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Original Article

Efficacy and safety of PANCREAZE® for treatment of exocrine pancreatic insufficiency due to cystic fibrosis☆

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Abstract

Background: Pancreatic enzyme replacement therapy (PERT) is critical for correction of exocrine pancreatic insufficiency (EPI) in patients with cystic fibrosis (CF).
Methods: This was a randomized, placebo-controlled PERT withdrawal study evaluating the efficacy and safety of PANCREAZE® (pancrelipase) in CF patients with EPI. Participants (n=49) entered an open-label, ≤14 day run-in phase, maintained a high-fat diet (100±15 g/day), and received PANCREAZE® (10.5 or 21). Participants with a coefficient of fat absorption (CFA)≥80% (n=40) were then randomized (1:1) to receive either PANCREAZE® or placebo during a double-blind, ≤7 day withdrawal phase.
Results: PANCREAZE® improved fat absorption as shown by significantly lower mean±SD change in CFA between open-label and double-blind phases for PANCREAZE® (−1.5±5.88%; $p<0.001$) compared to placebo (−34.1±23.03%). Protein absorption was similarly improved. No unexpected adverse events were reported.
Conclusions: This study demonstrated PANCREAZE® was effective in treating EPI due to CF and was safe and well tolerated.

Keywords: Coefficient of fat absorption; Cystic fibrosis; Exocrine pancreatic insufficiency; Pancreatic enzyme replacement therapy; Pancrelipase; PANCREAZE®

1. Introduction

Approximately 85 to 90% of cystic fibrosis (CF) patients suffer from pancreatic duct obstruction associated exocrine pancreatic insufficiency (EPI) [1]. The resultant enzyme deficiency causes malabsorption resulting in gastrointestinal symptoms, failure to thrive in infants, poor growth in children, and weight loss in adults [2]. Pancreatic enzyme replacement therapy (PERT) is the treatment of choice for EPI in CF patients and is critical to prevent malabsorption and maintain an optimal nutritional status [3]. PERT is considered effective and well tolerated based on clinical experience and well-controlled clinical trials [3–6].

Reports of fibrosing colonopathy associated with use of high doses of some enzyme supplements [7] and lower efficacy of some generic PERT preparations [8] prompted the United States Food and Drug Administration (US FDA) to evaluate the need for

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revised labeling, and registration of pharmaceutical preparations of pancreatic enzymes. Due to inconsistencies in formulation, activity, stability, and bioavailability of pancreatic enzyme preparations, the US FDA issued a requirement in 2004 that manufacturers of pancreatic enzyme supplements must file a New Drug Application (NDA) to ensure consistent efficacy, safety, and quality of these agents [9].

PANCREAZE® (pancrelipase) [10] is a PERT prescribed for use in infants, children, and adults for treatment of steatorrhea, secondary to EPI in CF or chronic alcoholic pancreatitis since 1988. The present study was conducted to reaffirm the efficacy and safety of PANCREAZE® in order to fulfill the US FDA requirements to submit an NDA for registration of the product. The primary objective of this randomized, double-blind, placebo-controlled, withdrawal study was to evaluate the efficacy of PANCREAZE® capsules on the quantitative change in fat absorption in pediatric, adolescent and adult patients with CF associated clinical symptoms of EPI. Secondary objectives included evaluation of effect of PANCREAZE® capsules on the quantitative change in protein absorption and improvement in clinical signs and symptoms of EPI in these patients. The safety of PANCREAZE® in this patient population was also assessed.

2. Methods

2.1. Study drug

PANCREAZE® 10.5 and 21 capsules are oral pancreatic enzyme supplements containing enteric coated microtablets of enzymes extracted from porcine pancreas. PANCREAZE® 10.5 capsules contain 10,500, 25,000, and 43,750 USP units of lipase, protease, and amylase respectively. PANCREAZE® 21 capsules contain 21,000, 37,000, and 61,000 USP units of lipase, protease, and amylase respectively.

2.2. Study population

Males and females aged 7 to 60 years were eligible if they had a diagnosis of CF confirmed by genotype analysis or sweat test (chloride levels >60 mmol/L), and CF-related EPI confirmed by documentation of an abnormal coefficient of fat absorption (CFA), or by a fecal elastase test (<100 μg fecal elastase/gram stool) ≤3 months of screening or a fecal elastase test during screening. Participants were on a stable diet and a PERT that adequately controlled EPI symptoms, and had received stable doses of any medications affecting the gastrointestinal tract for ≥1 month before screening. A CFA ≥80% during the 72-hour stool collection period was required for randomization and inclusion in the double-blind phase.

Participants were excluded for: extreme cachexia (<10th percentile of body mass index); severe/acute pulmonary disease unrelated to complications of cystic fibrosis; exacerbation of CF pulmonary disease ≤1 month before screening; congenital anomalies of gastrointestinal tract; distal intestinal obstruction syndrome ≤6 months of screening or requirement of surgical management to treat; hypersensitivity to porcine products; clinically significant gastrointestinal symptoms (e.g., vomiting, constipation); or disease or disorder that could interfere with assessment of study drug. Participants were excluded if they were taking drugs affecting blood uric acid concentrations or prokinetic agents (e.g., metoclopramide, cisapride,) ≤30 days of screening; concurrent supplemental enteral nutrition; immunosuppressant agents for organ transplantation; or systemic steroid therapy. Females were excluded if pregnant, planning to become pregnant, or nursing.

Use of other pancreatic enzyme preparations, mineral oil, magnesium, polyethylene glycol, and potassium supplementation was prohibited, as were agents affecting gastrointestinal motility (except a single dose of bisacodyl 10 mg during an inpatient visit). Stable use of other gastrointestinal medications was allowed. Recurrent antibiotic therapy was allowed if a stable dose had been administered for ≥1 month before screening.

The Independent Ethics Committee or Institutional Review Board at each study site approved the protocol. The study was conducted in accordance with Good Clinical Practices, the Declaration of Helsinki, all applicable regulatory requirements, and with the protocol. All participants or their legal representatives provided written informed consent.

2.3. Study design

The study was conducted from July 2008 to February 2009 at 11 centers in the United States and 1 center in Canada. The study consisted of a 7-day screening phase, ≤14-day open-label run-in phase, and ≤7-day placebo-controlled, double-blind, withdrawal phase. The duration of the double-blind phase ranged from 4 to 7 days, depending on patients' gastrointestinal transit time.

During the screening phase and after completion of laboratory assessments, participants' current PERT was discontinued, a high-fat diet (100±15 g fat/day or 3 g/kg/day) was initiated, and PANCREAZE® was administered based on the patient's lipase requirement during the previous 3 days. The number of PANCREAZE® (10.5 or 21) capsules administered was adjusted to optimize digestion of the high-fat diet based on clinical signs and symptoms according to CF Foundation PERT recommendations, to a maximum of 10,000 units of lipase/kg/day [11].

The PANCREAZE® dose was stabilized during screening (or, if not, within the first 72 h of the open-label phase) and maintained for ≥48 h. An initial inpatient, 72-hour stool collection was performed to measure CFA. Stool collection periods were marked by oral administration of a stool marker (FD&C blue dye, two 250 mg capsules) on the first day of the collection period and 72 h±1 h after taking the first dye marker. The collection period started with the first stool showing presence of blue marker and ended with the first blue stool following ingestion of the second stool marker. Stool samples were preserved at −20 °C and sent to a central laboratory for analysis of fecal fat and nitrogen content. End-of-study assessments were performed after the stool collection period or upon early withdrawal from the double-blind phase.

During the double-blind phase, participants with a CFA ≥80% were randomized (1:1) to continue their optimized dose of PANCREAZE® (10.5 or 21) or switched to placebo. A computer-generated randomization schedule achieved balancing, using randomly-permuted treatment blocks. After ≥1 day of double-