STUDY OF A NOVEL PANCREATIC ENZYME REPLACEMENT THERAPY IN PANCREATIC INSUFFICIENT SUBJECTS WITH CYSTIC FIBROSIS

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Objectives We studied a novel pancreatic enzyme product, ALTU-135, a proprietary formulation of microbially derived lipase, protease, and amylase, to determine its efficacy and safety in treatment of pancreatic insufficiency (PI) in patients with cystic fibrosis (CF).

Study design Ambulatory subjects with CF-PI (n = 117) had baseline coefficient of fat and nitrogen absorption (CFA and CNA, respectively) determined in an inpatient setting while not receiving pancreatic enzyme replacement therapy. Subjects were then randomized to treatment with ALTU-135 containing 5000 (low), 25,000 (mid), or 100,000 (highest) units of lipase (1:1:0.15 of lipase:protease:amylase) for 28 days. After 14 days, CFA and CNA were re-measured. The primary outcomes were change from baseline in CFA and CNA between treatments.

Results Treatment CFA was significantly greater in the mid and highest dose groups compared with that in the low dose group ($P = .0229$ and $P = .0041$, respectively); findings were similar for CNA. Subjects with baseline CFA ≤ 40% and >40% in the 2 higher dose groups had a mean increase of 31 and 8 percentage points in CFA, respectively ($P < .0001$).

Conclusion ALTU-135 was efficacious during the 1-month study period at the dose of 25,000 units of lipase, 25,000 units of protease, and 3750 units of amylase. *(J Pediatr 2006;149:658-62)*

Most patients with cystic fibrosis (CF) have severe exocrine pancreatic insufficiency (PI) and must take pancreatic enzyme replacement therapy (PERT) with each meal throughout their life.[1] Currently available PERTs are microencapsulated porcine pancreatic extracts. These products were on the market before the inception of the Food and Drug Administration and have a poorly defined profile of adverse events (AEs) or proof of efficacy.[2] A novel PERT, ALTU-135, contains a proprietary formulation of microbial lipase, protease, and amylase and was found to have good preliminary safety and clinical activity in patients with CF who have PI.[3] We conducted a phase 2 dose-ranging study of this novel PERT to assess its efficacy and safety in individuals with CF who have PI.

METHODS

We designed a randomized, double-blind, parallel dose-ranging study to identify the most efficacious dose of ALTU-135 on oral fat, protein, and carbohydrate absorption and to assess the safety of ALTU-135 in patients with CF who have PI.

All subjects signed a consent form approved by the local institutional review board and, in the case of pediatric patients, assent was also given. Inclusion and exclusion criteria were specified (see study NCT00095732 at www.ClinicalTrials.gov). Standard stopping rules were set with a study-specific committee of the CF Foundation's Data Safety Monitoring Board.

Subjects were stratified according to their use of acid suppression therapy before

AE	Adverse event	ITT	Intention to treat
ANOVA	Analysis of variance	mITT	Modified intention to treat
BMI	Body mass index	PERT	Pancreatic enzyme replacement therapy
CF	Cystic fibrosis	PI	Pancreatic insufficiency
CFA	Coefficient of fat absorption	SAE	Severe adverse event
CFQ-R	Cystic Fibrosis Questionnaire–Revised	SCT	Starch challenge test
CNA	Coefficient of nitrogen absorption	USP	United States Pharmacopoeia

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Study registered as NCT00095732 at www.ClinicalTrials.gov.

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randomization. We wanted to study subjects without changing their usual care, but becaue there is conflicting evidence about the influence of acid-suppressing agents on coefficient of fat absorption (CFA), we chose a balanced allocation strategy. Subjects received a fixed dose of 5000, 25,000, or 100,000 units United States Pharmacopoeia (USP) of lipase per meal or snack. To study a new dosing paradigm, doses were not adjusted on the basis of weight or food ingested. Lipase, protease, and amylase were fixed in a 1:1:0.15 ratio.

If subjects met study criteria at the screening visit, they were admitted to an inpatient facility within the next 10 to 14 days. Each subject's prescribed enzyme therapy was discontinued, and a fecal balance study for CFA and coefficient of nitrogen absorption (CNA) was determined by using a high-fat, controlled 72-hour diet. The appropriate period for measuring fat and nitrogen absorption was demarcated by using a blue dye stool marker (FD&C blue #2), which facilitated accurate and complete stool collection.[3] Subjects were randomized to 1 of the 3 treatment arms aforementioned, and began taking the study drug after the 72-hour controlled diet period. All subjects received an equal number of unlabeled capsules to take with each meal and snack. Subjects were discharged from the facility at the completion of the stool collection. Subjects were seen 1 week after beginning the study drug for a safety evaluation and were admitted to the inpatient facility 7 days later (on study day 14) for a second fecal fat balance study while taking the study drug. Subjects were seen for safety evaluation after 21 and 29 days of treatment. The study drug was discontinued, and subjects resumed their normal PERT. A follow-up visit was scheduled 1 week later.

A starch challenge test (SCT) was devised as an exploratory way to evaluate amylase efficacy. Subjects had a baseline blood glucose determination and then ingested 100 g of white bread (50 g of carbohydrate). Blood glucose levels were measured every 15 minutes for the first hour and then twice hourly for another 3 hours. The SCT was performed during each inpatient facility visit, once without taking PERT and once after taking the study drug with the white bread.

Safety monitoring included the incidence of AEs, the frequency of abnormal laboratory test results, and quality of life, as measured by the Cystic Fibrosis Questionnaire–Revised (CFQ-R).[4]

Description of the Product

The 3 components of ALTU-135 (formerly called TheraCLEC)—lipase, protease, and amylase—are manufactured and purified independently to provide a consistent amount and ratio of each enzyme per dose. Crystallized and cross-linked lipase (Lipase-CLEC), crystallized protease, and amorphous amylase are individually produced and formulated into separate drug substances, allowing rigorous in-process controls and quality control release testing designed to ensure that each production run results in a product meeting predetermined quality specifications. ALTU-135 has broad enzymatic specificity, which enables a single lipase to digest triglycerides fully without the need for bile salts, co-lipases, or other lipases. The specific protease and amylase components were selected after evaluating many different enzymes on the basis of their broad enzymatic activity and digestive properties. The rationale for the dosing proportions has been described previously.[3]

Analysis of Data

The sample size of 126 subjects for the phase 2 study was calculated on the basis of the CFA SD of 19.4% from the phase 1 study.[3] With 42 subjects per group, a 15.3% difference could have been detected in any ALTU-135 dose, with 80% power assuming a 2-sided type I error of $\alpha = .05$. The difference in mean CFA of the 3 arms during the treatment period was analyzed using a 1-way analysis of variance (ANOVA). To assess the 3 possible pairwise comparisons while controlling for the overall 5% type I error rate, Tukey's studentized range test was used.

We planned a linear regression analysis examining the simultaneous effects of the treatment arm, mean baseline CFA, and acid suppression status. Additional factors to be tested in the model included age, sex, race, and body mass index (BMI). We planned to display the absolute and percent changes in the mean CFA, CNA, and stool weights from the baseline period to the treatment period and to perform paired t tests. Descriptive statistics were to be used for baseline demographic data and for each of the 6 scale scores of the CFQ-R.

RESULTS

Study Population

A total of 139 subjects were screened at 26 CF Foundation-accredited centers. One subject withdrew consent before randomization; 9 other subjects did not meet entry criteria, including 5 subjects presumed to have PI, but who had fecal elastase >100 μg/g of stool. Thus, 129 subjects were enrolled as the intention-to-treat population (ITT) for the safety analysis. Of these 129 subjects, 12 withdrew early, 4 because of AEs. A total of 117 subjects received at least 1 randomized dose and underwent baseline (off-enzyme) and treatment assessments and formed the modified intention-to-treat population (mITT) for efficacy analysis; ≥75 % of stool was collected for these subjects. Demographic characteristics generally were well-matched in each treatment group (Table I).

Efficacy

Baseline CFA off-treatment was well-matched among groups (Table II). The mid- and highest-dose ALTU-135 groups increased CFA from baselines by 11.4% and 17.3%, respectively. Within group t tests showed the mean increases in CFA from off-enzyme to on-enzyme were significant for the mid- and highest-dose groups only ($P < .0005$ and $P < .0001$, respectively). Although CFA values (both absolute percentage and change from baseline) in the highest-dose group were greater than those in the mid-dose group, the