialised central laboratory by means of the Dumas combustion method [14].

Patients recorded in a diary the frequency and characteristics of stools and symptoms suggestive of malabsorption including bloating, abdominal pain, and flatulence. Entries from the last 2 weeks of each treatment period were used in the efficacy

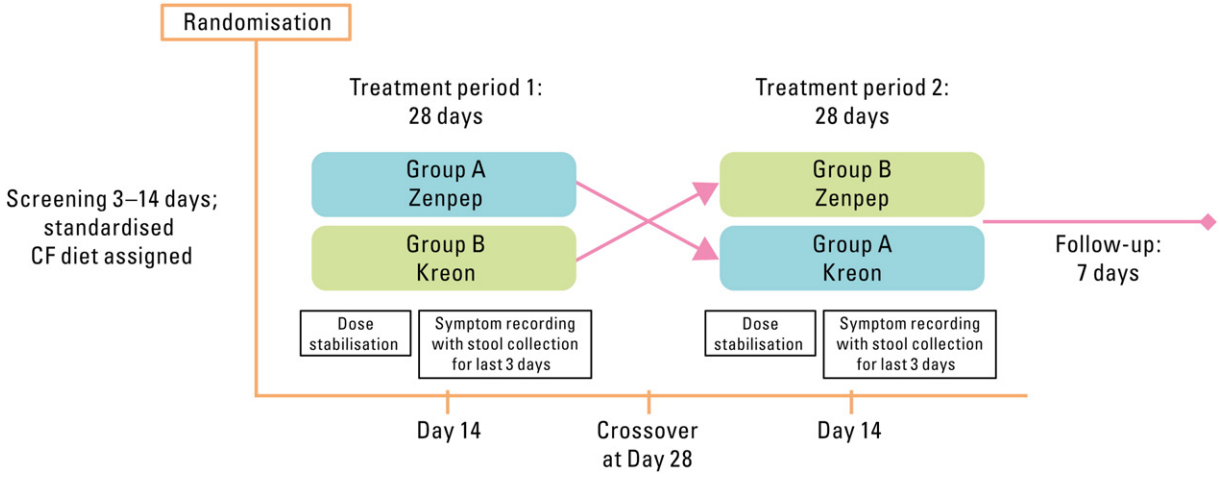

Fig. 1. Study design. CF, cystic fibrosis.

assessment of signs and symptoms. The diary also was used to record information regarding dietary and medication adherence. During each treatment period, patients were required to record in a diary each dose of study drug taken. Treatment adherence, defined as percentage ≥75% and ≤125% of capsules taken versus capsules prescribed, was determined on the basis of diary entries and study drug reconciliation and was evaluated at each visit.

The Cystic Fibrosis Questionnaire-Revised (CFQ-R) was administered to assess the impact of the treatment on overall health, daily life, perceived well-being, and symptoms. Parents and caregivers of children aged 13 years and younger received the CFQ-R-Parent version of the questionnaire; adults and adolescents aged 14 years and older received the CFQ-R-Teen/Adult version. The CFQ-R was completed at the beginning of each treatment period and at the end of the study.

Statistical analysis was performed using SAS® version 9.3 (SAS Institute Inc., Cary, NC, USA). The choice of 5% as the non-inferiority margin for CFA-72 h was based on the differences observed between Kreon and placebo in three randomised double-blind trials [15–17]. The primary efficacy analysis of CFA-72 h was based on the completers population, defined as all randomised patients who received at least one dose of Zenpep or Kreon and finished both treatment periods with complete CFA-72 h data.

Mixed linear models were used to analyse CFA-72 h, body weight changes, CNA-72 h, average number of stools per day, and CFQ-R scores. Logistic regression models with repeated proportions were used to analyse stool consistency, visible fat/grease in stools, and symptoms of abdominal pain, flatulence, and bloating.

3. Results

Of the 96 patients randomised, 86 completed the study, and CFA-72 h data were available from both treatment periods for 83 patients (completers population; Fig. 2) Patient mean age at screening in the 96 patients randomised was 19.2 years (SD 7.9) and 60.4% were male. Demographics and baseline characteristics were well balanced between groups A and B (Table 1). In the completers population, all patients achieved a study drug compliance level of ≥80% during the 72-h stool collection period and all (100% with Zenpep) or nearly all (98.8% with Kreon) patients achieved this level of compliance during the treatment period.

For the primary efficacy variable (CFA-72 h at the end of each treatment period), Zenpep demonstrated both non-inferiority and equivalence to Kreon in dietary fat absorption (least-squares [LS] mean CFA-72 h: Zenpep, 84.1% [SE 1.1] vs. Kreon, 85.3% [SE 1.1]; difference in LS means: −1.3% (95% CI, −3.6 to 1.1) p = 0.297; Table 2). The lower limit of the CI (3.6%) exceeded the non-inferiority margin of 5%, and the 95% CI was completely between −5% and 5% and included 0 to show equivalency. Non-inferiority of Zenpep to Kreon was demonstrated; furthermore, the equivalence of the two drugs also was demonstrated.

Efficacy results of Zenpep and Kreon also were similar for the secondary endpoints. Overall, the LS mean CNA-72 h values were similar for Zenpep (80.9% [SE 1.2]) and Kreon (82.0 [SE 1.2]), with a difference in LS means of −1.1 and a 95% CI (−3.3 to 1.2) and p = 0.334 (Table 2) Patients began the study with a mean baseline body weight of 54.1 kg. No difference in change in body weight from baseline was observed with Zenpep and Kreon (54.6 kg) at end of treatment. Both drugs resulted in an overall LS mean gain in body weight of 0.5 kg.

Signs and symptoms of EPI on treatment were not significantly different between Zenpep and Kreon. The average number of stools per day was similar for Zenpep (1.5 [SE 0.1]) and for Kreon (1.5 [SE 0.1]), resulting in a difference in LS means of 0.02, with a 95% CI (−0.05, 0.09) and p = 0.636. A nominally significant difference in the proportion of patient-days (i.e., the number of days that a symptom of any severity was reported divided by the total number of days that the symptom diary was completed) with bloating was observed between Zenpep and Kreon (p = 0.007), with the majority being reported as mild with both treatments; however, patient-days with bloating were infrequent with both Zenpep (0.2 overall mean proportion) and Kreon (0.1).

Zenpep and Kreon had a similar impact on overall health, perceived well-being, and CF symptoms as measured by the

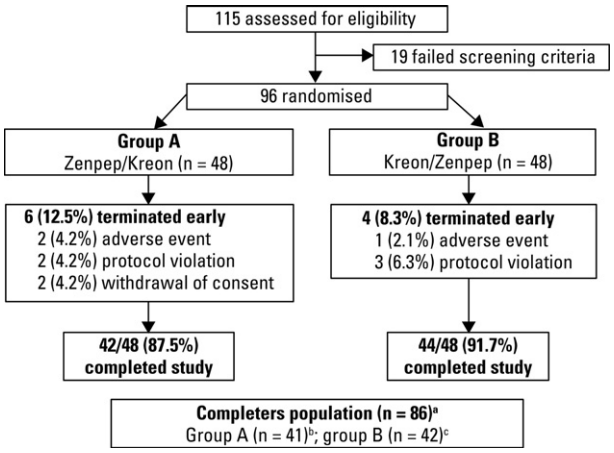

Fig. 2. Patient disposition, consort diagram. [a]Missing data for coefficient of fat absorption over 72 h (CFA-72 h) for three patients. [b]Missing CFA-72 h data for one patient. [c]Missing CFA-72 h data for two patients.

CFQ-R-Parent and CFQ-R-Teen/Adult. No significant differences were observed between Zenpep and Kreon for any domains of the CFQ-R-Parent. For the CFQ-R-Teen/Adult, a nominally significant difference in favour of Zenpep was observed only for the respiratory domain, with a higher LS mean change from baseline for Zenpep (6.8) than for Kreon (3.7), a 95% CI of the difference in LS mean changes (0.4, 5.9) and $p = 0.026$.

Treatment with Zenpep was generally safe and well tolerated. The safety results seen in this study were consistent with the known profile of Zenpep and comparable to Kreon. The proportion of patients reporting treatment-emergent adverse events (TEAEs) was relatively low with both treatments. The number of patients reporting TEAEs was numerically lower for Zenpep than for Kreon, 18 (19.6%) vs. 23 (25.6%), respectively. In five patients (5.4%) taking Zenpep and eight patients (8.9%) receiving Kreon, observed TEAEs were consistent with the underlying disease, with abdominal pain, diarrhoea, and flatulence reported most frequently. Most TEAEs were reported at a maximum intensity of mild. Investigators reported no serious adverse events (AEs) related to treatment and no deaths.

Table 2
Analysis of CFA-72 h (%), CNA-72 h (%), and change in body weight—completers population.

	Zenpep ($N = 83$)	Kreon ($N = 83$)
CFA-72 h, LS mean (SE)	84.1 (1.1)	85.3 (1.1)
Difference in LS means, 95% CI	−1.3 (−3.6, 1.1), $p = 0.297$	
CNA-72 h, LS mean (SE)	80.9 (1.2)	82.0 (1.2)
Difference in LS means, 95% CI	−1.1 (−3.3, 1.2), $p = 0.334$	
Change in body weight, LS mean kilograms (SE)	0.5 (0.1)	0.5 (0.1)
Difference in LS means, 95% CI	0.0 (−0.2, 0.2), $p = 0.966$	

CFA-72 h, coefficient of fat absorption over 72 h; CNA-72 h, coefficient of nitrogen absorption over 72 h; LS, least-squares.

4. Discussion

Overall, Zenpep demonstrated efficacy comparable with Kreon. Specifically, Zenpep demonstrated both non-inferiority and equivalence to Kreon in terms of control of dietary fat absorption (assessed as CFA-72 h). Kreon and Zenpep, which produced with no overfill, showed marginal differences in lipase activity. Kreon 10,000 lipase units was originally selected as the comparator to Zenpep 10,000 lipase units for this study; however, certificates of analysis revealed that Kreon contained a 40% to 50% overfill of lipase. Therefore, after the first patient was randomised, the study was stopped. To address this issue of overfill, a new comparator drug formulation, Kreon 25,000 lipase units, was tested and had less than 10% overfill; thus the study was re-started and used Kreon 25,000 lipase units and Zenpep 25,000 lipase units.

The efficacy results of Zenpep demonstrated in this study are broadly similar to those reported previously. In a placebo-controlled study involving 32 patients (mean age 15.4 years) with CF-associated EPI, 29 (91%) achieved an LS mean CFA above 80% after a 6- to 7-day treatment with Zenpep (LS mean CFA-72 was 88.3%) [18]. For the 83 completers in our study, the LS mean CFA-72 h was 84.1%. In the placebo-controlled study, an LS mean CNA of 87.2% was reported, a result that is broadly comparable to the LS mean CNA-72 h of 80.9% found for the completers population in our study.

Table 1
Patient demographics and baseline characteristics—intention-to-treat population.

Characteristic	Group A Zenpep/Kreon ($N = 48$)	Group B Kreon/Zenpep ($N = 48$)	Total ($N = 96$)
Age, mean (range) year	20.4 (12–42)	18.0 (12–43)	19.2 (12–43)
Male, *n* (%)	29 (60.4)	29 (60.4)	58 (60.4)
CF diagnosis based on, *n* (%)			
Clinical feature plus	48 (100.0)	48 (100.0)	96 (100.0)
Genotype with 2 CF mutations OR	40 (83.3)	44 (91.7)	84 (87.5)
Sweat chloride >60 mmol/L	36 (75.0)	39 (81.3)	75 (78.1)
Monoclonal faecal elastase <15 μg/g, n (%)	36 (75.0)	38 (79.2)	74 (77.1)
Body weight, mean (SD) kg	53.3 (13.3)	53.8 (13.9)	53.6 (13.5)

CF, cystic fibrosis; EPI, exocrine pancreatic insufficiency.

The efficacy of Kreon in this study was also consistent with published data. In a placebo-controlled study, 97 patients (aged 7 years and older) with CF-associated pancreatic insufficiency and steatorrhoea, received a high-fat diet and Kreon. After the patients had been stabilised, those with a CFA greater than 80% either continued with Kreon or received a placebo during a 72-h stool collection phase. In the Kreon group, patients maintained a mean CFA of 84.1%, whereas placebo was associated with a drop in mean CFA to 52.2% [19]. In a double-blind, placebo-controlled crossover study involving 32 patients with CF-associated EPI, 5 days of Kreon resulted in an LS mean CFA of 88.6% and an LS mean CNA of 85.1% [17]. In our study, results for the completers population were broadly similar, with LS means for CFA-72 h of 85.3% and CNA-72 h of 82.0% with Kreon.

Signs and symptoms associated with EPI, evaluated as secondary endpoints, showed that the proportion of patient-days with abdominal pain or flatulence with Zenpep was comparable to those seen with Kreon (Table 3). Abdominal pain and flatulence was of mild intensity in the majority of subjects with both treatments; however, a nominally significant difference in the proportion of patient-days with bloating was observed between Zenpep and Kreon ($p = 0.007$). The overall mean proportion of patient-days with bloating was low with both treatments (0.2 with Zenpep and 0.1 with Kreon), and the majority of bloating was of mild intensity with both treatments; therefore, the clinical significance of the difference in bloating is unclear. Zenpep and Kreon had similar effects on stool frequency, stool consistency, and visible fat/grease in the stool. For the CFQ-R-Teen/Adult, a nominally significant difference in favour of Zenpep was observed only for the respiratory domain, with a higher LS mean change from baseline for Zenpep than for Kreon ($p = 0.026$). Otherwise, Zenpep and Kreon showed a similar impact on overall health, perceived well-being, and CF symptoms as measured by the CFQ-R-Parent and CFQ-R-Teen/Adult.

The safety and tolerability of Zenpep was comparable to Kreon, with a numerically lower number of patients experiencing TEAEs with Zenpep. The safety findings for Zenpep in this study were consistent with the established safety profile summarised in the Zenpep US prescribing information. The most common known AEs (>6% of patients treated with Zenpep) are abdominal pain, flatulence, headache, cough, decreased weight, early satiety, and contusion [19,20]. Gastrointestinal events, including abdominal pain and flatulence, were the most frequently reported TEAEs in this study; however, no instances of weight loss, early satiety, or contusion were reported. None of the TEAEs in this study occurred at a rate of more than 3.3%, underscoring the favourable safety profile of Zenpep.

Table 3
Analysis of patient-reported signs and symptoms over the last 2 weeks of the treatment period—completers population.

	Zenpep ($N = 83$)	Kreon ($N = 83$)	p-value
Stool frequency per day, LS mean (SE)	1.5 (0.1)	1.5 (0.1)	0.636
Proportion of days with:			
Hard + formed/normal stool consistency, mean (SD)	0.7 (0.3)	0.8 (0.3)	0.698
Stools with visible fat/grease, mean (SD)	0.1 (0.1)	0.1 (0.2)	0.826
Bloating, mean (SD)	0.2 (0.3)	0.1 (0.2)	0.007
Abdominal pain, mean (SD)	0.1 (0.2)	0.1 (0.2)	0.691
Flatulence, mean (SD)	0.4 (0.4)	0.4 (0.4)	0.445

LS, least-squares.

5. Conclusions

Zenpep demonstrated both non-inferiority and equivalence to Kreon in the primary endpoint of dietary fat absorption. Further, efficacy results of Zenpep and Kreon were generally similar for the secondary endpoints. TEAEs were consistent with the known profile of Zenpep and comparable to Kreon. The distinctive lack of enzyme overfill with Zenpep enables more accurate dosing, thereby providing more predictable therapeutic effects. Moreover, with the increasing use of high-dose PEPs containing a stated dose of 25,000–40,000 lipase units/capsule, dosages in excess of the recommended 10,000 U lipase/Kg are easily reached. As this has been described as a potential risk factor for fibrosing colonopathy, more exact PEP dosing with zero overfill could theoretically reduce this risk.

Conflicts of interest

CJT is a consultant to Aptalis and Profile Pharma. SS, LM, and CG are employees of Actavis, Inc. RF and RTE are former employees of Forest Research Institute, an affiliate of Actavis, Inc., when the study was performed.

Author contributions and funding support

Funding for this study was provided by Aptalis Pharma US, Inc., an affiliate of Actavis, Inc. All authors contributed to the conception and design of the study, or acquisition of the data, or to data interpretation. All authors contributed to the initial draft of the manuscript, participated in review and revision of the manuscript and approved the final version.

Acknowledgements

We thank all of the participating sites as well as all of the patients and their families who participated in this study. Funded medical writing support was provided by Gayle Scott, PharmD, of Excel Scientific Solutions.

The authors would like to express gratitude to the following co-investigators for their contributions to this study:
Kristine Desager, University Hospital Antwerp-Universitair Ziekenhuis Antwerpen, Leuven, Belgium; Miroslava Bosheva, Clinic of Genetic and Paediatric Diseases at UMHAT Sveti Georgi, Plovdiv, Bulgaria; Vania Nedkova, Clinic of Genetic and Paediatric Diseases UMHAT Dr. Georgi Stranski JSC, Pleven, Bulgaria; Svetoslav Dachev, Specialized Hospital for Active Treatment of Pulmological and Phtisiatric Diseases, Ruse, Bulgaria; Ivan Galabov, Multiprofile Clinic for Specialized Pediatric Clinic at MHAT Sveta Marina, Varna, Bulgaria;

Ivanka Galeva, Clinic of Pediatric Diseases, UMHAT 'Alexandrovska', Sofia, Bulgaria; Joachim Riethmueller, Universitätsklinik für Kinder- und Jugendmedizin Tübingen, Tübingen, Germany; Jochen Mainz, Universitätsklinikum Jena, Klinik für Kinder- und Jugendmedizin, Jena, Germany; Manfred Ballmann, Ruhr-Universität Bochum—St. Josef Hospital, Klinik für Kinder- und Jugendmedizin, Bochum, Germany; Olga Bede, Peadiatric Clinic and Peadriatic Health Centre, University of Szeged, Szeged, Hungary; Kálmán Gyurkovits, Somogy County Kaposi Mor Teaching Hospital, Pulmonology for children, Mosdos, Hungary; Klara Holics, Heim Pal Hospital for children, Budapest, Hungary; Istvan Laki, Pediatric Department, Pest County Pulmonology Hospital, Torokbalint, Hungary; Ferenc Gonci, Kenezy Hospital, Pulmonology for Children, Debrecen, Hungary; Marco Cipolli, Azienda Ospedaliero Universitaria Integrata, Centro Fibrosi, Cistica-Ospedale Civile Maggiore, Verona, Italy; Rolando Gagliardini, Azienda Ospedaliero Universitaria, Ospedali Riuniti, Ospedale Pediatrico, Ancona, Italy; Mario La Rosa, University of Catania, Catania, Italy; Valeria Raia, University Federico II of Naples, Pediatrics Department, Naples, Italy; Vincenzina Lucidi, Bambino Gesu Hospital, Rome, Italy; Bruna Santini, Ospedale Infantile Regina Margherita, Turin, Italy; Antonio Manca, Azienda Ospedale Policlinico di Bari, Bari, Italy; Giuseppe Magazzu, Azienda Ospedaliera Universitaria Policlinico G. Martino, Messina, Gastroenterologia Pediatrica E. Fibrosi Cistica, Messina, Italy; Serenella Bertasi, University of Rome La Sapoenza, Dipartimento di Biotecnologia cellulare ed ematologia-Sezione ematologia, Rome, Italy; Maria Saracco, Clinica di Malattie dell'Apparato Respiratorio, A.S.O. San Luigi, Orbassano (Turin), Italy; Maria Trawinska-Bartnicka, Poradnia Leczenia Mukowiscydozy, Specjalistyczny Zespol Opieki Zdrowotnej, Gdansk, Poland; Henryk Mazurek, NZOZ Sanatorium Cassia Villa Medica, Rabka Zdroj, Poland; Dorota Sands, IRMED Irena Woojociechowska, Warsaw, Poland; Andrzej Emeryk, ALERGOTEST s.c. Specjalistyczne Centrum Medyczne, Lublin, Poland; Grzegorz Gaszczyk, Centrum Pulmonologi i Alergologii w Karpaczu, Karpacz, Poland; Iwona Stelmach, Wojewodzki Szpital Specjalistyczny im Kopernika, Lodz, Poland; Marek Woynarowski, Centrum Zdrowia Matki, Dziecka-Mlodziezy, Warsaw, Poland; Marta Rachel, NZOZ Podkarpacki Osrodek Pulmonologii i Alergologii, Warsaw, Poland; Christopher Taylor, Child Health Sheffield Children's NHS Trust Hospital, School of Medicine and Biomedical Sciences Academic Unit, Sheffield, UK; and Martin Walshaw, Liverpool Heart and Chest Hospital, Liverpool, UK.

References

[1] Ahmed N, Corey M, Forstner G, Zielenski J, Tsui LC, Ellis L, et al. Molecular consequences of cystic fibrosis transmembrane regulator (CFTR) gene mutations in the exocrine pancreas. Gut 2003;52(8):1159–64.

[2] Durie PR. Pathophysiology of the pancreas in cystic fibrosis. Neth J Med 1992;41(3–4):97–100.

[3] Freedman SD, Blanco P, Shea JC, Alvarez JG. Mechanisms to explain pancreatic dysfunction in cystic fibrosis. Med Clin North Am 2000;84(3):657–64 [x].

[4] Corey M, Edwards L, Levison H, Knowles M. Longitudinal analysis of pulmonary function decline in patients with cystic fibrosis. J Pediatr 1997;131(6):809–14.

[5] Steinkamp G, Wiedemann B. Relationship between nutritional status and lung function in cystic fibrosis: cross sectional and longitudinal analyses from the German CF quality assurance (CFQA) project. Thorax 2002;57(7):596–601.

[6] DeYoung JL. Development of pancreatic enzyme microsphere technology and US findings with pancrease in the treatment of chronic pancreatitis. Int J Pancreatol 1989;5:31–6 [suppl].

[7] Wier HA, Kuhn RJ. Pancreatic enzyme supplementation. Curr Opin Pediatr 2011;23(5):541–4.

[8] DiMagno EP, Malagelada JR, Go VL, Moertel CG. Fate of orally ingested enzymes in pancreatic insufficiency. Comparison of two dosage schedules. N Engl J Med 1977;296(23):1318–22.

[9] The European Directorate for the Quality of Medicines & HealthCare. European Pharmacopoeia Online 8.5 [cited 2015 Jun 17]. Available from: http://online.pheur.org/entry.htm.

[10] European Medicines Agency. Guideline on the clinical development of medicinal products for the treatment of cystic fibrosis [EMEA/CHMP/EWP/9147/2008] [cited 2015 Jun 17]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003507.pdf.

[11] FitzSimmons SC, Burkhart GA, Borowitz D, Grand RJ, Hammerstrom T, Durie PR, et al. High-dose pancreatic-enzyme supplements and fibrosing colonopathy in children with cystic fibrosis. N Engl J Med 1997;336(18):1283–9.

[12] Jeppesen PB, Mortensen PB. Colonic digestion and absorption of energy from carbohydrates and medium-chain fat in small bowel failure. JPEN J Parenter Enteral Nutr 1999;23(Suppl. 5):S101–5.

[13] Borowitz D, Konstan MW, O'Rourke A, Cohen M, Hendeles L, Murray FT. Coefficients of fat and nitrogen absorption in healthy subjects and individuals with cystic fibrosis. J Pediatr Pharmacol Ther 2007;12(1):47–52.

[14] PR Wilson. A new instrument concept for nitrogen/protein analysis. A challenge to the Kjeldahl method. Asp Appl Biol 1990:25443–6.

[15] D'Haese JG, Ceyhan GO, Demir IE, Layer P, Uhl W, Lohr M, et al. Pancreatic enzyme replacement therapy in patients with exocrine pancreatic insufficiency due to chronic pancreatitis: a 1-year disease management study on symptom control and quality of life. Pancreas 2014;43(6):834–41.

[16] Perano SJ, Couper JJ, Horowitz M, Martin AJ, Kritas S, Sullivan T, et al. Pancreatic enzyme supplementation improves the incretin hormone response and attenuates postprandial glycemia in adolescents with cystic fibrosis: a randomized crossover trial. J Clin Endocrinol Metab 2014;99(7):2486–93.

[17] Trapnell BC, Maguiness K, Graff GR, Boyd D, Beckmann K, Caras S. Efficacy and safety of Creon 24000 in subjects with exocrine pancreatic insufficiency due to cystic fibrosis. J Cyst Fibros 2009;8(6):370–7.

[18] Wooldridge JL, Heubi JE, Amaro-Galvez R, Boas SR, Blake KV, Nasr SZ, et al. EUR-1008 pancreatic enzyme replacement is safe and effective in patients with cystic fibrosis and pancreatic insufficiency. J Cyst Fibros 2009;8(6):405–17.

[19] Stern RC, Eisenberg JD, Wagener JS, Ahrens R, Rock M. doPico G, et al. A comparison of the efficacy and tolerance of pancrelipase and placebo in the treatment of steatorrhea in cystic fibrosis patients with clinical exocrine pancreatic insufficiency. Am J Gastroenterol 2000;95(8):1932–8.

[20] Zenpep [prescribing information]. Bridgewater, NJ, USA: Aptalis Pharma US, Inc.; 2014.