CLINICAL REVIEW

Application Type	NDA
Submission Number	22-222
Submission Code	N
Letter Date	31 July 2007
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Clinical Reviewer	Joanna W. Ku, MD
Clinical Team Leader	Anne R. Pariser, MD
Review Completion Date	30 June 2008
Established Name	Pancrelipase, USP
(Proposed) Trade Name	Ultrase® MT capsules
Therapeutic Class	New Molecular Entity (NME)
Applicant	Axcan Scandipharm, Inc.
Priority Designation	Priority Review (P)
Formulation	Oral Capsules
Dosing Regimen	500 to 1,000 lipase USP units/kg/meal, not to exceed 2,500 USP units/kg/meal or 4,000 lipase USP units/g fat/day
Indication	Pancreatic enzyme replacement
Intended Population	Adult and pediatric patients with pancreatic enzyme deficiency due to cystic fibrosis, chronic pancreatitis, or other related disorders

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

This Reviewer recommends an Approvable (AE) action. Deficiencies in chemistry, manufacturing and controls (drug substance and product) will need to be addressed in order to receive an Approval.

This Reviewer finds that the safety and efficacy of the to-be-marketed product (TbMP) of Ultrase® MT have been established for the treatment of steatorrhea in patients who are ages seven-years or older with exocrine pancreatic insufficiency (EPI). This is based on data from the pivotal study, Study UMT20CF05-01, in which patients with cystic fibrosis (CF) with EPI were treated with the TbMP Ultrase® MT coated with HP-55.

The two older studies conducted (Studies 96-01 and 96-02) using an older formulation of the product, Ultrase® MT coated with Eudragit®, could be used to provide supportive evidence for the safety and efficacy of Ultrase®. These older studies could be used to provide supportive—but not definitive--evidence for the safety and efficacy of the to-be-marketed product because the bridging *in vivo* bioactivity/bioavailability test failed to establish comparability between the two formulations in enzyme bioactivity/bioavailability at the physiologic site of action in the duodenum.

The Sponsor should be granted a Pediatric Deferral for infants less than two years of age to allow additional time to develop an infant-appropriate formulation. The Sponsor has been advised to conduct an additional clinical study in children between two and seven years of age should that age group be sought for inclusion in labeling.

1.2 Risk Benefit Analysis

Pancreatic enzyme products (PEPs) of porcine or bovine origin are used to treat exocrine pancreatic insufficiencies (EPI) in children and adults with cystic fibrosis (CF) and chronic pancreatitis (CP). On 28 April 2004 (69 FR 23410), the Food and Drug Administration (FDA) announced that all orally administered pancreatic enzyme products (PEPs) are new drugs that will need to be approved for prescription use only. This ruling stemmed from the concerns that although these products have been available for use more than 70 years in the United States (US), there are deficiencies in product quality and inconsistencies in enzyme bioactivity, and there is a need for continuous physician monitoring of patients who use these products as prescription medications.

The Agency has determined that there is an existing body of evidence that PEPs have clinical benefit for patients with CF and CP (69 FR 23410), in that safety and efficacy have already been established by consensus in the literature and the international medical community. Therefore, the requirement for a New Drug Approval (NDA) is less extensive and rigorous than that for a drug with less of a clinical track record. In a Guidance document for submitting NDAs of PEPs,

the Agency explained the type and amount of evidence that is required,[1] including the following discussion points, which could apply to this NDA. The duration of the entire pivotal trial could be days to two to three weeks, and the total number of patients in the study could be between 10 and 25, depending on the design chosen. One adequate and well-controlled clinical investigation and confirmatory evidence may be appropriate. A cross-over study in which each patient in the study is treated with the intended product and a control is an acceptable study design; and demonstration that administration of the PEP to patients with EPI causes a meaningful decrease in stool fat as evaluated in a 72-hour quantitative stool collection, a pharmacodynamic endpoint, is an acceptable clinical efficacy endpoint. Additionally, because CF is primarily a pediatric disease, the efficacy studies in the NDA should include clinical studies in pediatric patients with CF. Safety variables should include symptoms and signs of malabsorption, such as manifestations of steatorrhea; complaints of bloating; flatus; abdominal pain; loose and frequent stools; overt diarrhea; blood in the stool. The safety issues of uric acid elevations and fibrosing colonopathy should be addressed. This Reviewer finds that the present NDA for Ultrase® MT has satisfactorily addressed all of these issues.

The Sponsor submitted three short term clinical efficacy and safety trials of Ultrase® in patients with EPI due to CF. The pivotal study was UMT20CF05-01, in which the TbMP of Ultrase® (Ultrase® MT coated with HP55) was studied. The supporting studies were Studies 96-01 and 96-02, in which an older formulation of Ultrase® (Ultrase® MT coated with Eudragit®) was used.

The pivotal study (Study UMT20CF05-01) was a multi-center, randomized, double-blind, placebo-controlled, two-week, two-period cross-over study in which each patient was used as their own control. The study population comprised of 31 intent-to-treat patients who were older than seven years of age, and had EPI due to CF. Patients were randomized 1:1 to two groups, with one group undergoing one-week of treatment with Ultrase® MT 20 capsules, followed by one-week treatment with Placebo; and the other group, vice versa in their treatment sequence. The results showed that mean increase in fat absorption as measured by Coefficient of Fat Absorption (CFA %) with Ultrase® treatment compared to Placebo treatment was an improvement of + 34.7 (SD ± 25) points on the CFA %, a clinically and highly statistically significant result ($p < 0.0001$).[2] This magnitude of improvement in CFA % is similar to the results seen in other PEPs. Subgroup analysis showed that those patients who had a lower capacity for fat absorption on Placebo had a greater improvement with Ultrase® treatment, consistent with the theory that the more severely affected patients have a greater capacity to respond to treatment. This study supports the clinical effectiveness of the TbMP of Ultrase® MT.

The two supporting studies for efficacy were Studies 96-01 and 96-02, in which an older formulation of Ultrase® (coated with Eudragit®) MT 20 and MT 12 capsules, respectively, were used. This formulation is not to be marketed, and since the *in vivo* bioactivity/bioavailability

1 U.S. Department of Health and Human Services. Food and Drug Administration. Center for Drug Evaluation and Research (CDER). "Guidance for Industry. Exocrine Pancreatic Insufficiency Drug Products – Submitting NDAs." <http://www.fda.gov/cder/guidance/6275fnl htm> April 2006.
2 This delta value was the mean of the individual treatment differences in the 24 patients who completed both treatment periods and who had evaluable stool testing results for both periods.

testing failed to establish comparability between this older formulation and the to-be-marketed formulation, these study results are used as supportive evidence of efficacy and safety only. Similar to Study UMT20CF05-01, Studies 96-01 (N= 31) and 96-02 (N=26) were multi-center, randomized, double-blind, placebo-controlled, crossover-studies designed to evaluate the safety and efficacy of Ultrase® MT in the treatment of steatorrhea in CF patients older than seven years of age, with a history of EPI. Patients were randomized 1:1. One group underwent one-week of treatment with Ultrase® MT capsules, followed by one-week treatment with Placebo; and the other group, vice versa in their treatment sequence. The results showed that mean increase in fat absorption as measured by Coefficient of Fat Absorption (CFA %) with Ultrase® treatment compared to Placebo treatment was an improvement of + 29 points on the CFA %, a clinically and highly statistically significant result ($p = 0.0001$) for Study 96-01, and similarly, + 33 points on the CFA % ($p = 0.0002$) for Study 96-02. This magnitude of CFA % improvement on Ultrase® MT 20 and 12 using the Eudragit® formulation provides supportive evidence for efficacy, and is within the expected range with that of Ultrase® MT HP-55 (the TbMP), as well as other PEPs in the same drug class.

Approximately ninety patients in the three studies' safety population (Studies UMT20CF05-01, 96-01, and 96-02) had a mean age ranging from 16.5 (6.5 SD) to 19.6 years (6.6 SD), with an overall range of 7 to 37 years. This pooled safety population was comprised approximately of Caucasian (92%), Black (5%), Hispanic (2%), and Black/Caucasian (1%) patients. There were no deaths. Serious Adverse Events (SAEs) and Adverse Events (AEs) that caused dropouts, mostly respiratory and gastrointestinal events, were likely related to the underlying disease of CF. Common adverse events were predominantly gastrointestinal events (e.g., abdominal pain, flatulence, nausea, fecal fat increased, abnormal laboratory test), and all of these had a higher incidence in patients during the Placebo phase, likely reflecting not a "safety concern" per se, but rather, a lack of efficacy from absent PEP treatment. Given that dosing was within the established guideline, and the study population was small and the study treatment was very short, as expected, there were no cases of fibrosing colonopathy, a rare but serious condition thought to be related to excessively high dosing of PEPs. Additional supporting evidence of a favorable safety profile came from post marketing safety surveillance, as well as literature review. In sum, data on patients from the three short-term the placebo-controlled safety studies in conjunction with post-marketing safety data and published reports provided sufficient evidence for the safety of the product.

In the opinion of this Reviewer the risk benefit analysis for Ultrase® MT is favorable, and from a clinical standpoint Ultrase® MT could be approved to treat CF patients with EPI older than seven years of age. Furthermore, efficacy and safety could be extrapolated to patients who suffer EPI from other causes (for example, chronic pancreatitis due to alcoholism or pancreatectomy) given that there is a general consensus that EPI due to any cause has similar clinical findings and should respond similarly to this drug.

1.3 Recommendations for Postmarketing Risk Management Activities

None is warranted at this time.

1.4 Recommendations for other Post Marketing Activities/Phase 4 Commitments

None is warranted at this time.

2 Introduction and Regulatory Background

2.1 Disease Background and Product Information

Exocrine pancreatic insufficiency (EPI) is the inability to properly digest and absorb fats, proteins, and carbohydrates due to a lack of digestive enzymes produced by the pancreas. Pancreatic enzyme supplements improve digestion by catalyzing the hydrolysis of fats to glycerol and fatty acids, protein to proteoses and derived substances, and starch into dextrins and short chain sugars. These enzymes (lipase, proteases, and amylase), break down fats (lipase), proteins (proteases), and carbohydrates (amylase), into elementary units of small size that can traverse the intestinal mucosa, incorporate into the blood stream to work as sources of energy and building blocks of cells. EPI typically results from chronic loss of pancreatic tissue due to a number of underlying conditions. In children, cystic fibrosis (CF) is the most common cause of EPI. In adults, alcoholism or idiopathic pancreatitis-related chronic pancreatitis (CP) is the most common. A number of other less common causes are possible, such as pancreatic cancer, surgical removal of the pancreas, trauma to the pancreas, etc. Whatever the cause, the loss of digestive enzymes leads to mal-digestion and mal-absorption of nutrients. Symptoms can range from mild to severe, and can include a distended abdomen, flatulence, and frequent, bulky, greasy, foul-smelling stools. EPI can significantly impact on morbidity and mortality: retarded growth and development, impaired immune response, infections, and bleeding tendencies, etc.

Treatment of EPI includes treatment of the underlying condition to prevent further pancreatic damage; vitamin supplementation; diet modification that uses a low-fat, high-protein and high-calorie diet to maintain adequate nutrition and appropriate weight; and pancreatic enzyme replacement, which is prescribed to be taken in adequate amount with each meal and snack. Although carbohydrate and protein mal-absorption/digestion can be easily abolished using this strategy, fat mal-absorption/digestion (steatorrhea) is rarely abolished.[3] Still, due to advances in treatment strategies that include the use of PEPs, most CF patients born in the 1990's can expect to live for 40 years or more, whereas before the mid-1960's, the median age of death of children with CF was two years. The safety and efficacy of PEPs has been well established in clinical practice.

This New Drug Application (NDA) is for the New Molecular Entity (NME) pancrelipase. The proposed trade name is Ultrase® MT. Ultrase® is purified exocrine pancreatic enzymes extracted from the hog/porcine pancreas. Ultrase® mainly consists of the enzymes lipase, proteases, and amylase, and is intended to treat EPI due to CF and CP, and other related conditions. The drug substance (DS) (pancrelipase) is manufactured by (b) (4) (b) (4) and the drug product (DP) is manufactured by Eurand S.p.A. The

3 Pongprasobchai, S. & DiMagno, E.P. (2005). Treatment of Exocrine Pancreatic Insufficiency. In C. Forsmark (Ed.) *Pancreatitis and its Complications.* (pp. 295-312). Totowa, New Jersey: Humana Press.

Applicant/Sponsor is Axcan Scandipharm, Inc. (Axcan), who is also responsible for the final packaging and product release.

The drug is oral capsules. Each capsule contains enteric-coated minitablets. The minitablets are composed of pancrelipase and compendial excipients in a [redacted] (b) (4) form. The capsules are to be taken orally with each meal or snack. The proposed starting dose is 500 to 1,000 lipase USP units (units)/kg/meal, with titration to a maximum of <2,500 units/kg/meal or <4,000 units/g fat/day. The total daily dose is not to exceed 10,000 units/kg/day (accounting for 3 meals and 2 snacks, with the snack dose being half of the meal dose). These dosing recommendations follow the guidelines of the Cystic Fibrosis Foundation (CFF) in conjunction with the FDA in order to optimize therapy while minimizing the risk of fibrosing colonopathy. For a 70 kg man, this amounts to a starting dose of 35,000 to 70,000 units/meal, with titration up to 175,000 units/meal. For an average two year child who weighs 13 kg, this amounts a starting dose of 6,500 to 13,000 units/meal, with a titration up to 32,500 units/meal.

The inactive ingredients are: gelatin, hydrogenated castor oil, colloidal silicon dioxide, magnesium stearate, croscarmellose sodium, microcrystalline cellulose, hydroxypropyl methylcellulose phthalate (HP55), talc, triethyl citrate, iron oxides and titanium dioxide.

Three capsule strengths are available (see Table 1, copied electronically from the Sponsor's submission).

Table 1 Composition of pancrelipase in Ultrase® MT capsules

Product	Lipase (USP Units)	Protease (USP Units)	Amylase (USP Units)
ULTRASE® MT12 Capsules (13, 800 U/USPL)	[redacted] (b) (4)		
ULTRASE® MT18 Capsules (20, 700 U/USPL)			
ULTRASE® MT20 Capsules (23, 000 U/USPL)			

The TbMP Ultrase® MT Capsules contain a hydroxypropyl methylcellulose phthalate[4] (HP-55) coating. The purported advantage of this acid-resistant coating (which dissolves only at a relatively basic environment of pH ≥ 5.5) is that it can prevent inactivation of the pancreatic enzymes by gastric acid in the stomach, thereby delivering the drug in a predictable manner with high levels of biologically active enzyme reaching the duodenum at the intended site of biologic and therapeutic activity. This formulation was used in the pivotal study (Study UMT20CF05-01). The remaining clinical studies used an older formulation, Ultrase® MT capsules coated with the water-based Eudragit® LD 30, a formulation not intended for marketing.

4 Hypromellose phthalate (official USP nomenclature)

The Sponsor proposed the following indication:

(b) (4)

(b) (4)

2.2 Tables of Currently Available Treatments for Proposed Indications

Ultrase® MT is currently marketed in the US, and has been available on the US market since 1991. Given this long use record, it is appropriate that only limited, short-term studies are required for the submission of this NDA.

Numerous pancreatic enzyme products (PEPs) are currently available on the US market (see Table 2, which lists some of the available PEPs in the US), but none has an approved NDA. For a discussion on the regulatory status of these products see the following sections: Section 2.3 Availability of Proposed Active Ingredients in the United States, and Section 2.4 Important Issues with Consideration to Related Drugs.

Table 2 Selected pancreatic enzyme products that are available for clinical use in the US

Manufacturer	Brand Name
Solvay Pharma	Creon®
Axcan Scandipharm	Ultrase MT®
Axcan Scandipharm	Viokase®
Digestive Care	Digestizyme® (Pancrecarb)
Eurand SpA	Zentase™
McNeil Pediatrics	Pancrease MT®
Altus	TheraCLEC-Total™
Ethex	Multiple brands

2.3 Availability of Proposed Active Ingredient in the United States

Pancreatic enzyme products (PEPs) have been available in the US since before the enactment of the Federal Food, Drug, and Cosmetic Act (The Act) of 1938; and, the majority has also been available since pre-Drug Efficacy Study Implementation (DESI; pre-1962). Thus, the majority has never undergone formal evaluation either under Investigational New Drug (IND) applications or New Drug Applications (NDAs). The only product that has received an FDA NDA approval is Cotazym® (sponsored by Organon, Inc), but Cotazym® is not currently marketed. Therefore, no PEP currently on the market in the US holds an approved NDA.

PEPs that are on the market are available in a variety of ways, as non-prescription nutritional supplements, over-the-counter medications (OTC), or by prescription. Various dosage forms of pancreatic enzyme drug products are available as uncoated tablets, powders, capsules, enteric-

coated tablets, and encapsulated enteric-coated micro-spheres. These formulations are not considered to be clinically interchangeable. As part of an OTC drug review program in the 1990's, FDA evaluated the safety and effectiveness of PEPs, and found significant variation in bioavailability among the various dosage forms and among products from different manufacturers of the same dosage form. These variations in formulation, dosage, and manufacturing processes, both between the different PEPs and within the individual PEP brands (e.g., from lot to lot, and even within lots) were thought to have a critical effect on safety and efficacy. Based on this, FDA concluded that formal FDA review and pre-clearance of each product to standardize enzyme bioactivity would be needed. FDA also determined that since continuous physician monitoring of patients is necessary for the safe and effective use of PEPs, these products should be available by prescription only, hence the products should be approved through the new drug approval (NDA) process to standardize enzyme activity. FDA announced these requirements in the Federal Register on 28 April 2004 (herein referred to as the 2004 FR Notice). And, a Guidance document published by FDA for submitting NDAs for PEPs was published in the Federal Register of 14 April 2006, 71 FR 19524 (herein referred to as the Guidance).[5]

The 2004 FR notice advised the public that FDA intended to exercise its enforcement discretion until 28 April 2008, because the Agency considered PEPs medically necessary, and intended that PEPs would remain available on the market during the period necessary for manufacturers to conduct the required studies, prepare applications, and have the applications approved. In response to the 2004 FR Notice, however, a number of manufacturers indicated that they need an extension of time beyond the original deadline of 28 April 2008 to obtain approved applications. The manufacturers contend that additional time is needed because of numerous problems encountered during the drug development process, predominately manufacturing issues, and difficulty conducting all of the required studies needed for IND and NDA filling and approval. The Agency considered these requests, and extended the deadline. In an FR Notice dated 26 October 2007, FDA extended the period during which it intends to exercise its enforcement discretion until 28 April 2010. However, this extension applies only to any manufacturer of PEPs marketed on or before publication of the 2004 FR notice, and if the manufacturer has an active IND for its PEPs on or before 28 April 2008, has submitted an NDA on or before 28 April 2009, and is pursuing approval of its application with due diligence. For a complete listing of FR notices pertaining to the regulatory history of PEPs, see Appendix 1.

2.4 Important Safety Issues with Consideration to Related Drugs

Porcine-derived PEPs have been in clinical use in a global market for over 70 years, and as such, there is extensive clinical experience with these products in humans. The long-term safety experience shows that the PEPs are safe in the context of demonstrated clinical benefits of PEP treatment. In consideration of this long and extensive safety experience, the Guidance states that only short-term safety evaluation is required. The Guidance also specifies that since PEPs are locally acting agents in the gastrointestinal tract and are not absorbed systemically into the blood stream, safety monitoring should focus on gastrointestinal adverse events such as manifestations

5 U.S. Department of Health and Human Services. Food and Drug Administration. Center for Drug Evaluation and Research (CDER). "Guidance for Industry. Exocrine Pancreatic Insufficiency Drug Products – Submitting NDAs." <http://www.fda.gov/cder/guidance/6275fnl htm> April 2006.

of steatorrhea, complaints of bloating, flatus, abdominal pain, loose and frequent stools, overt diarrhea, and blood in the stool, and other known adverse events associated with PEPs administration, such as uric acid elevations.

A noteworthy concern of the PEPs is fibrosing colonopathy, a rare but serious condition, whose etiology has not been elucidated. It has been suspected that high or inappropriate dosing of PEPs may play a role, although theories about the role of the excipients (including Eudragit®) have also been discussed. In an effort to minimize the development of fibrosing colonopathy that has been assumed to be related to high doses of PEPs, the FDA, in conjunction with the Cystic Fibrosis Foundation (CFF), recommends a starting dose of 500 to 1,000 lipase units/kg/meal with titration to less than 2,500 units/kg/meal or less than 4,000 lipase units/g fat consumed/day.[6,7] Doses in excess of 2,500 units/kg/meal should be used with caution and only if their benefit is documented by a three-day fecal fat test. Doses in excess of 6,000 units/kg/meal have been associated with fibrosing colonopathy. This dosing recommendation, applicable to any formulation, was made on the basis of concern over dose-related colonic strictures in CF patients, and the likelihood that maximal efficacy is achieved at the recommended ceiling dose of 2,500 units/kg/meal.

2.5 Summary of Pre-submission Regulatory Activity Related to Submission

IND 41,387 was received on 24 December 1992. (b) (4) (b) (4) the Division recommended that the Sponsor conduct fat absorption studies in CF patients in two adequate and well-controlled studies, one using a higher strength of Ultrase®, and the second, a lower strength. Subsequently, Studies 96-01 (Ultrase® MT20) and 96-02 (Ultrase® MT12) were conducted under IND 41,387.

The Sponsor submitted a separate NDA (NDA 22,222) on 31 July 2007, but due to deficiencies in the Drug Master File (DMF), (b) (4) (b) (4) The Sponsor requested a rolling submission, which was granted with priority review status. The PDUFA goal date was extended from 1 April 2008 to 1 July 2008 due to a major amendment that was received on 12 March 2008.

Points for discussion during the pre-submission regulatory activities included the following:

- Clinical trials carried out with the Eudragit® formulation (the older formulation) can be applied to the drug product made with the HP-55 coating (the to-be-marketed formulation) only if both *in vitro* dissolution profile and *in vivo* bioavailability profile show comparability.
- For young pediatric patients, the Sponsor should develop an age-appropriate formulation with lipase content low enough to allow for flexibility for recommended weight based dosing.

6 FitzSimmons, SC, GA Burkhart, D Borowitz et al. High-dose pancreatic enzyme supplements and fibrosing colonopathy in children with cystic fibrosis. New England Journal of Medicine. 1997; 336:1283-1289
7 Borowitz, D, RD Baker, and V Stallings, Consensus report on nutrition for pediatric patients with cystic fibrosis. Journal of Pediatric Gastroenterology and Nutrition. 2002;35:246-259

- The Sponsor may (b) (4)

(b) (4)

2.6 Other Relevant Background Information

The Agency has determined that there is an existing body of evidence that shows that the PEPs have clinical benefit for patients with CF and CP (69 FR 23410), and that safety and efficacy have already been established by consensus in the literature and the international medical community. Therefore, the requirement for a New Drug Approval (NDA) is less extensive and rigorous than that for a drug with a lesser clinical track record. In the Guidance document for submitting NDAs of PEPs, the Agency explained the type and amount of evidence that is required,[8] including the following discussion points, which could apply to this NDA. The duration of the entire pivotal trial could be days to two to three weeks, and the total number of patients in the study could be between 10 and 25, depending on the design chosen. One adequate and well-controlled clinical investigation and confirmatory evidence may be appropriate. A cross-over study in which each patient in the study is treated with the intended product and a control is an acceptable study design; demonstration that administration of the PEP to patients with EPI causes a meaningful decrease in stool fat as evaluated in a 72-hour quantitative stool collection, a pharmacodynamic endpoint, is an acceptable clinical efficacy endpoint. Because CF is primarily a pediatric disease, the efficacy studies in the NDA should include clinical studies in pediatric patients with CF. Safety variables should include symptoms and signs of malabsorption, such as manifestations of steatorrhea, complaints of bloating, flatus, abdominal pain, loose and frequent stools, overt diarrhea, and blood in the stool. The safety issues of elevation in uric acid and fibrosing colonopathy should be addressed. This Reviewer finds that in the present NDA for Ultrase® MT all of these stipulations have been met.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

This Reviewer found that the overall submission quality to be acceptable, including responses by the Sponsor to FDA's Information Request letters.

The Division requested two site inspections for the pivotal study to be conducted by the Division of Scientific Investigation (DSI): Site 02 (Dr. Theodore Liou, of University of Utah School of Medicine), and Site 03 (Dr. Steven Strausbaugh, of Rainbow Babies and Children's Hospital in Cleveland, OH).

Site 02 had the highest enrollment (N=7) in this small pivotal study (N=36), and the highest incidence of "major protocol violations" (four incidents). Inspection by FDA DSI Inspector Khairy Malek, M.D. found that Site 02 had "many protocol violations… Four subjects were allowed in the study before confirmatory testing of pancreatic insufficiency by way of fecal

8 U.S. Department of Health and Human Services. Food and Drug Administration. Center for Drug Evaluation and Research (CDER). "Guidance for Industry. Exocrine Pancreatic Insufficiency Drug Products – Submitting NDAs." <http://www.fda.gov/cder/guidance/6275fnl htm> April 2006.

elastase testing… At the beginning of the study, the dietician was sick and the Principle Investigator allowed the study to proceed before getting another dietician. This resulted in poor dietary control and deviation from the protocol, which required 2 g of fat/kg of body weight ± 15% for almost all the subjects. In addition three subjects…had poor dietary compliance during various Stabilization and Treatment Periods." But despite of these findings, the conclusion reached by the inspector was that these violations would not affect the validity of the data or markedly affect the calculation of the coefficient of fat absorption, which is the primary efficacy parameter, and that the data from this site can be used in support of the NDA. A letter was sent to Dr. Liou by FDA, stating that he did not "adhere to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and protections of human subjects, specifically that he did not ensure that the investigation was conducted according to the investigational plan [21 CFR 312.60], and that he should make appropriate corrections in his procedures to assure that the findings noted are not repeated in any ongoing or future studies."

Site 03 (Dr. Strausbaugh) had the second highest enrollment (N=6), and had the most number of patients (N=2) who did not complete the study that was not due to a screening failure: one discontinuation was due to a major protocol deviation, and the other was due to a Serious Adverse Event (SAE). The inspection revealed "minor protocol violation: two subjects were enrolled before the results of the fecal elastase tests were received. The results were found later to be within the protocol requirement. The data from this site can be used in support of the NDA."

The overall assessment by FDA's DSI inspector was that the violations described for either site will not affect the validity or reliability of the data, and that the data from the two inspected sites can be used in support of the NDA.

Two Axcan-sponsored audits were conducted (Dr. Strausbaugh, site #03; Dr. Ahrens, site #05). The Sponsor submitted the audit certificates, which state that a qualified GCP auditor has performed an audit at each site and that both sites successfully passed the audit.

3.2 Compliance with Good Clinical Practices

The Sponsor states that Study UMT20CF05-01 (the pivotal clinical study using the TbMP) and Studies 96-01 and 96-02 (the supportive studies) were conducted in compliance with and monitored according to Good Clinical Practices (GCP).

For the pivotal study, the Cystic Fibrosis Foundation—Therapeutic Development Network (CFF-TDN) provided extensive support in the design, implementation, and analysis of the study. The Cystic Fibrosis Foundation also functioned as the study's Data and Safety Monitoring Board (DSMB), and Data Monitoring Committee (DMC).

3.3 Financial Disclosures

Pursuant to 21 CFR 54 and 21 CFR 314.50(k), financial disclosure information has been obtained from all investigators participating in Studies UMT20CP05-01 (the bioavailability

study) and UMT20CF05-01 (the pivotal clinical study using the TbMP): no investigator had any financial interest to disclose.

Study 96-01 was initiated on 1 April 1997 and completed in August 1998. Study 96-02 was initiated on 4 August 1997 and completed in August of 1999. These trials were sponsored by Scandipharm Inc., which was a privately-held company at the time the trials were conducted. Scandipharm Inc. was subsequently purchased by Axcan on 2 August 1999. Because these trials were initiated prior to the effective date of the final rule on financial disclosure requirements, no financial disclosure information was collected from the investigators at the time the trials were initiated. However, as per the FDA Guidance Document "Financial Disclosure by Clinical Investigators," Axcan has established that to the best of its knowledge there were no financial arrangements or interests in these studies of concern to FDA.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls (CMC)

At the time of this writing, the CMC reviews and recommendations are pending, although issues have been identified as deficiencies that will lead to an Approvable (AE) action. Please see reviews by FDA reviewers Wei Guo, Ph.D. (CMC) and Ennan Guan, Ph.D. (virology) for details.

4.2 Clinical Microbiology

Ultrase® MT is a dry solid oral dosage form of pancreatic enzymes derived from porcine pancreas. The drug substance (DS), pancrelipase, is not sterile. The drug product (DP), Ultrase® MT, consists of solid non-sterile capsules with a core of minitablets composed of pancrelipase and compendial excipients. The original submission proposed microbial limits of no more than (b) (4) for total plate count, and an absence of *E. coli and Salmonella* species. In a January 2007, in response to an FDA Information Request letter, the Sponsor changed the microbial limits specifications to no more than (b) (4) total plate count, no more than (b) (4) yeast and mold, and an absence of *E. coli and Salmonella* species. The (b) (4) For additional details, please see Microbiology Review by FDA microbiology reviewer Stephen Langille, Ph.D. Approval is recommended.

4.3 Preclinical Pharmacology/Toxicology

Preclinical pharmacology and toxicity studies of the active ingredient (pancrelipase) were not needed, given the long history of its use in patients with EPI. The submitted toxicology information was mostly related to the excipients and (b) (4) (a major impurity) in Ultrase® MT Capsule. The need for excipient toxicity information arose from the fact that the expected daily ingestion of PEPs is a large number of capsules, and therefore, the quantity of excipients ingested is substantial. The Sponsor provided toxicity and regulatory information about the

following excipients: croscarmellose sodium, hydroxypropyl methylcellulose phthalate (HP 55), triethyl citrate, talc, iron oxide, and gelatin, i.e., for excipients where the daily intake could exceed the maximum daily oral dose among all FDA-approved drug products, as determined from the maximum daily dose of Ultrase® and information from the FDA Inactive Ingredients Database. In his review, FDA pharmacology-toxicology reviewer David Joseph, Ph.D. concluded that the estimated maximum dose for these excipients and (b) (4) were not considered to be a safety concern. Approval is recommended.

A special toxicology study of a porcine PEP was also submitted, and the objective of the study was to investigate the underlying mechanism of fibrosing colonopathy, a condition that has occurred in children with CF apparently after treatment with high levels of pancreatic enzymes. Rats were treated with oleic acid and/or reserpine to produce a chemically-induced, increased intestinal permeability, a pathological condition that is characteristic of CF-related EPI. High doses of Ultrase® were then administered. The results suggest that high dose levels of pancreatic enzymes can produce injury in the small intestine under conditions of increased intestinal permeability. However, it should be emphasized that the intestinal lesions in this study differ from those of fibrosing colonopathy, which is characterized by submucosal fibrosis of the colon and rectum, and colonic strictures. The lesions in rats were limited to the ileum and jejunum in the form of muscle necrosis. While suggestive, this study does not fully characterize the relationship between high-dose PEP and fibrosing colonopathy lesions in humans.

4.4 Clinical Pharmacology

The purpose of the clinical pharmacology review was two fold: 1) to test equivalence by way of establishing comparable bioactivity and/or bioavailability of the active ingredient at the site of action between the two product formulations (Ultrase® MT coated with HP 55 and Ultrase® MT coated with Eudragit®); 2) to test the *in vitro* stability of the contents of the Ultrase® MT HP-55 capsules to establish that Ultrase® capsule content may be sprinkled on food to allow patients who cannot swallow capsules to take the medication as sprinkled powder mixed into foods.

The *in vivo* bioactivity/bioavailability study (Study UMT20CP05-01) could not establish that the two formulations were equivalent. The *in vitro* stability Study (No. RE-071211-01) did establish product stability in conditions that simulate real-world use. Therefore, the recommendations are 1) since the bridging study could not establish formulation equivalence, final approvability of the TbMP will need to be based on clinical findings conducted in patients who received the TbMP; and 2) the TbMP may be sprinkled on food for patients who cannot swallow capsules.

In a joint meeting between the Division of Clinical Pharmacology 3 and the Division of Gastroenterology Products, consensus was reached that based on the experiences gathered in reviewing the PEP NDAs submitted so far (for Creon®, Zentase®, and Ultrase®) regarding the *in vivo* bioactivity/bioavailability intubation studies. FDA now recognizes that there are many challenges in the study design, study conduct, and assay methodology that limit interpretation of the results of these studies, and in view of the timeline imposed by the Agency on sponsors for submitting NDAs for PEPs, it is decided that intubation studies of bioactivity/bioequivalent for PEPs will no longer be required for future PEP NDA submissions, though a formal public statement has not be released. And, from this point forward when demonstrating bioequivalence

between formulations is necessary, the Sponsor will be encouraged to conduct clinical studies rather than relying upon bridging bioactivity/bioavailability studies.

4.4.1 Mechanism of Action

Please see Section 2.1 Disease Background and Product Information.

4.4.2 Pharmacodynamics

Since lipase, amylase, and proteases act locally in the gastrointestinal tract and are not systemically absorbed, pharmacodynamic studies are not applicable and have not been conducted.

4.4.3 Pharmacokinetics

Since lipase, amylase, and proteases act locally in the gastrointestinal tract and are not systemically absorbed, pharmacokinetic studies are not applicable and have not been conducted.

5 Sources of Clinical Data

5.1 Tables of Clinical Studies

The clinical studies submitted are summarized in Table 3:

Table 3 List of clinical studies submitted by the Sponsor in support of NDA 22-222

Study	Design	Patient Population	Formulation Used
UMT20CF05-01* *pivotal study (Final clinical study report submitted) Study completed: 2007	Multi-center, randomized, double-blind, placebo-controlled, two-week, two-period cross-over study of the safety and efficacy of Ultrase® MT20 compared to placebo. Patients were administered Ultrase® and Placebo each for one week.	CF patients with EPI and steatorrhea ≥ seven years old Age range: 8-37 years Mean age: 20 years N=31	To-be-marketed formulation (HP-55 coating)
96-01 (Final clinical study report submitted) Study completed: 1998	Multi-center, randomized, double-blind, placebo-controlled, two-week, two-period cross-over, study of the safety and efficacy of Ultrase® MT20 compared to placebo. Patients were administered Ultrase® and Placebo each for one week.	CF patients with EPI and steatorrhea ≥ seven years old Age range: 7-36 N=31	Older formulation (Eudragit® coating)—not intended for marketing
96-02 (Final clinical study report submitted) Study completed: 1998	Multi-center, randomized, double-blind, placebo-controlled, two-week, two-period cross-over, study of the safety and efficacy of Ultrase® MT12 compared to placebo. Patients were administered Ultrase® and Placebo each for one week.	CF patients with EPI and steatorrhea ≥ seven years old Age range: 8-36 N=26	Older formulation (Eudragit® coating)—not intended for marketing
Study 01 (Final study report submitted as legacy report—no SAS datasets) Study reported: 1994	Open-label study of safety and efficacy comparing Ultrase® (MT12, 20, 24) vs. patient's one year history on their usual medication. Two weeks on Ultrase® treatment phase; one year of historical phase	CF patients with EPI and steatorrhea ≥ seven years old Age range 1-40 N=171	Older formulation (Eudragit® coating)—not intended for marketing
Study 02 (Abbreviated report submitted as legacy report—no SAS datasets) Study reported: 1994	Open-label study of safety and efficacy comparing Ultrase® (MT12, 20, 24) vs. patient's usual medication. Three weeks on patient's usual medication, and three weeks on Ultrase®	CF patients with EPI and steatorrhea from 9 months to 31 years Age range: 9 months-31 years N=25	Older formulation (Eudragit® coating)—not intended for marketing
UMT20CP05-01 Bioavailability study (Final clinical report submitted) Study completed: 2006	Single-center, randomized, open-labeled, cross-over study of lipase *in situ* availability in subjects with chronic pancreatitis using two enteric-coated formulations of Ultrase® MT (Eudragit® LD30 and HP55 coating).	Age range: 19-75 Median age: 56 N=13	To-be-marketed formulation (HP-55 coating) and older formulation (Eudragit® coating)—not intended for marketing

5.2 Review Strategy

The pivotal clinical study was Study UMT20CF05-01, the sole clinical study that used TbMP. Since the pivotal study was the only study that was conducted with TbMP, the entire clinical review and assessment of short-term efficacy rests on this study. A single, short-term efficacy (and safety) study is consistent with the Guidance recommendations, and is acceptable as a 505(b) (2) application.

The older two clinical studies (Studies 96-01 and 96-02) provide supportive evidence for efficacy and safety. These studies used an older Ultrase® MT formulation that contained the Eudragit® coating, a formulation not intended for marketing. Their efficacy findings are briefly summarized in this review (see Section 6.1.19 Additional Efficacy Issues/Analyses).

Together, Studies UMT20CF05-01, and Studies 96-01 and 96-02 provided data for an integrated safety analysis.

The two oldest studies (Studies 01 and 02) were submitted as legacy reports (with Study 02 submitted as a 12-page abbreviated report) in a format that did not permit review, and therefore, this Reviewer did not rely upon these results to support the claims of safety and efficacy.

The clinical bioavailability study, Study UMT20CP05-01 was reviewed for short-term safety data only in this clinical review. The results on bioavailability were reviewed by the Clinical Pharmacology Reviewer, Tien-Mien Chen, Ph.D. (See Section 4.4 Clinical Pharmacology).

5.3 Discussion of Individual Studies

This submission contains a single study (pivotal trial) that is used to support TbMP. This pivotal study (Study UMT20CF05-01) will be reviewed in depth in Section 6 Review of Efficacy. Supportive evidence for efficacy from Studies 96-01 and 96-02 will be reviewed in Section 6.1.10 Additional Efficacy Issues/Analyses. An integrated safety analysis of all three studies will be reviewed in Section 7 Review of Safety.

6 Review of Efficacy

6.1 Indication

The Sponsor proposed that Ultrase® receive the following indication:

(b) (4)

Since this application is recommended to receive an Approvable (AE) action, specific wording for the indication statement was not negotiated during this review cycle. In the opinion of this

Reviewer, the following indication statement would more accurately reflect the results of the clinical data:

(b) (4)

6.1.1 Methods

The pivotal study (study UMT20CF05-01) employed a cross-over design with relatively brief periods of treatment exposure of one week per treatment assignment (Ultrase® MT or Placebo). The cross-over design assumed that the condition being assessed is stable (limited drift over time), and that the treatment being assessed does not carry its therapeutic or adverse effects across the periods (carry-over effect). It also required that one period is not preferred over another on a systematic basis (period effect) and that one treatment sequence is not preferred over the other (sequence effect). The cross-over design is one of the study designs identified in the Guidance document provided by the FDA for the preparation and submission of an NDA for PEPs (April 2006; Section VI, E, 3). As identified in that Guidance, the strength of the cross-over design lies in its use of each patient as his/her own control and the use of a paired analysis. This statistical approach potentially decreases the effects of inter-patient variability, which otherwise might obscure true treatment effects. In general, fewer patients are needed to perform a cross-over study than a parallel study. One of the key elements required to ensure the validity of the cross-over study design is to ensure that the patients re-establish their Baseline between the treatment periods, which in the opinion of this Reviewer, was successfully accomplished by the design of the study.

Because the primary efficacy endpoint required precise assessment of fat and protein absorption from the marker-to-marker stool collection, it was not possible to provide for “escape” or “rescue” medication for steatorrhea or for other signs or symptoms as it might interfere with the results of the fat and protein absorption analyses. For this reason, it was important that the study treatment periods were designed to be as short as possible. Also, while these patients were established at Baseline as being ‘stable’ with respect to their clinical condition and optimal treatment, there was no guarantee that some changes might occur in a given patient during the study, a further reason for minimizing the study treatment period duration.

The Cystic Fibrosis Foundation - Therapeutics Development Network Coordinating Center (CFTDN) provided support in implementation and execution of the study, including participation in the discussion of the study design. This Reviewer agrees with the Sponsor that the study design was acceptable for achieving its study endpoint goals and reducing patient risks to a minimum.

The pivotal study and its efficacy results will be described next. All of the information in the Efficacy section of this review, with the exception of additional analyses in Section 6.1.10 Additional Efficacy Issues/Analyses (which describes the study designs and results of Studies 96-01 and 96-01) is limited to the pivotal study, given that it is the only study in the clinical development program that was conducted in TbMP.

6.1.1.1 Title of the Pivotal Study (Study UMT20CF05-01)

Study UMT20CF05-01 is titled: "A Multicenter, Randomized, Double-Blind, Cross-over Study to Compare the Safety and Efficacy of Ultrase® MT20 to Placebo for the Correction of Steatorrhea in Patients with Cystic Fibrosis (CF)." This is the pivotal study of the Ultrase® MT clinical development program, and it is the only study that used the to-be-marketed (TBM) formulation (Ultrase® MT capsules coated with HP-55).

6.1.1.2 Study Design

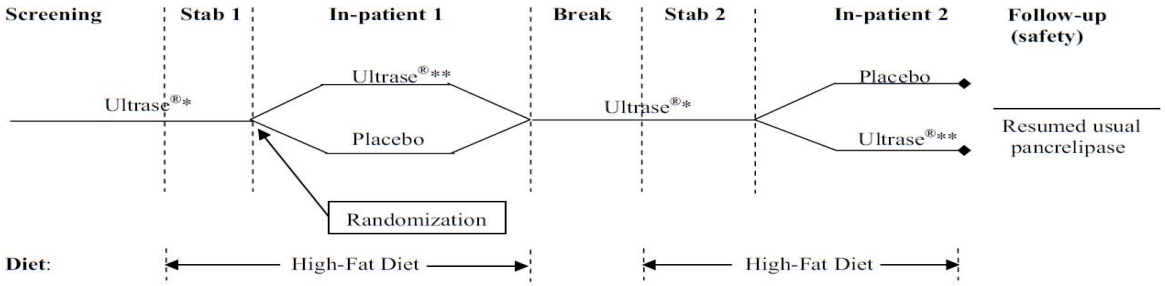
This was a multi-center, randomized, double-blind, placebo-controlled, two-week, two-period cross-over, study of 31 (Intent-to-Treat) patients that evaluated the efficacy, safety and tolerability of Ultrase® MT20 capsules coated with HP-55. The study drug was either Ultrase® MT 20 or Placebo, and each study patient was randomized to receive either Ultrase® MT20 or Placebo during the first study treatment period, and the other treatment during the second study treatment period. Eligible patients were CF patients with EPI, seven years or older, maintained clinically stable on a PEP treatment, with adequate body mass index (BMI). Patients were not required to have a particular Baseline Coefficient of Fat Absorption (CFA %) level. The primary efficacy endpoint was the difference in the percent absorption of dietary fat (CFA %) between Ultrase® MT20 and Placebo Treatment. The secondary objective was the percent absorption of dietary nitrogen (CNA %) between Ultrase® MT20 and Placebo Treatment. Patients served as their own controls.

The total duration of this study for a given individual was from 41 to 49 days (including the follow-up visit). The first patient consented to the study on 30 November 2007, and the last patient completed the study on 25 April 2007.

The study design consisted of the following periods: Screening Period (up to 11 days) → Stabilization Period 1 (up to 4 days) → Inpatient Study Drug Treatment Period 1 (6-7 days) → Break Period (3-6 days) → Stabilization Period 2 (up to 4 days) → Inpatient Study Drug Treatment Period 2 → Safety follow up visit (7-10 days after discharge from Study Drug Treatment 2 hospitalization).

Figure 1 depicts the study design schematically (electronically copied from the Sponsor's submission):

Figure 1 Schematic of study design of the pivotal study



* Ultrase® = Commercial Ultrase® MT18 or MT20 or open-label Ultrase® MT20 from Axcan (during Screening).
Open-label Ultrase® MT20 from Axcan (during Stabilization Period and Break Period).

** Ultrase® = Double-blind study drug
Note: Stab = Stabilization

The Screening Period lasted up to 11 days and was completed on an outpatient basis. The patients met with the investigator and the study staff for an explanation of the study, to review and sign the informed consent form, and to be assessed for study eligibility. The medical and surgical histories and the concomitant medication history taken in the three months prior to study entry were recorded. A physical examination with vital signs was performed and clinical laboratory determinations were made, including the collection of a single stool sample to determine fecal elastase-1 content. During the Screening Visit, the patients met with a registered dietician for development of the high fat diet to be used in the two Stabilization Periods and two Study Drug Treatment Periods. Patients received instructions on how to fill out all necessary information about food intake, study drug intake, bowel movements and characteristics of their stools in a diary. Patients already on Ultrase® MT18 or MT20 continued with that treatment for the Screening Period. Patients on enzyme preparations other than Ultrase® MT18 or MT20 at study entry were switched to open-label Ultrase® MT20 for the Screening Period, and received dose adjustments based on clinical symptoms while taking their usual diets. This Reviewer could not find further details about how these procedures were accomplished, e.g., whether patients were switched to an estimated equivalent dose or to a standardized starting dose, or whether the doses were titrated based on defined clinical criteria that were standardized from site to site.

During the first Stabilization Period (Stabilization Period 1), which was completed on an outpatient basis, all patients received Ultrase® MT20 and started on their high fat diet (2 grams ± 15% per kilogram of body weight), recording all necessary information in the diary card, as instructed. The patients were instructed to adjust the number of capsules of Ultrase® MT20 needed to account for the higher amount of fat in their diet. Patients were managed to reach a stabilized status according to the clinician's observations and the patient's symptoms. The patients were considered stabilized if they had three or fewer bowel movements per day, or if additional Ultrase® MT 20 did not cause any further reduction in their stool frequency. A Stabilized Dose was determined by the investigator from the average number of Ultrase® MT20 capsules the patient took during the last two days of Stabilization Period 1 and according to his/her medical judgment. This Stabilized Dose was the dose of study treatment to be used in the in-patient Study Drug Treatment Periods as well as during Stabilization Period 2. A Break

Period of (3 to 6 days) was included to follow the end of Study Drug Treatment Period 1. During the Break Period, the patient was free from high fat diet and food recording, and was on open-label Ultrase® MT20 regimen at an *ad lib* dose.

Reviewer's comment:
The issue of a four-day Stabilization Period was discussed when the protocol was reviewed by the CFTDN. It was debated and agreed upon that since patients would be stable on a PEP treatment prior to the study, a four-day stabilization would be sufficient. But, a second stabilization would also be required because the patients would have a Break Period between Inpatient Study Drug Treatment Periods during which time they will return to their normal diets and ad lib Ultrase® dosing if desired. It was requested by FDA that the dose used in the second stabilization period (Stabilization Period 2) be the same as that was used in the first stabilization period (Stabilization Period 1), i.e., that the dose given during the second Stabilization Period be defined by the first Stabilization Period in order to ensure a proper cross-over design (see 27 July 2006 FDA Meeting Minutes with Axcan Scandipharm Inc).

On the first day of Study Drug Treatment Period 1, the participants were randomized to receive Ultrase® MT20 or Placebo, and then they were switched to the opposite treatment for Study Drug Treatment Period 2. During each day of both inpatient Study Drug Treatment Periods, the patients continued their high fat diet and received the study drug from the study personnel with each meal and snack. The number of capsules administered was the number of capsules (i.e., the Stabilized Dose) established during the Stabilization Period 1. A 72-hour stool test was performed for each of the Study Drug Treatment Periods. On Days 3 and 6 (or 7) of each Study Drug Treatment Periods, two 250 mg capsules of FD&C Blue No. 2 dye indicator (stool marker) were administered with breakfast, and the patients went through a "marker to marker" stool collection. The administration of the second FD&C Blue No. 2 marker was delayed on Day 7 instead of Day 6, if the transit time of the patient was delayed, e.g. the first blue marker did not appear in the stool within 36 hours of administration. When the first blue tinted stool appeared after administration of the first marker, this blue tinted stool was not saved but all stools from subsequent bowel movements were saved until the appearance of the second stool marker, which was administered on Day 6 or Day 7. This first stool containing the second marker was saved and marked the end of the stool collection. The stools collected represented a 72-hour stool sample collection. The patients were discharged after the completed stool collection and after the completion of the procedures scheduled on Day 6 or Day 7.

Patients were monitored throughout the study for the occurrence of adverse events (AEs). A follow-up contact was made seven to ten days after discharge from hospitalization of Study Drug Treatment Period 2, either by a telephone call for those patients with no abnormal findings during the study, or by a clinic visit for those who showed any abnormal findings (physical examination, vital signs, and laboratory tests) during the study.

6.1.1.3 Study Objectives

The primary objective of this study was to demonstrate the efficacy and short term safety of HP55-coated Ultrase® MT20 for the correction of steatorrhea in CF patients with a history of EPI.

6.1.1.4 Patient Population

Key Inclusion Criteria

Patients were eligible for study participation if they fulfilled the following:

- Patients must have a confirmed diagnosis of CF based on one or more clinical features consistent with the CF phenotype, and one of the following:
    1. A genotype with two identifiable mutations consistent with CF.
    2. A sweat chloride test > 60mmol/L by quantitative pilocarpine iontophoresis.
- Patients must have pancreatic insufficiency as demonstrated by a fecal elastase (FE-1 < 100 µg/g of stools in ScheBo test) and must require pancreatic enzyme supplementation.
- Patients must be 7 years of age or older.
- Patients must have an adequate nutritional status based on Body Mass Index (BMI) measurements:
    1. Patients 7 to 20 years old must have a BMI $\geq 5^{th}$ percentile.
    2. Female patients >20 years old must have a BMI ≥16.
    3. Male patients >20 years old must have a BMI ≥16.5.
- Patients must be on an "optimal" (not otherwise defined by the Sponsor) clinical dose of pancreatic enzymes (Ultrase® MT 12, MT18 or MT20 or other pancreatic enzymes preparations) prior to entry in the study, and must tolerate this medication.
- Patients must be able to swallow capsules and must be able to eat a high fat diet, calculated as 2 g (± 15%) fat/kg of body weight per day.

Key Exclusion Criteria

Patients were excluded from study participation for any of the following:

- Patients who use narcotics or bowel stimulants and/or laxatives on a regular basis.
- Patients receiving enteral tube feeding and not willing to stop during the course of the study.
- Patients known to have a significant medical disease that would compromise their welfare or confound the study results including any of the following: acute pancreatitis, pulmonary infection, history of bowel resection, dysmotility disorders, chronic or severe abdominal pain, clinically significant portal hypertension, poorly controlled diabetes,
- Patients who have a condition known to increase fecal fat loss including any of the following: celiac disease, biliary cancer, biliary stricture, cholelithiasis, Crohn's disease, pancreatic cancer, radiation enteritis, tropical Sprue, Whipple's disease, lactose intolerance, pseudomembranous colitis.
- Female patients who are pregnant or lactating.

6.1.1.5 Concomitant and Prohibited Medications

Since the primary endpoint of this study is a measure of dietary fat absorption, drugs or products known to have an effect on fat absorption or to interfere with the fecal fat test were prohibited during the study, including the following: enema, barium, potassium chloride, mineral oil and castor oil, calcium carbonate, olestra, magnesium hydroxide, all fat-blocking nutritional supplements, over-the-counter enzymatic supplements, gastrointestinal motility modifiers, narcotics, erythromycin, acute use of broad-spectrum antibiotics, and all laxatives (with the exception of bisacodyl if prescribed by the investigator especially during the in-patient 72-hour stool collection period). It was not stated in the protocol that agents that could change the pH of the stomach content were specifically prohibited (e.g., H_2 antagonist, proton-pump inhibitors, sucralfate, antacid, etc).

6.1.1.6 Study Visits and Procedures

Study visits and procedures are presented in Table 4 below (copied electronically from the Sponsor's submission).

Table 4 Schedule of events

PROCEDURES	SCREENING PHASE	COMPARISON PHASE																
		Stab*	Treatment Period 1 in days (D)							OP**	Stab*	Treatment Period 2 in Days (D)							Follow-up
	D-15 to D-5	D-4 to D-1	D1	D2	D3	D4	D5	D6	D7	D-10 to D-7	D-4 to D-1	D1	D2	D3	D4	D5	D6	D7	7 to 10 days after discharge
Informed Consent	X																		
Inclusion/Exclusion	X																		
Medical History and Demographics	X																		
Physical Exam and Vital Signs	X							x[4]	x[4]								x[4]	x[4]	
Clinical Laboratory Tests and Urinalysis	X							x[5]	x[5]								x[5]	x[5]	
Serum Pregnancy Test[1]	X																x[5]	x[5]	
Fecal Elastase Determination[2]	X																		
Morning Weight	X		x	x	x	x	x	x				x	x	x	x	x	x		
Concomitant Medication[3]	X	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		
Dietician and Study Nurse Instructions	X																		
Dispense Diary/open label Ultrase MT20	X							x[5]	x[5]										

* Stabilization Period (at home) **Out Patient Phase

[1] For Women Of Child Bearing Potential only. [2] On a random sample of stool. [3] Taken in the last 3 months. [4] Any time during the day the second marker has passed. If an AE appears between the time the physical examination is done and the blue tinted stool has passed, another physical examination is needed to assess this AE. . [5] After second dye marker is passed.

Source: Appendix 16.1.1 Protocol UMT20CF05-01

PROCEDURES	SCREENING PHASE	COMPARISON PHASE															
		Stab*	Treatment Period 1 in days (D)							OP**	Stab*	Treatment Period 2 in Days (D)							Follow-up
	D-15 to D-5	D-4 to D-1	D1	D2	D3	D4	D5	D6	D7	D-10 to D-5	D-4 to D-1	D1	D2	D3	D4	D5	D6	D7	7 to 10 days after discharge
Ultrase Treatment (personal or newly introduced)	x																		
Stabilization on open label Ultrase MT20		x									x								
High Fat Diet		x	x	x	x	x	x	x[7]	x[7]		x	x	x	x	x	x	x[7]	x[7]	
Diary Records[6]		x	x	x	x	x	x	x			x	x	x	x	x	x	x		
Randomization/ Kit number assigned			x																
Double-blind Ultrase MT20 vs Placebo			x	x	x	x	x	x[7]	x[7]			x	x	x	x	x	x	x	
FD&C Blue No 2 dye with breakfast (stool marker)					x			x[8]	x[8]					x			x[8]	x[8]	
72-hour stool collection					x	x	x	x[9]	x[9]					x	x	x	x[9]	x[9]	
Adverse Events		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Discharge of period treatment								x[4]	x[4]								x[4]	x[4]	
Follow up visit																			x[10]

* Stabilization Period (at home) ** Out Patient Phase

[6] Diary to include food records, capsules count, number and characteristics of stools and abdominal symptoms. Diary to be completed by patient during stabilization and by the study personnel from D1 to D6-7. [7]To stop at discharge. [8]If the first dye marker is not passed within 36 hours of administration, administer the second dye marker 96 hours after the first dye marker (Day 7). [9]Stool collection until second dye marker is passed. [10]Assessment to be performed by phone or during a visit with the investigator if judged necessary, to follow any abnormal findings during the study (physical exam, vital signs, lab tests, AE, etc.)

Source: Appendix 16.1.1 Protocol UMT20CF05-01

6.1.1.7 Randomization, Blinding, Control

Randomization was 1:1, and by central randomization, not stratified by center or any other criteria. The study was double-blind only during the two Study Drug Treatment Periods, and was achieved using identical capsules for the two treatments and identical packaging. The study was placebo-controlled. The placebo capsules used in this study had the same appearance as the Ultrase® MT20 capsule with respect to size, color and imprinting. The placebo capsules were composed of size 0 capsules (body yellow/cap grey opaque) containing uncoated Avicel® spheres (Avicel® is microcrystalline cellulose, USP). In the opinion of this Reviewer, however, blinding might not have been entirely possible, due to the likelihood of an increased incidence/severity of steatorrhea while on placebo, after patients having been stabilized to having <3 stools per day on the Stabilizing Dose during the Stabilization Period. But, given that the primary endpoint was an object measure of CFA %, this should not have affected the study results.

6.1.1.8 Study Medication Dose Selection, Dispensing, and Compliance

Pre-selection of set dose or dose ranges was not possible for this study since the daily dose to be used by a patient was determined on an individual patient basis according to their EPI signs and symptoms.

In this study, optimal Ultrase® MT20 dosages were based upon adjustment of the patient's usual pancrelipase dose, modified in response to the introduction of the high fat diet. The dose to be administered during the treatment periods was established for each patient during the first

stabilization period (Stabilization Period 1), at which time the high fat diet was initiated. The patients adjusted their dose of open-label Ultrase® MT20 to account for the increase of fat in their diet. They were medically managed to reach a "stabilized" status according to the clinician's observations and the patient's symptoms. The patients were considered "stabilized" if they had three or fewer bowel movements per day or if additional Ultrase® MT 20 did not cause any further reduction in stool frequency. The Stabilized Dose was determined by the investigator from the average number of Ultrase® MT20 capsules the patient took in the last two days of Stabilization Period 1 and according to his/her medical judgment. This Stabilized Dose was the dose of the Study Drug used in both Study Drug Treatment Periods as well as during both Stabilization Periods. The total daily number of capsules was then dispensed with each meal and snack throughout the day. The dose was not to exceed 2,500 lipase units/kg/meal or snack.

Compliance was calculated from the capsule counts reported during the double-blind Study Drug Treatment Periods. There were two compliance measurements, one for Study Drug Treatment Period 1 and one for Study Drug Treatment Period 2. There was no measurement of compliance during the Screening Phase and the Stabilization Periods.

As for the extent of exposure, the patient's last day of treatment was not taken into account in the treatment compliance calculation. These two compliance measurements were computed as follows:

$$\frac{\text{Total number of capsules taken during the treatment period*}}{\text{Number of prescribed capsules/day x treatment period extent of exposure*}} \times 100\%$$

* Excluding the last day of treatment for both Treatment Periods.

Non-compliance was defined as taking less than 80% or more than 120% of the dose established during Stabilization Period 1 (the Stabilized Dose).

6.1.1.9 Efficacy and Endpoint Measurements in the Pivotal Study

The primary outcome measures were stool CFA % and safety.

The primary efficacy parameter is the Coefficient of Fat Absorption (CFA %), defined as:

$$\frac{\text{72-hour fat intake (g)} - \text{72-hour fat excretion (g)}}{\text{72-hour fat intake (g)}} \times 100\%$$

The primary efficacy endpoint was Ultrase® MT20 Treatment CFA % minus Placebo Treatment CFA %.

The Sponsor also performed a secondary efficacy analysis on the results of Coefficient of Nitrogen Absorption (CNA %).

Other efficacy assessments included the total number of daily bowel movements, and the proportion of the characteristics of the stools (hard, formed/normal, soft, or watery) between the study treatment groups.

The intent-to-treat (ITT) population was defined as all randomized patients. The safety population was defined as all patients who received at least one dose of Pancrease® MT. The per-protocol (PP) population was defined as all patients who completed the two Study Drug Treatment Periods, and had all bowel movements appropriately collected in the two complete stool collection periods with no major protocol violations. This Reviewer also analyzed an "at-lease-one CFA %" population, consisting of patients who had at least one CFA % recording from either one of the two Study Drug Treatment Periods. For additional details, please see Section 6.1.4 Analysis of Primary Endpoints.

6.1.1.10 Safety Analysis

Safety was assessed by type and incidence of Adverse Events (AEs); discontinuation due to AEs; drug-related AEs, Serious Adverse Events (SAEs), and severe AEs; changes from Screening Visit or Baseline in physical exams, vital signs, or clinical laboratory assessments. All AEs reported during this study were "treatment emergent," i.e., they were not present prior to exposure to study medication, or they were any event already present that worsened in duration, intensity or frequency following exposure to study medication. All AEs, whether or not considered causally related to the treatment, were recorded.

Serious Adverse Events (SAEs) were monitored by Axcan Pharma Inc. throughout the trial. Monitoring of SAEs was performed with special attention on intestinal obstruction. All SAEs, regardless of relationship to study treatment, were to be reported by the investigator to Axcan Pharma Inc within 24 hours of learning of the event. This included SAEs occurring as soon as the ICF/assent form was signed by the patient (i.e. pre-treatment SAEs). SAEs that were possibly related to treatment and were assessed as being unexpected could have qualified for expedited reporting by Axcan to the regulatory authorities.

Axcan Pharma Inc. sent all SAE reports within the next working day via fax or email to the Data Monitoring Committee chair of the Data and Safety Monitoring Group and to Endpoint Research. All SAEs that occurred in the 30 days following the last dose of study drug were to be reported to Axcan Pharma Inc. The Sponsor had a legal responsibility to notify the Health Products and Food Branch (HPFB) of Canada, the FDA, the European Agency for the Evaluation of Medicinal Products (EMEA) of European Union, and all other foreign regulatory agencies about the safety of the drug.

6.1.1.11 Statistical Analysis Plan

The results from a similar, earlier, cross-over study of Ultrase M20 (Study 96-01) showed a difference of 29% between Ultrase and the Placebo treatment the primary efficacy outcome measures. The mean CFA% was 59% with placebo and 87% with Ultrase, with N=25 patients. The treatment difference was highly significant. Based on these results, the Sponsor planned to have 24 completed patients. Assuming a standard deviation of 30% between Placebo and Ultrase and a two-sided alpha of 0.05, a sample size of 24 would give a power of 80% to detect a

minimum difference of 18%. The intent-to-treat (ITT) population was defined as all randomized patients. Please see the FDA Statistical Reviewer Stella Grosser, Ph.D.'s review for further details.

6.1.1.12 Protocol Amendment

The first patient consented to the study on 30 November 2007, and the last patient completed the study on 25 April 2007. The original study protocol was issued on 4 August 2006. There was one protocol amendment (dated 8 January 2007), which was instituted midstream during the study, involving mainly administrative and personnel changes, and the following amendments: addition of CNA % as a secondary objective and enteral tube feeding as an exclusion criterion; modification/clarification of the process to establish the Stabilized Dose during Stabilization Period 1; addition of the prohibited use of erythromycin; and modification of the targeted amount of fat to eat per day. Regarding the last item, it appears to this Reviewer that the amount of daily fat to be consumed was changed midstream in the study to allow more flexibility. The revised version was, "2 grams (± 15%) per kilogram of body weight, while taking into account the patient's activity level and appetite." The provision of ± 15% modifier was probably instituted because the actual amount of fat consumed by patients was more variable than that had been originally anticipated. It is unlikely that the results of the study were significantly impacted by this amendment, however.

6.1.2 Demographics

The intent-to-treat (ITT) patient population was comprised predominantly of Caucasian patients (93.5%), the remainder being Black patients (6.5%). Since CF is a disease predominantly of Caucasians, the study population is representative of the CF population. There were more males in the study (64.5%). Since CF is a genetic disease that is autosomal recessive in nature, both males and females are equally affected. The small imbalance in the gender distribution is likely a function of the small number of patients studied. The patients were between the ages of 8 to 37 years; the mean age was 20. Since CF patients live into their third or fourth decades, this represents the median age in the expected lifespan. In the ITT population, the mean years from CF diagnosis to study Screening was 19 years (range 3-27 years). The majority of patients (60%) had been on Ultrase® MT18 or 20 prior to the study start; the rest were on Ultrase® MT12 or another PEP. Age breakdown of children, adolescents, and adults is as follows in Table 5. It is worth noting that very few children younger than 12 years were enrolled in the study, which is a significant limitation in the Sponsor's clinical development program performed to date. The Sponsor intends to conduct additional clinical studies in the pediatric patients (see Section 6.1.7 Subpopulations).

Table 5 Age categorization of the ITT population in Study UMT20CF05-01

ITT population (N=31)
2-11 year group (children): 2 patients
12-18 year group (adolescents): 13 patients
>18 year group (adults): 16 patients

Additional demographics and other Baseline characteristics of the ITT population can be found in Table 6 (electronically copied from the Sponsor's submission).

Table 6 Summary of demographics and other Baseline characteristics (ITT population)

Parameter	Statistic	Overall
Number of Patients in the ITT Population	N	31
Age at Informed Consent (years)	n	31
	Mean	19.6
	STD	6.6
Gender	n	31
Male	n (%)	20 (64.5)
Female	n (%)	11 (35.5)
Race	n	31
Caucasian	n (%)	29 (93.5)
Black	n (%)	2 (6.5)
Weight at Screening (kg)	n	31
	Mean	55.56
	STD	11.61
Alcohol Habits	n	31
No, never	n (%)	10 (32.3)
Yes	n (%)	21 (67.7)
Smoking History	n	31
Non-smoker	n (%)	30 (96.8)
Ex-smoker	n (%)	1 (3.2)
Smoker	n (%)	0
Fecal Elatase-1 (µg/g of stool)	n	31
<15	n (%)	30 (96.8)
=34	n (%)	1 (3.2)

Notes:
1. Percentages based on the total number of Safety patients with available data.
Source: Table 14.1-10

6.1.3 Patient Disposition

Thirty-six (36) patients were screened; five patients were screening failures (see Table 7 for the reasons for screening failures). The remaining 31 patients were randomized, all of whom having received at least one dose of study drug, constituting the ITT population. Five of the 31 ITT patients discontinued the study prematurely either as a result of violating the protocol, withdrawing consent, or experiencing SAEs. Twenty-eight (28) patients had at least one CFA value recorded; and, 24 patients completed both Study Drug Treatment Periods and had stool results available for each treatment periods. Nine patients had at least one major protocol violations (i.e., not compliant with the high fat diet, did not have any high-fat diet diary recording, or discarded stool during stool collection). Therefore, the per-protocol population (PP) consisted of 18 patients who were not screen failures, did not have any major protocol violations, did not withdraw consent or drop-out due to an SAE, and had at least one CFA collection. Table 7 lists the disposition of all patients as described. Table 8 lists disposition of patients by study sites.

Table 7 Disposition of patients UMT20CF05-01

Patient ID	Treatment sequence	ITT	Reason for not completing the Study	Study completed	Major protocol violation	PP
0103	Screening Failure	No	SAE (increased coughing while on Ultrase®)	No	-	No
0603	Screening Failure	No	SAE (hemoptysis while on Ultrase®)	No	-	No
1002	Screening Failure	No	Patient withdrew consent during Screening (while on Ultrase®)	No	-	No
1003	Screening Failure	No	AE (increased coughing while on Ultrase®)	No	-	No
1007	Screening Failure	No	Failed inclusion criteria (Fecal Elastase >100).	No	-	No
0102	Placebo / ULTRASE	Yes	Patient withdrew consent during Study Drug Treatment Period 2 (while on Ultrase®)	No	-	No
0301	ULTRASE/ Placebo	Yes	SAE (abdominal pain) during Study Drug Treatment Period 2 (while on Placebo)	No	-	No
0505	Placebo / ULTRASE	Yes	SAE (cough, fever) during Break Period (while on Ultrase®), coming from the Placebo period	No	-	No
0601	ULTRASE/ Placebo	Yes	AE (abdominal pain, decreased appetite, flatulence, steatorrhea) during Study Drug Treatment Period 2 (while on Placebo)	No	-	No
0304	Placebo / ULTRASE	Yes	Subject inadvertently discarded stool during stool collection during Study Drug Treatment Period 2 (while on Ultrase®)	No	(Ø stool)	No
0201	ULTRASE / Placebo	Yes		Yes	Yes (Ø fat)	No
0204	Placebo/ULTRASE®	Yes		Yes	Yes (Ø fat)	No
0205	ULTRASE/ Placebo	Yes		Yes	Yes (Ø fat)	No
0207	Placebo / ULTRASE	Yes		Yes	Yes (Ø fat)	No
1005	Placebo / ULTRASE	Yes		Yes	Yes (Ø fat)	No

0602	ULTRASE/ Placebo	Yes		Yes	Yes (? fat)	No
0604	Placebo / ULTRASE	Yes		Yes	Yes (? fat)	No
0101	Placebo / ULTRASE	Yes		Yes	No	Yes
0104	ULTRASE/ Placebo	Yes		Yes	No	Yes
0105	ULTRASE/ Placebo	Yes		Yes	No	Yes
0202	ULTRASE/ Placebo	Yes		Yes	No	Yes
0203	Placebo / ULTRASE	Yes		Yes	No	Yes
0206	Placebo / ULTRASE	Yes		Yes	No	Yes
0302	ULTRASE/ Placebo	Yes		Yes	No	Yes
0303	Placebo / ULTRASE	Yes		Yes	No	Yes
0305	Placebo / ULTRASE	Yes		Yes	No	Yes
0306	ULTRASE / Placebo	Yes		Yes	No	Yes
0501	Placebo / ULTRASE	Yes		Yes	No	Yes
0502	Placebo ULTRASE	Yes		Yes	No	Yes
0503	ULTRASE / Placebo	Yes		Yes	No	Yes
0504	ULTRASE/ Placebo	Yes		Yes	No	Yes
0701	Placebo / ULTRASE	Yes		Yes	No	Yes
0901	Placebo / ULTRASE	Yes		Yes	No	Yes
0902	ULTRASE/ Placebo	Yes		Yes	No	Yes
1001	ULTRASE / Placebo	Yes		Yes	No	Yes
1006	Placebo / ULTRASE	Yes		Yes	No	Yes

(Ø stool)—no stool sample for a Study Drug Treatment Period
(Ø fat)—did not comply with high fat diet
(? fat)—did not have sufficient fat diary recording
Shaded area: 24 patients who completed both Study Drug Treatment Periods, for whom CFA % was available for both periods

Table 8 Patient disposition by site

Investigator Site	Number of patients screened	Disposition of patients (patient's ID in parenthesis)
Dr. Gavin Graff	5	1 withdrew (0102); 1 screening failure (0103)
Dr. Theodore Liou	7	4 had a major protocol violation (0204, 0205, 0207. and 0201)
Dr. Jamshed Kanga	6	3 screening failures (1002, 1003, 1007); 1 had a major protocol violation (1005)
Dr. Kathryn Moffett	4	2 had a major protocol violation—no fat/CFA % recording (0602, 0604); 1 did not complete the study due to gastrointestinal worsening while on double-blind Placebo treatment (0601); 1 screening failure (0603)
Dr. Richard Ahrens	5	1 did not complete the study due to an SAE (0505)
Dr. Samya Nasr	1	-
Dr. Steven Straughsbaugh	6	1 did not complete the study due to an SAE (0301); 1 did not finish the study--discarded stool (0304)
Dr. Susan Millard	2	-
Total	36	24 patients completed both Study Drug Treatment Periods, for whom CFA % was available for both periods

6.1.3.1 Concomitant Medication

This Reviewer used the **CV_conmd.xpt** dataset to arrive at the following observations:

- The majority of the concomitant medications were CF related.
- The most common concomitant medications (other than PEPs) were the following: Salbutamol® (91% of patients), Dornase Alfa® (69%); Tobramycin® (64%), ADEKS® (64%), Azithromycin® (53%), Ibuprofen® (39%), Seretide® (31%), Fluticasone® (31%), and Multivitamin (28%).
- There were 19/36 patients (53%) of the safety population who were taking proton pump inhibitors or H_2 blockers during the study. Except for one patient, all had started the medication before the start of the study and the vast majority had been on a stable dose of the medication for chronic use for several years. There did not appear to be a change in the pattern of use over the course of the study.

6.1.3.2 Protocol Deviations and Violations

Protocol deviations that were considered major and that were not authorized by the Sponsor were reported in nine patients; one had Study Drug non-compliance, and eight patients (22%) were non-compliant with the required high fat diet (Table 9) (copied electronically from the Sponsor's submission). Along with these major protocol violations, this Reviewer noted that there were numerous "minor' protocol deviations, mostly relating to non-compliance of the high fat diet. In most cases, the compliance was towards taking more than the allowable amount of fat, which would have probably enhanced the likelihood of seeing a treatment effect (i.e., more fat intake, more room to improve). But, the Reviewer does not believe that these protocol violations/deviations rendered the conclusions of the study unreliable.

Table 9 Summary of major protocol violations (all screened patients) in Study UMT20CF05-01

Parameter	Statistic	Overall
Number of Screened Patients	N	36
Major Protocol Violations		
Study Drug Compliance <80% or >120%	n (%)	1 (2.8)
Non-compliance with High-Fat Diet[a]	n (%)	8 (22.2)

[a] Without any protocol deviations granted by the Sponsor.
Notes:
1. Patients could have more than one major protocol violation.
2. Non-compliance with high fat diet is defined as deviating by ±10% from the targeted amount of fat (1.7 – 2.3 g of fat per kg of body weight) on multiple occasions during the stool collection periods.
3. Percentage based on the total number of screened patients.

Source: Table 14.1-3

6.1.3.3 Measurements of Treatment Compliance

Compliance to the required treatment regimen was high and consistent in the ITT population as calculated using capsule counts. Average compliance was 98.3% (SD ± 9.2 %) for the Ultrase®

treatment period, and 97.4% (SD ± 9.2 %) for the Placebo treatment period. Compliance values tended towards a slightly higher use than required, with 76.7% of patients on Ultrase® treatment being between 100% and 120% as compared to 13.3% of patients being between 80% and 100%. A similar profile was seen with Placebo (Table 10) (copied electronically from the Sponsor's submission).

Table 10 Summary of treatment compliance (ITT population) in Study UMT20CF05-01

		Treatment	
Parameter	**Statistic**	**Ultrase® MT20**	**Placebo**
Number of Patients in the ITT Population	N	30	31
Treatment Compliance (%)	n	30	30
	Mean	98.3	97.4
	STD	9.2	7.6
< 20%	n (%)	0	0
20% to 40%	n (%)	0	0
40% to 60%	n (%)	0	0
60% to 80%	n (%)	2 (6.7)	3 (10.0)
80% to 100%	n (%)	4 (13.3)	6 (20.0)
100% to 120%	n (%)	23 (76.7)	21 (70.0)
> 120%	n (%)	1 (3.3)	0

Notes:
1. Treatment compliance has been calculated as follows:
$$\frac{\text{Total number of capsules taken during the Treatment Period (excluding the last day of treatment)}}{\text{(Number of prescribed capsules/day) x (Treatment Period extent of exposure in days (excluding the last day of treatment))}}$$
2. The number of prescribed capsules/day corresponds to the number of capsules/day that has been determined to be the patient's stabilized dose at the end of Stabilization Period 1 by the investigator after discussion with the Sponsor.
3. Five patients (0103, 0603, 1002, 1003, and 1007) received open-label study medication during the study Screening Phase but did not enter the study Comparison Phase.

Source: Table 14.1-22

Table 11 (copied electronically from the Sponsor's submission) presents a summary of treatment exposure in patients who were randomized to Study Drug treatment (ITT population). On average, patients were exposed to 5.4 (±1.1) and 5.0 (±1.1) days of treatment while on Ultrase® MT20 and Placebo, respectively. The mean daily number of capsules administered was similarly comparable between the treatments with 18.2 (±6.6) and 17.9 (±6.8) capsules while on Ultrase® and Placebo, respectively.

Table 11 Summary of extent of exposure and mean total daily number of capsules taken (Study UMT20CF-05-01)

		Treatment	
Parameter	**Statistic**	**Ultrase® MT20**	**Placebo**
Number of Patients in the Safety Population Who Entered the Treatment Period	N	30	31
Extent of Exposure (days)	n	30	31
	Mean	5.4	5.0
	STD	1.1	1.1
	Median	5.5	5.0
	(Min., Max.)	(1, 7)	(0, 6)
Mean Total Daily Number of Capsules Taken	n	30	30
	Mean	18.2	17.9
	STD	6.6	6.8
	Median	18.0	18.0
	(Min., Max.)	(6, 30)	(6, 32)

Notes:
1. Extent of exposure, in days, has been calculated as follows within each study period:
   (Next to the last dose date of the concerned study period – First dose date of the concerned study period) + 1
2. Mean total daily number of capsules taken has been calculated as follows within each study period:
   Total number of capsules taken during the concerned study period (excluding the last day of treatment) / Extent of exposure
3. Five patients (0103, 0603, 1002, 1003, 1007) received open-label study medication during the study Screening Phase but did not enter the study Comparison Phase.

Source: Table 14.1-21

Reviewer's comment:

Due to the constraint of the review clock, it has not be ascertained by this Reviewer whether the dosing in terms of lipase units used by patients in the study fell into the CFF/FDA recommendations, or whether the dosing is representative of how it will be used post-approval. These issues will need to be revisited and clarified with the Sponsor at the time of labeling negotiations.

6.1.4 Analysis of Primary Endpoint(s)

Primary efficacy analysis was based on an evaluation of the percent absorption of dietary fat (CFA %).

This method is clearly identified as an appropriate assessment for the purposes of this study in the CDER guidance document, Guidance for Industry - Exocrine Pancreatic Insufficiency Drug Products – Submitting NDAs (CDER 2006). The Guidance states that although demonstrating a beneficial effect on clinical outcomes is desirable in clinical trials (e.g., weight gain or nutritional status), efficacy can also be demonstrated by showing a meaningful beneficial effect on appropriate pharmacodynamic measures such as steatorrhea. For example, a Sponsor could

demonstrate that administration of the PEP to patients with exocrine pancreatic insufficiency causes a meaningful decrease in stool fat as evaluated in a 72-hour quantitative stool collection.

The Guidance bases its recommendations on published consensus documents[9] that describe that decreased CFA is an accepted indicator of EPI, and an increase in CFA is associated with enhanced pediatric growth and development.[10] A clinically meaningful increase in CFA in CF patients is accepted to be an increase of 30% or greater in the most severely affected patients, where "severely affected patients" is defined as those patients who have Baseline CFA less than 40%. In patients with a Baseline CFA greater than 40%, however, there is no accepted change in CFA that has been shown to be clinically meaningful. Patients with higher CFAs at Baseline tend to have smaller increases in CFA with PEP administration, as these patients have a lesser capacity to respond. Conversely, patients with the lowest CFAs at Baseline tend to have greater increases with PEP treatment as there is more "room" to improve.

No accepted clinically meaningful increase in CFA has been determined for patients with EPI due to causes other than CF. However, as EPI due to any cause has similar clinical findings as in CF, this degree of change could reasonably be applied as meaningful in EPI due to other conditions that cause EPI, such as CP. In accordance with the Guidance, the Division accepts the use of CFA as the primary efficacy measure in the clinical studies conducted in the Ultrase® clinical development program. However, the Division expects to see that the magnitude of change in patients' CFA with PEP administration would depend upon the Baseline (or no treatment/Placebo CFA), and expect to see larger increases in CFA (approaching 30%) in patients with the lowest Baseline/Placebo CFA (e.g., <40%), and lesser increases in CFA in patients with higher Baseline/Placebo CFA (e.g., >40% to <80%).

Although the Sponsor had pre-specified that the primary efficacy variable was to be analyzed in the ITT population--which is defined as all randomized patients (N=31)--the Sponsor's efficacy analyses found in Table 12 (copied electronically from the Sponsor's submission) actually reflect the results of the 24 patients who completed both Study Drug Treatment Periods, who had stool testing completed in both study periods (See Table 7: only patients in the shaded gray area). The primary efficacy endpoint is defined as change in CFA, determined by mean CFA % measured in patients in the Ultrase® Treatment Period minus the mean CFA % measured in patients during the Placebo Treatment Period. Each patient served as his/her own control in this cross-over study.

The Sponsor's efficacy analyses are given below in Table 12 (copied electronically from the Sponsor's submission). In these 24 patients (not the ITT population), the difference in CFA % between the Ultrase® Treatment Period and the Placebo Treatment period was 35 points (SD ± 25), $p < 0.0001$, a clinically and statistically significant result. There were no apparent sequence or period effects. Dropouts were not replaced, and missing observations were not imputed. There were no apparent sequence or period effects. The FDA Statistical Reviewer (Stella Grosser, Ph.D.) noted some differences in the statistical manipulation between the Sponsor's and

9 Borowitz, DS; Grand, RJ; Durie, PR Consensus Committee (supplement A). Use of pancreatic enzyme supplement for patients with cystic fibrosis in the context of fibrosing colonopathy. 1995; J Ped 127(5): pp 681-684
10 Dodge, JA, Turck D. Cystic fibrosis: nutritional consequences and management. Best Pract Res Clin Gastroenterol. 2006; 20(3):531-46.

her independent analyses, but the statistical conclusions reached remained the same: significant treatment effect was demonstrated with no effect of period or sequence. For more details, please see Dr. Grosser's Statistical Review.

Table 12 Summary and analysis of the coefficient of fat absorption (ITT population)

		Treatment		
Parameter	**Statistic**	**Ultrase® MT20**	**Placebo**	**Delta**
Number of Patients in the ITT Population	N	30	31	30
CFA%	n	25	27	24
	Mean	88.550	55.614	34.742
	STD	4.943	25.104	25.049
	Median	89.190	51.950	40.385
	(Min., Max.)	(77.36, 97.08)	(13.59, 97.12)	(-7.24, 75.22)
Mixed Model Fixed Effect [a]				
Sequence	p-value	0.9060		
Period	p-value	0.3204		
Treatment Group	p-value	<0.0001**		
Note: n for CFA% includes all randomized patients who completed at least one treatment period; the delta value is the mean of the individual treatment differences in patients who completed both treatment periods.				

** Indicates statistical significance at the 0.010 level.

[a] P-values from a semi-parametric mixed model on ranked CFA% values including sequence, period, and treatment group as fixed effects, and patient ID as random effect.

Notes:

1. CFA%= Coefficient of Fat Absorption
2. CFA% has been calculated as follows (in some instances, the CFA% has been calculated over 96 hours instead of 72 hours):

$$\frac{\text{72-hour fat intake (g)} - \text{72-hour fat excretion (g)}}{\text{72-hour fat intake (g)}} \times 100\%$$

3. The fat excretion value (g/24h) transferred by the Central Lab has been multiplied by 3 before analysis in order to convert it to total fat content.
4. For each patient, Delta is the difference between CFA% Ultrase MT20 value and CFA% Placebo value.

Source: Table 14.2-1

This Reviewer performed an independent analysis of the results shown in the 24 selected patients. Table 13 lists the results of patients, ranked in the order from low to high based on their CFA % with Placebo treatment (no treatment). The mean delta CFA % was a 35 point increase (SD ± 25) with Ultrase® MT treatment, a clinically significant result.

Table 13 Δ CFA % between Ultrase® treatment and Placebo in the 24 patients who completed both Study Drug Treatment Periods and who had stool results for both periods in Study UMT20CF05-01

Patient	CFA Placebo	CFA Ultrase	Change in CFA
0207	13.59	88.51	74.92
0302	17.14	92.36	75.22
0206	23.06	81.91	58.85
0503	25.86	89.87	64.01
0105	26.54	89.89	63.35
0203	35.14	91.96	56.82
0902	40.47	83.41	42.94
0303	40.58	87.76	47.18
0306	41.94	90.24	48.30
0204	44.07	92.69	48.62
0504	45.7	84.21	38.51
0901	46.6	88.86	42.26
0501	51.16	89.19	38.03
1005	51.95	94.39	42.44
0101	54.03	81.11	27.08
0104	57.24	80.87	23.63
0305	63.07	77.36	14.29
0205	78.58	89.53	10.95
0502	84.48	94.63	10.15
1006	84.61	97.08	12.47
0701	87.3	95.59	8.29
0201	89.5	89.05	-0.45
1001	93.28	86.04	-7.24
0202	97.12	90.3	-6.82
			Mean Δ CFA= 34.7 SD=25 Median 40.4

6.1.4.1 Additional Analyses of Primary Endpoint

This Reviewer performed additional clinical analyses to further verify that clinically meaningful improvement was seen with Ultrase®. Table 14 shows the ITT patients' results listed by ranking of Placebo (no treatment) CFA % values from low to high. For the purpose of this analysis, patients without both CFA % measurements for Ultrase® Treatment Period and the Placebo Treatment Periods were conservatively assigned a Δ CFA % of zero (which assumed that for these patients, there was no improvement seen in CFA % with Ultrase® treatment). It was also assumed that Δ CFA % would not be a negative number (i.e., that PEP treatment would not result in a worsening in CFA %) based on the knowledge that PEPs are known to be efficacious. This Reviewer recognizes, however, that the latter assumption may not entirely valid given that even in this study some patients were shown to have negative CFA % change with Ultrase® treatment. Nonetheless, the changes in the negative directions were relatively small, probably within the error of the test, so the assumption is likely reasonable. In any event these analyses are not meant to arrive at mathematically rigorous conclusions, but are intended to be used as sensitivity analyses to see if the results conform to a biologically/physiologically plausible hypothesis.

The results in Table 14 show that patients with the lowest Placebo CFA % had the highest gain in CFA % improvement on Ultrase® treatment, which is consistent with the presumption that patients with the lowest CFA % should have greater increases with PEP treatment as there is more "room" to improve. CFA % < 40 has been accepted in the literature as severe malabsorption. Divided into three groups (with the moderate to mild groups being arbitrarily defined by this Reviewer): Placebo CFA % < 40 % (severe); between 40 and 80% (moderate); and, > 80% (mild), the results demonstrated that the patients' CFA increase with Ultrase® treatment (Δ CFA) was +40, +30, and +2, respectively, with a median Δ CFA of +27. The results are summarized in Table 14.

Table 14 UMT20CF05-01 (Pivotal Study) Analysis of Δ CFA % in the ITT population (N=31)

SUBJECT	CFA Placebo	CFA Ultrase®	CFA DELTA
0207	13.59	88.51	74.92
0302	17.14	92.36	75.22
0206	23.06	81.91	58.85
0503	25.86	89.87	64.01
0105	26.54	89.89	63.35
0203	35.14	91.96	56.82
0902	40.47	83.41	42.94
0303	40.58	87.76	47.18
0306	41.94	90.24	48.30
0204	44.07	92.69	48.62
0504	45.7	84.21	38.51
0901	46.6	88.86	42.26
0501	51.16	89.19	38.03
1005	51.95	94.39	42.44
0505	52.86	.	0.00
0101	54.03	81.11	27.08
0104	57.24	80.87	23.63
0305	63.07	77.36	14.29
0102	63.93	.	0.00
0205	78.58	89.53	10.95
0502	84.48	94.63	10.15
1006	84.61	97.08	12.47
0701	87.3	95.59	8.29
0201	89.5	89.05	-0.45
0304	91.79	.	0.00
1001	93.28	86.04	-7.24
0202	97.12	90.3	-6.82
0301	.	86.93	0.00
0601	.	.	0.00
0602	.	.	0.00
0604	.	.	0.00

Median Δ CFA= 26.9

SD= 26.4

By Placebo CFA:

Median Δ CFA in patients with Placebo CFA % <40 = 39.3
SD = 34.3

Median Δ CFA in patients with Placebo CFA % >40 and <80 = 30.3
SD = 17.6

Median ΔCFA in patient with Placebo CFA % >80 = 2.3
SD = 8.0

These data demonstrates that in patients with severe EPI (CFA % <40), treatment with Ultrase® result in clinically meaningful benefit, as demonstrated by a median increase in the CFA % of > 30%.

A similar analysis was performed for patients who at least one CFA % measurement (either in the Placebo Treatment Period or in the Ultrase® Treatment Period) (Table 15). Once again, missing values were assigned a Δ CFA % of zero. Similar results were obtained, with increase (i.e., improvement) of the median Δ CFA % during Ultrase® treatment. The Δ CFA % for this population was better than that for the ITT population (+30 vs. +27 in the ITT population), which is to be expected given that in this analysis population more patients actually had CFA % values and were not assigned a change of CFA % of zero.

Table 15 UMT20CF05-01 (Pivotal Study) analysis of Δ CFA % in the "at-least-one CFA" patient population (N=28)

SUBJECT	CFA Placebo	CFA Ultrase	CFA DELTA
0301	.	86.93	0.00
0207	13.59	88.51	74.92
0302	17.14	92.36	75.22
0206	23.06	81.91	58.85
0503	25.86	89.87	64.01
0105	26.54	89.89	63.35
0203	35.14	91.96	56.82
0902	40.47	83.41	42.94
0303	40.58	87.76	47.18
0306	41.94	90.24	48.30
0204	44.07	92.69	48.62
0504	45.7	84.21	38.51
0901	46.6	88.86	42.26
0501	51.16	89.19	38.03
1005	51.95	94.39	42.44
0505	52.86	.	0.00
0101	54.03	81.11	27.08
0104	57.24	80.87	23.63
0305	63.07	77.36	14.29
0102	63.93	.	0.00
0205	78.58	89.53	10.95
0502	84.48	94.63	10.15
1006	84.61	97.08	12.47
0701	87.3	95.59	8.29
0201	89.5	89.05	-0.45
0304	91.79	.	0.00
1001	93.28	86.04	-7.24
0202	97.12	90.3	-6.82

Median Δ CFA = 29.8

SD = 26.2

By Placebo CFA:

Median Δ CFA in patients with Placebo CFA % <40 = 56.2
SD = 25.8

Median Δ CFA in patients with Placebo CFA % >40 and <80 = 30.3
SD = 17.6

Median Δ CFA in patient with Placebo CFA % >80 = 2.3
SD = 8.0

Based on the sensitivity analyses performed in the various efficacy populations, the conclusion reached by this Reviewer is that Ultrase® MT is efficacious. The results in the moderately to severely affected groups of patients are clinically significant. The worse/lower the CFA % at Baseline (i.e., on Placebo, or no treatment), the more the increase in the CFA% was observed. The clinical implication is that patients who have the most severe form of EPI have the most to gain to Ultrase® MT treatment.

Finally, this Reviewer examined the effect of treatment sequence on whether there was a difference in the results obtained for change in CFA % depending on whether the patients were treated first with Ultrase® or Placebo in the ITT population. Once again, for patients with missing CFA values, the Δ CFA was assigned a value of zero. The median increase in CFA % in patients who were treated first with Ultrase® MT was 25.2, as compared to 28.3 in those who were treated first with Placebo. As shown in Table 16 there does not appear to be a sequence effect.

Table 16 UMT20CF05-01 (Pivotal Study) analysis of Δ CFA % based on sequence of treatment in the ITT population (N=31)

Sequence 1: Ultrase®→Placebo (N=14)

SUBJECT	CFA Placebo	CFA Ultrase®	CFA DELTA
0301	.	86.93	0.00
0601	.	.	0.00
0602	.	.	0.00
0302	17.14	92.36	75.22
0503	25.86	89.87	64.01
0105	26.54	89.89	63.35
0902	40.47	83.41	42.94
0306	41.94	90.24	48.30
0504	45.7	84.21	38.51
0104	57.24	80.87	23.63
0205	78.58	89.53	10.95
0201	89.5	89.05	-0.45
1001	93.28	86.04	-7.24
0202	97.12	90.3	-6.82
			Median Δ CFA = 25.2 SD = 29.5

Sequence 2: Placebo→Ultrase® (N=17)

SUBJECT	CFA Placebo	CFA Ultrase	CFA DELTA
0604	.	.	0.00
0207	13.59	88.51	74.92
0206	23.06	81.91	58.85
0203	35.14	91.96	56.82
0303	40.58	87.76	47.18
0204	44.07	92.69	48.62
0901	46.6	88.86	42.26
0501	51.16	89.19	38.03
1005	51.95	94.39	42.44
0505	52.86	.	0.00
0101	54.03	81.11	27.08
0305	63.07	77.36	14.29
0102	63.93	.	0.00
0502	84.48	94.63	10.15
1006	84.61	97.08	12.47
0701	87.3	95.59	8.29
0304	91.79	.	0.00
			Median Δ CFA = 28.3 SD = 24.4

An analysis by race could not be performed since too few non-Caucasian patients were enrolled in the study. This Reviewer did not find an age or gender effect in the efficacy results.

In sum, this clinical Reviewer is in agreement with the Sponsor's and FDA Statistical Reviewer's analyses that the primary efficacy endpoint was been met and that the results of this pivotal study in the TbMP of Ultrase® MT demonstrate that Ultrase® is effective in improving

fat absorption in CF patients seven years or older with steatorrhea due to EPI, and that the efficacy results are both statistically significant and clinically meaningful. The most gain in the CFA % was observed in patients with the lowest Baseline (i.e., with no treatment, or Placebo) CFA%.

6.1.5 Analysis of Secondary Endpoints(s)

The secondary efficacy measure was the Coefficient of Nitrogen Absorption (CNA %), defined as:

> CNA% = [(72-hr protein intake (g)/6.25) – 72-hr nitrogen excretion (g) x100] ÷ (72-hr protein intake (g)/6.25)

The effects seen in the assays for CNA % were smaller than were observed with fat absorption but the direction of the effects remained the same. The CNA % was highly statistically significantly greater for the Ultrase® MT20 treatment than for the Placebo ($P < 0.0001$). The Period and Sequence effects were not statistically significant. In patients who completed both treatment periods (N=24), the difference between the treatment was +26. Table 17 summarizes the Sponsor's analysis, which was verified by FDA statistician (S. Grosser).

Table 17 Summary and analysis of the coefficient of nitrogen absorption (ITT population) (Copied electronically from the Sponsor's submission)

		Treatment		
Parameter	**Statistic**	**Ultrase® MT20**	**Placebo**	**Delta**
Number of Patients in the ITT Population	N	30	31	30
CNA%	n	25	27	24
	Mean	84.051	58.784	25.676
	STD	7.244	20.569	17.695
	Median	84.050	49.710	29.230
	(Min., Max.)	(61.83, 95.05)	(29.98, 96.14)	(-8.86, 52.27)
Mixed Model Fixed Effect [a]				
Sequence	p-value	0.5287		
Period	p-value	0.2547		
Treatment Group	p-value	<0.0001**		
Note: n for CFA% includes all randomized patients who completed at least one treatment period; the delta value is the mean of the individual treatment differences in patients who completed both treatment periods.				

** Indicates statistical significance at the 0.010 level.

[a] P-values from a semi-parametric mixed model on ranked CNA% values including sequence, period, and treatment group as fixed effects, and patient ID as random effect.

Notes:

1. CNA%= Coefficient of Nitrogen Absorption
2. CNA% has been calculated as follows (in some instances, the CNA% has been calculated over 96 hours instead of 72 hours):

$$\frac{\text{(72-hour protein intake (g)/6.25) – 72-hour nitrogen excretion (g)}}{\text{72-hour protein intake (g)/6.25}} \times 100\%$$

3. The nitrogen excretion value (g/24h) transferred by the Central Lab has been multiplied by 3 before analysis in order to convert it to total nitrogen content.
4. For each patient, Delta is the difference between CNA% Ultrase® MT20 value and CNA% Placebo value.

Source: Table 14.2-3

Although an improvement in the CNA % was observed, the clinical relevance of this is finding unknown. Hence findings regarding the CNA % should not be included in the label to support an indication.

6.1.6 Other Endpoints

The Sponsor also studied 1) the number of bowel movements per day, and 2) proportion of daily stools by characteristic (formed, soft, and watery) between the two treatment groups. The Reviewer did not independently verify these results, which are summarized below based on material taken from the Sponsor's submission. The endpoints have not been validated and their clinical significance is unknown, and the descriptive data are not intended for informing the label. Therefore they are included here only for the sake of completion.

Day 3 of the two Study Drug Treatment Periods is representative of the effects of the treatments on the daily number of stools as reported by patients and includes the largest number of patients reporting this frequency while on both treatments. Treatment with Ultrase® resulted in a mean

of about half as many daily stools as did Placebo Treatment (see Table 18, copied electronically from the Sponsor's submission).

Table 18 Summary of total daily number of bowel movements on Day 3 of treatment (ITT)

		Treatment	
Parameter	**Statistic**	**Ultrase® MT20**	**Placebo**
Number of Patients in the ITT Population	N	30	31
Total Daily Number of Bowel Movements	n	29	30
	Mean	1.5	3.1
	STD	1.0	1.8
	Median	1.0	3.0
	(Min., Max.)	(0, 5)	(0, 7)

Notes:
1. Hypothesis testing of this data was not performed.
Source: Table 14.2-5

Day 4 of the Study Drug Treatment Periods is representative of the effects of treatment on the characteristics of the stools as reported by patients and includes the largest number of patients reporting this frequency while on the Ultrase® MT20 treatment. As shown in Table 19 (copied electronically from the Sponsor's submission), Ultrase® treatment resulted in a preponderance of patients with normal stools (76.19% ± 39.13%) as compared to a much smaller percentage of patients taking placebo (25.71% ± 43.84%). The Placebo resulted in most patients having soft stools (66.73% ± 45.08%).

Table 19 Proportion of total daily stools by characteristic on Day 4 of treatment

		Treatment	
Parameter	**Statistic**	**Ultrase® MT20**	**Placebo**
Number of Patients in the ITT Population	N	30	31
Daily Proportion of Hard Stools (%)	n	28	28
	Mean	11.31	3.57
	STD	27.98	18.90
	Median	0.00	0.00
	(Min., Max.)	(0.0, 100.0)	(0.0, 100.0)
Daily Proportion of Formed/Normal Stools (%)	n	28	28
	Mean	76.19	25.71
	STD	39.13	43.84
	Median	100.00	0.00
	(Min., Max.)	(0.0, 100.0)	(0.0, 100.0)
Daily Proportion of Soft Stools (%)	n	28	28
	Mean	12.50	66.73
	STD	29.27	45.08
	Median	0.00	100.00
	(Min., Max.)	(0.0, 100.0)	(0.0, 100.0)
Daily Proportion of Watery Stools (%)	n	28	28
	Mean	0.00	3.99
	STD	0.00	13.65
	Median	0.00	0.00
	(Min., Max.)	(0.0, 0.0)	(0.0, 66.7)

Notes:
1. For each patient, the daily proportion (%) of Hard stools have been calculated as follows: (Total number of Hard stools on a particular day / Total number of stools on that day) * 100%.
2. For each patient, the daily proportion (%) of Formed/Normal stools have been calculated as follows: (Total number of Formed/Normal stools on a particular day / Total number of stools on that day) * 100%.
3. For each patient, the daily proportion (%) of Soft stools have been calculated as follows: (Total number of Soft stools on a particular day / Total number of stools on that day) * 100%.
4. For each patient, the daily proportion (%) of Watery stools have been calculated as follows: (Total number of Watery stools on a particular day / Total number of stools on that day) * 100%.
5. Hypothesis testing of these data was not performed.

Source: Table 14.2-7

6.1.7 Subpopulations

A significant portion of the target population for PEPs includes pediatric patients with CF, in which there is chronic EPI dating from birth, and treatment can begin as early as one month of age, if not earlier. Current recommendations state that enzyme should be administered to all CF infants who are fed infant formula and solid foods containing macronutrients.[11, 12] As such, data from clinical experience in children are essential to support the appropriate use of these products starting at one month of age (if not earlier). Furthermore, in accordance with the Pediatric Research Equity Act (PREA), applications for new active ingredients, new indications, new dosage forms, new dosing regimens, and new routes of administration must contain a pediatric assessment--unless the sponsor has obtained a waiver or deferral of pediatric studies (Section 505B of the Federal Food Drug and Cosmetic Act).

The Ultrase® clinical development program has been conducted exclusively in CF patients with EPI. The pivotal study, which provided safety and efficacy information for the TbMP included patients down to eight years of age, though neither one of these youngest patients completed the study (Patient 0102 withdrew consent during Study Drug Treatment Period 2 while he was on Ultrase® treatment; Patient 0103 was a Screening failure, but he was part of the Safety Population). The next older patient in this study was a ten-year-old child. Supportive evidence for safety and efficacy that came from the two studies that used an older formulation not intended for marketing included data from patients as young as seven years of age (Study 96-01), and eight years of age (Study 96-02). As part of this NDA submission the Sponsor provided a pediatric assessment. Data shown in Table 20 (copied electronically from the Sponsor's submission) are for patients for whom complete data were available.

11 Borowitz D, Grand R, Durie P. Use of pancreatic enzyme supplements for patients with cystic fibrosis in the context of fibrosing colonopathy. Consensus Committee. J Pediatr 1995; 127:681-694.
12 Borowitz D, Baker R, Stallings V. Consensus report on nutrition for pediatric patients with cystic fibrosis. J Pediatr Gastroenterol Nutr 2002; 35: 246-259.

Table 20 Coefficient of fat absorption (CFA %) for patients 10-16 years of age (Studies UMT20CF05-01 and 96-01 and 96-02)

Patient #	Age*	CFA (%) ULTRASE**	CFA (%) Placebo**	Difference % ULTRASE - Placebo
Study UMT20CF05-01				
0104	10	80.87	57.24	23.63
0202	15	90.30	97.12	-6.82
0204	13	92.69	44.07	48.62
0205	15	89.53	78.58	10.95
0207	14	88.51	13.59	74.92
0302	15	92.36	17.14	75.22
0305	16	77.36	63.07	14.29
0901	15	88.86	46.60	42.26
0902	12	83.41	40.47	42.94
1001	16	86.04	93.28	-7.24
1006	16	97.08	84.61	12.47
Mean %CFA	-	87.91%	57.8%	30.1%

*From Study Report Listing 5.1, 5.3.5.1 Study UMT20CF05-01 Appendix 16.2.4, Vol. 14, p. 2
**From Study Report Listing 16.1, 5.3.5.1 Study UMT20CF05-01 Appendix 16.2.6, Vol. 14, p. 175; CFA is defined as: (72-hour fat intake (g) – 72-hour fat excretion (g)) x 100 / 72-hour fat intake (g)

Patient #	Age*	CFA (%) ULTRASE**	CFA (%) Placebo**	Difference % ULTRASE - Placebo
Study 96-01				
A01	9	72.5	51.5	21.0
A02	8	92.2	37.3	54.9
A04	16	88.3	63.9	24.4
A05	14	88.9	69.0	19.9
A06	12	85.5	35.0	50.4
A09	15	99.1	82.8	16.2
A10	15	92.6	51.1	41.4
B02	16	91.9	75.5	16.5
B06	11	83.4	59.9	23.5
F01	12	90.9	59.0	31.9
F04	10	90.8	58.1	32.7
F05	7	89.9	49.9	40.0
F06	13	88.9	55.3	33.5
F09	15	95.0	72.6	22.4
F10	16	90.3	29.9	60.4
Mean %CFA	-	89.3%	56.7%	32.6%
Study 96-02				
C02	11	49.7	-42.5***	92.2
C03	14	64.3	50.7	13.6
C05	16	81.5	63.2	18.3
C06	15	91.9	86.3	5.5
D01	10	78.5	54.5	24.0
D03	13	72.5	66.0	6.6
D08	13	95.9	79.8	16.2
D09	8	91.9	74.5	17.4
E01	13	76.0	55.6	20.4
E02	10	76.0	88.1	-12.1
E04	11	92.4	59.7	32.8
E07	16	93.0	90.5	2.5
E08	11	79.4	38.7	40.7
E09	11	55.9	40.5	15.4
Mean %CFA	-	78.5%	57.5%	21.0%

*From Study Report Listings 16.2.5, 5.3.5.1 Study 96-01, Vol. 4, p. 515; 5.3.5.1 Study 96-02, Vol. 8, p. 471

**Calculated from Study Report Listings 16.2.11A and 16.2.21, 5.3.5.1 Study 96-01, Vol. 4, p. 555, 783; 5.3.5.1 Study 96-02, Vol. 8., p. 504, 681; CFA is defined as: (72-hour fat intake (g) (Days 3-5) – 72-hour fat excretion (g)) x 100 / 72-hour fat intake (g)

***Excretion was greater than the fat intake for this patient

Such is the extent of evidence for efficacy in children studied in the Ultrase® clinical program. Data to date in patients less than twelve years of age are limited, which is not consistent with the use of the product in the post-marketing experience. In a Type C meeting held between the Division and the Sponsor on 16 January 2008, the Division expressed that the two oldest studies conducted by Scandipharm Inc. (Studies 01 and 02) that included younger pediatric patients (≤ seven years of age) could not be used to provide evidence of safety and efficacy because these studies were only available as legacy reports whose data were not available in a reviewable format. Since labeling can only reflect the patient population actually studied (i.e., patients older than eight years), the Division recommended that studies in pediatric patients seven years and younger be initiated as soon as possible so to be able to broaden the treatment population statement in the labeling should Ultrase® be approved. Accordingly, the Sponsor is planning to conduct the following study, which has submitted a draft protocol for Study UMT12CTF0801 titled: "*Efficacy and safety of Ultrase® MT12 in the control of steatorrhea in Cystic Fibrosis (CF) and Pancreatic Insufficient (PI) children Aged 2 to 6 years old."* Enrollment is expected to begin in the third quarter (Q3) of 2008.

One potential concern about the use of Ultrase® in younger children is the fact that solid oral dosage forms like capsules can be hard for younger patients to swallow. However, Ultrase® MT capsules contain enteric-coated minitablets of pancreatic enzymes, and the delayed-release properties of the product are imparted by the minitablets, not the capsule. In situations where young patients cannot swallow an intact capsule, this formulation allows the capsule to be broken open and the minitablets dispersed in food without impacting the integrity of the enteric coating. The most appropriate dosing for Ultrase® MT Capsules is based on body weight, with a recommended starting dose of 500 lipase unit/kg body weight/meal. Although for younger children who cannot swallow whole capsules, Ultrase® MT Capsules can be broken to release the enteric-coated minitablets, accurate sub-division of the minitablets once the capsule has been opened would be difficult; for this reason, doses of < 1 capsule per meal are not recommended. This limits the use of the lowest strength of Ultrase® (MT12) to a child of 14 kg body weight or higher. (b) (4)

This Reviewer assessed the primary endpoint by gender and by age (<16 and >16), and found no gender or age effect. It was not possible to assess the primary endpoint by ethnicity since there were too few non-Caucasian patients studied. Since CF patients are mostly Caucasian, the homogeneity of race in the clinical development program is not a critical factor. It appears that the only patter that could be seen on subgroup analysis was that the patients who were the most severely affected, gained the most benefit by having an increase in CFA % of at least 30 points, an improvement defined by the medical literature as clinically meaningful.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Due to the time constraint, this Reviewer has not independently verified, but assumes that all patients in the study were treated according to CFF/FDA Guidelines and the patients were titrated on an individual basis within these Guidelines according to symptoms, in which case the dosing regimen would be reflective of the expected clinical use in the post marketing experience. Dosing is to follow the guidelines set by the CFF and FDA due to a safety concern for fibrosing colonopathy (FC). See Section 2.4 Important Safety Issues with Consideration to Related Drugs, and Section 6.1.3.3. Measurement of Treatment Compliance.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

In this short-term study, effects of persistence of efficacy and/or tolerance were not studied. However, given the extensive experience of PEP, it has not been reported in the medical literature that persistence of efficacy or tolerance effects have been observed.

6.1.10 Additional Efficacy Issues/Analyses

6.1.10.1 Supportive evidence: Studies 96-01 and 96-02

Results of these studies were reviewed in less detail than that for the pivotal trial, as these studies were mainly supportive. The Sponsor's analysis and FDA statistician Dr. Grosser's confirmatory analysis were reviewed. The following is taken from Dr. Grosser's review, paraphrased, with additional clinical comments made by this Reviewer where relevant.

Studies 96-01 and 96-02 were carried out nearly a decade prior to submission of this NDA (last patient completed Study 96-01 on 24 August 1998; and last patient completed Study 96-02 on 29 August in 1999). They were nearly identical in design with the main difference being that Study 96-01 used a higher strength Ultrase® MT20 capsules, and Study 96-02, a lower strength Ultrase MT 12. They were also similar in many ways to study UMT20CF05-010 - except that in these supportive studies, an older formulation of Ultrase® (coated with Eudragit®) - a formulation not intended for marketing - was used. Because the *in vivo* bioactivity/bioavailability testing did not establish comparability linking the two formulations (Ultrase® MT Eudragit® and Ultrase® MT HP-55), the results of these two older studies could not be used to inform labeling for the TbMP. But, they are still relevant being that they could provide supportive evidence for the drug's safety and efficacy, and therefore, are cited and briefly summarized here.

Similar to Study UMT20CF05-01, Studies 96-01 and 96-02 were multi-center, randomized, double-blind, placebo-controlled, crossover-studies designed to evaluate the safety and efficacy of Ultrase® MT in the treatment of steatorrhea in CF patients with a history of EPI. Each study consisted of a diet and enzyme Stabilization Period (7 days) followed by a Treatment Period of approximately six days and then, after a switch of treatments, a second Treatment Period of approximately six days. Patients were randomized to receive the Study Drug Treatment either in the sequence of Ultrase® MT → Placebo, or Placebo → Ultrase® MT. The evaluation of efficacy was based on a within-subject comparison of the CFA % between Ultrase® and Placebo treatment periods; a secondary comparison was the CNA %.

For both Studies 96-01 and 96-02, it was assumed that there would be at least a 30% difference between the Ultrase® MT and Placebo treatment periods with respect to percent fat absorption and percent protein absorption. Further assuming a standard deviation of 30% between Placebo and Ultrase, and a two-sided alpha of 0.05, a sample size of 21 would give a power of 90% to detect a minimum difference of +18 in CFA %.

6.1.10.1.1 Study 96-01

Results for Study 96-01 showed that 31 patients were randomized. Twenty-seven patients (14 on Ultrase MT20 and 13 on Placebo) completed Treatment Period 1, and they constitute what the Sponsor calls the ITT population. Of these, 25 patients completed both treatment periods. Patients ranged from 7 to 36 years of age, with 19 males (70%) and eight females in the ITT population. Twenty-six (96%) were Caucasian. Results for fat and protein percent absorption are shown below in Table 21 (copied electronically from the Sponsor's submission). A difference of +29 in CFA % was seen in improvement with Ultrase® to Placebo, with the results being highly statistically significant.

Table 21 Overall summary results of percent fat and nitrogen absorption in the ITT population of Study 96-01

OVERALL SUMMARY OF PERCENT ABSORPTION – INTENT-TO-TREAT SUBJECTS			
Variable	**Ultrase (N=27) [1]**	**Placebo (N=25)**	**Treatment Comparison (p-value)**
Dietary Fat (g) Mean ± SD Range N	 87.7 ± 10.1 46.8 to 99.1 26	 58.7 ± 16.5 29.9 to 96.2 25	0.0001*
Dietary Protein (g) Mean ± SD Range N	 88.8 ± 6.1 70.3 to 98.7 26	 62.9 ± 18.2 33.5 to 97.3 25	0.0001*

Source: Table 14.8B
* Significant at .05 significance level
[1] Stool collection for subject F12 was incomplete

6.1.10.1.2 Study 96-02

Twenty-six patients were randomized. Twenty-three patients completed Treatment Period 1 and constitute the (modified) ITT population; twelve patients received Ultrase MT12, and 11 received Placebo during Treatment Period 1. Of these, 22 completed both treatment periods (the evaluable population). Patients ranged from 8 to 36 years of age, with 16 males (70%) and seven females in the ITT population; 20 (87%) were Caucasian. Results for percent absorption are shown below in Table 22 (copied electronically from the Sponsor's submission). The results show that a difference of +33 in CFA % was seen in improvement with Ultrase® to Placebo, with the results being highly statistically significant.

Table 22 Overall summary results of percent fat and nitrogen absorption in the ITT population of Study 96-02

OVERALL SUMMARY OF PERCENT ABSORPTION FOR INTENT-TO-TREAT SUBJECTS			
Variable	**Ultrase (N=23)**	**Placebo (N=22)** [1]	**Treatment Comparison (p-value)**
Dietary Fat (g) Mean ± SD Range N	 79.4 ± 12.5 49.7 to 95.9 23	 46.7 ± 35.8 -51.3 to 90.5 22	0.0002*
Dietary Protein (g) Mean ± SD Range N	 83.9 ± 11.0 45.4 to 96.8 23	 58.4 ±24.8 -18.1 to 92.7 22	0.0001*

Source: Table 14.8A
* Significant at .05 significance level
[1] Subject C02 protein/fat input was less than protein/fat output

The magnitude of CFA % improvement on Ultrase® MT 20 and 12 using the Eudragit® formulation provides supportive evidence for efficacy, and is within the expected range with that of Ultrase® MT HP-55 and other PEPs in the same drug class.

7 Review of Safety

7.1 Methods

7.1.1 Clinical Studies Used to Evaluate Safety

This Reviewer used safety information from the individual double-blind, placebo-controlled clinical studies (Studies 96-01, 96-02, and UMT20CF-05-01) to generate an integrated safety analysis for Ultrase® MT in the treatment of EPI in CF patients seven years and older. Supportive information in the form of spontaneous reporting and publications from the medical literature on PEPs was also reviewed. The Sponsor submitted an original integrated safety summary (ISS) on 31 July 2007, a reorganized version (but containing no new data) on 20 December 2007, and an 120-day Safety Update on 1 February 2008, all of which were reviewed, including the electronic datasets and the Sponsor's interpretation of the safety data.

A brief description of the clinical studies that were used to evaluate safety is as follows.

Studies 96-01 and 96-02
Studies 96-01 and 96-02 assessed Ultrase® MT capsules that contained minitablets coated with Eudragit®; study designs were identical except for the dosage of Ultrase® used as study drug (Ultrase® MT20 and MT12, respectively). These studies were both randomized, double-blind, placebo-controlled, two-week, two-period cross-over studies. Each CF patient was required to

consume a high-fat diet at home, and to be stabilized on an optimized dose of Ultrase® based on clinical observations and symptoms. The high fat diet was to include at least 2 g of fat per kg of body weight daily. During Treatment Period 1, patients were randomized to receive either Ultrase® or Placebo for at least six days; a 72-hour fecal fat test was performed. Patients then entered Treatment Period 2, where they were crossed over to the opposite treatment, i.e., patients who received Placebo were now to receive active study drug and vice versa; a 72-hour fecal fat test was collected during the second six-day treatment period.

Patients were monitored throughout for the occurrence of AEs until the end of the two-week study period. Laboratory studies, physical exams and vital sign measurements were performed on Day 6 of each of the Treatment Periods, and a 24-hour urine collection for creatinine and uric acid was collected on Day 5 of both Treatment Periods. A 24-hour urine uric acid collection was performed because of the concern for hyperuricemia and hyperuricosuria associated with PEP treatment.

Study UMT20CF05-01
The pivotal study, Study UMT20CF05-01 was a randomized, double-blind, placebo-controlled crossover study in CF patients using Ultrase® MT capsules containing minitablets enteric coated with HP55. This was a Phase 3, multi-center trial conducted in two phases: a screening phase and a treatment comparison phase. During the screening phase (up to 11 days) patients were maintained/switched to open-label Ultrase® MT (either Ultrase® MT 18 or 20) to adjust to a stable high-fat diet, defined as 2 g (± 15%) of fat per kg of body weight per day, also taking into account the patient's activity level and appetite. During the Comparison Phase, patients were hospitalized for the two inpatient Study Drug Treatment Periods of six to seven days each. Before each Study Drug Treatment Period there was a Stabilization Period of four days, during which patients consumed the high-fat diet and were treated with a "stabilizing" dose of Ultrase® MT20 titrated to tolerate the high-fat diet. This Stabilized Dose was the dose used for both Stabilizing Periods (Ultrase® MT20) and Treatment Periods of the Study Drug (Ultrase® MT20 or Placebo). Randomization assigned one group of patients to receive Ultrase® MT20 for Treatment Period 1, then Placebo for Treatment Period 2; and, the other group the opposite sequence. A 72-hour fecal fat testing was performed for each of the Treatment Periods. A break of three to six days was taken between the two Study Drug Treatment Periods (i.e., after the end of Treatment Period 1 and before the start of Stabilization Period 2) to provide a break/washout for patients to be liberated from the high-fat diet, during which they could take taking Ultrase® MT 20 at an *ad lib* dose.

Patients were monitored for the occurrence of treatment emergent AEs throughout the study period, including a seven to ten day follow up after discharge of the second Treatment Period. The full reporting study window was from successful screening to ≤ 30 days after the last dose of study medication. During Treatment Periods, laboratory studies, physical exams and vital sign measurements were performed. Unlike for Studies 96-01 and 96-02, a 24-hour urine uric acid collection was not done.

This Reviewer did not review the safety data from the two oldest studies (Study 01 and 02) because only legacy reports were available for them (the data were not in a reviewable format),

and AEs were not collected for Study 02. The Sponsor did not include these two studies in their ISS analysis.

7.1.2 Adequacy of Data

The AE terms in the double-blind, placebo-controlled Studies 96-01 and 96-02 were originally coded in COSTART, but the integrated summary table was recoded using MedDRA v10.0 for the purpose of this submission. The Phase 3 study, UMT20CF05-01 was coded using MedDRA v.9.0. The Sponsor's coding appeared adequate.

7.1.3 Pooling Data Across Studies to Estimate and Compare Incidence

This reviewer pooled data across the three double-blind placebo controlled studies (Studies UMT20CF05-01, and 96-01 and 96-02) to increase the number of patients analyzed for safety. But given that only Study UMT20CF05-01 administered the TbMP product, a separate safety analysis was also performed where possible.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

It appears to this Reviewer that in the randomized, double-blind, placebo-controlled studies (Studies UMT20CF05-01, 96-01 and 96-02), a total of 94 patients were treated with at least one dose of Ultrase®, which should have constituted the true safety population analysis (Note: The Sponsor submitted the safety analyses on various "modified" safety populations, e.g., patients who completed the study, patients who were randomized, etc. The differences in the numbers of patients between these modified safety populations and the "true" safety population of 94 were small, a handful of patients, which does not change the overall conclusion about the safety profile. Final labeling should reflect the safety experience gathered in studies that were conducted in the TbMP). In these 94 patients, there were 16 patients under the age of 12 (3 patients in Study UMT20CF05-01; 5 patients in Study 96-01; and 8 patients in Study 96-02). The age distribution of the 94 patients in the "true" safety population can be found in Table 23 for Study UMT20CF05-01 and in Figure 2 for Studies 96-01 and 96-02 (Figure 2 was copied electronically from the Sponsor's submission since no electronic datasets for the patient demographics were submitted).

Table 23 Age distribution in Study UMT20CF05-01 (N=36, safety population)

SUBJECT	AGE
0102	8
0103	8
0104	10
0902	12
0204	13
0207	14
0202	15
0205	15
0302	15
0901	15
0301	16
0305	16
1001	16
1006	16
0201	17
0601	18
0304	19
0306	19
1007	19
0502	20
1002	20
0101	21
0503	21
0701	21
0303	23
1003	23
1005	23
0203	24
0501	24
0206	25
0105	27
0505	27
0604	27
0603	34
0602	35
0504	37

Figure 2 Age distribution of the safety population in Studies 96-01 and 96-02

Study 96-01 (N=32, safety population)

SCANDIPHARM, INC. - ULTRASE STUDY, PROTOCOL NO. 96-01

DATA LISTING 16.2.5
DEMOGRAPHICS

(b) (6)

SITE	PATIENT NUMBER	TREATMENT SEQUENCE	AGE (years)	SEX	RACE
A - DR. STERN	A01	ULTRASE-PLACEBO	9	MALE	CAUCASIAN
	A02	PLACEBO-ULTRASE	8	FEMALE	CAUCASIAN
	A03	PLACEBO-ULTRASE	19	MALE	CAUCASIAN
	A04	ULTRASE-PLACEBO	16	MALE	CAUCASIAN
	A05	ULTRASE-PLACEBO	14	MALE	CAUCASIAN
	A06	ULTRASE-PLACEBO	12	FEMALE	CAUCASIAN
	A07	PLACEBO-ULTRASE	36	MALE	CAUCASIAN
	A08	PLACEBO-ULTRASE	20	MALE	CAUCASIAN
	A09	PLACEBO-ULTRASE	15	MALE	CAUCASIAN
	A10	PLACEBO-ULTRASE	15	MALE	CAUCASIAN
	A11	ULTRASE-PLACEBO	32	MALE	CAUCASIAN
B - DR. EIGEN	B01	ULTRASE-PLACEBO	19	FEMALE	CAUCASIAN
	B02	PLACEBO-ULTRASE	16	MALE	CAUCASIAN
	B03	ULTRASE-PLACEBO	17	FEMALE	CAUCASIAN
	B04	PLACEBO-ULTRASE	20	MALE	CAUCASIAN
	B05	ULTRASE-PLACEBO	20	FEMALE	CAUCASIAN
	B06	ULTRASE-PLACEBO	11	FEMALE	CAUCASIAN
	B07	PLACEBO-ULTRASE	18	FEMALE	CAUCASIAN
	B08	PLACEBO-ULTRASE	19	MALE	CAUCASIAN
	B09	PLACEBO-ULTRASE	17	MALE	CAUCASIAN
F - DR. DUGGAN	F01	ULTRASE-PLACEBO	12	MALE	CAUCASIAN
	F02	PLACEBO-ULTRASE	15	MALE	CAUCASIAN
	F04	ULTRASE-PLACEBO	10	MALE	HISPANIC
	F05	PLACEBO-ULTRASE	7	MALE	CAUCASIAN
	F06	PLACEBO-ULTRASE	13	MALE	CAUCASIAN
	F07	ULTRASE-PLACEBO	13	MALE	CAUCASIAN
	F08	ULTRASE-PLACEBO	31	MALE	CAUCASIAN
	F09	ULTRASE-PLACEBO	15	FEMALE	CAUCASIAN
	F10	PLACEBO-ULTRASE	16	MALE	CAUCASIAN
	F11	PLACEBO-ULTRASE	16	MALE	CAUCASIAN
	F12	ULTRASE-PLACEBO	22	MALE	CAUCASIAN

Study 96-02 (N= 26, safety population)

SCANDIPHARM, INC. - ULTRASE STUDY, PROTOCOL NO. 96-02

DATA LISTING 16.2.5
DEMOGRAPHICS

SITE	PATIENT NUMBER	TREATMENT SEQUENCE	(b) (6)	AGE (years)	SEX	RACE
C - DR. STERN	C01	ULTRASE-PLACEBO		17	MALE	HISPANIC
	C02	PLACEBO-ULTRASE		11	MALE	CAUCASIA
	C03	ULTRASE-PLACEBO		14	MALE	CAUCASIA
	C04	PLACEBO-ULTRASE		21	MALE	CAUCASIA
	C05	ULTRASE-PLACEBO		16	MALE	CAUCASIA
	C06	PLACEBO-ULTRASE		15	MALE	BLACK
D - DR. SHERMAN	D01	ULTRASE-PLACEBO		10	MALE	CAUCASIA
	D02	ULTRASE-PLACEBO		17	FEMALE	CAUCASIA
	D03	PLACEBO-ULTRASE		13	MALE	CAUCASIA
	D04	PLACEBO-ULTRASE		22	MALE	BLACK
	D05	PLACEBO-ULTRASE		32	MALE	CAUCASIA
	D06	ULTRASE-PLACEBO		20	MALE	CAUCASIA
	D07	PLACEBO-ULTRASE		36	MALE	CAUCASIA
	D08	ULTRASE-PLACEBO		13	FEMALE	CAUCASIA
	D09	PLACEBO-ULTRASE		8	FEMALE	CAUCASIA
	D10	ULTRASE-PLACEBO		17	FEMALE	CAUCASIA
	D11	PLACEBO-ULTRASE		16	FEMALE	CAUCASIA
E - DR. ACCURSO	E01	PLACEBO-ULTRASE		13	MALE	CAUCASIA
	E02	ULTRASE-PLACEBO		10	FEMALE	CAUCASIA
	E03	PLACEBO-ULTRASE		18	MALE	CAUCASIA
	E04	ULTRASE-PLACEBO		11	FEMALE	CAUCASIA
	E05	ULTRASE-PLACEBO		19	FEMALE	CAUCASIA
	E06	PLACEBO-ULTRASE		22	MALE	CAUCASIA
	E07	PLACEBO-ULTRASE		16	FEMALE	CAUCASIA
	E08	ULTRASE-PLACEBO		11	MALE	CAUCASIA
	E09	ULTRASE-PLACEBO		11	MALE	CAUCASIA

Approximately a third of patients received Ultrase® MT 12 coated with Eudragit®; a third received Ultrase® MT 20 coated with Eudragit®; and a third received Ultrase® MT 20 coated with HP 55 (TbMP). The mean daily Ultrase® dose in the study was approximately 7000-7500 lipase units/kg/day.

Demographic characteristics for the randomized patients (one of the Sponsor's modified safety populations) enrolled in these double-blind, placebo-controlled studies are displayed in Table 24 (copied electronically from the Sponsor's submission). The data illustrate that the majority of randomized patients (n=88) in these studies were Caucasian (81 of 88; 92%) and there was a higher prevalence of male patients (60 patients; 68%) in all three studies. Study patients were generally young (mean ages ranging from 16.5 to 19.6 years of age) with a mean history since diagnosis of CF from 15.9 to 19.2 years.

Table 24 Demographic of safety populations in the placebo controlled studies

Variable	Study	96-01 n=31*	96-02 n=26*	UMT20CF05-01 n=31*
Age (years)	mean (SD)	16.9 (6.6)	16.5 (6.5)	19.6 (6.6)
	range	7.0 - 36.0	8.0 – 36.0	8 - 37
Weight (kg)	mean (SD)	50.9 (17.5)	49.8 (14.7)	55.56 (11.61)
	range	19.0 - 91.0	26.8 – 80.0	31.1 - 88.0
Height (cm)	mean (SD)	158.6 (18.1)	157.8 (16.1)	164.3 (13.2)
	range	113.0 – 183.0	127.0 – 185.4	1.22 - 1.89
Years since CF diagnosis	mean (SD)	16.2 (6.8)	15.9 (6.4)	19.2 (7.4)
	range	4.0 – 35.0	6.0 – 33.0	3 - 37
Gender, n (%)	male	23 [74]	17 [65]	20 (64.5)
	female	8 [26]	9 [35]	11 (35.5)
Race, n (%)	Caucasian	30 [97]	22 [85]	29 (93.5)
	Black	0	2 [8]	2 (6.5)
	Hispanic	1 [3]	1 [4]	0
	Caucasian/Black	0	1 [4]	0

*All randomized patients
Source: 5.3.5.1 Study 96-01, Vol. 3, p. 77; Study 96-02, Vol. 7, p. 77; Study UMTCF05-01 14.0 Tables, Vol. 11, p. 2

A major limitation of the safety data is that patients younger than seven years were not studied. The data in the Ultrase® MT clinical program were also limited by other factors, including small study size, use of only one study in the TbMP, homogeneous population, and short study duration. However, for the purpose of this NDA safety review since this application is a 505(b)(2), it is acceptable that the Ultrase® MT clinical program is limited to short-term efficacy and safety studies. The long-term safety of PEPs has been established over the many years of their use and this application relied on the published medical literature for full descriptions of AE profiles.

7.2.2 Explorations for Dose Response

No formal dose-response investigations were performed, but all patients were titrated to relief of symptoms, and this Reviewer presumes that patients' dosing during the studies remained within the CFF/FDA guidelines, and if that was true, this Reviewer is in the opinion that the Sponsor

has adequately addressed the issue of dose response. Of note, the Sponsor proposed to market three strengths of Ultrase® MT (MT12, 18, and 20). In the TbMP, only Ultrase® MT 18 or 20 was used in the Screening Period, and only Ultrase® 20 was used in the Ultrase® MT Study Drug Treatment Period.

A Pediatric Deferral to allow the Sponsor to develop an infant-appropriate formulation to be administered to children less than two years of age is a reasonable approach and should be granted.

7.2.3 Special Animal and/or In Vitro Testing

Given the extensive human exposure to PEPs, the PEP Guidance for submitting NDAs states that animal pharmacology studies with the active ingredient (pancrelipase) are not required to support the EUR-1008 clinical development program. In addition, this was a 505(b)(2) application thus no special animal or in vitro testing was required.

This Reviewer will not attempt a general assessment of the preclinical program, only to comment that preclinical testing appeared adequate to explore certain potential adverse reactions (i.e., fibrosing colonopathy and the high dosing of excipients and impurities). Please see Section 4.3 Preclinical Pharmacology/Toxicology, and FDA pharmacology-toxicologist Dr. Joseph's review for details.

7.2.4 Routine Clinical Testing

Routine clinical testing of study patients, including efforts to elicit adverse event data and monitor laboratory parameters, vital signs, and physical exams appeared adequate both in terms of the methods and the frequency of testing.

7.2.5 Metabolic, Clearance, and Interaction Workup

Knowledge of how a drug is metabolized and excreted is critical to anticipating safety problems in patients with impaired excretory or metabolic function and problems resulting from drug-drug interactions. PEPs are locally acting agent in the gastrointestinal tract, and therefore are not systemically absorbed. The Sponsor conducted a dog study, using radio-label amylase, to allow for increased sensitivity in the detection of intestinal absorption. The results indicated the absorption of amylase was either "negligible or completely absent." Since PEPs act locally in GI tract and are not systemically absorbed, so absorption, distribution, metabolism and elimination (ADME) assessments were not performed.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

The following statements apply to Ultrase® as well and are taken directly from the Clinical Review by FDA clinical reviewer Ethan Hausman, M.D. for Creon®, however the statements have been paraphrased to suit Ultrase® by this Reviewer.

Rare cases of fibrosing colonopathy (FC) have been reported with PEP use, and are thought to be associated with high-dose PEP administration in younger patients. Given the severity of this

diagnosis, surveillance for FC in PEP clinical development program is relevant to the assessment of safety in this class of medications. No instances of FC were reported in the Ultrase® ISS, but there are limitations in the safety surveillance program; and, conclusions regarding the adequacy of FC case detection are not possible for several reasons. First FC is a histopathologic diagnosis and routine surveillance with colonoscopy and biopsy was not performed in any study. Second, while FC is commonly described as a symptomatically severe and acute process, literature suggests it may actually have a chronic, indolent course; therefore, though severely symptomatic cases might have come to clinical attention during safety assessments, incipient cases might not have been recognized. Third, though fibrosing colonopathy is classically described following high-dose lipase treatment, the doses of Ultrase® administered were within current guidelines promulgated to decrease the risk of FC. Fourth, though the time of exposure required developing FC is undetermined, the short duration of the studies (two weeks) may not have provided a long enough exposure to precipitate FC. Finally, cases of FC in the medical literature appear to have been reported only sporadically. The population studied was relatively small and given the rarity of FC may not have been large enough to detect an FC safety signal. Therefore, this Reviewer believes that although there were no obvious cases of FC reported in this NDA, no conclusions can be drawn regarding the adequacy of FC case detection for the overall ISS population, and monitoring for FC is likely best performed in the post-marketing setting. The issue regarding FC should be included in the label.

It has also been reported that hyperuricemia/hyperuricosuria may be associated with PEP use, which is thought to be related to the purine content of pancreatic extracts from which the PEPs are produced. As more evidence becomes available, it may be relevant to follow this trend in patients with impaired liver function commonly seen in older patients with CF and in patients with CP. The finding might also be relevant in patients with impaired renal function and/or impaired uric acid metabolism (e.g., gout). Given the small study population and short duration of studies, it is unlikely that a single case of clinically significant hyperuricemia or hyperuricosuria would have been seen. The issue regarding hyperuricemia/hyperuricosuria, like FC, should be included in the label and be followed with special attention as part of worldwide Pharmacovigilance in the post-marketing setting.

7.3 Major Safety Results

7.3.1 Deaths

There were no deaths reported during any of the short-term studies supporting this submission.

7.3.2 Nonfatal Serious Adverse Events

There were eight SAEs—and except for one case of newly diagnosed diabetes, all were either GI or respiratory related. All were likely CF related.

Study 96-01
One patient experienced abdominal cramping due to obstruction during Placebo treatment. Another patient was diagnosed with pulmonary exacerbation of CF during Placebo treatment.

One patient was diagnosed with diabetes mellitus during the screening period while on Ultrase® MT20. None of these events appeared to be related to Ultrase® treatment.

Study 96-02
No SAEs were reported.

Study UMT20CF05-01
There were two patients (Patient 0103 and 0603) who experienced SAEs during Screening, at which time they were on open-label Ultrase® MT18 or MT20. One patient experienced worsening chest x-ray attributed to pulmonary exacerbation of CF, which was successfully treated with antibiotics. The other patient experienced hemoptysis, also diagnosed as CF-related pulmonary exacerbation, which also resolved with standard medical treatment.

Three patients experienced SAEs within the reporting study window (from successful Screening to ≤ 30 days after the last dose of study medication). One patient (Patient 0505) experienced a CF-related pulmonary exacerbation, an acute bronchiectasis caused by methicillin-resistant *Staphylococcus aureus (MRSA)* and *Pseudomonas aeruginosa* during the Placebo treatment. The two other patients experienced SAEs after returning to using their usual pancrelipase product following study discharge. Patient 0602 experienced dyspnea, productive cough, chills, nausea, vomiting, and abdominal pain, as well as non-serious hemoptysis; Patient 1005 experienced cystic fibrosis lung, hypokalemia, and lymphadenopathy.

7.3.3 Dropouts and/or Discontinuations

Ten patients dropped out due to an AE/SAE, all related to either GI or respiratory symptoms. All appeared to be related to the underlying disease.

Study 96-01
In Study 96-01, SAEs caused three patients to withdraw from the study. While taking Placebo, one patient experienced intestinal obstruction and another reported increased cough; while on Ultrase® therapy during Screening, one patient was diagnosed with diabetes mellitus, identified during the Screening blood work as a concurrent medical condition.

Study 96-02
In Study 96-02 three patients were withdrawn due to non-serious AEs while on Placebo: one due to intestinal obstruction, another due to an intestinal disorder, and a third due to a rectal disorder.

Study UMT20CF05-01
In Study UMT20CF05-01, two patients on open-label Ultrase® failed Screening due to an SAE (one patient experienced worsening chest x-ray abnormality due to CF pulmonary exacerbation, and the other person experienced hemoptysis diagnosed as a CF-related pulmonary exacerbation). One patient experienced SAEs resulting in discontinuation during the study while on the Break Periods between treatment periods (CF lung, bronchiectasis, upper respiratory tract infection, gastrointestinal infection, non-serious vaginal infection, non-serious malnutrition); this patient having received Placebo during Treatment Period 1, which preceded immediately the Break Period. Two other patients experienced non-serious AEs while on Placebo that also

resulted in study discontinuation (abdominal pain in one, and abdominal pain, flatulence, and steatorrhea in the other).

7.3.4 Significant Adverse Events

There were no other significant Adverse Events reported.

7.3.5 Submission Specific Primary Safety Concerns

There were no submission specific primary safety concerns. The issues that have already been discussed elsewhere in this Review regarding fibrosing colonopathy, hyperuricemia or hyperuricosuria, and the safety of Eudragit® coating are of concern to all PEPs, and are not specific to this PEP or submission.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

In the pooled safety analysis of the three randomized, double-blind, placebo-controlled studies (UMT20CF05-01, 96-01 and 96-02), the most frequently observed AEs were predominantly gastrointestinal (GI) related, as would be expected in a CF patient population. The most common AEs experienced by patients in during the Ultrase® Study Drug Treatment Period were flatulence (experienced by 26% of patients), abdominal pain (17%), headache (11%), and diarrhea (10%). Of note, these gastrointestinal AEs occurred at a greater incidence in patients during the Placebo Study Drug Treatment Period: flatulence (44%), abdominal pain (50%), and diarrhea (15%), giving support to the hypothesis that these GI AEs were related to the underlying disease, and that without treatment (during Placebo administration), these events reflect a lack of treatment efficacy rather than an AE profile that might have been related to Ultrase® treatment.

Table 25 (copied electronically from the Sponsor's submission) lists the most common AEs affecting ≥ 2% of patients on Ultrase® and occurring in more patients on Ultrase® than placebo in combined data from the double-blind, placebo-controlled studies (Studies UMT20CF05-01, 96-01, and 96-02). This Reviewer notes that headache occurred in almost twice as many patients (11%) during the Ultrase® Study Drug Treatment Period than during the Placebo (6%).

Table 25 Most common adverse events affecting ≥ 2% of patients on Ultrase® and occurring in more patients on Ultrase® than Placebo: combined data from the double-blind, placebo-controlled studies (Studies UMT20CF05-01, 96-01 and 96-02)

Treatment	Combined ULTRASE® Number of patients (%) n=82	Combined Placebo Number of patients (%) n=84
MedDRA SOC		
Preferred Term		
Nervous System Disorders		
Headache	9 (11)	5 (6)
Dizziness	2 (2)	1 (1)
Respiratory, Thoracic, And Mediastinal Disorders		
Cough	4 (5)	3 (4)
Epistaxis	2 (2)	1 (1)
Pharyngolaryngeal pain	2 (2)	1 (1)
Gastrointestinal Disorders		
Constipation	4 (5)	3 (4)
Infections And Infestations		
Pharyngitis	2 (2)	0 (0)
Source: Appendix 2.7.4.7 Table 2.7.4.7-4		

This Reviewer noted that the AEs profiles for the pivotal study and the bioactivity/bioequivalence study were similar to that of the pool analysis of the three double-blind, placebo-controlled studies[13]. Safety information (predominantly AE collection) obtained in the BA study that was of limited utility given the design of the study and the small numbers of patients exposed to two, single-doses of Ultrase®.

In summary, the overall AE profile assessment is that no new safety signal attributable to Ultrase® has been identified in the clinical review (with the possible exception that headache occurred in more patients during the Ultrase® treatment period than in Placebo). Most AEs were likely related to the underlying disease, and were either GI or respiratory related. It should be kept in mind that these short-term safety studies could only give limited data on the safety profile of the product, and they are to be supplemented with information from the post-marketing Pharmacovigilance experience, should the product be approved and marketed.

13 A summary of AE by system organ class and preferred terms of the pivotal study (UMT20CF-05-01) can be found in Section 9.6 Appendix 3.

7.4.2 Laboratory Findings

This Reviewer found that there were no clinically significant mean changes for any hematology, chemistry, or urinary parameters that could be attributed to Ultrase® treatment in the three placebo-controlled studies.

The Sponsor notes the following observations:

- In Study 96-01, it was noted that patients receiving Ultrase® MT20 experienced a +28.83 mg mean change (28.83 ± SD 267.48) in urine uric acid within a 24-hour collection period, compared with a mean change of -23.17 mg (-23.17 ± SD 316.16) for patients receiving Placebo although it was also observed that the standard deviations of these values were more than ten times greater than their means, indicating a likely contribution of outliers. Moreover, in the opinion of this Reviewer, this magnitude of increase is unlikely clinically significant given the wide range of the normal value. (NIH normal values range from 250 to 750 mg/24 hours).
- Similarly in Study 96-02, patients while receiving MT12 had a statistically significant mean increase from Screening in uric acid (112.87 ± SD 200.64 mg/24hr; p=0.018) while the Placebo treatment results in a significant mean decrease (-93.70 ± SD 200.64 mg/24 hrs; p=0.036), a differential effect that was statistically significant for the treatment comparison (p=0.001).
- However, in Study UMT20CF05-01, there were no clinically meaningful effects of either Ultrase® or Placebo treatment on mean spot urine uric acid concentration (a 24-hour urine collection for uric acid was not performed for this study). The significance of the differences seen in Studies 96-01 and 96-01 using the Ultrase® MT Eudragit® formulation in evaluating what may be the potential implication of this in the Ultrase® HP55 formulation is unknown.
- In Study UMT20CF05-01 a few patients while on Ultrase® (2; 6.9%) and more patients while on Placebo treatment (9; 30%) developed green urine likely due to the FD&C blue #2 dye stool marker ingested as part of the 72-hour stool sampling process. It is unknown why more patients while on Ultrase® would experience this affect, which is likely an artifact.

7.4.3 Vital Signs

In Studies 96-01 and 96-02, post-treatment vital signs were not recorded. A summary of the Treatment Period physical examinations demonstrated no clinically significant changes between the Screening and the Treatment Periods. In Study UMT20CF05-01, there were no effects of Ultrase® treatment on mean vital signs.

7.4.4 Electrocardiograms (ECGs)

ECGs were not collected or examined because PEPs are products that act locally in the GI tract, and are not expected to have systemic effect, or to affect cardiac function.

7.4.5 Special Safety Studies

There were no special safety studies performed during the Ultrase clinical development program.

7.4.6 Immunogenicity

Ultrase® is not systemically absorbed, and there were no assessments performed specifically related to immunogenicity (i.e., antibody testing).

7.5 Other Safety Explorations

No other safety explorations were performed.

7.6 Additional Safety Explorations

7.6.1 Human Carcinogenicity

Ultrase® is not systemically absorbed and human carcinogenicity studies were not part of the clinical development program.

7.6.2 Human Reproduction and Pregnancy Data

FDA Pharmacology Toxicology Reviewer (Dr. Joseph) recommends that the following statement be included in the label:

"Animal reproduction studies have not been conducted with Ultrase®. It is also not known whether Ultrase® can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Ultrase® should be given to a pregnant woman only if clearly needed. It is not known whether this drug is excreted in human milk. Caution should be exercised when Ultrase® is administered to a nursing mother."

Ultrase® is almost certainly going to be used by women of reproductive potential and may be used by pregnant and lactating women. The effect of Ultrase® and the excipients on the fetus is unknown, therefore a request for a pregnancy and lactation registry should be considered (b) (4) (b) (4)

7.6.3 Pediatrics and Effect on Growth

These short-term studies are not capable of elucidating whether Ultrase® MT might pose a safety issue in the growth and development in pediatric patients. But, based on long-term information from public literature, pediatric patients with CF derive benefits from PEP treatment in terms of growth, development, functional status, and survival: the standard of care is that PEP treatment should be started as soon as CF is diagnosed.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

The following is taken from the Sponsor's clinical safety summary:

Acute toxicity determination in animals has not been possible since the maximum dose that could be given orally produced no toxic reaction. In chronic feeding tests with a related product, rats developed swollen salivary glands. This is believed to be due to a proteolytic activity of the pancreatic enzyme resulting in mucosal irritation caused by tissue digestion. No acute toxic reactions have been reported. Extremely high doses of PEPs have been associated with hyperuricemia and hyperuricosuria. Over dosage of pancreatic enzyme concentrate may cause diarrhea or transient intestinal upset.

Ultrase® is not known to be subject to drug abuse.

Ultrase® is not known to cause withdrawal or rebound signs or symptoms.

7.7 Additional Submissions

There were no additional submissions.

8 Postmarketing Experience

Ultrase® (pancrelipase) is an orally administered, enteric-coated porcine pancreatic enzyme preparation that is indicated for the treatment of exocrine pancreatic insufficiency (EPI) in adults and children. It has been commercially available on the U.S. market since November 1991, first by Scandipharm Inc., then by Axcan Inc.

The Sponsor of this NDA, Axcan Pharma Inc., has been marketing Ultrase® MT Capsules since August 1999 in the U.S. Ultrase® is currently marketed by the Sponsor in Canada and by distributors in Argentina, Brazil, Chile, and Costa Rica. Few adverse events have been reported during this time, either in the literature or directly to the Manufacturer or Sponsor. Nevertheless it should be mentioned that since the product has not been under an NDA in the US, and therefore has been essentially unregulated, no Pharmacovigilance requirements have been set forth, making it likely that AEs are grossly underreported.

Ultrase® is not absorbed into tissues or the general circulatory system, and therefore, systemic reactions to pancrelipase are unlikely to occur. The enzymes in Ultrase® are digested within the stomach and intestinal lumen and are metabolized as dietary protein. For these reasons, Ultrase® is not likely to have effects such as carcinogenesis or effects on fertility or reproduction. The effects of the excipients on these functions are unknown.

In the 16 years that Ultrase® has been marketed, there have been no marketing suspensions or restrictions on the distribution of pancrelipase or changes in target population or indications due to safety reasons. In a January 1994 publication, Smyth et al, described five children with cystic fibrosis in the United Kingdom who had switched from standard strength enteric-coated

formulation to high-strength products, 12 to 15 months before presentation with meconium ileus equivalent that failed to respond to medical management.[14] In response to this study, many high strength enzyme preparations (i.e., those containing >20,000 IU lipase/capsule) were withdrawn from the market by pharmaceutical companies in the U.S.[15] The higher strengths Ultrase® MT Capsules (MT24 and MT30) were voluntarily discontinued by Scandipharm Inc. in 1994.
The safety of Ultrase® from post-marketing reports and literature has been discussed extensively by the Sponsor in the NDA submission with regards to the following:

1. Postmarketing reports for Ultrase® from Axcan's Drug Safety Database.

2. Literature review of experimental and controlled studies and case reports. The studies/reports were sorted according to the associated adverse event:

- Hypersensitivity
- Hyperuricosuria and hyperuricemia
- Intestinal obstruction and stricture (fibrosing colonopathy)
- Esophageal injury
- Other gastrointestinal related adverse effects
- Treatment failure or nutrient interactions

Axcan Pharma Inc. markets Ultrase® as well as Viokase® and Panzytrat®, two other formulations of pancreatic enzymes. The Sponsor submitted a discussion on the post-marketing experience of Ultrase® and other formulations of pancreatic enzymes from the drug safety database maintained by Axcan Pharma Inc. and its subsidiaries. The drug safety database includes spontaneous cases from health care professional and non-health-care professional as well as cases from scientific literature and regulatory authorities. Axcan Pharma Inc. performed a reconciliation process with the World Health Organization's (WHO's) Vigibase in February 2007. During this process, the Vigibase adverse event cases involving Ultrase®, Viokase® and unspecified formulation of pancrelipase were included in the Axcan Pharma Inc. safety database.

An estimate of the patient exposure to Ultrase® MT Capsules was calculated by the Sponsor for October 1999 to January 2007 from the number of product units distributed in the US. While Ultrase® MT Capsules are marketed in other countries (Argentina, Brazil, Chile, Costa Rica and Canada), US sales overwhelmingly constitute the greatest percentage globally (98-99%). Since pancrelipase products are administered on weight based dosing, the calculation of patient exposure required the following assumptions:

1) The majority of patients taking Ultrase® ® MT Capsules for the treatment of steatorrhea are CF patients. The median age of survival for CF patients according to the Cystic Fibrosis Foundation's (CFF) 2005 Annual Report is 36.8 years; and, 40% of the CF population is over 18 years of age. The average age for all patients in the CFF Registry is > 16 years. Annual Report Data for the year 2004 from the Cystic Fibrosis

14 Smyth, RL, van Velzen, D, Smyth AR, et al. Strictures of ascending colon in cystic fibrosis and high-strength pancreatic enzymes. The Lancet 1994; 343:85-86
15 FitzSimmons, SC., Burkhard, GA, Borowitz, D, et al. High-dose pancreatic-enzyme supplement and fibrosing colonopathy in children with cystic fibrosis. N Engl J Med 1997; 336: 1283-1289.

Foundation shows that between the ages of birth to 20 years, cystic fibrosis patients generally sit between the 20th and 40th percentile for weight.[16] Therefore, an average weight of 54.3 kg was used for dosing calculations, assuming an average weight value for a 16 year old representing the 30th percentile average weight value approximated from CDC (Centers for Disease Control and Prevention) clinical growth charts for males and females between the ages of 2 to 20 years.

2) A starting dose of 500-1,000 USP lipase units/kg/meal with titration to less than 2,500 USP lipase units/kg/meal for pancreatic enzyme supplementation has been recommended by the FDA in conjunction with the CFF. Therefore, an average dose of 1,500 USP lipase units/kg/meal from Ultrase® MT capsule supplementation was assumed for calculation purposes.

3) It was assumed that patients would be consuming a total of four meals/day, equivalent to three meals and two snacks.

Based on these assumptions, the minimal number of capsules administered per day for Ultrase® MT12, Ultrase® MT18 and Ultrase® MT20 was calculated to be 23.6 capsules, 15.7 capsules and 14.2 capsules, respectively. Table 26 (copied electronically from the Sponsor's submission) lists U.S. unit sales information for Ultrase® MT Capsules as well as the calculation of patient-exposure-years.

16 Cystic Fibrosis Foundation Patient Registry: Annual Data Report 2004, Vol. 17

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Reviewer's comment:
The exposure has been significant, but only relatively few AEs have been reported in the Pharmacovigilance database, as shown in Table 27 (copied electronically from the Sponsor's submission). The most commonly reported AEs were GI system related. Most of the events reported during post-marketing experience were assessed as non-serious. The types of AEs were similar to what has been reported with PEPs in general.

As mentioned above, it is likely that AEs have been grossly under reported because the product has not been approved under an NDA so the reporting requirement has been nil. The data accompanying spontaneous reports are often incomplete and the total number of reactions occurring during post-marketing experience is unknown. In other words, considering that post-marketing surveillance is essentially based on voluntary reporting from health professional and

customers, the frequency provided in the Table 27 should not be used to estimate the incidence of an event in the overall population treated with pancrelipase.

Table 27 Adverse events (preferred term) recorded for pancreatic enzymes in the Axcan Pharma Safety Database classified by system organ class

SOC / PREFERED TERM	NUMBER OF OCCURRENCE
BLOOD AND LYMPHATIC SYSTEM DISORDERS	
Lymphadenopathy	2
GASTROINTESTINAL DISORDERS	
Abdominal discomfort	10
Abdominal pain	13
Abdominal pain upper	3
Abnormal faeces	6
Anorectal disorder	2
Ascites	1
Colitis	4
Constipation	6
Diaorrhea	23
Diarrhoea haemorrhagic	1
Dyspepsia	3
Faeces discoloured	1
Fibrosing colonopathy	11
Flatulence	9
Frequent bowel movements	7
Gastric disorder	1
Gastrointestinal disorder	1
Gastrointestinal haemorrhage	3
Gastrointestinal inflammation	1
Gastrointestinal necrosis	1
Ileitis	1
Ileus	1
Intestinal functional disorder	1
Intestinal obstruction	12
Intestinal perforation	1
Intestinal stenosis	7
Intussusception	1
Lip blister	1
Malabsorption	4

Coded by MedDRA v.10.0 dictionary. Database lock point: May 30, 2007.

SOC / PREFERED TERM	NUMBER OF OCCURRENCE
GASTROINTESTINAL DISORDERS (CONT'D)	
Melaena	3
Mouth ulceration	1
Nausea	4
Oesophageal stenosis	1
Oesophagitis	1
Oral pain	3
Rectal haemorrhage	1
Steatorrhoea	8
Stomach discomfort	2
Stomatitis	2
Tongue ulceration	1
Vomiting	4
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	
Drug ineffective	15
Drug ineffective for unapproved indication	1
Drug interaction	1
Drug intolerance	1
Fatigue	1
Feeling abnormal	1
Granuloma	1
Hunger	1
Malaise	1
Non-cardiac chest pain	1
Pain	3
IMMUNE SYSTEM DISORDERS	
Hypersensitivity	1
INFECTIONS AND INFESTATIONS	
Rash pustular	1
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	
Oral administration complication	1

Coded by MedDRA v.10.0 dictionary. Database lock point: May 30, 2007.

SOC / PREFERED TERM	NUMBER OF OCCURRENCE
INVESTIGATIONS	
Blood glucose increased	2
Liver function test abnormal	1
Medication residue	1
Pancreatic enzymes increased	1
Prothrombin level decreased	1
Weight decreased	2
Weight increased	1
METABOLISM AND NUTRITION DISORDERS	
Dehydration	1
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	
Growth retardation	1
Muscle spasms	1
Musculoskeletal chest pain	1
NERVOUS SYSTEM DISORDERS	
Dizziness	2
Hyperaesthesia	1
Paraesthesia	1
Syncope	1
PREGNANCY, PUERPERIUM AND PERINATAL CONDITIONS	
Abortion	1
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	
Throat irritation	1
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	
Blister	1
Dermatitis diaper	1
Erythema	2
Pruritus	3
Pruritus generalised	1
Rash	6
Skin exfoliation	1
Urticaria	1

Coded by MedDRA v.10.0 dictionary. Database lock point: May 30, 2007.

The Sponsor received 17 individual reports assessed as serious. The SAE case reports are listed below.

Eleven cases of fibrosing colonopathy (FC) were reported from spontaneous notification (10 cases) and literature (1 case). These cases were reported in CF patients who were taking multiple PEPs including Ultrase®. FC has been reported in CF patients treated with both high and lower-strength enzyme supplements.[17]

Reviewer's comment:
The Sponsor has not specified whether there were cases of FC reported since the release of the CFF/FDA Guidelines. It is not also not known whether there are other risk factors for FC, such as whether patients who are younger (i.e., with lower body weight) might be at greater risk.

Three reports involving an unspecified formulation of PEPs were received from the WHO Vigibase database and were assessed as serious by the initial reporter. These cases include: diarrhea, abdominal distension and weight increase in one patient, weight decreased, pain and malabsorption in another patient, as well as stomach discomfort, diarrhea, abdominal pain, pain, nausea, malaise, frequent bowel movements, dizziness and dehydration in the third patient.

One case of three episodes of intestinal obstruction requiring hospitalization was reported in a pediatric patient who was treated with Ultrase®. The patient was dispensed a three-month supply of the drug that was not stored in the original container. As per the reporter's narrative, the treating health professional stated that the obstruction episodes were related to degraded enzyme ingestion.

One case of intussusception was reported in a 15-year-old patient treated with Ultrase® as well as Pancrease®. The patient was switched to Ultrase®, used it for nine days and was switched back to his previous PEP formulation (Pancrease®). One week later, the patient was diagnosed with intussusception. The patient was treated with ileostomy, received total parenteral nutrition (TPN) and was recovering from the event at the time of the report.

One case of fatal intestinal perforation was reported in a 4-year-old patient who was treated with generic formulation of pancrelipase as well as Ultrase®. This report was received from the father of the patient and was not "medically confirmed."

17 Smyth, RL, van Velzen, D, Smyth AR, et al. Strictures of ascending colon in cystic fibrosis and high-strength pancreatic enzymes. The Lancet 1994; 343:85-86

9 Appendices

9.1 Literature Review

The Sponsor conducted a literature review on safety related to Ultrase® pertaining to the issues of hypersensitivity, hyperuricosuria and hyperuricemia, intestinal obstruction and stricture, esophageal injury, other gastrointestinal-related adverse effects, treatment failure, and nutrient interactions. Extensive citation of literature has been provided, which is beyond the scope of this review to copy or describe in depth; therefore, the reader is referred to the NDA, under section 2.7.4 Summary of Clinical Safety for details and for specific references. However, the Reviewer highlights the following points to be considered and negotiated with the Sponsor at the time of labeling negotiation, should this NDA be approved in a future review cycle.

1. Hypersensitivity: Although case reports or experimental/controlled studies demonstrating hypersensitivity associated specifically with Ultrase® have not been published, the literature contains many reports of hypersensitivity associated with various other PEPs. The reaction is thought to be IgE-mediated because specific IgE antibodies against the extracts have been identified. All reported hypersensitivity type reactions have been due to inhalation of pancreatic enzyme powder. Symptoms included skin reactions such as urticaria and pruritus, and respiratory reactions such as wheezing and dyspnea. The potential for hypersensitivity reactions has led to the recommendation in the prescribing information for Ultrase® that it not be crushed or chewed prior to ingestion. There is also a specific warning for individuals who may be allergic to pork proteins. For younger pediatric patients who will be dispensed the content of the capsules as powder form to be sprinkled on and dispersed in food (because they cannot swallow capsules), a warning statement about hypersensitivity reactions might be included in the labeling.

2. Hyperuricemia and hyperuricosuria: Uric acid is the metabolic product of nucleic acids, a contaminant found in a variety of pancreatic enzyme formulation, which is ultimately excreted by the kidneys. Because of the low solubility of uric acid, it will precipitate in acidic urine (pH 4.5-6). Therefore, a patient with hyperuricosuria (urinary excretion of uric acid >800 mg/1.73 m^2/24 h) is at risk of uric acid crystallization and damage to the renal tubules. Hyperuricemia is the term applied to settings in which the serum urate concentration is elevated, but neither symptoms nor signs of urate deposition have occurred. Although no studies specific to Ultrase® have been reported, hyperuricosuria and hyperuricemia have been described in patients receiving large doses of pancreatic supplements. Currently marketed enteric-coated PEPs are not expected to cause hyperuricosuria or hyperuricemia, however, because these formulations are more pure and the urate load from enteric coated enzymes is substantially less compared to non-enteric coated preparations, since fewer capsules are used. Furthermore, it is unclear whether the nucleic acid contaminants of the products or an unrecognized manifestation of CF causes the hyperuricosuria. It appears that, in some CF patients, hyperuricemia and/or hyperuricosuria may actually be part of the disease complex. However, in other patients, it appears that PEPs caused these side effects. Therefore, it may be prudent to

evaluate uric acid metabolism in CF patients, who consume large amounts of lipase units per meal on a daily basis. Unfortunately the medical literature does not provide a specific threshold for lipase units beyond which more intensive evaluation of uric acid is warranted.

3. Intestinal Obstruction and Stricture: There have been reports of fibrosing colonopathy in patients receiving high doses of PEPs. Fibrosing colonopathy is characterized pathologically by dense submucosal fibrosis which leads to narrowing and shortening of the colon. The disease begins in the cecum and ascending colon, and extends distally, and can eventually progress to involve the entire colon. Damage to the colon appears to be irreversible. Clinically, the presenting symptoms of fibrosing colonopathy include chronic abdominal pain particularly after meals, abdominal distension, a change in bowel habits, bloody stools and failure to thrive. In the later stages of the disease, patients develop vomiting and signs of subacute or acute intestinal obstruction. Symptoms of fibrosing colonopathy usually present within 12 months of starting high-dose pancreatic enzyme therapy but the pathogenesis of fibrosing colonopathy is still unclear. Risk factors noted in case-control studies include high-dose PEP, younger age (2-13 years), a history of gastrointestinal symptoms, prior gastrointestinal surgery, use of histamine H_2 receptor blockers, corticosteroids and recombinant human deoxyribonuclease. Other studies have suggested a role for the enteric coating of the microspheres in some preparations, in particular, the methacrylic acid and ethylacrylate copolymer Eudragit® L30 D-55, but this role remains controversial.[18] Potential etiological factors for fibrosing colonopathy may, therefore, include toxic damage by either the high-dose enzymes themselves, impurities or the coatings. In addition, an immune-mediated mechanism of tissue damage through an antigenic response to the porcine enzymes has been suggested.[19] Increased intestinal permeability, as is observed in CF, may also contribute to the development of fibrosing colonopathy. Epidemiological case-control studies have supported an association between higher doses of PEPs and increased risk. High-strength formulations, which contained 20,000 U or more of lipase per capsules, first became available in 1991, and were intended to improve patient compliance by decreasing the number of capsules needed each day. In 1994, there were three separate reports of CF patients with symptomatic colonic submucosal fibrosis, all of whom had been started on high strength enzymes in the 12 to 20 months prior to diagnosis. Intake of >6,000 lipase units/kg/meal or >10,000 lipase units/kg per day are most often associated with this development. The Cystic Fibrosis Foundation and the FDA surveyed CF centers to determine their experience with fibrosing colonopathy from 1991 through 1993; 45 cases were reported, 15 of which met a formal case definition. Since then, additional case reports have appeared occasionally in the literature. Several workshops have been organized to decide how to use pancreatic enzyme supplements in light of the reports of fibrosing colonopathy. It was agreed that these products are highly valuable for the management of nutrition in CF children, and their use should continue. Recommendations by the Cystic Fibrosis Foundation in conjunction with the FDA

18 FitzsSimmons SC, Burkhard, GA, Borowitz, D, et al. High-dose pancreatic-enzyme supplements and fibrosing colonopathy in children with cystic fibrosis. N Engl J Med 1997; 336: 1283-9.
19 Lee, J, Wan, I, and Durie, P Is fibrosing colonopathy an immune mediated disease? Arch Dis Child 1997; 77:66-70

included keeping doses to a range of 500 to 2,500 lipase units/kg per meal, and to keep doses below a maximum of 10,000 lipase units/kg/day. The enteric-coated pancrelipase has been recommended due to the achievement of the desired pharmacological activity at the relative lower dosage. Ultrase® MT capsules are currently manufacture with HP55 and are not methacrylic acid as the enteric-coating, (b) (4) (b) (4)

4. Esophageal Injury: A single case report of odynophagia and endoscopic documentation of an esophageal ulcer appears in the literature. In this patient, part of a series of 17, with the other 16 having different types of medication involved, odynophagia prompted endoscopic evaluation. An esophageal ulcer was documented with particles of the PEP (Pantozyme®) discovered in the ulcer base. Other causes of esophageal ulcer (e.g., carcinoma, herpes simplex, cytomegalovirus and moniliasis were excluded by appropriate testing.

5. Other Gastrointestinal Related Adverse Effects: The Sponsor submitted various sporadic case reports in the literature of other gastrointestinal related adverse effects, including the following: three cases in which prolonged retention of PEP powder in the mouth or chewing of enteric-coated tablets by children caused mouth ulceration and stomatitis; four cases of dryness of the mouth; one case of intolerance to PEP (the child vomited the drug while ingesting); unspecified number of cases of nausea, cramping and/or diarrhea; unspecified number of cases of severe constipation from too rapid increase in enzyme dosage; unspecified number of cases of peri-anal irritation from too rapid passing of significant enzyme activity in the stools due to excessive dosing or too rapid intestinal transit time.

6. Treatment failure: Although not specific to Ultrase®, treatment failure with the use of enteric-coated pancrelipase products has been reported. Three patient cases reported treatment failure after using generic pancrelipase capsules. The patients were diagnosed with CF and the pharmacists had substituted generic pancrelipase capsules for the Pancrease® brand. The *in vitro* analysis on enzyme activity was investigated after the treatment failure reported. The analysis discovered that lipase activity was less than 200 units per capsule compared to 6,820 units per capsules from Pancrease® after one-hour exposure to simulated gastric fluid. These *in vitro* data indicated that the enteric-coating of the generic product was not bioequivalent to the prescribed brand drug Pancrease®. The patients' gastrointestinal symptoms and fat malabsorption rapidly resolved after the brand Pancrease® therapy was reinstituted. The authors concluded that non-bioequivalent generic products should not be used to treat patients. They also recommended that physicians should mark their prescriptions for pancreatic enzyme products "do not substitute" and that pharmacists should not substitute one brand of PEP for another without consulting the prescribing physician.

7. Nutrient Interactions: Enteric-coated pancreatic enzymes such as Ultrase® given as digestive aids can have a number of effects on the absorption of nutrients, both positive and negative. Adequate absorption of fat-soluble vitamins requires proper fat absorption, and treatment with pancreatic enzymes in combination with vitamin supplementation has

been used to improve the absorption of Vitamins A and D in CF patients. However, PEPs can form insoluble complexes with folic acid, and may, therefore, impair folate absorption. The extent of this impairment and its consequences are unknown, but may be an important consideration in women of child-bearing age since adequate folate intake during pregnancy is associated with a reduced risk of neural tube defects in infants. PEPs have been shown to contain selenium at concentrations that result in improved absorption of selenium in patients. Iron absorption, on the other hand, may be reduced by pancreatic enzyme preparations, and some authors recommend that the iron status of patients with CF should be routinely monitored, that the serum ferritin level may be the most appropriate measurements of total body iron stores, and that iron should not be administered in close proximity in time of PEPs. However, since the study that gave rise to these recommendations enrolled only young adults, the results from the study may not be applicable to growing children.[20]

9.2 Labeling Recommendations

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Other general comments regarding labeling recommendations are as follows:

1. The literature case reports described in Section 9.3 Literature Review should be considered.
2. Only those studies that were conducted in the TbMP should be included in the labeling (i.e., results from Studies 96-01 and 96-02 should not be included).
3. Dose recommendation should comply with the CFF/FDA dosing Guidelines.
4. The indication statement should state that Ultrase® has been shown to treat steatorrhea caused by EPI due to CF, CP, and other related disorders.
5. A brief discussion of fibrosing colonopathy and hyperuricemia/hyperuricosuria should be included. The following description of the former may be considered: Fibrosing colonopathy is a term used to describe a condition seen in patients with CF who have taken high amounts of PEP (>6,000 lipase units/kg/meal). At its most advanced stage, this condition leads to colonic strictures. Colonic strictures have been reported in CF patients treated with both high and lower-strength enzyme supplements.[21] The possibility of bowel stricture should be considered if symptoms suggestive of gastrointestinal

20 Tempsky, WT, Rosenstein, BJ, Carroll JA, et al. Effect of pancreatic enzyme supplement on iron absorption. AJDC 1989; 143: 969-972.
21 Smyth, RL, van Velzen, D, Smyth AR, et al. Strictures of ascending colon in cystic fibrosis and high-strength pancreatic enzymes. The Lancet 1994; 343:85-86

obstruction occur. Since impaired fluid secretion may be a factor in the development of intestinal obstruction, care should be taken to maintain adequate hydration particularly in warm weather.[22]

9.3 Advisory Committee Meeting

No Advisory Committee was convened for this application.

9.4 Appendix 1: Federal Register (FR) Notice and Regulatory History of PEPs

To address the problems with variations between the PEPs, the Food and Drug Administration (the Agency) published the following notices in the Federal Register (FR): [23]

- In 1979, the Agency proposed establishing monographs for OTC PEPs.
- In 1985, recommendations of the PEP Advisory Review Panel were published that stated that OTC monographs would not be sufficient to regulate the PEPs, pre-clearance of each product to standardize enzyme bioactivity would be necessary, and PEPs should be made available by prescription only.
- In 1991, the Expert panel proposed that the FDA withdraw the 1985 proposed OTC rule, declared that the PEPs are not Generally Recognized as Safe (GRAS) and Generally Recognized as Effective (GRAE), and the PEPs are misbranded.
- In 1995, a Notice of Final Rule was published that stated all PEPs must obtain FDA approval (under NDA) in order to remain on the market.
- In 2004, the Notice of Requirement for NDA Approval was published that stated all PEPs must get NDA approval within the next four years (deadline 28-April-2008), and the expectation of the Agency was that only NDAs under 505(b)(2), not Abbreviated New Drug Applications (ANDAs), would be received. To be approved, PEP NDAs must meet the requirements for content and format of an application as stated in 21CFR 314.50. A draft Guidance for submitting NDAs for PEPs was also published at that time.
- In 2006, the Final Guidance for submitting NDAs for PEPs was published ("the Guidance").[24]

22 Lands, L, Zinman, R, Wise, M, et al. Pancreatic function testing in meconium disease in CF: Two case reports. J of Ped Gastroenterol and Nutrition 1988; 7:276-279
23 This regulatory history of pancreatic enzyme products was compiled by FDA's clinical review team leader, Anne Pariser, M.D. (see Clinical Team Leader Summary Review of NDA 20-725, July 31, 2007)
24 U.S. Department of Health and Human Services. Food and Drug Administration. Center for Drug Evaluation and Research (CDER). "Guidance for Industry. Exocrine Pancreatic Insufficiency Drug Products – Submitting NDAs." <http://www.fda.gov/cder/guidance/6275fnl htm> April 2006.

Note: These FR notices and the Guidance only apply to the currently-marketed, animal (porcine or bovine)-derived PEPs containing pancreatin and pancrelipase.

9.5 Appendix 2: Listing of Individual Site Investigator and Study Sites for Study UMT20CF05-01

Principal/Coordinating Investigator:
Michael Konstan, MD (Cleveland, OH)

Individual Site Investigator:
Site 01 Gavin Graff, MD (Pennsylvania State University and the Hershey Medical Center)
Site 02 Theodore Liou, MD (University of Utah)
Site 03 Steven Strausbaugh (University Hospitals of Cleveland)
Site 05 Richard Ahrens, MD (University of Iowa)
Site 06 Katryn Moffett (West Virginia University Research Corporation)
Site 07 Samya Nasr, MD (University of Michigan)
Site 09 Susan Millard, MD (Spectrum Health Hospital)
Site 10 Jamshed Kanga (University of Kentucky Research Foundation)

9.6 Appendix 3: Summary of AEs by SOC and PT, Pivotal Study

System Organ Class		Treatment	
Preferred Term	Statistic	Ultrase® MT20	Placebo
Number of Patients in the Safety Population Who Entered the Treatment Period	N	30	31
Number of TEAEs	n	33	109
BLOOD AND LYMPHATIC SYSTEM DISORDERS	n (%)	0	1 (3.2%)
WHITE BLOOD CELL DISORDER	n (%)	0	1 (3.2%)
GASTROINTESTINAL DISORDERS	n (%)	8 (26.7%)	19 (61.3%)
ABDOMINAL DISCOMFORT	n (%)	0	1 (3.2%)
ABDOMINAL DISTENSION	n (%)	0	1 (3.2%)
ABDOMINAL PAIN	n (%)	2 (6.7%)	12 (38.7%)
ABDOMINAL PAIN UPPER	n (%)	4 (13.3%)	6 (19.4%)
ABDOMINAL TENDERNESS	n (%)	0	2 (6.5%)
CONSTIPATION	n (%)	2 (6.7%)	2 (6.5%)
DIARRHOEA	n (%)	0	3 (9.7%)
FAECAL VOLUME INCREASED	n (%)	0	1 (3.2%)
FLATULENCE	n (%)	1 (3.3%)	5 (16.1%)
NAUSEA	n (%)	0	5 (16.1%)
STEATORRHOEA	n (%)	0	1 (3.2%)
VOMITING	n (%)	0	3 (9.7%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	n (%)	0	3 (9.7%)
CHILLS	n (%)	0	1 (3.2%)
FATIGUE	n (%)	0	1 (3.2%)
GENERAL PHYSICAL HEALTH DETERIORATION	n (%)	0	1 (3.2%)
LETHARGY	n (%)	0	1 (3.2%)
PYREXIA	n (%)	0	2 (6.5%)
INVESTIGATIONS	n (%)	6 (20.0%)	12 (38.7%)
ALANINE AMINOTRANSFERASE INCREASED	n (%)	1 (3.3%)	2 (6.5%)
ASPARTATE AMINOTRANSFERASE INCREASE	n (%)	0	1 (3.2%)
BLOOD ALKALINE PHOSPHATASE INCREASED	n (%)	1 (3.3%)	0
BLOOD CALCIUM DECREASED	n (%)	0	1 (3.2%)
BLOOD GLUCOSE INCREASED	n (%)	0	2 (6.5%)
BLOOD POTASSIUM INCREASED	n (%)	0	1 (3.2%)
BLOOD TRIGLYCERIDES INCREASED	n (%)	0	1 (3.2%)
BREATH SOUNDS ABNORMAL	n (%)	0	1 (3.2%)
FAECAL FAT INCREASED	n (%)	4 (13.3%)	9 (29.0%)
FORCED EXPIRATORY VOLUME DECREASED	n (%)	1 (3.3%)	0
GAMMA-GLUTAMYLTRANSFERASE INCREASED	n (%)	0	1 (3.2%)
LABORATORY TEST ABNORMAL	n (%)	3 (10.0%)	7 (22.6%)
LABORATORY TEST ABNORMALITY	n (%)	0	1 (3.2%)
NEUTROPHIL COUNT INCREASED	n (%)	0	1 (3.2%)
PULMONARY FUNCTION TEST DECREASED	n (%)	0	1 (3.2%)
WEIGHT DECREASED	n (%)	0	3 (9.7%)
METABOLISM AND NUTRITION DISORDERS	n (%)	0	2 (6.5%)
DECREASED APPETITE	n (%)	0	2 (6.5%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	n (%)	1 (3.3%)	3 (9.7%)
ARTHRALGIA	n (%)	0	1 (3.2%)
MUSCULOSKELETAL DISCOMFORT	n (%)	0	1 (3.2%)
MYALGIA	n (%)	1 (3.3%)	1 (3.2%)
NERVOUS SYSTEM DISORDERS	n (%)	2 (6.7%)	2 (6.5%)
DIZZINESS	n (%)	0	1 (3.2%)

HEADACHE	n (%)	2 (6.7%)	1 (3.2%)
PSYCHIATRIC DISORDERS	n (%)	0	1 (3.2%)
PANIC ATTACK	n (%)	0	1 (3.2%)
	n (%)		
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	n (%)	0	1 (3.2%)
DYSMENORRHOEA	n (%)	0	1 (3.2%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	n (%)	6 (20.0%)	6 (19.4%)
COUGH	n (%)	1 (3.3%)	1 (3.2%)
DYSPHONIA	n (%)	0	1 (3.2%)
DYSPNOEA	n (%)	0	1 (3.2%)
NASAL CONGESTION	n (%)	0	1 (3.2%)
NASAL TURBINATE HYPERTROPHY	n (%)	1 (3.3%)	0
PERITONSILLAR ABSCESS	n (%)	1 (3.3%)	0
PHARYNGOLARYNGEAL PAIN	n (%)	2 (6.7%)	1 (3.2%)
PLEURITIC PAIN	n (%)	0	1 (3.2%)
PRODUCTIVE COUGH	n (%)	0	1 (3.2%)
RALES	n (%)	2 (6.7%)	2 (6.5%)
RHINORRHOEA	n (%)	1 (3.3%)	3 (9.7%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	n (%)	1 (3.3%)	0
RASH MACULO-PAPULAR	n (%)	1 (3.3%)	0
SURGICAL AND MEDICAL PROCEDURES	n (%)	0	1 (3.2%)
PAIN MANAGEMENT	n (%)	0	1 (3.2%)
VASCULAR DISORDERS	n (%)	2 (6.7%)	0
EPISTAXIS	n (%)	2 (6.7%)	0

Notes:
1. Adverse events have been coded using the MedDRA dictionary, version 9.0.
2. Treatment emergent adverse events (TEAEs) include all new AEs that occurred during the Treatment Periods. AEs already present at the beginning of one of these study periods that worsen in intensity following exposure to the study period medication have also been considered as treatment emergent.
3. Patients with more than one occurrence of the same preferred term/system organ class during a particular study period have been counted only once within the preferred term/system organ class of that study period.
4. Percentages based on the total number of Safety patients within each treatment group and each study period.
5. Terms 'lacrimation increased' and 'rhinitis' were removed from this derivative table as these events only occurred during the Stabilization Periods, data that are presented in the more detailed Section 14 Tables

Source: Table 14.3-2

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/s/

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7/1/2008 02:05:10 PM
MEDICAL OFFICER

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