ELSEVIER

Journal of Cystic Fibrosis 14 (2015) 275 – 281

Journal of Cystic Fibrosis

www.elsevier.com/locate/jcf

Original Article

Safety and efficacy of Creon® Micro in children with exocrine pancreatic insufficiency due to cystic fibrosis☆

Nataliya Y. Kashirskaya [a], Nikolay I. Kapranov [a], Suntje Sander-Struckmeier [b,*], Vladimir Kovalev [c]

[a] Department of Cystic Fibrosis, Research Centre for Medical Genetics RAMS, Moskvorechye str. 1, Moscow 115478, Russia
[b] Abbott Laboratories GmbH, Freundallee 9A, 30173 Hannover, Germany
[c] Abbott Laboratories, Leningradskoye shosse 16A, Moscow 125171, Russia

Received 28 March 2014; received in revised form 8 July 2014; accepted 9 July 2014
Available online 25 July 2014

Abstract

Background: Pancreatic enzyme replacement therapy is the foundation of nutritional management for exocrine pancreatic insufficiency (EPI).
Methods: A 3-month, open-label, multicentre study in Russia assessing safety, efficacy, and ease-of-use of Creon® Micro (5000 lipase units/spoon) in children aged 1 month to <4 years with EPI due to cystic fibrosis. Efficacy assessments included growth parameters.
Results: All 40 subjects (mean age 26.5 months) completed treatment. Adverse events occurred in 40% of the subjects (most commonly respiratory tract infection [15%], frequent bowel movements [8%], rhinitis, stomatitis, nasopharyngitis, and diarrhoea [all 5%]), none were serious or led to discontinuation. After 3 months, mean ± SD increases from baseline z-scores were height/length-for-age 0.13 ± 0.48, weight-for-age 0.20 ± 0.39, and BMI-for-age 0.29 ± 0.65. Treatment was rated 'easy' to administer by 95% caregivers and acceptance 'good'/'very good' by 90%.
Conclusions: Creon Micro was well tolerated. Growth development parameters increased over the 3-month treatment period. Treatment was considered easy to use and acceptance was good.

Keywords: Clinical trial; Creon; Cystic fibrosis; Pancreatic enzyme replacement therapy; Exocrine pancreatic insufficiency; Pancreatin

1. Introduction

Exocrine pancreatic insufficiency (EPI) affects approximately 80–90% patients with cystic fibrosis (CF). It is often present at birth and is identified in the majority of patients within their first year [1–3]. EPI results in the maldigestion of food and malabsorption of nutrients, including fat soluble vitamins, leading to malnutrition and symptoms such as poor weight gain, steatorrhea, and abdominal pain [4]. Several studies have shown that adequate nutrition and normal growth are associated with better pulmonary function, fewer complications, and increased survival in patients with CF [5–10]. If EPI is untreated or undertreated, poor growth and development is likely to adversely affect disease course and survival. Early diagnosis of CF, and early detection and treatment of EPI, is therefore vital. In Russia, children with CF are now detected mainly through the national neonatal screening program, initiated in January 2007, which facilitates early diagnosis and treatment.

The standard of care for EPI is pancreatic enzyme replacement therapy (PERT) in combination with dietary management, regardless of its aetiology. Guidelines for the management of CF include the use of PERT for the treatment of EPI [10–12]. Creon® (pancreatin; Abbott Laboratories GmbH, Hannover, Germany) is a PERT indicated for the treatment of EPI due to CF, chronic pancreatitis, pancreatectomy, or other conditions, and is available in several different formulations worldwide. Creon® Micro (pancreatin gastro-resistant granules in

☆ Trial registration: clinicaltrials.gov NCT01747330.

* Corresponding author at: Established Pharmaceuticals Division (EPD), Abbott Laboratories GmbH, Freundallee 9A, 30173 Hannover, Germany. Tel.: +49 511 6750 3254; fax: +49 511 6750 2916.
E-mail addresses: kashirskayanj@mail.ru (N.Y. Kashirskaya), nikolay.i.kapranov@gmail.com (N.I. Kapranov), suntje.sander@abbott.com (S. Sander-Struckmeier), vladimir.kovalev@abbott.com (V. Kovalev).

http://dx.doi.org/10.1016/j.jcf.2014.07.006

a glass bottle) is a capsule-free preparation that was developed in particular for infants and young children to allow accurate dosing in those who require lower doses or are unable to swallow capsules. Each 100 mg of gastro-resistant granules (equivalent to one measuring spoonful) contains 60.12 mg of pancreatin, which contains the following pancreatic enzymes: lipase 5000 Ph. Eur. units, amylase 3600 Ph. Eur. units, and protease 200 Ph. Eur. units [13]. Clinical trials have demonstrated the efficacy and safety of Creon Micro in infants and young children [14,15] and Creon Minimicrospheres capsules in children <7 years [16] and 7–11 years [17] with EPI due to CF. This prospective, open-label, multicentre study was carried out in Russia for compliance with local regulatory requirements, and its objective was to assess the safety, efficacy, and ease-of-use of Creon Micro in children with EPI due to CF.

2. Methods

This was a prospective, open-label, multicentre study comprising a screening period, a baseline assessment ≤14 days after screening, a 3-month treatment period (starting on Day 1), and a safety follow-up phone call 30 + 3 days after end of treatment. The study was carried out at eight centres in Russia between June and December 2012 (clinicaltrials.gov identifier NCT01747330) and was conducted in accordance with the EU Clinical Trial Directive, the International Conference on Harmonization guideline for Good Clinical Practice, and the principles of the Declaration of Helsinki. The study protocol and informed consent form were approved by an Independent Ethics Committee that complied with local regulatory requirements. Voluntary written informed consent was provided by the caregiver (or a legally acceptable representative) prior to performing any study-related procedures.

2.1. Participants

Participants were enrolled by the study investigators. Males and females aged 1 month to <4 years with a confirmed CF diagnosis and EPI were eligible for inclusion. CF diagnosis was confirmed by pilocarpine iontophoresis (chloride concentration ≥60 mmol/L) or sweat conductivity testing [18] (Macroduct®/Nanoduct® conductivity ≥80 mmol/L sodium chloride equivalents) and/or a genotype with two identifiable mutations consistent with CF accompanied by one or more clinical features of the CF phenotype. EPI was determined by a faecal elastase-1 level <100 μg/g stool. Subjects were also required to have a body weight of at least 2 kg and a clinically stable condition without evidence of acute respiratory disease or any other acute condition. Key exclusion criteria were: surgery due to meconium ileus with intestinal resection; history of fibrosing colonopathy, distal intestinal obstruction syndrome or acute abdomen; solid organ transplant or surgery affecting the large bowel (excluding appendectomy), or small bowel surgery that significantly affected absorptive capacity; use of immunosuppressive drugs except steroids; any type of malignancy involving the digestive tract; known allergy to pancreatin or inactive ingredients of treatment; intake of experimental drug within 30 days prior to study start; subjects on parenteral or enteral nutrition; any clinically relevant disease that could limit participation in or completion of the study.

Use of other PERT preparations, narcotic analgesics, anti-diarrhoeals, antispasmodics, and laxatives during the study was prohibited, but medications influencing duodenal pH, gastric emptying, and bile secretion were permitted if taken at a stable dose.

Subjects were categorized as infants and toddlers (<2 years) or children (≥2 years) based on their age at screening according to the European Medicines Agency age classification [19].

2.2. Treatment

If applicable, subjects received their previously-prescribed PERT at the usual dose until start of treatment with Creon Micro. During the study, Creon Micro was administered at a dose of 5000 lipase units per 120 mL of formula or breast feed, or 1000 lipase units/kg body weight/meal, according to the Cystic Fibrosis Foundation guidelines [12,20]. The minimum dose was 5000 units/meal, corresponding with one spoon of Creon Micro (100 mg), and increased if needed in increments of 5000 lipase units/meal. The maximum dose permitted was 2500 units/kg body weight per feeding, or 4000 units/g fat intake, or 10,000 lipase units/kg body weight/day [11,12]. Caregivers were instructed to give Creon Micro during or immediately after meals with liquid (pH < 5.5) or by adding it to small amounts of acidic soft food (pH < 5.5) that did not require chewing (e.g., applesauce), which was to be swallowed immediately and followed with water or juice to ensure complete ingestion. Caregivers were also asked to ensure that no drug was retained in the mouth.

2.3. Safety

Safety was assessed by monitoring adverse events (AEs). AEs were recorded by investigators using standard medical terminology and then coded according to the Medical Dictionary for Regulatory Activities version 15.1. The severity of AEs, their likely relationship to study drug (unrelated, unlikely, possible, probable), related changes in study medication, outcome, and whether serious or not were also recorded.

Other safety assessments including physical examination, vital signs, and laboratory safety tests were performed. Blood samples were analyzed at Laboratory INVITRO, Moscow, Russia.

2.4. Efficacy assessments

Efficacy was evaluated by assessing the growth parameters of height/length and body weight at baseline, Month 1, and Month 3. To assess development relative to a standard population, height/length-for-age, weight-for-age, and BMI-for-age percentiles and z-scores were calculated by comparison with the respective age and gender-specific percentiles of the US population published by the Centers for Disease Control and Prevention in 2000 [21]. The US population was used as specific percentiles for the Russian paediatric population are not available. The clinical symptoms of