Gastrointestinal Drug Advisory Committee Meeting
FDA White Oak Campus
White Oak Conference Center
Building 31, The Great Room (Room 1503)
10903 New Hampshire Avenue
Silver Spring, Maryland
January 12, 2011

Meeting to discuss: the Safety and efficacy of New Drug Application (NDA) 022486/Solpura (liprotamase) Capsules, by Alnara Pharmaceuticals for the proposed indication (use) in the treatment of exocrine pancreatic insufficiency due to cystic fibrosis, chronic pancreatitis, pancreatectomy, or other conditions that may impair or limit function of the pancreas

Department of Health & Human Services
Food & Drug Administration
Center for Drug Evaluation & Research
Office of New Drugs
Division of Gastroenterology Products

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Food and Drug Administration
Center for Drug Evaluation and Research
January 12, 2011 GIDAC Advisory Committee Meeting

Briefing Materials – Table of Contents

1 Executive Summary

1.1 Statement of Purpose

The purpose of the Advisory Committee meeting is to obtain advice from the Committee regarding the efficacy, safety, and indication of Solpura (liprotamase). Liprotamase is a biotechnology product that contains microbially-derived enzymes: crystallized cross-linked lipase, crystallized protease, and amorphous amylase. The proposed indication is: "…treatment of patients with exocrine pancreatic insufficiency due to cystic fibrosis, chronic pancreatitis, pancreatectomy, or other conditions." The applicant proposes that the product will be used across all age groups and includes dosing recommendations in the product label for patients less than seven years of age, the lowest age studied in the clinical trials. Porcine derived pancreatic enzyme products (PEPs), which have for years been the mainstay for treatment of exocrine pancreatic insufficiency, are complex mixtures of different types of lipases, proteases and amylases, in addition to other enzymes/proteins. Approval of liprotamase would result in marketing of the first product for exocrine pancreatic insufficiency that is not a porcine-derived PEP. FDA review issues include concerns about the adequacy of submitted efficacy data to support approval of this new product. FDA reviewers have questioned whether the change in coefficient of fat absorption observed with liprotamase is comparable to that observed with the porcine derived PEPs, and whether the substantial body of evidence in the literature that supports the clinical benefit of porcine derived PEPs is applicable to liprotamase, in light of the magnitude of observed changes in CFA associated with liprotamase, relative to the changes reported with porcine derived PEPs.

1.2 Background

1.2.1 Exocrine Pancreatic Insufficiency

Exocrine pancreatic insufficiency (EPI) typically results from chronic loss of pancreatic tissue due to a number of underlying diseases. The most common cause of EPI in children is cystic fibrosis (CF); common causes of EPI in adults are CF and chronic pancreatitis (CP).

The predominant clinical manifestations of EPI are steatorrhea, abdominal pain, weight loss, and nutritional problems (e.g., fat-soluble vitamin deficiencies) due to malabsorption. Pancreatic enzyme replacement therapy with exogenous sources of PEPs (i.e., porcine-derived PEPs) is the mainstay of therapy for steatorrhea and malabsorption due to EPI, regardless of cause.

1.2.2 Porcine Derived Pancreatic Enzyme Products

FDA required all marketed PEPs to have undergone the NDA application and review process. Key to the approval of each PEP was the Agency's long-standing determination

that replacement of pancreatic enzymes has clinical benefit for patients with exocrine pancreatic insufficiency (EPI), and the body of evidence in the literature that supports efficacy and safety of PEPs. In light of this evidence, only a short-term demonstration of the efficacy and safety of the particular PEP to be marketed was required to support its NDA approval. The body of evidence in the literature also allowed each PEP to be indicated for all pediatric age groups and for all etiologies of EPI *regardless of whether patients in these subpopulations were included in the short-term trial for that PEP*.

The primary endpoint used to support approval of PEPs has been the change in Coefficient of Fat Absorption (CFA) (comparison of CFA on treatment with CFA without treatment).[1] CFA is an objective measure of fat absorption, and evaluates the lipase component of the PEP.

A secondary endpoint included in studies of PEPs is the change in Coefficient of Nitrogen Absorption (CNA) (comparison of CNA on treatment with CNA without treatment).[2] Although CNA is not the basis for the demonstration of efficacy because of its limitations as a measure of protein absorption (e.g., urine nitrogen is not measured and movement of nitrogen across the bowel wall is not measured), documentation of an increase in CNA supports that proteases present in the PEP are physiologically active.

Evaluation of the amylase component of PEPs has not been done in clinical trials because there is no standard, feasible method to measure the physiological activity of amylase. Although amylase deficiency can result in starch malabsorption, intracolonic polysaccharide loads are metabolized rapidly by the colonic flora, and therefore fecal carbohydrate measurements are not representative of starch malabsorption.

The Dosage and Administration instructions for PEPs are based on lipase units even though all three enzyme classes (i.e., lipase, protease, and amylase) are listed as "active ingredients" in the product label, and the activity (Units) of each component is also specified. Porcine-derived PEPs are mixtures from a single source; the active ingredients are identified in the product labels as measures of quality control ("lipase", "protease", and "amylase" do not each refer to a single specific enzyme, but a class of multiple different enzymes with shared activities).

Dosing of PEPs for EPI is individualized based on age, body weight, fat content of the diet, and control of clinical symptoms such as steatorrhea. The major dosing guidelines for PEPs are the Consensus Conferences guidelines established by the Cystic Fibrosis Foundation (CFF); see Clinical Review.

[1] CFA is determined from a 72-hour stool collection; the formula for CFA is CFA [%] = {[Fat intake (g/day) – Fat excretion (g/day)] / Fat intake (g/day)} X 100.

[2] CNA is determined from a 72-hour stool collection; the formula for CNA is CNA [%] = {[Nitrogen intake (g/day) – Nitrogen excretion (g/day)] / Nitrogen intake (g/day)} X 100.

1.3 Clinical Summary

The two controlled clinical trials submitted in support of this NDA were, Study 726 (a randomized, double-blind placebo-controlled trial) and Study TC-2A (a randomized, double-blind, dose-ranging trial). However, the products used in the two trials are not comparable to one another; therefore, clinical efficacy and safety results cannot be directly compared between trials.[3] The Applicant proposed a third study, Study 767 (a long term open label safety study that used the same drug product as that in Study 726), to be considered as additional evidence to support the safety and efficacy of liprotamase. Studies 726, TC-2A, and 767 are summarized in the table below. No children less than age 7 years were enrolled in these trials.

Table 1. Key Clinical Trials for Liprotamase

Study	Design	Population	N*	Duration of Treatment	Treatment Arms[#]
726[†] (Pivotal Trial)	R, DB, PC	▪ EPI due to CF ▪ Ages 7 to 44 years	138	34-44 days	➢ Liprotamase 32,500 units (n=70*) ➢ Placebo (n=68*)
TC-2A[‡] (Dose Ranging)	R, DB, dose-ranging	▪ EPI due to CF ▪ ages 11 to 55 years	125	28 days	➢ Liprotamase 6,500 units (n=41) ➢ Liprotamase 32,500 units (n=43) ➢ Liprotamase 130,000 units (n=41)
767[§] (Long Term Safety)	OL	▪ EPI due to CF ▪ Ages 7 to 62 yrs	214	48-52 weeks	➢ Liprotamase 32,500 units[£]

*ITT; R: Randomized; DB: Double-blind; PC: Placebo-controlled
[#]Dose of active treatment arms in USP units of lipase per meal or snack (3 meals and 2 snacks per day)
[†]An additional 25 patients received up to 31 days of treatment prior to randomization to allow for determination of baseline CFA levels (subjects with baseline CFA levels > 80% were excluded from the randomization).
[‡]Product used in TC-2A not comparable to Phase 3 product (i.e., product used in Studies 726 and 767).
[§]includes 88 patients who received prior treatment in 726 and 5 patients who received prior treatment in TC-2A
[£]Protocol-specified dose increases (to 2 capsules per meal and 1 capsule per snack) allowed in cases of involuntary weight loss, steatorrhea, or lack of weight gain.
(Table modified from Clinical Efficacy Review.)

Key features of Studies 726 and TC-2A are summarized below. See Clinical Review for details.

- Primary Endpoint: The primary endpoint in Study TC-2A was the CFA during the treatment period. The primary endpoint in Study 726 was the change in CFA from the baseline (no treatment) period to the treatment period in the subgroup of patients with baseline CFA ≤ 40%.
- Secondary Endpoints: A key secondary endpoint in each of these trials was the change in CNA from the baseline period to the treatment period. The starch challenge test (SCT) was included as an exploratory endpoint.

Key features of Study 767 are summarized below.

- Study Period: The study, which included patients who continued from Studies 726 or TC-2A and patients who were newly enrolled, was 12 months in duration.
- Efficacy Endpoints: Efficacy endpoints were not defined in the protocol. [Height, weight, and BMI z-scores (based on CDC growth charts) were presented over time;

[3] There are only limited differences between the product in Study 726 and the to-be-marketed product (TBMP); these would be unlikely to have an impact on clinical efficacy and safety (see CMC Review).

qualitative comparisons were made to 2008 CFF Registry data and to a retrospective collection of data from 5,660 patients in the CFF Registry ("group-matched external control").]

- Dose: The dose was one capsule (i.e., 32,500 units) per meal or snack; there was a protocol-specified dose increase to two capsules per meal and one capsule per snack allowed in cases of involuntary weight loss, steatorrhea, or lack of weight gain.

Another open label long term safety study, Study 810, was conducted in patients with CP or pancreatectomy. That study used the same product and dose as Study 767. Of the 39 patients that entered the study, 29 patients completed three months, and four patients completed one year.

1.3.1 Efficacy

Study TC-2A:

In this dose ranging trial, which was conducted utilizing a product which was not comparable to the product in Study 726, there was evidence of a dose response; however, the increase in CFA was not proportional to the increase in the dose.

Table 2. Change in CFA* (Study TC-2A)

Baseline CFA Category	Low 6,500 U	Middle 32,500 U	High 130,000 U	**Middle – Low**[#] (p-value[†])	**High – Low**[#] (p-value[†])
Overall[‡]	**1%** (±15%) (n=39)	**11%** (±19%) (n=41)	**17%** (±18%) (n=37)	**10%** (p=0.028)	**16%** (p=0.0004)
Baseline CFA < 40%[§]	**11.5%** (±14.2%) (n=8)	**35%** (±18.5%) (n=8)	**28%** (±16%) (n=13)	**23.5%**	**16.5%**
Baseline CFA ≥ 40%[§]	**-1%** (±13%) (n=33)	**5%** (±14%) (n=35)	**10%** (±16%) (n=26)	**6%**	**11%**

*Change in CFA from baseline period to treatment period. Mean (±SD).
[#]Arithmetic difference in means between treatment groups shown.
[†]p-values calculated using Tukey's studentized range test for pairwise comparisons between treatment groups for the change in CFA from baseline results
[‡]mITT population
[§]ITT population used for subgroup analyses (Baseline CFA<40% and Baseline CFA ≥40%)
(Table above modified from the Clinical Efficacy Review. Source is Page 52 of the TC-2A Study Report.)

Study 726:

The primary efficacy results of Study 726 are in the table below. There was a statistically significantly higher change in CFA in the liprotamase group compared to placebo in both patients with baseline CFA <40% (primary efficacy analysis) and in the subgroup of patients with baseline CFA ≥40%.

Table 3. Change in CFA* (Study 726)

Subgroup	Liprotamase	Placebo	Liprotamase-Placebo[#]	p-value
Overall Study Population	**11%** (±17) (n=70)	**0.2%** (±16) (n=68)	**11%**	p<0.001
Baseline CFA<40% Subgroup (Primary Efficacy Analysis)	**20%** (±16) (n=24)	**5%** (±15) (n=20)	**15%**	p=0.001
Baseline CFA≥40% Subgroup	**7%** (±15) (n=46)	**-2%** (±16) (n=48)	**9%**	p=0.006

*Change in CFA from baseline period to treatment period. Mean (±SD). Baseline observation carried forward.
[#]LSM Difference. For baseline CFA<40% subgroup, change in CFA was analyzed using an ANCOVA model with fixed effects for treatment group, CFA subgroup, and acid suppression usage with adjustment for baseline CFA. For baseline CFA≥40% subgroup and overall study population, change in CFA was analyzed using an ANCOVA model with fixed effects for treatment group and acid suppression usage with adjustment for baseline CFA.
(Table above modified from the Clinical Efficacy Review. Source is Page 73 of the 726 Study Report.)

Subgroup analyses by age (7 to 11 years, 12 to 16 years, and 17 to 44 years) presented in the Clinical Review suggested that age 12 to 16 years patients had a numerically lower treatment difference than the other two age groups in the overall baseline CFA category and in the baseline CFA ≥ 40% category.

The change in CFA observed in Study 726, and studies of Creon, Zenpep, and Pancreaze are summarized in the table below. Although there are limitations of cross-study comparisons, the results suggest that the magnitude of change in CFA with liprotamase is lower than that of the porcine-derived PEPs.

Table 4. Change in CFA Results (Creon, Zenpep, Pancreaze, Liprotamase)

Baseline CFA Category	Porcine-derived PEPs			Study 726	Study TC-2A	
	Creon* 4,000 U/g fat/day (n=29[£])	Zenpep* 5,700 U/kg/day (n=32)	Pancreaze[#] 6,400 U/kg/day (n=40)	Liprotamase 32,500 U (per meal or snack) (n=138)	Liprotamase 32,500 U (per meal or snack) (n=41[‡])	Liprotamase 130,000 U (per meal or snack) (n=37[‡])
Overall	41%	26%	33%	11%	11%	17%
Baseline CFA < 40%	61% (n=8[£])	47% (n=5)	--[#]	15% (n=44)	35% (n=8[§])	28% (n=13[§])
Baseline CFA ≥ 40%	31% (n=23[£])	20% (n=27)	--[#]	9% (n=94)	5% (n=35[§])	10% (n=26[§])

*The pivotal studies for Creon and Zenpep each had a cross-over design. Change in CFA was calculated as the mean difference in CFA between the PEP treatment and placebo treatment.
[#]The pivotal study for Pancreaze had a randomized withdrawal design; 20 patients received Pancreaze and 20 patients received placebo. Treatment difference between change in CFA in Pancreaze group and change in CFA in placebo group shown. Baseline CFA was not available because of the randomized withdrawal design.
[‡]mITT population used for primary efficacy analysis
[§]ITT population used for subgroup analyses (Baseline CFA<40% and Baseline CFA ≥40%)
[£]Overall results for Creon taken from the approved Creon label (modified Full Analysis Population; n=29). Subgroup results taken from the FDA Clinical Review for Creon dated April 30, 2009 (Full Analysis Population [n=31]; n=8 in Baseline CFA < 40% category, and n=23 in the Baseline CFA ≥ 40% category).

The dose used in the liprotamase pivotal trial (32,500 units/meal or snack) corresponds to a weight-based daily dose of 3,250 units/kg/day for a person weighing 50 kg (the median body weight in the study) and to weight-based daily doses of 2,770 and 4,330

units/kg/day for the 75th percentile (58.6 kg) and 25th percentile (37.5 kg) body weights in the study, respectively (see table below).

Table 5. Weight-based Daily Dose Corresponding to Body Weight Percentiles in Study Population – Liprotamase (Study 726)

Body Weight in Study Population		Liprotamase Weight-based Daily Dose
Percentile	Body Weight	
75th percentile	58.6 kg	2,770 units/kg/day
Median	50 kg	3,250 units/kg/day
25th percentile	37.5 kg	4,330 units/kg/day

This range of weight-based daily doses is lower than that the mean weight-based daily dose in the Zenpep and Pancreaze pivotal studies (5,700 units/kg/day and 6,400 units/kg/day, respectively); although it is difficult to compare the weight-based daily dose of liprotamase to the 4,000 units/gram of fat per day dose used in the Creon pivotal study, the latter is the maximum dose recommended by the CFF Consensus Conferences guidelines (see Clinical Review).

It is possible that the lower weight-based daily doses in Study 726 for liprotamase compared to those in the pivotal trials of porcine-derived PEPs may explain the numerically lower change in CFA compared to the change in CFA observed in the trials of porcine-derived PEPs (see Table 4). A higher dose of this product has not been studied in a controlled, clinical trial. The higher dose of the product evaluated in the dose ranging trial was not associated with a dose proportional increase in CFA; a four-fold higher dose than the dose studied in the pivotal trial resulted in a higher change in CFA (17% vs. 11%) in that study.

Study 767:

The height, weight, and BMI z-scores from the 12-month, open label, single arm trial are shown in the table below. Mean height, weight and BMI z-scores appeared to decline for the first two to three months, and then appeared to stabilize.

Table 6. Safety Population - Height, Weight and BMI Z-scores (Selected Visits) [Study 767]

Visit	Safety Population Z-score (Mean ± SD)		
	Height	Weight	BMI
Baseline, n=214	-0.490 (±0.989)	-0.607 (±1.031)	-0.493 (±0.994)
Week 8, n=192*	-0.526 (±0.987)	-0.753 (±1.048)	-0.649 (±0.991)
Mo 3 (Wk 12), n=176	-0.581 (±0.977)	-0.802 (±1.070)	-0.682 (±1.013)
Mo 6 (Wk 24), n=157	-0.617 (±0.980)	-0.868 (±1.071)	-0.733 (±1.031)
Mo 12 (Wk 52), n=145	-0.655 (±1.020)	-0.836 (±1.060)	-0.681 (±1.054)

n presented is for height and BMI; *the number of subjects with weight data was 193 at Week 8.
(Table above is modified from the Clinical Review; Source is Page 86 of the 767 Study Report.)

Subgrouping results by age (7 to 11 years, 12 to 16 years, and 17 years and older) suggested that mean height, weight, and BMI z-scores declined for the 7 to 11 years and 12 to 16 years patients but were stable for the 17 years and older patients (see Clinical

Review). BMI shift analysis by age subgroup suggested patients 7 to 11 years old had the greatest shift to worse BMI category compared to the other subgroups (see Clinical Review).

Efficacy Discussion:

The Applicant proposes that substantial evidence of efficacy comes from:

(a) Study TC-2A
(b) Study 726
(c) Study 767

"Substantial evidence" is defined in Section 505(d) of the Food, Drug, and Cosmetic Act as "evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof."

We question whether the Applicant has provided substantial evidence of efficacy.

There are four key issues to consider in determining whether this application provides substantial evidence of efficacy:

(i) clinical meaningfulness of the magnitude of change in CFA observed;
(ii) physico-chemical comparability of the product used in TC-2A versus 726;
(iii) contribution of Study 767 to the body of evidence for liprotamase; and
(iv) level of evidence for a single study.

Clinical Meaningfulness of the Magnitude of Change in CFA Observed: We question whether the observed magnitude of change in CFA is clinically meaningful. The magnitude appears lower than that observed in the trials for porcine-derived PEPs (see Table 4 above). In multiple pre-submission meetings with the sponsor, the Division stated that in the subgroup of patients with baseline CFA <40%, a ≥30% difference in CFA between liprotamase and placebo would be considered clinically meaningful.

Physico-chemical Comparability of the Product used in TC-2A versus 726: Study TC-2A cannot be considered a second adequate and well-controlled trial of liprotamase because the products used in the two trials are not physico-chemically comparable (see CMC Review included in this Briefing Document).

Contribution of Study 767 to the Body of Evidence for Liprotamase: Study 767 contributes to the safety data for liprotamase. Neither efficacy endpoints nor comparisons to an external control were prospectively defined in the protocol; however, the applicant performed numerous exploratory analyses of clinical outcomes, and provided discussion based on qualitative comparisons with external control data. We continue to explore this data.

Level of Evidence for a Single Study: We question whether the level of evidence requirements for a single study (Study 726) have been met as described in 21 CFR 314.126 and the Evidence of Effectiveness Guidance. The Guidance states, in general terms, that a single study would be acceptable for approval if it provides strength of evidence equal to two adequate and well-controlled trials. Key considerations (also described in the Guidance) include: (1) whether the observed outcome is statistically very persuasive; and (2) whether there is consistency across study subsets. The statistical reviewer determined that the observed outcome in Study 726 is statistically very persuasive. However, subgroup analyses suggest that the treatment difference is not consistent across subsets defined by age, country, and concomitant acid suppression therapy. (See Clinical review.)

In summary, we ask the Committee to consider the strength of evidence that liprotamase is effective given the efficacy data presented in light of the issues discussed above. If the Committee determines that the evidence supports approval of the product in the population studied, we seek the Committee's advice regarding whether the observed efficacy supports labeling in ages younger than age 7 years, who were not studied. (The body of evidence in the literature of the efficacy of porcine derived PEPs in children has been the basis of approval of porcine derived PEPs in pediatric age groups, without requiring pediatric clinical trial data for the to be marketed product.)

1.3.2 Safety

Exposure

The clinical trial safety database for liprotamase is considerably larger than that of the approved porcine-derived PEPs combined; the safety database of each PEP was generally limited to data from one short term trial of approximately 30 patients.

The total liprotamase safety database consists of:

- 433 patients with EPI due to CF,
- 39 patients with EPI due to CP or pancreatectomy, and
- 20 healthy subjects

Exposure by duration was as follows:

- 117 patients for 4 weeks (Study TC-2A)[4]
- 138 patients for 5.5 weeks (Study 726)
- 189 patients for 4 months, 163 patients for 6 months, and 149 patients for 1 year (Studies 767 and 810)[5]

[4]Of the 117 patients that received liprotamase for 4 weeks in Study TC-2A, 39 received the 6,500 U dose (TC-2A), 41 received the 32,500 U dose, and 37 received the 130,000 U dose (TC-2A)

[5]Mean number of capsules/day was 5.5 in Study 767 and 4.1 in Study 810; 29 of the 39 patients in Study 810 completed 3 months, and 4 completed 1 year.

It should be noted that the product used in TC-2A is not comparable to the product used in Study 726 and the long-term safety studies (Studies 767 and 810).

Safety Concerns

Safety concerns identified are:

- transaminase elevations (ALT and/or AST);
- distal intestinal obstruction syndrome (DIOS);
- potential for inadequate growth and malnutrition in pediatric patients, and
- risk of fibrosing colonpathy (FC).

Transaminase Elevations (ALT and/or AST)

There were no Hy's Law cases (i.e., no cases of three-fold or greater elevations above the ULN of ALT or AST accompanied with a two-fold or greater elevation of serum bilirubin) in any of the studies.

Short-Term Studies (726 and TC-2A):

Five-fold or greater elevations above the upper-limit of normal (ULN) of AST and/or ALT in Studies 726 and TC-2A are summarized in the table below.

Table 7. Elevations In Liver Enzymes ≥ 5 X ULN (ALT and/or AST) – 726 and TC-2A

Studies of Liprotamase					
	Study 726		Study TC-2A		
	Placebo	Liprotamase	Low	Mid	High
Number of patients	1	3	1*	2	4
Elevations	• 5.2 X ULN	• 5.7 X ULN • 7.8 X ULN • 9.9 X ULN	• 7.3 X ULN*	• 5.1 X ULN • 5.8 X ULN	• 6.0 X ULN • 6.0 X ULN • 9.5 X ULN • 14.9 X ULN

*Elevation at screening.

In Study 726, there was a numerically higher number of patients with elevations ≥ 5 X ULN in the liprotamase group than the placebo group; in Study TC-2A, there appeared to be a trend of a higher number of patients with elevations ≥ 5 X ULN with increasing dose. In Study 726, the magnitude of the transaminase elevations appeared to be higher in the treatment group compared to the placebo group; in Study TC-2A, there appeared to be a trend of a higher magnitude of transaminase elevations with increasing dose.

Long-term Safety Studies (767 and 810):

The proportion of subjects with Liver Function Test (LFT) elevations in the long term studies, 767 and 810, is shown in the table below. Approximately one-third of the patients in the long term studies had received prior treatment in the short-term trials.

Table 8. Proportion of Subjects with LFT Elevations Long Term Studies 767 and 810 (Safety Population): Maximum Value Observed

Range	Number of Patients [n (%)]			
	Baseline or screening	Maximum value on liprotamase treatment	Last value	Discontinued Treatment Due to Elevated LFT
AST and/or ALT	(N = 253)	(N = 245)*	(N = 245)*	(N = 253)‡
Normal	200 (79%)	105 (43%)	167 (68%)	0
> ULN to < 2.5*ULN	48 (19%)	106 (43%)	69 (28%)	3 (1%)
≥ 2.5*ULN to < 5*ULN	4 (2%)	27 (11%)	7 (3%)	1 (0%)
≥ 5*ULN to < 10*ULN	1 (0%)	7 (3%)	2 (1%)	0
≥ 10*ULN	0	0	0	0

Note: Summaries based on events exclusive of those occurring more than 14 days after discontinuation of treatment.
* Eight patients did not have any post-treatment laboratory values.
‡ Discontinued due to elevated transaminase.
(Table above modified from table found on page 3 of the Applicant's Response to Information Request received September 20, 2010.)

The proportion of patients in the 2.5-5 X ULN and 5-10 X ULN categories was numerically higher on treatment compared to at baseline/screening or last value.

Distal Intestinal Obstruction Syndrome (DIOS)

DIOS cases occurred in the liprotamase trials (6 patients total; occurring twice in one patient). In contrast, no cases of DIOS were observed in the clinical trials of the approved porcine-derived PEPs.

Distal Intestinal Obstruction Syndrome (DIOS) cases are summarized below

- Study 726 (1 patient):
  - (1) A case of DIOS (reported as an SAE) occurred during the no-treatment phase when the patient's usual PEP therapy was withdrawn.
- Study TC-2A (2 patients):
  - (1) A case of DIOS (reported as an SAE) occurred in a 24 year old male randomized to the low dose group three days after start of liprotamase.
  - (2) A case of DIOS (reported as an SAE) occurred in a 21 year old female randomized to the high dose group; she was diagnosed the first day of treatment (symptoms started before treatment in no-treatment phase); the patient's condition worsened during the study.
- Study 767 (3 patients):
  - (1) An 18 year old male developed symptoms consistent with DIOS (reported as an SAE) within one week after starting liprotamase in 767 (patient was

discontinued from the study); note this patient continued from TC-2A, and was diagnosed with 'bowel obstruction" (actually DIOS) in TC-2A two days after the patient's usual PEP therapy was withdrawn.

(2) DIOS was reported on Day 31 in a 21 year old male; the event was assessed as moderate in severity and the patient completed the study without recurrence of DIOS.

(3) DIOS was reported on Day 85 in a 13 year old male; the event was assessed as mild in severity and the patient completed the study without recurrence of DIOS.

It is difficult to determine if the greater number of DIOS cases observed in the liprotamase clinical trials than in the PEP clinical trials is due to lower efficacy of liprotamase than PEPs, or if this is due to a greater number of patients observed for a longer period of time in the liprotamase trials than in the PEP trials. The first case in Study TC-2A and the three cases in Study 767 appear related to liprotamase because of the timing of symptom onset relative to withdrawal from each patient's usual PEP and the start of liprotamase; in addition, the second case in Study TC-2A appears to be related to liprotamase because the patient's condition worsened during the course of the study.

Potential for Inadequate Growth and Malnutrition in Pediatric Patients:

If there is lower efficacy than porcine derived PEPs, there is the potential for inadequate growth and malnutrition in pediatric patients. Questions about the relative magnitude of changes in CFA between liprotamase and porcine derived PEPs can only be addressed through cross study comparisons at this time. The studies conducted in the liprotamase development program were not designed to make direct comparisons to porcine derived PEPs.

Fibrosing Colonopathy (FC):

Fibrosing colonopathy, a rare but serious condition that may result in colonic stricture, has been associated with prolonged high-dose PEP administration.[6] The risk of FC with liprotamase could be higher than with PEPs if the dose is excessively increased in response to lower efficacy. (PEP products are routinely titrated to optimize treatment effect.) In addition, theoretically, liprotamase might be associated with a higher potential risk for FC because its chemical features may render it more resistant to proteolytic activity, causing it to be persistently active in the colon.

There were no FC cases in the liprotamase studies; however, FC is rare and would not be expected to occur in a safety population of this size. It is impossible to determine if the FC risk is higher with liprotamase than with approved PEPs with the current safety database.

[6] FitzSimmons SC, Burkhart GA, Borowitz D, Grand RJ. High-Dose Pancreatic-Enzyme Supplements and Fibrosing Colonopathy in Children with Cystic Fibrosis. NEJM. 1997; 336(18): 1283-1289.

2 Points for Consideration by the Advisory Committee

- Does the New Drug Application (NDA) provide substantial evidence of efficacy for the treatment of patients with: (a) EPI due to CF (i.e., the population studied in Study 726)? (b) EPI due to other conditions (e.g., chronic pancreatitis, pancreatectomy)?

- Has a clinically meaningful difference in the primary endpoint (change in CFA) between the liprotamase and placebo groups been demonstrated?

- Are there additional efficacy studies that should be obtained prior to approving liprotamase for EPI? If so, please describe the design of the studies (e.g., placebo-controlled, active-control; dose-ranging), including selection of endpoints (e.g., change in CFA versus clinical outcome such as weight gain).

- Are the efficacy data adequate to support labeling the product at the time of marketing approval for use in children less than age 7 years?

- Are there safety concerns associated with the use of liprotamase in EPI (e.g., transaminase elevations, potential for inadequate growth and malnutrition in pediatric patients, distal intestinal obstruction syndrome, fibrosing colonpathy, other)? Please explain what risks you have considered.

- Are there additional safety data or studies that should be obtained prior to approving liprotamase for EPI? If so, please describe.

- Based on currently available data, do the potential benefits outweigh the potential risks of liprotamase for the treatment of patients with EPI (specify the particular subpopulation(s) defined by age, etiology of EPI, or other factors)?

1 Quality

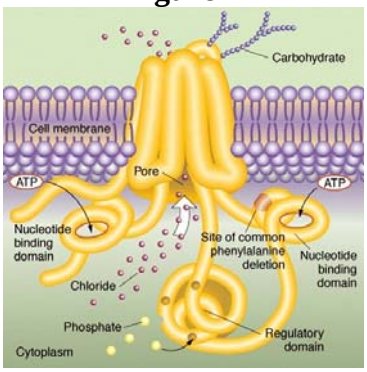
1.1 Introduction

Liprotamase is a mixture of three enzymes, lipase, amylase and protease, combined together with excipients in a solid dosage form. The mixture is designed to degrade proteins, complex carbohydrates and triglycerides in the digestive tract and function as replacement for pancreatic enzymes in patients with exocrine pancreatic insufficiency (EPI).

The pancreas produces and secretes digestive enzymes in the upper gastrointestinal (GI) tract. In the intestinal tract, the enzymes are in contact with food partially digested in the stomach and mixed with bile. The food components (lipids, proteins and carbohydrates) are further degraded into compounds that can be easily absorbed (monoglycerides, amino acids and simple sugars). In diseases such as cystic fibrosis (CF), chronic pancreatitis (CP) and pancreatic cancer, the exocrine function of the pancreas is compromised, resulting in severely impaired secretion of the digestive enzymes. Consequently, patients cannot digest and absorb food and experience weight loss and malnutrition, accompanied by a series of GI tract disturbances that include pain, steatorrhea, diarrhea and abdominal distension.

The most severely affected population is the CF population. CF is a genetically inherited disease caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene, which encodes for a protein that forms an ion channel that transports chloride across epithelial cell membranes. The putative structure of the CFTR protein is depicted in Figure 1. The most common mutation is deletion of phenylalanine 508 (identified in Figure 1), while other mutations occur only sporadically.

Figure 1



In CF patients, the pancreatic function may be compromised at birth, leading to failure to thrive, very low growth rates and death in the early teenage years, due both to the inability to absorb food and to the additional complications that result from the inactivation of the CFTR protein in the epithelium of various other organs. The lungs are particularly severely affected.

The main treatment for pancreatic insufficiency consists of administration of extracts of porcine pancreas (pancreatic enzyme products; PEPs). The enzymes contained in the pancreatic extract replace the enzymes no longer produced by the diseased human pancreas. This replacement therapy was established in the early 20th century, well before the enactment of the Federal Food, Drug and Cosmetic Act. Therefore, PEPs were marketed without regulatory oversight. Due to inconsistencies in manufacturing and formulation strategies, the potency of the early PEP products declined over the shelf-life. Thus, to compensate for the loss of potency, manufacturers were filling the product above the label claim, resulting in patients being exposed to higher than expected doses of lipase. In response to concerns about potency and adverse events such as fibrosing colonopathy, FDA requested that PEPs be submitted under NDA, in order to ensure that high quality, consistent products would be marketed.

2 Comparison of critical quality attributes of liprotamase and PEPs linked to the safety and efficacy profile

The pancreatic enzymes are derived from porcine pancreatic glands, and there are risks associated with the use of PEPs, which mainly relate to contamination of the source material with animal pathogens (bacteria and viruses). While porcine viruses that can infect humans are monitored in PEPs and PEP preparations testing positive for the presence of such viruses cannot be marketed, FDA was concerned with the possibility that porcine viruses might mutate and become able to infect humans. Albeit theoretical, patients and health care providers have been made aware of the risk via information provided in the package insert and medication guide.

In contrast to the porcine derived PEPs, the enzymes in liprotamase are produced via microbial fermentation and are purified through a series of purification steps. Liprotamase is manufactured in bacteria and fungi, organisms that do not permit replication of animal viruses. In addition, the manufacturing process allows control over raw materials. Consequently, there is a negligible risk of contamination of liprotamase with viruses that can infect humans.

While the porcine derived PEPs contain multiple enzyme classes, including lipases, amylases and proteases, each of which may contain multiple enzymes with the same catalytic activity, liprotamase only contains one enzyme for each class. The bacterial lipase does not have a requirement for colipase for maximal activity, as is the case for triacylglycerol lipase in the PEPs. The enzymes are purified and lipase was formulated at higher activity compared to PEPs. The sponsor proposes that this offers the advantage that patients may need a lower number of capsules per meal or snack compared to PEPs.

The complex nature of pancreatic enzymes is due to the fact that the crude extracts represent the typical enzyme output provided by the pancreas. As such, multiple enzymes in each major class (i.e., phospholipases for the lipase class and chymotrypsin, trypsin and carboxypeptidases for the protease class) function in digesting the components present in food. Therefore, it is biologically plausible that porcine derived PEPs might allow for a more efficient digestion of food in the intestine.

3 Liprotamase drug product

Specific amounts of each of the three purified enzymes are blended with inactive excipients and filled into hard gelatin capsules. Each 200 mg liprotamase capsule contains 48,960 Units of lipase (measured using the tributyrin substrate and defined as TBU), 25,000 Units of protease and 3,750 Units of amylase. The sponsor maintains that the 48,960 TBU are equivalent to 32,500 USP Units of lipase (measured using olive oil as enzyme substrate), but has not provided data to support this claim. Except for the difference in substrate, the tributyrin assay and the USP/olive oil assay are similar. The recommended dose of liprotamase is one capsule per each meal or snack consumed.

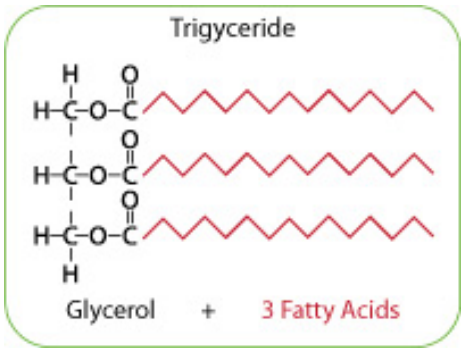
4 Description of the enzymes in liprotamase

4.1 Lipase

Lipase is of bacterial origin and is produced by recombinant DNA technology. The enzyme is secreted in the culture medium, and the production process provides for purification and crystallization of the purified enzyme. After crystallization, the lipase crystals are chemically and covalently cross-linked. In vitro studies suggest that this modification increases stability of the lipase (i.e., protection from proteolysis), and that the cross-linked enzyme is insoluble at acidic pH representative of the stomach and soluble at neutral pH representative of the duodenum.

Lipase is a 30 kDa bacterial protein with a broad pH range of activity, which is optimal at pH 8. The enzyme catalyzes the hydrolysis of triglycerides in fatty acids (as illustrated in Figure 2 below), glycerol and mono and diglycerides at the interface of an emulsified substrate. In contrast to the porcine triglycerol lipase, which requires colipase for maximal activity, the bacterial lipase does not require colipase for activity.

Figure 2: Structure of the lipase substrate

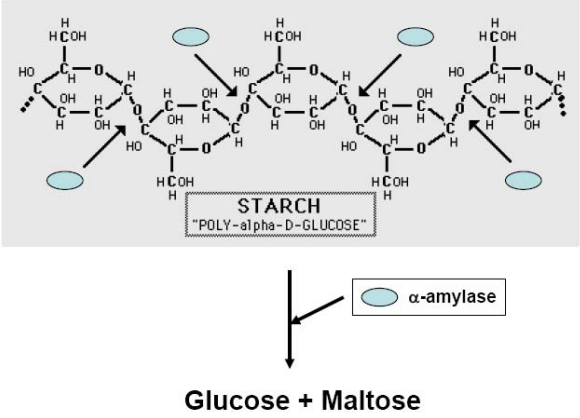


4.2 Amylase

The α-amylase is a non-recombinant, fungal amylase, produced by fermentation and secreted in the culture medium, from which it is extracted and purified. The purified enzyme is dried into an amorphous powder.

α-amylase is a globular glycoprotein with a molecular weight of about 54 kDa. α-amylase has optimal activity at pH 5. The enzyme is a glucanohydrolase and catalyzes the hydrolysis of glucosidic linkages of starch, glycogen and related polysaccharides to produce monosaccharides (as exemplified in Figure 3 below).

Figure 3: α-amylase substrate and reaction products



4.3 Protease

Protease is a non-recombinant, semi-alkaline fungal protease, produced by fermentation and secreted in the culture medium from which it is extracted and purified. The purified enzyme is crystallized and dried into a powder, to prevent auto-proteolysis and increase stability.

Protease hydrolyzes peptide bonds nonspecifically into constituent amino acids. The enzyme has a molecular weight of about 28 kDa and optimal activity at pH 8.0.

4.4 Summary of manufacturing development

The sponsor has introduced a number of manufacturing changes during clinical development, mostly between Phase 1/2 and Phase 3, and between Phase 3 and commercial manufacture. The latter consisted of changes in facility and scale-up. The Phase 1/2 product and the Phase 3 product are not physico-chemically comparable; therefore, clinical efficacy and safety results observed with these products cannot be directly compared. However, the limited differences observed between the Phase 3 product and the to-be-marketed product (TBMP) are unlikely to have an impact on clinical safety and efficacy.

1 Nonclinical Background

Liprotamase was evaluated in a comprehensive program of nonclinical studies which included pharmacology studies, ADME studies, acute toxicology studies, repeated-dose toxicology studies ranging in duration from 2 weeks to 6 months in rats and 9 months in dogs, and evaluation of reproductive effects in rats (Segment I, II and III) and rabbits (Segment II). In addition, a complete battery of genotoxicity studies was also conducted with liprotamase and with individual enzymes.

Liprotamase was tested in the dog and minipig models of exocrine pancreatic insufficiency (EPI). In the EPI dog study, liprotamase restored co-efficient of fat absorption (CFA) up to 78-87% of pre-operative values. Liprotamase restored co-efficient of nitrogen absorption (CNA) up to 44-64% of pre-operative values. There was an apparent lack of dose response for both CFA and CNA. Liprotamase caused reduction in stool weight, stool number and stool index when compared to pre-operative values; however, it did not fully restore the pre-operative values for these parameters. In the EPI minipig, liprotamase increased body weight by approximately 1 kg (9.4% increase) when compared to basal level. Liprotamase also caused significant reduction (about 62%) in mean stool weight when compared to pre-operative values. In addition, liprotamase significantly improved fat and protein absorption. Moreover, liprotamase significantly improved postprandial lipid absorption, as demonstrated by increased lipemic index, increased non-esterified fatty acid (NEFA) concentration in the blood and increased triglyceride (TG) concentration in the blood. In addition, liprotamase stimulated epithelial growth in the small intestine with improved morphology and thickness of intestinal villi. Overall, liprotamase showed significant efficacy in the dog and minipig models of EPI, however, it was more efficacious in the EPI minipig than in the EPI dog.

Conventional pharmacokinetic (PK) studies were not conducted with liprotamase since it consists of a combination of digestive enzymes (lipase, protease and amylase). A tissue biodistribution study was conducted in rats using radiolabeled Lipase-CLEC which had been crosslinked with ^{14}C-BS^{3} (a cross-linking agent). A fraction of the ^{14}C dose administered as [^{14}C]TheraCLEC-Lipase was absorbed following oral administration in rats. Tmax for radioactivity ranged from 2 to 3 hours. The highest amount of radioactivity was found in the tissues and contents of the gastrointestinal tract (GIT), followed by adipose tissue, skeletal muscle, kidney, liver and skin. Over 70% of the radiolabel dose was recovered in the feces, with approximately 15% found in the urine, through 168 hours post-dose. At 168 hours post-dose, carcasses contained less than 1% of the radiolabel dose, suggesting that little of the radiolabel was retained in the body one week after dosing. Overall, following oral administration of radiolabeled Lipase, radioactivity was found in several tissues and organs. The highest concentration of radioactivity was found in the GIT and its contents, indicating limited absorption. Minimal radioactivity was found in the blood. However, it is not known whether this radioactivity in the blood is due to intact enzyme. Radioactivity was primarily excreted through the feces.

In a 30-day toxicology study in rats, animals were administered liprotamase at daily doses of (lipase:amylase:protease) (20,000:3,000:20,000), (80,000:12,000:80,000) and 200,000: 30,000:200,000 USP U/kg). Aspartate aminotransferase (AST) was increased by 20%, 16% and 11% at the low-, mid-, and high-dose males, respectively. Alanine aminotransferase (ALT) was increased by 10%, 21% and 7% at the low-, mid-, and high-dose males, respectively. Alkaline phosphatase (ALP) was increased by 23% and 31% in the intermediate- and high-dose males, respectively. These changes were not typically dose-related and were not seen in females. In addition, there were no histopathological findings in the liver. There was a treatment-related increase in lactate dehydrogenase (LDH) in males; however, this increase in LDH was also not dose-related. In males, creatine kinase (CK) was increased by 2.6, 1.2 and 1.3-fold (not dose-related), at low, mid and high dose, respectively, over the control. Overall, serum chemistry changes were generally not dose-related, only seen in males, and did not have a histopathological correlate. In addition, these serum chemistry changes were not seen in the 6-month chronic toxicology study in rats. Thus, the serum chemistry changes in rats did not appear to be toxicologically meaningful. Minimal to slight submucosal edema was observed in the cecum of 2 of 20 males at high-dose. However, this finding was not seen in the 6-month chronic toxicology study in rats. Similar submucosal edema in the stomach was also observed in control animals. Relation to the treatment and the toxicological significance of this finding is not clear. In a 6-month oral toxicology study in rats at 150, 450 and 1500 mg/kg/day, no significant treatment-related organ toxicities or histopathological changes were observed.

In a 90-day oral (capsule) toxicity study in Beagle dogs, animals were administered liprotamase at total daily doses of lipase: protease:amylase at (5,000/5,000/750; 20,000/20,000/3,000 and 50,000/50,000/7,500 USP U/kg/day). Small testicle was noted in one high dose animal. At the interim sacrifice on Day 30, small size in both testes was observed in the intermediate- and high-dose groups (1 of 2 males in both groups). A relationship to the treatment may not be ruled out in the absence of this finding in the control animals. However, this effect was not seen in the 9-month chronic toxicology study in dogs. In a 9-month oral toxicology study in Beagle dogs at 176, 527 and 1582 mg/kg/day, no significant treatment-related organ toxicity was observed at any of the tested doses.

Liprotamase was negative in a battery of genotoxicity assays.

In an oral Segment I fertility and early embryonic development study in male rats, animals were treated with liprotamase at 150, 450 and 1500 mg/kg/day. Histopathological changes were seen in the testes (1 of 22, 1 of 22 and 2 of 22 animals had slight/mild Sertoli cell only tubules at low, mid and high dose, respectively; and 1 of 22 animals at the high dose had intratubular cellular debris) and epididymides (1 of 22 and 2 of 22 animals at mid and high dose, respectively, had cellular debris in the tubular lumen) predominantly at the mid and the high dose. A relationship to the treatment may not be ruled out in the absence of this finding in the control animals. In an oral Segment II teratology study in rats, animals were tested at 150, 450 and 1500 mg/kg/day. Umbilical hernias were noted at 1500 mg/kg/day (about 35 to 94 times the recommended

maximum human dose based on the body surface area) in two fetuses from two litters, one of which also had an overriding aorta, interrupted aortic arch, pulmonary trunk atresia and an absent pulmonic valve. These external malformations were not observed at 450 mg/kg or lower doses. These findings at the high dose were considered treatment-related. In a Segment II teratology study in rabbits, animals were treated at 75, 225 and 750 mg/kg/day. No treatment-related effects were observed in rabbits at the tested doses.

1 Summary of Clinical Pharmacology and Biopharmaceutics Findings

1.1 Negligible Systemic Absorption

Pharmacokinetics (PK) was assessed in the Phase 2 study TC-2A. In all three treatment groups, samples were taken on Day 1 (pre-dose), Day 15 (0, 15 and 30 minutes, 1, 1.5, 2, and 3 hours after dosing), and Day 16 (prior to administration of the first capsule). Serum levels of lipase-CLEC, protease and amylase were determined by ELISAs, which are expected to detect not only intact enzymes, but also their breakdown products due to the use of polyclonal antisera. The claimed lower limit of quantitation of assays for lipase, protease and amylase, are 15 pg/mL, 100 ng/mL, and 15 pg/mL, respectively.

However, the ELISAs were not adequately validated. Reproducible, quantitative recovery of lipase-CLEC, protease and amylase spiked into normal human serum could not be demonstrated in this study. For each enzyme, the coefficient of variance (CV) of analytical recovery exceeded the targeted CV of <=20%. Moreover, in terms of inter- and intra-assay accuracy and precision, the LLOQ QC samples (15pg/ml) and low QC samples (20pg/ml) for both lipase and amylase had either the bias or the CV greater than 25%.

With these caveats, baseline values for amylase and lipase varied greatly among subjects (from <15 pg/ml to over 1,000 pg/ml) and all baseline values for the protease were < 100 ng/mL. While on treatment, the ELISA absorbance values of lipase-CLEC and protease in majority of the patients were below LLOQ and thereby no PK profile could be characterized for these two enzymes. Although the concentration of amylase was quantifiable in majority of the patients, no PK profile could be characterized because many of these patients had high baseline amylase concentration.

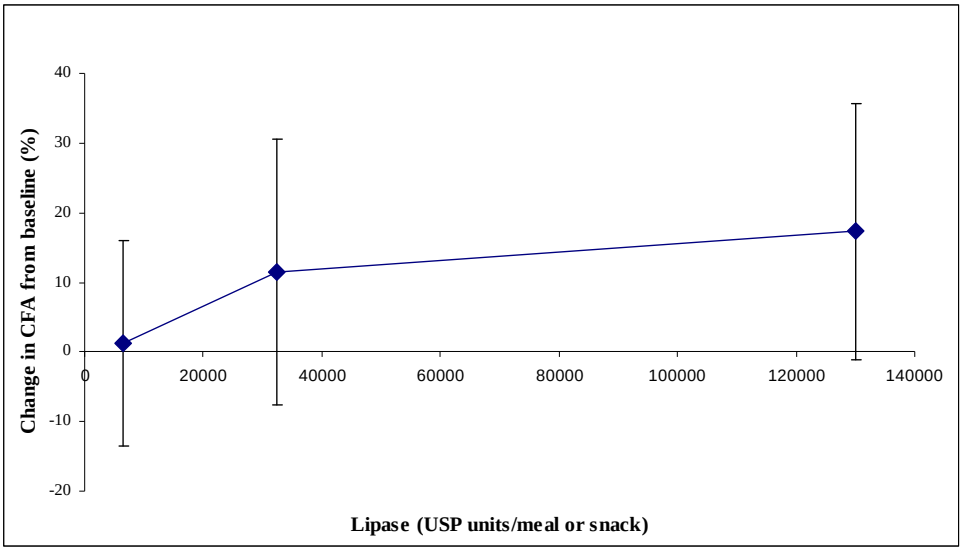
1.2 Dose-response

The dose tested in Phase 3 studies was mainly based on results of the Phase 2, dose ranging study[1]. In this Phase 2 study (Study TC-2A), three dose levels (liprotamase/protease/amylase USP units/meal or snack): 6,500/5,000/750, 32,500/25,000/3,750 and 130,000/100,000/15,000 were tested in cystic fibrosis patients. The value of primary endpoint, change in mean coefficient of fat absorption (CFA) from baseline, was 1.2%, 11.4% and 17.3% for low, mid, and high-dose treatment arms, respectively. Change in mean CFA from baseline increased from 1.2% to 11.4% when the dose of lipase was increased from 6,500 to 32,500 units. There was no corresponding increase in change in mean CFA from baseline when the dose of lipase was increased from 32,500 to 130,000 units; change in mean CFA from baseline increased about 6% when lipase dose was increased four-fold (See Figure 1). In addition, there was a suggestive dose-response relationship for number of patients who had elevated liver function test in this study; the number of patients who had elevated liver function test (>5X upper limit of normal) was 1, 2 and 4 for low, mid, and high-dose treatment arms.

[1] The Phase 1/2 product and the Phase 3 product are not physico-chemically comparable; therefore, clinical efficacy and safety results observed with these products cannot be directly compared.

The sponsor selected the mid-dose 32,500/25,000/3,750 (liprotamase/protease/amylase USP units/meal or snack) for their phase 3 studies.

Figure 1: Change in CFA from baseline (Mean ± S.D.) in Study TC-2A



1.3 Water Stability and Food Compatibility

Water stability and food compatibility of TBMP liprotamase[2] was assessed because the sponsor proposed to administer liprotamase to patients that cannot swallow a full capsule, or do not need a full capsule.

After 15 minutes of contact with water (c.a. pH 6.5), apple juice (pH 2.9-3.3), apple sauce (pH 3.5-4.0) and yogurt (pH 4.0-4.1), the activity of lipase, protease and amylase remained unchanged and ranged from 95 to 108%, from 94 to 102%, from 93 to 105% of the control, respectively. Moreover, while the activities of protease and amylase remained unchanged over 2 hour period in all matrices tested, the activity of lipase-CLEC remained unchanged over 2 hours in apple juice but showed a progressive decrease to 50-70% of activity over 2 hours in water, apple sauce and yogurt.

FDA has requested the applicant to provide validation of assays used in the water stability and food compatibility studies to determine lipase, protease and amylase activities. The response is still pending.

[2] The limited differences observed between the Phase 3 product and the TBMP liprotamase are unlikely to have an impact on clinical safety and efficacy.

CLINICAL REVIEW

TABLE OF CONTENTS

1 Introduction and Regulatory Background

1.1 Product Information

Liprotamase is the investigational agent studied in this application; if approved, it would be the first biotechnology product for treatment of exocrine pancreatic insufficiency. Liprotamase contains only microbially derived enzymes, more specifically:

- crystallized, cross-linked lipase
- crystallized protease and
- amorphous amylase

Each enzyme is manufactured separately. Liprotamase is comprised of three purified digestive enzymes obtained from microbial fermentation: a lipase, a protease, and an amylase. The lipase is crystallized and cross-linked (Lipase-CLEC) to increase stability against acid hydrolysis and proteolysis. The protease is crystallized to prevent proteolysis. The amylase component is a fermentation product.

Liprotamase is available in one capsule strength containing a purified preparation of 48,690 tributyrin units (TBU) crystallized cross-linked lipase, 25,000 U USP crystallized protease, and 3,750 U USP amorphous amylase.

Currently, the indication proposed for liprotamase by Alnara Pharmaceuticals is:

> "… for the treatment of patients with exocrine pancreatic insufficiency (EPI) due to cystic fibrosis, chronic pancreatitis, pancreatectomy, or other conditions."

The Applicant has proposed recommendations for starting and maximum doses (based on lipase activity) in age-specific categories (see table below). Lipase activity for liprotamase is labeled in tributyrin units (TBU); as per the Applicant, 48,690 TBU is the equivalent of 32,500 USP lipase units (i.e., 1.5 TBU corresponds to 1 USP lipase unit). However, the Applicant has not provided data to support this conversion (see CMC section). Throughout the remainder of the document, lipase will be referred to as USP units based on this conversion.

Table 1. Proposed Dosing Recommendations for Liprotamase

Age	Starting Lipase Dose / Meal or Snack[†]	Maximum Lipase Dose / Day	
Up to 12 months	~10,000 TBU*[,†,£]	---[#]	
1 to 3 years	~25,000 TBU*[,£]	243,450 TBU[‡]/day	15,000 TBU/kg/day or 6,000 TBU/gram of fat
4 to 6 years	~35,000 TBU*[,£]	340,830 TBU[‡]/day	
7 to 11 years	48,690 TBU[‡]	438,210 TBU[‡]/day	
12 years and older	48,690 TBU[‡]	535,590 TBU[‡]/day	

*Contents of one capsule (48,690 TBU) mixed with 5 mL water into a suspension; 1 mL of suspension will contain approximately 10,000 TBU
[†]For infants, 1 mL of the suspension mixed with 10,000 TBU per 120 mL of formula or per breast feeding
[£]Liprotamase-water suspension can be swallowed directly or mixed in specific soft acidic foods
[#]Maximum lipase dose for infants not stated in proposed label
[‡]1 capsule=48,690 TBU; 5 capsules=243,450 TBU; 7 capsules=340,830 TBU; 9 capsules=438,210 TBU ; 11 capsules= 535,590 TBU
(Table above summarized from the Applicant's proposed label for liprotamase.)

1.2 Treatments for Proposed Indications

Currently, there are three approved pancreatic enzyme products or PEPs (all of porcine origin) being used in the US to treat EPI in adults and children, including neonates. PEPs were first marketed in the US in the 1920's prior to the Food Drug and Cosmetic Act of 1938 (the Act). The PEPs are widely available in the US and throughout the world as nutritional supplements, and as over-the-counter (OTC) and prescription therapies; however, in the US, PEPs were never evaluated for safety and efficacy under NDA until recently when the FDA required that all PEPs be marketed under an approved NDA by April 28, 2010. (Cotazym was approved in 1996, but is not currently marketed.) On April 30, 2009, Creon (pancrelipase) was approved for the treatment of EPI due to CF or other conditions; on April 30, 2010, an efficacy supplement for Creon was approved so that the current indication for Creon is for the treatment of EPI due to CF, chronic pancreatitis, pancreatectomy, or other conditions. In addition, Zenpep (pancrelipase) was approved for the treatment of EPI due to CF or other conditions on August 27, 2009, and Pancreaze (pancrelipase) was approved for the treatment of EPI due to CF or other conditions on April 12, 2010.

1.3 Availability of Proposed Active Ingredient in the United States

Liprotamase is not currently marketed in the United States for any indication.

1.4 Important Safety Issues with Consideration to Related Drugs

The most serious safety concern with PEP administration has been fibrosing colonopathy (submucosal fibrosis). Fibrosing colonopathy (FC) is a condition that has been reported mainly in young children with CF who are being administered delayed-release PEP formulations. Although the exact etiology of FC is not known, studies have shown that the majority of the patients in whom FC developed were taking high dose PEPs.[1] As a result of these potential efficacy and safety concerns, the Cystic Fibrosis Foundation (CFF) and FDA published weight-based dosing guidelines for PEP administration as following:

[1] FitzSimmons, SC, Burkhart, GA, Borowitz, D et al. High Dose Pancreatic-Enzyme Supplements and Fibrosing Colonopathy in Cystic Fibrosis. New England Journal of Medicine. May 1997; 336 Number 18; 1283-9.

"Dosing should not exceed the recommended maximum dosage set forth by the Cystic Fibrosis Foundation Consensus Conferences Guidelines:

- Begin with 500 lipase units/kg of body weight per meal to a maximum of 2,500 lipase units/kg of body weight per meal (or less than or equal to 10,000 lipase units/kg of body weight per day), or less than 4,000 lipase units/g fat ingested per day.
- Individualize dosage based on clinical symptoms, the degree of steatorrhea present and the fat content of the diet."

See also Appendix 1.

Of note, the above dosing guidelines are given in USP lipase units as all of the currently approved PEPs are dosed in USP lipase units. Liprotamase uses TBU as a measurement for lipase activity.

Thus, monitoring for FC should be addressed in any future labeling, and should be a component of ongoing safety assessment for all pancreatic enzyme products, as should the CFF/FDA weight-based dosing guidelines.

Hyperuricemia and hyperuricosuria have been reported in patients with EPI treated with porcine derived PEPs. Caution should be exercised when prescribing porcine derived PEPS to patients with gout, renal impairment, or hyperuricemia as they contain purines that may increase blood uric acid levels. Since liprotamase is a biotechnology product and contains only microbially derived purified enzymes (lipase, protease and amylase), hyperuricemia and hyperuricosuria should not theoretically be a safety concern.

1.5 Summary of Pre-submission Regulatory Activity Related to Submission

This is the initial NDA submission for liprotamase.

In multiple pre-submission meetings, the Division has stated that in the subgroup of patients with baseline coefficient of fat absorption (CFA) <40%, a ≥30% difference between the liprotamase and placebo groups would be considered clinically meaningful.

Relevant clinical pre-submission regulatory activity for liprotamase includes the following:

Table 2. Relevant Clinical Pre-submission Regulatory Background

Date	Action
Aug 2003	End of Phase 1 Meeting: ➢ The Division established that CFA is acceptable as a primary endpoint. ➢ For a Phase 2 study, DGP stated that an intra-subject or inter-treatment difference of "≥10% for CFA would be acceptable as long as the baseline fat malabsorption is not severe". ➢ The Division recommended a minimum drug exposure of 200 patients for six months and 100 patients for one year.
Aug 2004	Teleconference with Applicant: ➢ The Division clarified that the Draft Guidance for Industry: Exocrine Pancreatic

	Insufficiency Drug Products which was published (PEP Guidance) only applied to currently marketed PEPs *of animal origin.*
Sept 2005	End of Phase 2 Meeting: ➢ A dose-dependent effect in CFA was demonstrated by the limited information which was provided. ➢ There was a potential concern regarding abnormal transaminase levels. ➢ The Division recommended including both pediatric and adult patients in the clinical trials.
Oct 2005	Phase 3 Study Design Meeting: ➢ There was an agreement reached on the randomized, withdrawal study design and the primary endpoint of "change in CFA from baseline between treated and placebo patients". ➢ The Division stated: ▪ An "increase of ≥ 10% in mean CFA is not sufficient to provide clinically meaningful improvement in fat malabsorption." ▪ "In those patients who have a low CFA baseline, an increase of 30% in mean CFA would be considered clinically meaningful." ▪ "A lesser mean change may be acceptable in those patients whose baseline CFA indicates less severe fat malabsorption." ▪ "In general, two adequate and well controlled studies are required to support an indication for the intended population; however, a single study may be acceptable if the evidence presented is highly persuasive statistically."
July 2006	Clinical SPA Submitted: ➢ The Division's response reiterated that: ▪ "An increase of 10% in mean coefficient of fat absorption (CFA) over placebo group is not sufficient to provide a clinically meaningful improvement in fat malabsorption, particularly in those with severe fat malabsorption at baseline." ➢ The Division stated: "In general, two adequate and well controlled studies are required to support an indication for the intended population, however, a single study may be acceptable if the evidence presented is highly persuasive statistically and clinically meaningful."
Oct 2006	Teleconference with Applicant: ➢ The Applicant asked whether the Phase 2 statistical proposal for defining "clinical benefit" is acceptable for approval of an NDA for liprotamase. The Applicant's proposal defined a "meaningful benefit [as …] an increase of 30% in mean change in CFA over placebo in patients with baseline CFA of ≤40% and an increase of 10% in mean change in CFA over placebo for the overall population." ➢ The Division reiterated: "An increase of 10% in mean coefficient of fat absorption (CFA) over placebo group is not sufficient to provide a clinically meaningful improvement in fat absorption, particularly in those with severe fat malabsorption at baseline. As previously noted, the Division considers an increase of 30% in mean CFA as clinically meaningful." ➢ The Division encouraged the Applicant to conduct studies with larger representation of more severely affected patients (patients with a baseline CFA of ≤40%).
Feb 2007	Phase 3 clinical protocol meeting: ➢ The Division was "unwilling to stipulate to a mean increase in %CFA of 10% over

	placebo for the overall study population as being sufficient to provide evidence of a clinically meaningful benefit of treatment." ➢ The Division stated that the totality of the data from this clinical study would need to be considered in addition to the change in %CFA to assess the efficacy results in the overall study population.
Nov 2008	Pre NDA Meeting: ➢ The discussion included the content and formatting of the proposed NDA submission.
March 2010	The NDA was submitted.

(The table above was compiled by this reviewer using Meeting Minutes and SPA Responses from the Document Archiving, Reporting & Regulatory Tracking System [DARRTS].)

1.6 Other Relevant Background Information

PEPs are currently used by adult patients as well as pediatric patients for the treatment of EPI due to a variety of causes. To date, there are three PEPs approved for the treatment of EPI due to CF or other conditions (Creon, Zenpep and Pancreaze), all of which are enteric-coated. There is a substantial body of literature to support dosing, safety and efficacy of the enteric-coated PEPs in adult and pediatric patients with EPI due to CF or other conditions.[2]

2 Sources of Clinical Data

2.1 Table of Clinical Studies Relevant for Efficacy

There were two controlled studies included in the liprotamase clinical development program which are reviewed in this briefing document. See table below. It should be noted that the product used in the Phase 2 study (TC-2A) was not physico-chemically comparable to the product used in the Phase 3 study (726). Therefore, clinical efficacy and safety results observed with these products cannot be directly compared. (See CMC Review.)

[2] Domínguez-Muñoz JE. Pancreatic enzyme therapy for pancreatic exocrine insufficiency. *Curr Gastroenterol Rep.* 2007;9(2):116-22.

Table 3. Clinical Studies Relevant for Efficacy

Study	Study Design	Total N Gender M:F	Age Mean Range (years)	N per Treatment Group; Population	Liprotamase Dose USP U/Meal (Lipase/Protease/Amylase)	Duration of Treatment
726 (Phase 3 trial)	MC, R, DB, PC, W	ITT: 138 85:53	18 (7-44)	Liprotamase: 70 Placebo: 68	32,500/25,000/3,750	44-54 days
TC-2A (Phase 2 trial)	MC, R, DB, P, DR, concurrent dose-controlled	ITT: 125 76:49 mITT: 117 71:46	ITT: 21 (11-55) mITT: 22 (12-55)	ITT: Arm 1: 41 Arm 2: 43 Arm 3: 41 mITT: Arm 1: 39 Arm 2: 41 Arm 3: 37	A1: 6,500/5,000/750 A2: 32,500/25,000/3,750 A3: 130,000/100,000/15,000	28 days

R-randomized
DB-double blind
PC-placebo controlled
MC-multi-center
P-parallel
DR-dose ranging

3 Review of Efficacy

Efficacy Summary

3.1 Indication

In the "Indications and Usage" section, the Applicant proposed the underlined wording below:

SOLPURA (liprotamase) is an orally administered biotechnology product containing a purified preparation of crystallized cross-linked lipase, crystallized protease, and amorphous amylase indicated for the treatment of patients with exocrine pancreatic insufficiency due to cystic fibrosis, chronic pancreatitis, pancreatectomy, or other conditions.

3.1.1 Methods

The clinical data from two studies (Pivotal trial 726 and Dose ranging trial TC-2A) were analyzed to determine whether a clinically meaningful therapeutic effect was seen for patients with EPI secondary to CF who received treatment with liprotamase versus placebo (or low dose liprotamase).

3.1.2 Efficacy Results by Study

Study 726

General Design

Study 726 was a multi-center, randomized, double-blind, placebo-controlled, parallel study in 138 patients with CF and EPI, ages greater than or equal to 7.

The primary efficacy endpoint was the change in coefficient of fat absorption (CFA) in the subgroup of patients with baseline CFA <40%. The CFA during the Double-Blind treatment period was compared to the CFA during the Baseline period for patients treated with liprotamase versus placebo.

CFA is a measure of fat absorption defined as:

$$\text{CFA} = \frac{\text{Dietary Fat Ingested} - \text{Fat Excreted in Stool}}{\text{Dietary Fat Ingested}} \times 100\%$$

There were several secondary efficacy endpoints, including Coefficient of Nitrogen Absorption (CNA), Blood Glucose Response/Starch Challenge Test and Stool Weight and Frequency. These endpoints are defined as follows:

1. *CNA*$= \frac{\text{Dietary Nitrogen Ingested} - \text{Nitrogen Excreted in Stool}}{\text{Dietary Nitrogen Ingested}} \times 100\%$

2. *Blood Glucose Response / Starch Challenge Test:* The proportion of patients who had a maximum increase in blood glucose of ≥10 mg/dL in the Starch Challenge Test (SCT) during the Double-Blind Treatment Period was compared between the two treatment groups. Diabetic patients were excluded from the SCT.

For the SCT, patients consumed a diet consisting of at least 150 g per day of carbohydrate for 3 days and fasted overnight for at least 8 hours. On Days Baseline Day 2 (B2) and Double Blind Day 2 (DB2), patients underwent the SCT. Patients rested for 30 minutes before the test began and activity was required to be limited during the evaluation. In place of breakfast, patients ingested a standard test meal of white flour bread comprising 50 g of carbohydrate. On the Day B2 test, no study drug was taken; on Day DB2, blinded study drug was taken in the middle of the test meal. A blood sample of approximately 1 – 2 mL was taken before the test meal and then at the following times: immediately after consuming the test meal, 15, 30, 45, 60, 75, 90, 105, and 120 minutes, and 2.5 and 3 hours after consuming the test meal.

At the time of this study, there were no accepted or validated tests that directly measured starch digestion and absorption for assessing the activity of the amylase component of liprotamase. Previous Phase 1 and 2 studies explored this endpoint as a potential measure of amylase activity; however, no correlation was found with dose and amylase activity.

3. *Stool Weight and Frequency:*
The secondary efficacy variables of stool weight and frequency were difficult to analyze accurately given the nature of the underlying disease and the lack of validated endpoint

measures. In the review of similar endpoints for porcine derived PEPs, the results have repeatedly shown no clinically definable change that was considered clinically meaningful.

Study 726 included the following periods as represented by the table below.

Table 4. Pertinent Features of Study Design (Study 726)

Period	Treatment
Screening Period	Usual PEP
Inpatient off-enzyme Baseline Period (6-7 days)*	None
Open-Label Treatment Period (21 days)	Liprotamase
Inpatient, Double-Blind Treatment Period (6-7 days)*	Liprotamase or Placebo[#]
Second Open-Label Treatment Period (7 days)	Liprotamase
Follow-up Period (14 days)	Usual PEP[†]

*Stool collection for CFA and CNA

[#] Patients were withdrawn from liprotamase treatment and randomized (1:1) to liprotamase or placebo

[†]After the last dose of liprotamase, the usual PEP was resumed (unless rolled over into Study 767)

Key Eligibility Criteria

Patients included in the study had to be 7 years or older with a confirmed diagnosis of CF and EPI and have a baseline CFA ≤ 80%. Patients were excluded if they had: a history of fibrosing colonopathy, any acute illness, a history of solid organ transplant or significant bowel resection, or known hypersensitivity to food additives.

Diet and Dosing Regimen

During the inpatient stays, patients were placed on a 72-hour controlled, 100 g/day high-fat diet; during the open-label phases, patients took one capsule of liprotamase with each of three meals and two snacks per day. Liprotamase is a fixed combination of: Lipase-CLEC (32,500 USP Units Lipase-CLEC), 25,000 Units USP of protease and 3,750 Units USP of amylase.

Efficacy Findings

Patient Disposition

There were 200 patients screened with 163 included in the safety population, 138 in the ITT population, with about equal numbers in both treatment groups. There were 134 patients who completed the study (four withdrew and three had adverse events (AE's) and one did not meet entry criteria). See the table below.

Table 5. Patient Disposition

Patient Disposition			
Parameter	**Liprotamase n (%)**	**Placebo n (%)**	**Total n (%)**
Screened			200
Safety population			163 (100)
Randomized (ITT pop.)	70 (100)	68 (100)	138 (100)
Per Protocol	61 (87)	51 (75)	112 (81)
Completed Treatment	68 (97)	66 (97)	134 (97)
Early Withdrawal	2 (3)	2 (3)	4 (3)
Adverse Event	2 (3)	1 (2)	3 (2)
CFA > 80%	0	1 (2)	1 (1)

Patient Demographics and Disease Characteristics

Mean age was approximately the same in both treatment groups (18 or 19 years). There were 29 pediatric patients (defined as age less than 17) in the liprotamase group and 35 in the placebo group, with similar distribution in each pediatric age sub-category. There were more males than females in each treatment group, but about the same percent. Almost all of the patients were Caucasian; however, Caucasians represent the majority of the CF population. See table below for complete demographic data.

Table 6. Patient Demographics*

	Liprotamase (n=70)	**Placebo (n=68)**	**Total (n=138)**
Age (years)			
Mean (SD)	19 (7.3)	18 (7.4)	18 (7.4)
*7-11	13	15	28
*12-16	16	20	36
*≥17	41	33	74
Min, Max	7, 37	8, 44	7, 44
Gender, n(%)			
Male	45 (64)	40 (59)	85 (62)
Female	25 (36)	28 (41)	53 (38)
Race, n(%)			
White	69 (99)	65 (96)	134 (97)
Black	1 (1)	3 (4)	4 (3)

*Reviewer's calculations

Baseline CFA values between the two treatment groups were compared and had similar mean values of 47 and 50 for the liprotamase and placebo groups, respectively. See the table below.

Table 7. Baseline CFA Values*

	Mean CFA (±SD)	CFA (Min, Max)	Median CFA
Liprotamase (N=70)	46.9 (±15.9)	14.7, 76.6	45.5
Placebo (N=68)	49.5 (±17.9)	11.8, 87.2	50.9

*Reviewer's calculations

Other disease characteristics were compared between treatment groups in the table below. The liprotamase group has a slightly larger percentage of patients with baseline CFA values <40%. The Division has considered a CFA of < 40%, without treatment, as defining a severe EPI population. About 38% of patients in both arms were on acid suppression therapy.

Table 8. Disease Characteristics

CHARACTERISTIC	STATISTICS	ALTU-135 (N = 70)	PLACEBO (N = 68)	TOTAL (N = 138)
Baseline CFA (%)	< 40 CFA	24 (34.3%)	20 (29.4%)	44 (31.9)
	≥ 40 CFA	46 (65.7%)	48 (70.6%)	94 (68.1)
Acid Suppression Use	Yes	27 (38.6%)	26 (38.2%)	53 (38.4)
	No	43 (61.4%)	42 (61.8%)	85 (61.6)

(Table above is taken from Applicant's 726 Study Report)

Primary Efficacy Results

Refer to the summary table below.

For the subgroup of patients with baseline CFA < 40% (primary efficacy analysis), which constituted nearly one- third of the study population, the mean change in CFA from Baseline to Double-Blind Treatment was 20.2% in the liprotamase group compared to 5.1%, in the placebo group. The treatment difference between arms was about 15% ($p = 0.001$).

In the overall group, the mean change in CFA from Baseline to Double-Blind Treatment was 11% in the liprotamase group compared to 0.2%, in the placebo group, so the treatment difference was about 11% ($p < 0.001$).

In the baseline CFA ≥ 40% subgroup, the mean change in CFA from Baseline to Double-Blind Treatment was 7% in the liprotamase group compared to -2%, in the placebo group, so the treatment difference was about 9% ($p = 0.006$).

These results were replicated by the FDA statistical reviewer.

Table 9. Applicant's Primary Efficacy Results

Subgroup	Statistic	Change in CFA[a]		
		ALTU-135	Placebo	p-Value
Baseline CFA < 40%	n	24	20	
	Mean (SD)	20.2 (15.7)	5.1 (15.3)	
	LSM Difference[b]	15.1		0.001
	95% CI for LSM Difference	6.4; 23.8		
Overall	n	70	68	
	Mean (SD)	11.3 (16.5)	0.2 (15.8)	
	LSM Difference[c]	10.6		< 0.001
	95% CI for LSM Difference	5.6; 15.5		
Baseline CFA ≥ 40%	n	46	48	
	Mean (SD)	6.7 (15.1)	-1.8 (15.7)	
	LSM Difference[c]	8.6		0.006
	95% CI for LSM Difference	2.5; 14.7		

[a] Baseline observation carried forward
[b] Change in CFA was analyzed using an ANCOVA model with fixed effects for treatment group, CFA subgroup, and acid suppression usage with adjustment for baseline CFA.
[c] Change in CFA was analyzed using an ANCOVA model with fixed effects for treatment group and acid suppression usage with adjustment for baseline CFA.
References: *Table 14.2.1.1.1, Listing 16.2.6.1*

(Table above is taken from Page 73 of the Applicant's 726 Study Report.)

These results were statistically significant; however, mean changes in CFA observed in registration trials for porcine-derived PEPs have ranged from approximately 25-40% in the patients with baseline CFAs of all values (corresponding to "overall" category above). For the subgroup of patients with baseline CFA< 40%, mean change in CFA values observed in studies of porcine-derived PEPs were approximately 40-60%. See discussion in Section 3.1.4 below.

Relevant Secondary Efficacy Results

Change in CNA

The mean change in CNA from Baseline to Treatment was greater in the liprotamase group than in the placebo group for the CFA < 40% subgroup (21.1% and 8.4%), overall group (12.8% and 2.4%), and the CFA ≥ 40% subgroup (8.4% and -0.1%), respectively. The adjusted mean difference for change in CNA between the liprotamase and placebo groups for the baseline CFA < 40% subgroup was 12.7% (p = 0.001). The adjusted mean differences were 9.2%, and 6.6% for the overall and baseline CFA ≥ 40% subgroup, respectively. See table below.

Table 10. Change in CNA from the Baseline Period to the Double-Blind Treatment Period, ITT Population

Subgroup	Statistics	Change in CNA[a]		
		ALTU-135 (N = 70)	Placebo (N = 68)	p-Value
< 40% Baseline CFA	n	24	20	
	Mean (SD)	21.1 (16.6)	8.4 (15.4)	
	LSM Difference	12.7		0.001
	95% CI for LSM	5.7; 19.7		
Overall	n	70	68	
	Mean (SD)	12.8 (14.4)	2.4 (15.2)	
	LSM Difference	9.2		< 0.001
	95% CI for LSM	5.0; 13.4		
≥ 40% Baseline CFA	n	46	48	
	Mean (SD)	8.4 (11.0)	-0.1 (14.6)	
	LSM Difference	6.6		0.012
	95% CI for LSM	1.5; 11.7		

[a] Baseline observation carried forward
Change in CNA was analyzed using an ANCOVA model with fixed effects for treatment group and acid suppression usage with adjustment for baseline CNA.
References: Table 14.2.2.1.1, Listing 16.2.6.1

(Table above is taken from Page 81 of the Applicant's 726 Study Report)

Starch Challenge Test

The Division did not critically review the outcomes observed in the Starch Challenge Test because of the lack of correlation between amylase dose and measure of amylase activity (see General Design section above).

Additional Efficacy Results – Subgroup Analyses

Subgroup analyses by age, country, and by concomitant acid suppression therapy were conducted by categories of baseline CFA.

Age

Subgroup analyses by age are shown in the table below by categories of baseline CFA. The treatment difference does not appear to be consistent across age categories.

Table 11. Subgroup Analyses by Age Categories - Change in CFA [%]* (Study 726)

Baseline CFA Category	**Age (years)**	Liprotamase	Placebo	Liprotamase-Placebo[#]
Overall	**7 to 11**	7.9 (±14.2) (n=13)	-3.4 (±16.3) (n=15)	**11.3**
	12 to 16	7.8 (±10.3) (n=16)	5.4 (±13.2) (n=20)	**2.4**
	17 to 44	13.8 (±18.8) (n=41)	-1.2 (±16.6) (n=33)	**15.1**
Baseline CFA < 40%	**7 to 11**	7.3 (±16.7) (n=3)	5.4 (±15.0) (n=3)	**1.9**
	12 to 16	17.2 (±12.5) (n=4)	5.9 (±11.6) (n=5)	**11.3**
	17 to 44	23.1 (±15.9) (n=17)	5.7 (±18.4) (n=11)	**18.9**
Baseline CFA ≥ 40%	**7 to 11**	8.1 (±14.3) (n=10)	-5.6 (±16.5) (n=12)	**13.8**
	12 to 16	4.8 (±17.8) (n=12)	5.2 (±14.1) (n=15)	**-0.5**
	17 to 44	7.2 (±18.2) (n=24)	-4.6 (±15.3) (n=21)	**11.6**

*Change in CFA from baseline period to treatment period. Mean (±SD).
[#]Arithmetic Difference of Means
(Table above generated from this clinical reviewer using dataset from the Applicant.)

The results in the baseline CFA<40 subgroup are difficult to interpret because of the small number of patients in the pediatric age categories by treatment arm (three in each treatment arm for the 7 to 11 year old group; four and five in the liprotamase and placebo arms, respectively, for the 12 to 16 year old group).

Twelve to 16 year old patients had a numerically lower treatment difference than the other age categories in the overall baseline CFA category and in the baseline CFA ≥ 40 category.

The Applicant conducted additional analyses for the population that included both pediatric patients, and young adults, which are summarized in the table below. The FDA defines the pediatric age group as less than 17 years of age.

Table 12. Applicant's Primary Efficacy Results in patients 7-20 yrs of age (including young adults)

Subgroup	Statistic	Change in CFA[a]		
		ALTU-135	Placebo	p-Value[a]
Baseline CFA < 40%	n	10 (0)	8 (0)	
	Mean (SD)	13.0 (11.6)	5.7 (11.9)	
	LSM Difference[b]	8.4		0.133
	95% CI for LSM Difference	-2.9; 19.6		
Overall	n	45 (0)	45 (1)	
	Mean (SD)	7.7 (14.3)	0.3 (16.0)	
	LSM Difference[c]	7.9		0.010
	95% CI for LSM Difference	1.9; 14.0		
Baseline CFA ≥ 40%	n	35 (0)	37 (1)	
	Mean (SD)	6.2 (14.7)	-0.9 (16.7)	
	LSM Difference[c]	5.6		0.137
	95% CI for LSM Difference	-1.8; 13.0		

Note: Subject 701001 had baseline CFA > 80% and was randomized in error. It is included in the ≥ 40% Baseline Group.
[a] Change in CFA was analyzed using an ANCOVA model with fixed effects for treatment group and acid suppression usage with adjustment for baseline CFA.
References: *Table 14.2.1.2.1, Listing 16.2.6.1*

(Table above is taken from Page 78 of the Applicant's 726 Study Report)

To further examine the efficacy of liprotamase, this Reviewer divided the pediatric patients by age subgroup (ages 7-11 and 12-16) and listed the individual changes in CFA per patient (displayed below). Even in the patients with more severe disease (baseline CFA< 40%), the changes in CFA were not very sizeable (see highlighted values). As noted above, the mean change in CFA was 7.9% for pediatric patients ages 7-11 in the liprotamase treatment group.

Table 13. Study 726 children 7-11 on Liprotamase*

Age	Baseline CFA [%]	CFA on Liprotamase [%]	Change in CFA [%]
7	56.11	53.09	-3.03
7	51.07	40.47	-10.60
7	26.89	14.99	-11.90
8	69.57	86.29	16.72
9	52.13	73.07	20.95
9	71.07	60.37	-10.70
10	47.29	80.89	33.60
10	30.05	47.25	17.20
10	36.58	53.26	16.67
11	47.64	47.64	0.00
11	72.83	79.38	6.55
11	64.37	78.01	13.64
11	67.33	81.10	13.77
Mean (min, max)	**53 (26.9, 72.8)**		**7.9 (-11.9, 33.6)**

*Reviewer's calculations
Highlighted: severely affected patients

The placebo group's individual changes in CFA were examined below. The mean Baseline value was similar to that of the liprotamase group at approximately 55%; the mean change in CFA was -3.4%.

Table 14. Study 726 ages 7-11 Placebo Patients*

Age	Baseline CFA [%]	CFA on placebo [%]	Change in CFA [%]
8	45.62	30.45	-15.17
8	31.06	29.12	-1.94
8	79.00	60.72	-18.28
9	51.32	6.95	-44.37
9	50.90	42.28	-8.63
10	40.36	51.08	10.72
10	72.10	83.77	11.67
10	71.08	66.76	-4.32
10	54.47	71.71	17.24
10	87.26	87.26	0.00
11	11.76	34.40	22.64
11	62.89	59.91	-2.98
11	30.95	26.53	-4.42
11	60.94	61.02	0.08
11	67.80	54.13	-13.67
Mean (SD) **Min, max**	**54.5 (20.3)** **11.8 , 87.3**		**-3.4 (16.3)** **-44.4, 22.6**

*Reviewer's calculations
Highlighted: severely affected patients

For the pediatric subgroup (ages 12-16) on liprotamase, the individual changes in CFA data are presented below. Once again, mean Baseline CFA is about 54%; individual changes in CFA from Baseline are modest, even in the most severely affected patients. The mean change in CFA was 7.8%.

Table 15. Study 726 ages 12-16 Liprotamase Patients*

Age	Baseline CFA [%]	CFA on Liprotamase [%]	Change in CFA [%]
12	76.56	91.33	14.77
12	71.56	66.30	-5.26
12	54.54	67.36	12.82
12	60.41	52.08	-8.33
12	56.80	53.71	-3.09
12	33.54	42.03	8.49
13	67.24	71.83	4.59
13	37.26	41.88	4.62
13	44.85	51.02	6.16
13	62.08	73.45	11.37
14	57.84	72.45	14.61
14	55.14	60.78	5.64
14	44.72	46.44	1.72
15	73.65	74.98	1.32
16	22.87	53.05	30.18
16	39.87	65.19	25.32
Mean (SD) **Min, max**	**53.7 (15.37)** **22.9, 76.6**	**61.5**	**7.8** **-8.3, 30.2**

*Reviewer's calculations
Highlighted: severely affected patients

The table below displays the placebo group individual changes in CFA data for the 12-16 year old subgroup. The mean Baseline value was similar at approximately 52%. The mean change in CFA was 5.4%.

Table 16. Study 726 ages 12-16 Placebo Patients*

Age	Baseline CFA [%]	CFA on Placebo [%]	Change in CFA [%]
12	15.97	14.55	-1.42
12	53.84	84.43	30.59
12	53.93	69.90	15.97
12	33.99	39.99	6.00
12	62.18	72.13	9.94
12	56.77	63.14	6.37
13	55.58	76.26	20.67
13	40.76	18.16	-22.60
13	74.46	85.93	11.48
13	34.80	49.07	14.27
13	39.64	30.54	-9.11
13	45.62	53.87	8.26
14	53.39	47.99	-5.40
14	78.98	71.82	-7.16
15	68.29	67.72	-0.57
15	63.86	54.38	-9.48
16	73.83	69.92	-3.91
16	47.84	70.91	23.07
16	24.36	43.94	19.57
16	52.93	54.21	1.27
Mean (SD) **Min, max**	**51.6 (16.7)** **16, 79**	**56.9**	**5.4** **-22.6, 30.6**

*Reviewer's calculations
Highlighted: severely affected patients

Thus, the difference in mean change in CFA between treatment groups was 7.8% minus 5.4% or approximately 2.4%. Once again, this is a very modest difference between the liprotamase group and the placebo group in this pediatric sub-population.

Country

Subgroup analyses by country are shown in the table below by categories of baseline CFA.

Table 17. Subgroup Analyses by Country Category - Change in CFA [%]* (Study 726)

Baseline CFA Category	**Country Category**	Liprotamase	Placebo	**Liprotamase-Placebo[#] (Mean Difference)**
Overall	**U.S.**	15.7 (±17.9) (n=34)	-2.1 (±17.7) (n=31)	**17.8**
	Non-U.S.	7.7 (14.4) (n=34)	2.4 (14.3) (n=35)	**5.3**
Baseline CFA < 40%	**U.S.**	28.4 (±16.1) (n=10)	3.4 (±18.7) (n=11)	**25.0**
	Non-U.S.	15.4 (12.8) (n=13)	8.2 (11.0) (n=8)	**7.2**
Baseline CFA ≥ 40%	**U.S.**	10.4 (16.0) (n=24)	-5.2 (16.9) (n=20)	**15.6**
	Non-U.S.	2.9 (±13.5) (n=21)	0.6 (±14.8) (n=27)	**2.3**

*Change in CFA from baseline period to treatment period. Mean (±SD). Baseline observation carried forward.
[#]Arithmetic Difference of Means
(Subgroup analysis by country conducted by the Applicant; source is Table 14.2.1.2.1 - Pages 122 to 127 of tables and figures of Study 726 Study Report.)

The treatment difference does not appear to be consistent by country category (U.S. sites versus non-U.S. sites). The magnitude of the treatment difference is numerically higher in the U.S. sites than in the non-U.S. sites across baseline CFA categories.

Concomitant Acid Suppression Therapy

Subgroup analyses by concomitant acid suppression therapy are shown in the table below by categories of baseline CFA. Across baseline CFA categories, both the liprotamase and placebo arms appear to have a numerically higher change in CFA in the acid suppression group compared to the non-acid suppression group.

Table 18. Subgroup Analyses by Concomitant Acid Suppression Therapy - Change in CFA [%]* (Study 726)

Baseline CFA Category	**Acid Suppression**	Liprotamase	Placebo	**Liprotamase-Placebo[#] (Mean Difference)**
Overall	**Yes**	17.9 (±20.7) (n=25)	6.4 (±15.5) (n=25)	**11.5**
	No	8.1 (±12.6) (n=43)	-3.5 (±15.3) (n=41)	**11.6**
Baseline CFA < 40	**Yes**	33.5 (±12.7) (n=9)	8.8 (±19.0) (n=7)	**24.7**
	No	13.0 (±11.4) (n=14)	3.4 (±14.0) (n=12)	**9.6**
Baseline CFA ≥ 40	**Yes**	9.1 (±19.3) (n=16)	5.5 (±14.4) (n=18)	**3.6**
	No	5.7 (±12.6) (n=29)	-6.4 (±15.1) (n=29)	**12.1**

*Change in CFA from baseline period to treatment period. Mean (±SD). Baseline observation carried forward.
[#]Arithmetic Difference of Means
Acid suppression therapy defined as either daily proton pump inhibitor or H2-receptor antagonist
(Subgroup analysis by acid suppression therapy use conducted by the Applicant; source is Table 14.2.1.2.1 - Pages 122 to 127 of tables and figures of Study 726 Study Report.)

The treatment difference for the acid suppression group is numerically higher than that of the non-acid suppression group for the baseline CFA <40 category, and numerically lower than that of the non-acid suppression group for the baseline CFA ≥ 40 category; the treatment difference for the overall baseline CFA category appears to be comparable for the acid suppression and non-acid suppression groups.

Responder Analyses

The Division of Gastroenterology Products has generally accepted that for the most severely affected EPI patients (defined as baseline CFA < 40%) an increase in CFA of 30% represents a clinically meaningful result. At the request of the Division, a post-hoc "responder" analysis was performed in which a "responder" was defined as an increase in CFA of ≥ 30% from baseline. See table below.

Table 19. Proportion of Subjects with an Increase in CFA by ≥ 30% From Baseline, by Baseline CFA (Study 726)

BASELINE CFA	LIPROTAMASE		PLACEBO	
	N/N	%	N/N	%
CFA < 40%	8/24	33.3	1/20	5.0
Overall	12/70	17.1	2/68	2.9
CFA ≥ 40%	4/46	8.7	1/48	2.1

(Table above is taken from Applicant's Response to Information Request dated October 15, 2010)

Among patients receiving liprotamase, the greatest percentage of responders (33.3%) was seen in patients with severe EPI (i.e., baseline CFA < 40%) as compared to patients receiving placebo, who were 5% responders. For the overall liprotamase group, there were 17.1% responders as compared to 2.9% for the placebo group.

Study TC-2A

General Design

Study TC-2A was a Phase 2, randomized, double blind, parallel, dose ranging study in 125 patients with CF and EPI. The product used in this trial was not physico-chemically comparable to the product used in the Phase 3 trial.

The primary efficacy endpoint was the CFA during the treatment period; CFA at Baseline, at treatment, and change from Baseline were summarized by treatment group. The secondary efficacy endpoints included Coefficient of Nitrogen Absorption (CNA), Blood Glucose Response / Starch Challenge Test and Stool Weight and Frequency; the definitions were the same as those in Study 726.

Dosing Regimen

Dose: lipase/protease/amylase units per meal or snack:
Treatment Arm 1 (n=41): 6,500/5,000/750
Treatment Arm 2 (n=43): 32,500/25,000/3,750
Treatment Arm 3 (n=41): 130,000/100,000/15,000

Study TC-2A included the following four periods as represented in the table below.

Table 20. Pertinent Features of Study Design (Study TC-2A)

Period	Treatment
Screening Period (10-14 days)	Usual PEP
Inpatient off-enzyme Baseline Period (6-7 days)*	None
Treatment Period (28 days)*	Liprotamase (dose ranging)[#]
Follow-up Period (7 days)	Usual PEP[†]

*Stool collection for CFA and CNA during baseline period and inpatient phase of treatment period
Patients received liprotamase in one of the three doses
[†]After the last dose of liprotamase, the usual PEP was resumed (unless rolled over into Study 767)

Key Eligibility Criteria

Patients included in the study had to be 7 years or older with a confirmed diagnosis of CF and EPI documented by fecal elastase < 100 μg/g measured at the screening visit. Patients had to have a forced expiratory volume over one second (FEV_1) ≥ 30% predicted. Patients were excluded if they had: a history of fibrosing colonopathy, a history liver or lung transplant or a known hypersensitivity to food additives.

Efficacy Findings

Patient Disposition

Of the 139 patients that were enrolled, there were nine patients that failed screening (five had fecal elastase >100 μg/g, one had FEV1<30% predicted, and two were clinically unstable) and one patient that withdrew consent before being randomized.

Patient Demographics and Disease Characteristics

In each treatment arm, the mean age was about 21, with standard deviations ranging from 8-9.3. There were more males vs. females in each treatment arm, with the largest difference in distribution present in Treatment arm 1. The majority of patients in the trial were Caucasian. See table below for demographic information.

Table 21. Demographics Data

Demographic Parameter	mITT Population			
	Arm 1 (N = 39)	Arm 2 (N = 41)	Arm 3 (N = 37)	Total (N = 117)
Age (years)				
Mean (SD)	21.3 (8.04)	22.2 (9.26)	20.9 (8.33)	21.5 (8.52)
Sex [N (%)]				
Male	28 (71.8%)	22 (53.7%)	21 (56.8%)	71 (60.7%)
Female	11 (28.2%)	19 (46.3%)	16 (43.2%)	46 (39.3%)
Race/Ethnicity [N (%)]				
American Indian/ Alas.Native	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Asian/ Pac. Islander	0 (0.0%)	1 (2.4%)	0 (0.0%)	1 (0.9%)
African-American (not of Hispanic Origin)	1 (2.6%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Hispanic	0 (0.0%)	1 (2.4%)	1 (2.7%)	2 (1.7%)
Caucasian (not of Hispanic Origin)	37 (94.9%)	39 (95.1%)	36 (97.3%)	112 (95.7%)
Other	1 (2.6%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Height (cm)				
Mean (SD)	168.9 (9.38)	165.9 (8.54)	165.4 (9.03)	166.7 (9.04)
Weight (kg)				
Mean (SD)	58.9 (9.45)	57.2 (10.61)	58.4 (11.78)	58.1 (10.57)
BMI (kg/m²)				
Mean (SD)	20.6 (2.47)	20.7 (2.98)	21.3 (3.32)	20.8 (2.93)

Reference: Appendix 9 (Tables 3.1, 3.2, 3.3)
Note: BMI was calculated as body weight (kg) divided by height (in meters) squa

(Table above is taken from Page 50 of the Applicant's TC-2A Study Report)

Baseline CFA values between the treatment groups were compared (see table below).

Table 22. Baseline CFA* (Study TC-2A)

Baseline CFA	6,500 U (n=41)	32,500 U (n=43)	130,000 U (n=39)
Subgroup [n; %]			
Baseline CFA <40%	8 (19.5%)	8 (18.6%)	13 (33.3%)
Baseline CFA ≥ 40%	33 (80.5%)	35 (81.4%)	26 (66.7%)
Descriptive statistics			
Mean ± SD	54.6% (±17.4%)	56.2% (±20.7%)	54.2% (±19.9%)
Median (Min, Max)	54.9% (14.3%, 94.6%)	58.5% (10.7%, 92.8%)	49.5% (25.1%, 98.5%)

*ITT population
(Table above generated from this clinical reviewer using datasets from the Applicant.)

The proportion of patients in each of the low, middle, and high dose groups whose baseline was CFA< 40% was 19.5%, 18.6% and 33.3%, respectively. The mean baseline CFA was approximately 55% in each dose group.

Primary Efficacy Results

The primary efficacy analysis showed that the change in CFA from Baseline, was 1.2%, 11.4% and 17.3% for the low, middle, and high-dose treatment arms, respectively. Although there appeared to be a dose-response relationship for efficacy, with the highest dose of 130,000 demonstrating the greatest efficacy, the increase in change of CFA is not dose-proportional (see Clinical Pharmacology section).

Table 23. Primary Efficacy Results: Mean Coefficient of Fat Absorption – Study TC-2A

OUTCOMES (MITT; N = 117)		TREATMENT ARM 1 (N = 39)	TREATMENT ARM 2 (N = 41)	TREATMENT ARM 3 (N = 37)
Pre-Treatment Baseline	Mean	55.0%	55.6%	52.2%
	SD	17.54%	20.29%	19.14%
On-Treatment	Mean	56.2%	67.0%	69.7%
	SD	18.16%	18.08%	17.86%
Change From Baseline	Mean	1.2%	11.4%*	17.3%†
	SD	14.77%	19.10%	18.37%

* p = 0.0005 paired t-test for within group change from baseline
† p < 0.0001 paired t-test for within group change from baseline

(Table above is taken from Page 52 of the Applicant's TC-2A Study Report)

The change in CFA results by baseline CFA subgroup are shown in the table below. A dose response was not evident beyond the 32,500 U dose level in the patient subgroup with baseline CFA<40%.

Table 24. Mean Change in CFA by Baseline CFA Subgroup* (Study TC-2A)

Baseline CFA Subgroup	Treatment Arm 1 6,500 U	Treatment Arm 2 32,500 U	Treatment Arm 3 130,000 U
Baseline CFA <40%	11.5% (±14.2%) (n=8)	35.3% (±18.5%) (n=8)	27.8% (±16.1%) (n=13)
Baseline CFA ≥ 40%	-1.4% (±13.5%) (n=33)	5.3% (±13.9%) (n=35)	10.0% (±16.5%) (n=26)

*ITT population
(Table above generated from this clinical reviewer using datasets from the Applicant.)

Relevant Secondary Efficacy Results

Change in CNA

Change in CNA results for Study TC-2A are shown in the table below.

Table 25. Mean Coefficient of Nitrogen Absorption (Study TC-2A)

OUTCOMES (MITT; N = 117)		TREATMENT ARM 1 (N = 39)	TREATMENT ARM 2 (N = 41)	TREATMENT ARM 3 (N = 37)
Pre-Treatment Baseline	Mean	60.6%	58.8%	56.8%
	SD	16.38%	17.88%	16.36%
On-Treatment	Mean	61.6%	71.3%	74.6%
	SD	15.46%	16.38%	13.51%
Change From Baseline	Mean	1.1%	12.5%*	17.5%*
	SD	14.89%	18.37%	18.00%
(* $p < 0.001$ paired t-test for within group change from baseline)				

(Table above taken from Page 56 of the Applicant's TC-2A Study Report.)

There was a statistically significantly higher change in CNA in the high dose group compared to the low dose group, and in the middle dose group compared to the low dose group.

There was a trend of a higher change in CNA with increasing dose, but the increase from the middle to high dose group was not dose proportional.

Additional Efficacy Results – Subgroup Analyses

Subgroup analyses of change in CFA by age and by concomitant acid suppression therapy were conducted. These subgroup analyses were presented for the overall, baseline CFA<40% and baseline CFA ≥ 40% categories.

Age

Subgroup analyses by age are shown in the table below.

Table 26. Subgroup Analyses by Age Categories - Change in CFA [%]* (Study TC-2A)

Baseline CFA Category	Age (years)	Low Dose 6,500 U	Middle Dose 32,500 U	High Dose 130,000 U
Overall	11	--	--	0 (n=1)
	12 to 16	-0.02 (±18.9) (n=11)	9.5 (±19.6) (n=12)	11.4 (±18.6) (n=11)
	≥ 17	1.5 (±12.7) (n=30)	11.4 (±18.8) (n=31)	18.4 (±18.1) (n=27)
Baseline CFA < 40%	11	--	--	--
	12 to 16	22.8 (±1.4) (n=2)	33.9 (±17.9) (n=3)	2.3 (n=1)
	≥ 17	7.8 (±14.7) (n=6)	36.0 (±20.9) (n=5)	30.0 (±14.7) (n=12)
Baseline CFA ≥ 40%	11	--	--	0 (n=1)
	12 to 16	-5.1 (±17.0) (n=9)	1.4 (±12.2) (n=9)	12.3 (±19.3) (n=10)
	≥ 17	-0.02 (±12.0) (n=24)	6.6 (±14.5) (n=26)	9.2 (±15.3) (n=15)

*ITT population

(Table above generated from this clinical reviewer using dataset from the Applicant.)

Concomitant Acid Suppression Therapy

Subgroup analyses by concomitant acid suppression therapy are shown in the table below.

Table 27. Subgroup Analyses by Concomitant Acid Suppression Therapy - Change in CFA [%]* (Study TC-2A)

Baseline CFA Category	Acid Suppression	Low Dose 6,500 U	Middle Dose 32,500 U	High Dose 130,000 U
Overall	Yes	8.0 (±10.7) (n=20)	16.6 (±19.6) (n=21)	20.8 (±18.4) (n=21)
	No	-5.5 (±14.6) (n=21)	5.4 (±16.7) (n=22)	10.3 (±16.8) (n=18)
Baseline CFA < 40%	Yes	11.8 (±12.7) (n=4)	45.3 (±22.0) (n=4)	28.5 (±18.4) (n=9)
	No	11.2 (±17.7) (n=4)	25.2 (±7.0) (n=4)	26.3 (±11.1) (n=4)
Baseline CFA ≥ 40%	Yes	7.1 (±10.4) (n=16)	9.8 (±11.6) (n=17)	15.0 (±16.9) (n=12)
	No	-9.4 (±11.0) (n=17)	1.0 (±14.9) (n=18)	5.7 (±15.5) (n=14)

*ITT population
(Table above generated from this clinical reviewer using dataset from the Applicant.)

Responder Analyses

An exploratory "responder" analysis was performed in which a "responder" was defined as a patient who had a change in CFA of ≥ 30% from baseline. See table below.

Table 28. Proportion of Subjects with an Increase in CFA by ≥ 30% from Baseline (TC-2A)

Baseline CFA Category	Liprotamase 6,500 U	Liprotamase 32,500 U	Liprotamase 130,000 U
CFA < 40%	**12.5%** (1/8)	**50.0%** (4/8)	**61.5%** (8/13)
Overall	**2.6%** (1/38)	**18.4%** (7/38)	**31.4%** (11/35)
CFA ≥ 40%	**0%** (0/30)	**10.0%** (3/30)	**13.6 %** (3/22)

Note: Two subjects from the liprotamase 130,000 U treatment group (116002, 116005) are missing baseline CFA and therefore could not be included in this analysis.
(Table above is modified from a table in the Applicant's Response to Information Request dated October 15, 2010)

For the baseline CFA < 40% subgroup, patients in the highest dose treatment arm (130,000 U) had the highest percentage responders. In addition, overall, patients who were in the 130,000 U treatment arm had the highest percentage responders.

Study 767

The Applicant conducted an open label long-term (12-month) safety study (Study 767). Efficacy endpoints were not prospectively defined in the study protocol.

The Applicant presented z-scores for BMI, height, and weight over time for the overall Study 767 safety population and for three age subgroups (7 to 11 years; 12 to 16 years; and 17 years and older); z-scores were determined using the 2000 CDC growth charts based on the normal population.

Because of the concern that there is lower change in CFA with liprotamase compared to porcine-derived PEPs, the FDA reviewers explored this data to determine if there is evidence of inadequate growth. The FDA reviewers determined that mean height, weight and BMI z-scores appeared to decline for the first two to three months, and then appeared to stabilize for the duration of the study, 12 months. This trend was observed in both the U.S. and non-U.S. subgroups. The U.S. subgroup had numerically higher mean height, weight and BMI z-scores than the non-U.S. subgroup at each of the visits. Mean height, weight, and BMI z-scores declined for the patients ages 7 to 11 years and 12 to 16 years, but were stable for the 17 years and older patients. A BMI shift analysis by age subgroups suggested that patients 7 to 11 years of age had the greatest shift to worse BMI category compared to the other subgroups.

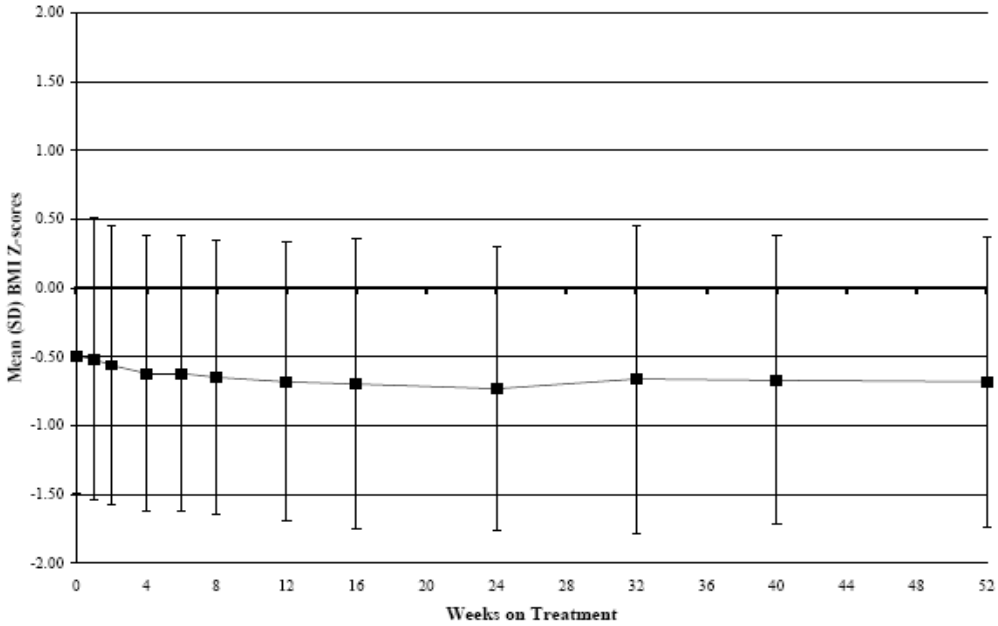
To address the lack of a comparator, the Applicant provided discussion in the Clinical Study Report for Study 767 based on qualitative comparisons with graphic displays of CFF Registry Data (obtained from the published CFF Registry Annual Data Report; see Appendix 2); a comparison to this data was not defined in the Study 767 protocol. The displays of CFF Registry data show median height, weight and BMI in CF patients plotted as percentiles based on the normal population (using CDC growth charts); the published CFF Registry Annual Data Report 2008 states that the data includes more than 25,500 patients who receive care at CFF-accredited care centers. The Applicant also provided discussion based on qualitative comparisons to a retrospective collection of data from the CFF Registry ("group-matched external control study"); this external control was also not defined in the Study 767 protocol. The "group-matched control" data was from 5,660 CF patients in the CFF registry that were selected based on similarity to patients in Study 767; key selection criteria were age $\geq$ 7 years old, on treatment for EPI with PEPs, and having a visit in the database occurring in 2007 or 2008. Descriptive tables (demographic characteristics; and baseline BMI, height, and weight z-scores); and figures (BMI z-scores over time; BMI z-scores by age subgroups over time; and BMI z-score shift analyses) are provided in Appendix 3. Comparisons between Study 767 data and the group-matched external control data were difficult to interpret because neither efficacy endpoints nor comparisons to an external control were prospectively defined in the protocol. The FDA Reviewers continue to explore these data.

Safety Population (BMI, Height and Weight):

BMI

BMI z-scores over time for the safety population (n=214) are shown in the figure below.

Figure 1. BMI Z-scores (Mean ± SD) Over Time - Safety Population (N=214)



(Figure above taken from Page 83 of the 767 Study Report.)

Height, Weight, and BMI

Height, weight and BMI z-scores (actual values and changes from baseline) in the safety population (n=214) are shown in the table below.

Table 29. Height, Weight and BMI Z-scores (Mean ± SD): Actual Values and Changes from Baseline, Safety Population (N=214)

Visit	Z-scores (Mean ± SD)					
	Height		Weight		BMI	
	Actual Value	Δ from Baseline	Actual Value	Δ from Baseline	Actual Value	Δ from Baseline
Baseline n=214	-0.490 (±0.989)		-0.607 (±1.031)		-0.493 (±0.994)	
Week 1 n=203*	-0.491 (±0.951)	-0.008 (±0.092)	-0.621 (±1.023)	-0.014 (±0.139)	-0.519 (±1.025)	-0.015 (±0.214)
Week 2 n=203*	-0.512 (±0.987)	-0.011 (±0.147)	-0.670 (±1.038)	-0.033 (±0.132)	-0.562 (±1.015)	-0.034 (±0.189)
Week 4 n=196*	-0.509 (±0.975)	-0.004 (±0.084)	-0.715 (±1.055)	-0.055 (±0.174)	-0.621 (±1.004)	-0.064 (±0.237)
Week 6 n=199	-0.517 (±0.993)	-0.004 (±0.110)	-0.724 (±1.052)	-0.066 (±0.168)	-0.622 (±0.998)	-0.078 (±0.238)
Week 8 n=192*	-0.526 (±0.987)	-0.015 (±0.106)	-0.753 (±1.048)	-0.069 (±0.188)	-0.649 (±0.991)	-0.073 (±0.275)
Mo 3 (Wk 12) n=176	-0.581 (±0.977)	-0.007 (±0.130)	-0.802 (±1.070)	-0.096 (±0.206)	-0.682 (±1.013)	-0.120 (±0.304)
Mo 4 (Wk 16) n=166*	-0.581 (±0.979)	-0.015 (±0.120)	-0.811 (±1.101)	-0.115 (±0.237)	-0.698 (±1.054)	-0.139 (±0.344)
Mo 6 (Wk 24) n=157	-0.617 (±0.980)	-0.038 (±0.173)	-0.868 (±1.071)	-0.154 (±0.268)	-0.733 (±1.031)	-0.172 (±0.410)
Mo 8 (Wk 32) n=154	-0.636 (±1.007)	-0.059 (±0.225)	-0.813 (±1.172)	-0.122 (±0.403)	-0.662 (±1.119)	-0.116 (±0.561)
Mo 10 (Wk 40) n=149	-0.642 (±1.007)	-0.052 (±0.254)	-0.825 (±1.088)	-0.111 (±0.297)	-0.671 (±1.048)	-0.113 (±0.411)
Mo 12 (Wk 52) n=145	-0.655 (±1.020)	-0.070 (±0.259)	-0.836 (±1.060)	-0.108 (±0.326)	-0.681 (±1.054)	-0.099 (±0.481)

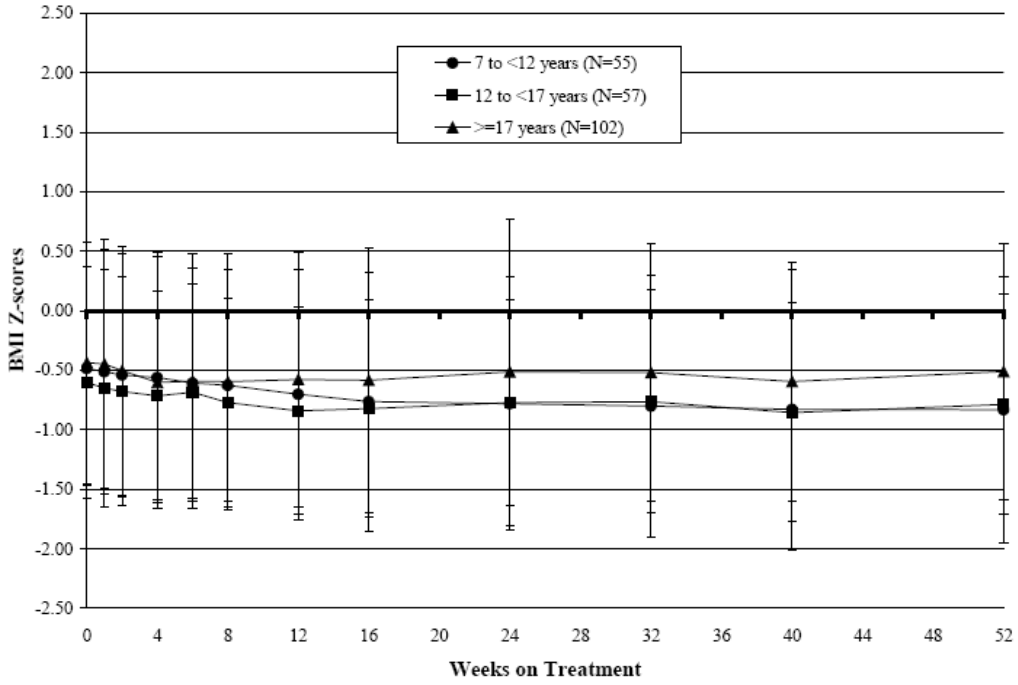
n presented is for height and BMI; the number of subjects with weight data was 206 at Weeks 1 and 2, 198 at Week 4, 193 at Week 8, and 167 at Month 4.
(Table above is taken from Page 86 of the 767 Study Report.)

Age Subgroups (BMI, Height and Weight)

BMI by Age Subgroups

BMI z-scores by age subgroups in the safety population (n=214) are shown in the figure below.

Figure 2. BMI Z-scores (Mean ± SD) Over Time by Age Subgroups - Safety Population (N=214)

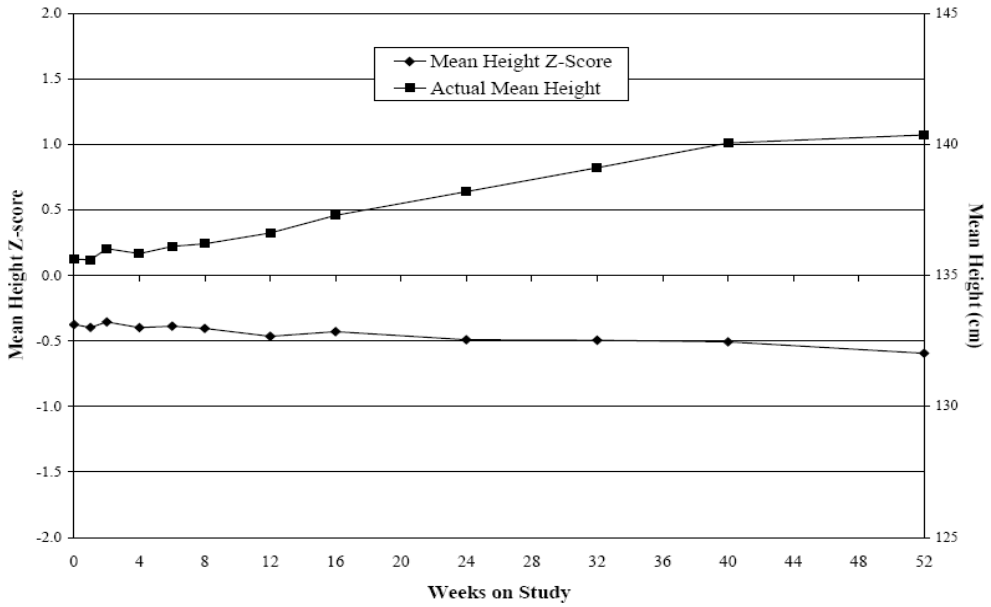


(Figure above is taken from Page 89 of the 767 Study Report.)

Height and Weight (Ages 7 to 11):

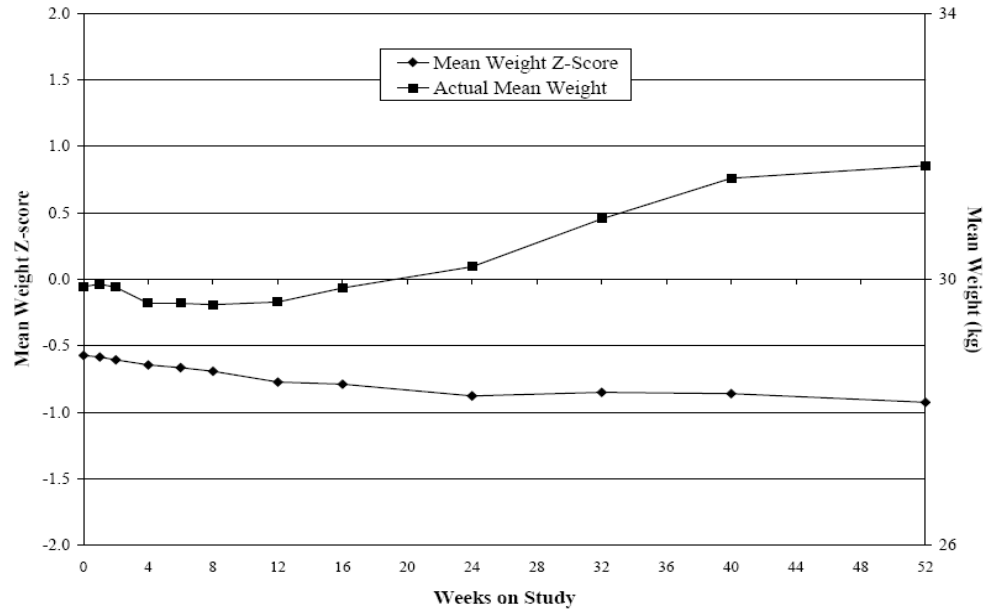
Height and weight (actual values and z-scores) over time on study for patients age 7 to 11 years (n=57) are shown in the figures below.

Figure 3. Height (Actual Values and Z-Scores) Over Time for Patients Age 7 to 11 Years (N=57)



(Figure above taken from page 94 of the 767 Study Report.)

Figure 4. Weight (Actual Values and Z-Scores) Over Time for Patients Age 7 to 11 Years (N=57)

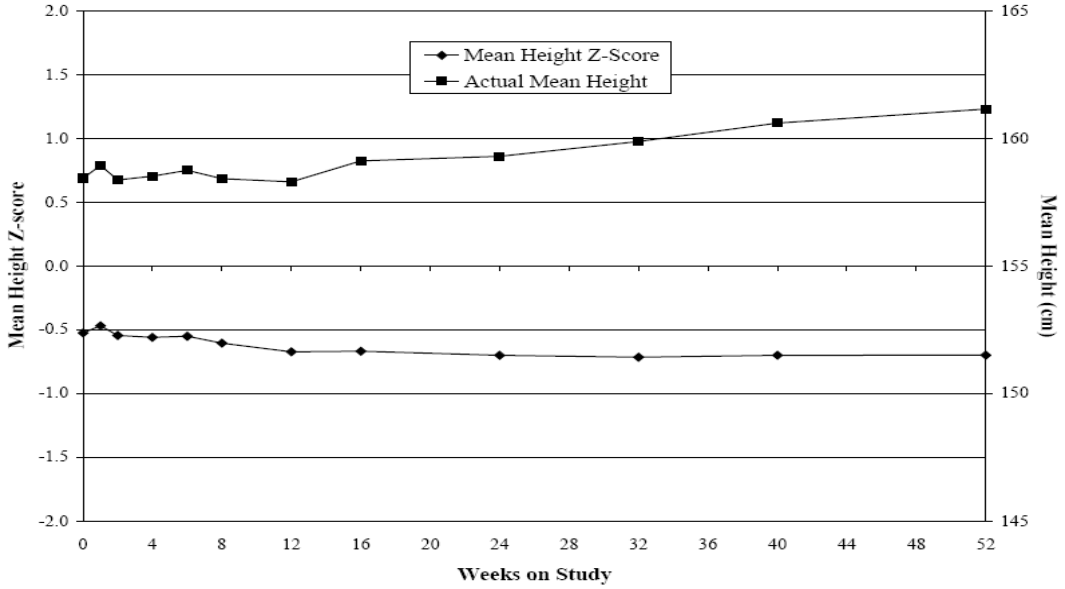


(Figure above taken from page 94 of the 767 Study Report.)

Height and Weight (Ages 12 to 16):

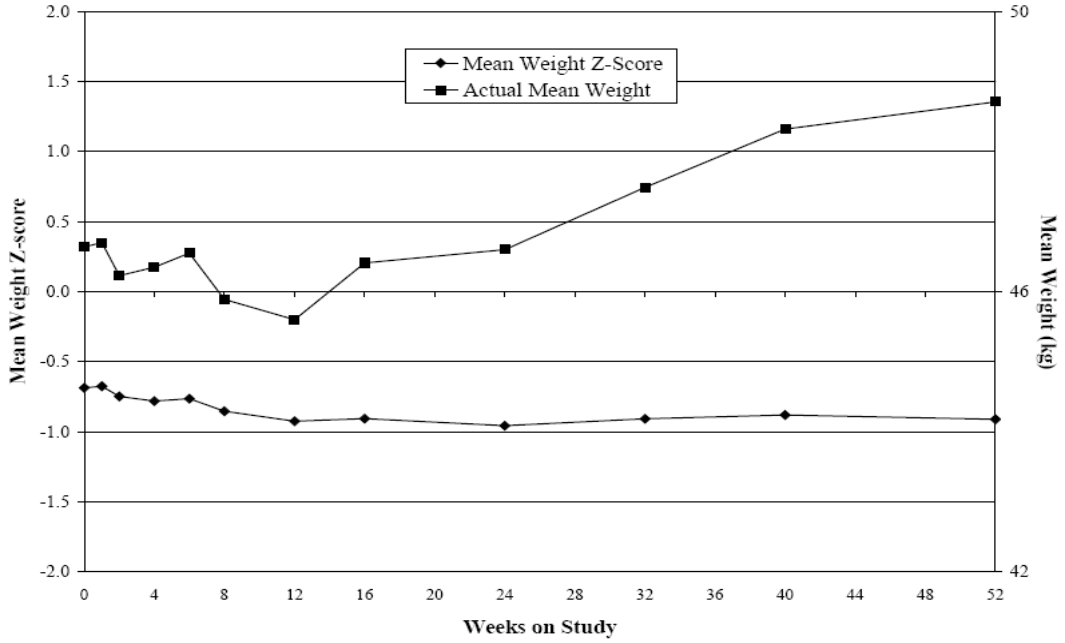
Height and weight (actual values and z-scores) over time on study for subjects age 12 to 16 years (n=57) are shown in the figure below.

Figure 5. Height (Actual Values and Z-Scores) Over Time for Patients Age 12 to 16 Years (N=57)



(Figure above taken from page 95 of the 767 Study Report.)

Figure 6. Weight (Actual Values and Z-Scores) Over Time for Patients Age 12 to 16 Years (N=57)



(Figure above taken from page 95 of the 767 Study Report.)

BMI Shift Analyses

Presented in the table below are BMI shifts by age subgroups which occurred throughout the study.

Table 30. BMI Shift Analysis Overall and by Age Subgroups, Safety Population

Visit	Age Subgroups (years): 7 to <12 (N=55)		12 to <17 (N=57)		≥17 (N=102)		All Subjects n (%) (N=214)	
	Improvement* n/N (%)	Worsening† n/N (%)	Improvement* n/N (%)	Worsening† n/N (%)	Improvement* n/N (%)	Worsening† n/N (%)	Improvement* n/N (%)	Worsening† n/N (%)
Week 4	6/54 (11.1)	3/54 (5.6)	0/53	1/53 (1.9)	6/90 (6.7)	10/90 (11.1)	12/197 (6.1)	14/197 (7.1)
Week 8	6/54 (11.1)	7/54 (13.0)	3/49 (6.1)	4/49 (8.2)	3/89 (3.4)	9/89 (10.1)	12/192 (6.3)	20/192 (10.4)
Month 3	4/50 (8.0)	5/50 (10.0)	2/46 (4.3)	3/46 (6.5)	6/80 (7.5)	12/80 (15.0)	12/176 (6.8)	20/176 (11.4)
Month 4	4/48 (8.3)	9/48 (18.8)	2/44 (4.5)	3/44 (6.8)	5/74 (6.8)	8/74 (10.8)	11/166 (6.6)	20/166 (12.0)
Month 6	4/46 (8.7)	10/46 (21.7)	4/42 (9.5)	4/42 (9.5)	5/69 (7.2)	6/69 (8.7)	13/157 (8.3)	20/157 (12.7)
Month 8	4/44 (9.1)	10/44 (22.7)	3/43 (7.0)	4/43 (9.3)	6/67 (9.0)	9/67 (13.4)	13/154 (8.4)	23/154 (14.9)
Month 10	5/43 (11.6)	11/43 (25.6)	3/43 (7.0)	6/43 (14.0)	5/63 (7.9)	10/63 (15.9)	13/149 (8.7)	27/149 (18.1)
Month 12	5/40 (12.5)	9/40 (22.5)	2/43 (4.7)	7/43 (16.3)	4/62 (6.5)	10/62 (16.1)	11/145 (7.6)	26/145 (17.9)

Source: Table 14.3.8.3.5

* Improvement represents subjects who shifted from 'At Risk' to 'Acceptable' or from 'Unacceptable' to 'At Risk' or 'Acceptable' (see Section 9.7.4.3 for definitions)

† Worsening represents subjects who shifted from 'Acceptable' to 'At Risk' or' Unacceptable' or from 'At Risk' to 'Unacceptable' (see Section 9.7.4.3 for definitions)

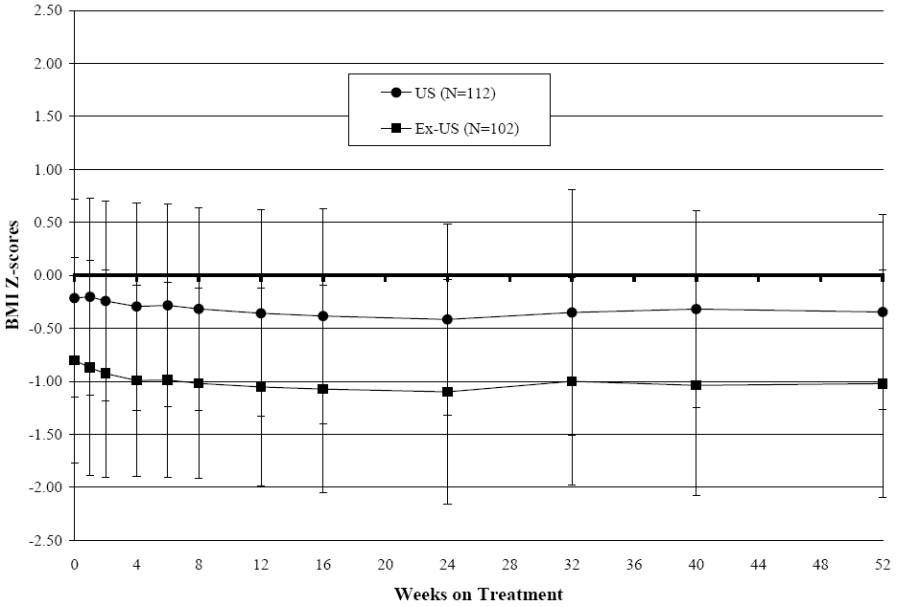
See Appendix 4 for definitions of "At Risk", "Acceptable", and "Unacceptable."
(Table above taken from page 106 of the 767 Study Report.)

<u>Region Subgroups (US vs. Non-US)</u>:

BMI – US vs. Non-US

BMI z-scores over time in geographic region (U.S. versus Non-U.S.) subgroups of the safety population (n=214) are shown in the figure below.

Figure 7. BMI Z-scores (Mean ± SD) by Geographic Region Subgroups - Safety Population (N=214)



(Figure above taken from Page 96 of the 767 Study Report.)

Height, Weight and BMI – U.S. vs. Non-U.S.

Height, weight and BMI z-scores (actual values and changes from baseline) by geographic region subgroups in the safety population (n=214) are shown in the table below.

Table 31. Height, Weight, and BMI Z-scores – Selected Visits (Mean ± SD) by Geographic Region Subgroups, Safety Population (N=214)

Visit	Z-scores (Mean ± SD)					
	Height		Weight		BMI	
	U.S. (n=112*)	Non-U.S. (n=102[#])	U.S. (n=112*)	Non-U.S. (n=102[#])	U.S. (n=112*)	Non-U.S. (n=102[#])
Baseline n=214	-0.379 (±0.962)	-0.611 (±1.009)	-0.327 (±1.037)	-0.915 (±0.936)	-0.214 (±0.932)	-0.801 (±0.973)
Week 8 n=192[†]	-0.421 (±0.953)	-0.643 (±1.015)	-0.424 (±1.048)	-1.114 (±0.928)	-0.316 (±0.956)	-1.020 (±0.897)
Mo 3 n=176	-0.410 (±0.973)	-0.777 (±0.951)	-0.456 (±1.080)	-1.198 (±0.915)	-0.358 (±0.975)	-1.053 (±0.930)
Mo 6 n=157	-0.434 (±0.964)	-0.828 (±0.963)	-0.531 (±1.040)	-1.255 (±0.977)	-0.415 (±0.900)	-1.099 (±1.056)
Mo 12 n=145	-0.420 (±1.006)	-0.893 (±0.984)	-0.467 (±1.074)	-1.210 (±0.910)	-0.346 (±0.922)	-1.021 (±1.075)

*US: n (for height and BMI) = 112 at Baseline, 101 at Wk 8, 94 at Mo 3, 84 at Mo 6, and 73 at Mo 12, respectively. (For US subjects, n for weight same as n for height and BMI data.)
[#]Non-US: n (for height and BMI) = 102 at Baseline, 91 at Wk 8, 82 at Mo 3, 73 at Mo 6, and 72 at Mo 12, respectively. (For non-US subjects, n for weight n for weight same as n for height and BMI data except n for weight is 92 at Wk 8.)
[†]n presented is for height and BMI; the number of subjects with weight data was 193 at Week 8.
(Table above is modified from Table 14.3.8.1.6 - Pages 292-316 of the Tables and Figures supporting the 767 Study Report.)

3.1.3 Additional Efficacy Issues/Analyses

Analysis of Primary Endpoint(s)

The primary efficacy analysis in Study 726 was a comparison of the change in coefficient of fat absorption (CFA) following oral administration of liprotamase and placebo in the subgroup with baseline CFA ≤ 40%. In addition, Study TC-2A compared the change in CFA from Baseline for three different doses of liprotamase to identify the dose that provided the highest degree of clinically meaningful CFA improvement from baseline (off enzyme).

As described in published consensus documents (e.g., Borowitz DS, Grand RJ, Durie PR, et al., J Pediatrics, Nov 1995), decreased CFA is an accepted indicator of EPI, and an increase in CFA is associated with enhanced pediatric growth and development. Thus, the change in CFA can be used as a reasonable marker for pancreatic enzyme activity. For porcine-derived PEPs, the Division of Gastroenterology Products has considered an increase in CFA to be clinically meaningful if it was 30% or greater in the most severely affected patients (i.e., those patients who have baseline CFA less than 40%). There is no accepted change in CFA that has been shown to be clinically meaningful in patients with a Baseline CFA greater than 40%. 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. The Division accepted the use of CFA as the

primary efficacy measure as reasonable and appropriate for the liprotamase clinical development plan, but informed the Applicant that the clinically meaningful change in patients whose baseline CFA is less than 40 % would be ≥30%.

Efficacy of Approved Porcine-Derived PEPs

There are currently three approved and marketed porcine-derived PEPs indicated for treatment of EPI secondary to CF and other causes: Creon, Zenpep and Pancreaze. Their approval was based upon success in meeting the recommendations set forth in the PEP Guidance, including reliance on the primary endpoint of change in CFA. Studies of each of these PEPs showed changes in CFA for the overall population from approximately 25-40%. In the approved porcine-derived PEPs, for the subgroup of patients with baseline CFA < 40% the mean change in CFA ranged from approximately 40-60%. These CFA changes exceed those observed for liprotamase in the major efficacy trial submitted in this application (Study 726). See table below.

Table 32. Cross-Study Comparisons of Change in CFA Results (Creon, Zenpep, Pancreaze, Liprotamase)

	Porcine-derived PEPs			Study 726	Study TC-2A	
Baseline CFA Category	Creon* 4,000 U/g fat/day (n=29[£])	Zenpep* 5,700 U/kg/day (n=32)	Pancreaze[#] 6,400 U/kg/day (n=40)	Liprotamase 32,500 U (per meal or snack) (n=138)	Liprotamase 32,500 U (per meal or snack) (n=41[‡])	Liprotamase 130,000 U (per meal or snack) (n=37[‡])
Overall	41%	26%	33%	11%	11%	17%
Baseline CFA < 40%	61% (n=8[£])	47% (n=5)	--[#]	15% (n=44)	35% (n=8[§])	28% (n=13[§])
Baseline CFA ≥ 40%	31% (n=23[£])	20% (n=26)	--[#]	9% (n=94)	5% (n=35[§])	10% (n=26[§])

*The pivotal studies for Creon and Zenpep each had a cross-over design. Change in CFA was calculated as the mean difference in CFA between the PEP treatment and placebo treatment.

[#]The pivotal study for Pancreaze had a randomized withdrawal design; 20 patients received Pancreaze and 20 patients received placebo. Treatment difference between change in CFA in Pancreaze group and change in CFA in placebo group shown. Baseline CFA was not available because of the randomized withdrawal design.

[‡]mITT population used for primary efficacy analysis

[§]ITT population used for subgroup analyses (Baseline CFA<40% and Baseline CFA ≥40%)

[£]Overall results for Creon taken from the approved Creon label (modified Full Analysis Population; n=29). Subgroup results taken from the FDA Clinical Review for Creon dated April 30, 2009 (Full Analysis Population [n=31]; n=8 in Baseline CFA < 40% category, and n=23 in the Baseline CFA ≥ 40% category).

3.1.4 Efficacy Discussion/Conclusions

Study 726 demonstrated efficacy of liprotamase by achieving a statistically significant increase in CFA compared to the placebo group. However, the differences observed in this trial do not appear as large in magnitude as have been observed in studies of porcine derived PEPs; we note that there are limitations of cross-study comparisons. The overall change in CFA was 11% for liprotamase versus approximately 25-40% in the trials that supported marketing approval for the

porcine derived PEPs. Although the more severely affected patients had numerically larger increases in CFA than less severely affected patients, the changes in this subgroup were not numerically as large as observed with porcine derived PEPs. In the subgroup with baseline CFA < 40%, the change in CFA was 15% for liprotamase vs. approximately 40-60% in the porcine derived PEPs. If this observation is a true reflection of a smaller therapeutic effect on CFA associated with liprotamase relative to porcine derived PEPs, administration of this product to children could result in impaired growth relative to treatment with porcine derived PEPs. For young children where adequate nutrition is a necessity for continued growth, less efficacy is a safety concern, since it could result in growth retardation and failure to gain appropriate weight.

Long-term study 767 was an open-label, uncontrolled study that did not have prospectively defined efficacy endpoints. The Applicant performed numerous exploratory analyses of clinical outcomes, and these data are currently under review. In the future, randomized, double blind, active controlled studies could be helpful in the evaluation of long-term outcomes.

4 Review of Safety

Safety Summary

4.1 Methods

4.1.1 Clinical Studies Used to Evaluate Safety

Safety data were reviewed from all of the clinical studies performed in the liprotamase clinical development program. These studies included a Phase 3 placebo-controlled study (Study 726), two long-term Phase 3 open label studies (Study 767 and prematurely terminated Study 810), a dose ranging Phase 2b study (Study TC-2A), and three short-term Phase 1 studies (Study TC-1A, Study TC-1B and Study TC-1C). See table below. In all studies, (except Study TC-1A and Study 810 whose populations were healthy volunteers and EPI patients with chronic pancreatitis/pancreatectomy, respectively), the population was the same: patients with EPI secondary to CF. Safety was assessed in these studies by the review of all of the AE data, in addition to careful examination of abnormal liver function tests.

The most important study reviewed for safety was Study 726, which was the double blind, placebo-controlled study in CF patients; however, all of the safety data from the liprotamase clinical studies were reviewed in their entirety.

Table 33. Tabular Overview of Clinical Safety Studies

Study ID	Number of Centers (Locations)	Study Status (Study Dates)	Study Design	Patient Population	Liprotamase Dose USP U/Meal or Snack (Lipase/Protease /Amylase) [Duration of Treatment]	No. of Subjects Treated	M/F% W/B/O% Mean age (yrs) (Range)
Phase I, Short-term treatment, Uncontrolled							
TC-1A	1 (US)	Complete (08/02-11/02)	OL, dose ranging, multiple dose	Healthy volunteers	5 cohorts dosed by USP U/kg BW/meal: 1: 1,000/1000/150 2: 2,500/2,500/375 3: 5,000/5,000/750 4: 7,500/7,500/1,125 5: 10,000/10,000/1,500 [6 days]	Total: 20 N=4 N=4 N=4 N=4 N=4	50/50 50/35/15 29 (18-44)
TC-1B	11 (US)	Complete (11/02-07/03)	OL, dose ranging, multiple dose	Cystic fibrosis	5 cohorts dosed by USP U/kg BW/meal: 1: 500/500/75 2: 1,000/1000/150 3: 2,500/2,500/375 4: 5,000/5,000/750 5: 100/100/15 [3 days]	Total: 23 N=5 N=4 N=5 N=4 N=5	61/39 96/0/4 24 (15-44)
TC-1C	1 (US)	Complete (05/03-08/03)	OL, multiple dose	Cystic fibrosis	1,000/1,000/150 dosed by USP U/kg BW/ meal [14 days]	Total: 8	63/38 100/0/0 22 (14-40)
Phase II, Short-term treatment, Controlled							
TC-2A	26 (US)	Complete (06/04-03/05)	R, DB, parallel, dose ranging, concurrent dose-controlled	Cystic fibrosis	3 treatment groups:[a] A1: 6,500/5,000/750 A2: 32,500/25,000/3,750 A3: 130,000/100,000/15,000 [28 days]	Total: 125 N=41 N=43 N=41	61/39 95/1/4 21 (11-55)
Phase III, Short-term treatment, Controlled							
726	34[b] (US:23; Slovakia:3 Poland:3 Italy:2 Argentina:1 Serbia:1 Russia:1)	Complete (05/07-06/08)	Randomized withdrawal, DB, parallel, placebo-controlled	Cystic fibrosis	32,500/25,000/3,750 [34-44 days]	Total: 138[d] LIP: 70 PBO: 68[c,e]	62/38 97/3/0 18 (7-44)
			Non-randomized[c]		32,500/25,000/3,750 [≤ 31 days]	Total: 25 LIP: 25	60/40 92/8/0 22 (7-51)
Phase III, Long-term treatment, Open-label							
767	44 (US:33; Slovakia:3 Poland:3 Italy:2 Argentina:1 Serbia:1 Israel:1)	Complete (06/07-04/09)	Open-label, extension treatment for Study 726 and open-enrollment for de novo patients	Cystic fibrosis	32,500/25,000/3,750[f] [48-52 weeks]	Total: 214[g]	58/42 97/1/1 18 (7-62)
810	9 (US)	Complete (12/07-03/09)	Open-label	Chronic pancreatitis/ pancreatec-tomy	32,500/25,000/3,750[f] [48-52 weeks]	Total: 39	51/49 87/10/3 53 (27-82)

Abbreviations: B=Black, BMI=body mass index, BW=body weight; DB=double-blind, F=female, ITT=intent-to-treat, LIP=liprotamase, M=male, O=other, OL=open-label, PBO=placebo, R=randomized, US=United States, W=White

a Note that dose levels in the CSR describe the A1 dose to be 5,000/5,000/750, A2 dose to be 25,000/25,000/3,750, and A3 dose to be 100,000/100,000/15,000. However, re-evaluation conducted after completion of the study revealed that the actual doses are as displayed in this table (see Module 3.2.P.2.2.1.2).

b Sites that enrolled subjects

(Table above is taken from Pages 12 to 13 of the Applicant's Summary of Clinical Safety)

4.2 Adequacy of Safety Assessments

4.2.1 Overall Exposure at Appropriate Doses/Durations

The safety of liprotamase was evaluated in seven clinical studies. Overall, a total of 492 patients received at least one dose of liprotamase across seven clinical studies, including 20 healthy volunteers, 433 patients with CF-related EPI, and 39 patients with EPI related to chronic pancreatitis or pancreatectomy.

Fifty-one patients received liprotamase for 3-14 days across the three Phase 1 studies. In the Phase 2b study, 117 patients received one of three fixed doses of liprotamase for 28 days. In the Phase 3 study, 138 patients received a fixed dose of liprotamase for 5 ½ weeks. In the two long-term studies, 189 patients received liprotamase for 4 months, 163 patients received liprotamase for 6 months, and 149 patients for 1 year. It should be noted that the product used in the Phase 1 and 2 studies is not comparable to the product used in the pivotal study and the two long-term studies.

The safety data were not pooled for this review. Because the study designs and doses differed, each study was analyzed separately.

The clinical development program for liprotamase followed the current CFF recommendations on limiting the dosages (by lipase units). Even the highest dose administered (130,000 lipase units) fell within these limits. No cases of fibrosing colonopathy were reported in the clinical development program; however, cases of FC are rare, and the finding of even a single case of FC in a safety population of this size would not be expected.

4.2.2 Safety Results by Study

Study 726

Exposure

The exposure to liprotamase is displayed in the table below.

Table 34. Study Drug Exposure by Treatment Group, Safety Population (Study 726)

CHARACTERISTIC	STUDY DRUG EXPOSURE MEAN (SD)		
	ALTU-135 (N = 70)	PLACEBO (N = 68)[a]	NOT RANDOMIZED (N = 25)[b]
Time on Study (Weeks)	6.5 (0.75)	6.6 (0.60)	3.9 (1.37)
Time on Treatment (Weeks)	5.5 (0.71)	5.5 (0.65)	3.1 (1.35)
Number of Capsules	176.6 (26.93)	174.2 (31.01)	94.2 (45.1)

[a] Includes time on ALTU-135 during open-label period
[b] Includes exposure to ALTU-135 during the open-label period
Reference: Table 14.1.12.3

(Table above is taken from Page 93 of the Applicant's 726 Study Report)

Common Adverse Events

Review of the adverse event data showed most events were in the gastrointestinal system category (67% for liprotamase vs. 62% for placebo). A large percentage of adverse events also occurred in the respiratory system (49% for liprotamase vs. 34% for placebo). No clear association between gastrointestinal or respiratory AEs with treatment group was found. In a CF patient population, in which the GI and respiratory systems are the most affected organ systems, adverse events in these systems would be expected, secondary to underlying disease. See table below for complete listing of AEs that occurred in ≥ 5 % of patients.

Table 35. Most Common Treatment Emergent Adverse Events (Reported in ≥ 5% of Subjects) – Study 726

	ALTU-135		PLACEBO		NOT RANDOMIZED	
SYSTEM ORGAN CLASS PREFERRED TERM	SUBJECTS N = 70 n (%)	EVENTS N = 308 n (%)	SUBJECTS N = 68 n (%)	EVENTS N = 277 n (%)	SUBJECTS N = 25 n (%)	EVENTS N = 77 n (%)
Any TEAE	60 (85.7)	308 (100.0)	57 (83.8)	277 (100.0)	20 (80.0)	77 (100.0)
Gastrointestinal Disorders	47 (67.1)	158 (51.3)	42 (61.8)	141 (50.9)	15 (60.0)	39 (50.6)
Abdominal Discomfort	4 (5.7)	5 (1.6)	3 (4.4)	3 (1.1)	0	0
Abdominal Distension	10 (14.3)	12 (3.9)	3 (4.4)	3 (1.1)	3 (12.0)	4 (5.2)
Abdominal Pain	25 (35.7)	34 (11.0)	19 (27.9)	41 (14.8)	7 (28.0)	11 (14.3)
Abdominal Pain Upper	7 (10.0)	10 (3.2)	13 (19.1)	21 (7.6)	3 (12.0)	4 (5.2)
Constipation	3 (4.3)	6 (1.9)	1 (1.5)	1 (0.4)	3 (12.0)	3 (3.9)
Diarrhoea	13 (18.6)	20 (6.5)	12 (17.6)	17 (6.1)	4 (16.0)	4 (5.2)
Flatulence	13 (18.6)	15 (4.9)	11 (16.2)	17 (6.1)	3 (12.0)	4 (5.2)
Frequent Bowel Movements	6 (8.6)	8 (2.6)	5 (7.4)	6 (2.2)	0	0
Nausea	9 (12.9)	10 (3.2)	4 (5.9)	5 (1.8)	0	0
Steatorrhoea	12 (17.1)	15 (4.9)	7 (10.3)	7 (2.5)	2 (8.0)	2 (2.6)
Vomiting	5 (7.1)	5 (1.6)	6 (8.8)	6 (2.2)	2 (8.0)	4 (5.2)
General Disorders & Administration Site Conditions	11 (15.7)	15 (4.9)	9 (13.2)	11 (4.0)	2 (8.0)	2 (2.6)
Pyrexia	5 (7.1)	7 (2.3)	1 (1.5)	1 (0.4)	2 (8.0)	2 (2.6)
Infections & Infestations	4 (5.7)	5 (1.6)	7 (10.3)	7 (2.5)	5 (20.0)	5 (6.5)
Nasopharyngitis	0	0	3 (4.4)	3 (1.1)	2 (8.0)	2 (2.6)
Investigations	13 (18.6)	22 (7.1)	17 (25.0)	31 (11.2)	1 (4.0)	1 (1.3)
Weight Decreased	3 (4.3)	3 (1.0)	5 (7.4)	7 (2.5)	0	0
Nervous System Disorders	16 (22.9)	22 (7.1)	7 (10.3)	9 (3.2)	5 (20.0)	6 (7.8)
Headache	9 (12.9)	12 (3.9)	4 (5.9)	6 (2.2)	4 (16.0)	5 (6.5)
Sinus Headache	4 (5.7)	6 (1.9)	1 (1.5)	1 (0.4)	0	0
Respiratory, Thoracic & Mediastinal Disorders	34 (48.6)	61 (19.8)	23 (33.8)	46 (16.6)	8 (32.0)	15 (19.5)
Cough	11 (15.7)	12 (3.9)	4 (5.9)	4 (1.4)	4 (16.0)	4 (5.2)
Nasal Congestion	6 (8.6)	6 (1.9)	2 (2.9)	3 (1.1)	2 (8.0)	2 (2.6)
Pharyngolaryngeal Pain	4 (5.7)	4 (1.3)	4 (5.9)	4 (1.4)	0	0
Productive Cough	4 (5.7)	4 (1.3)	4 (5.9)	5 (1.8)	0	0
Rales	2 (2.9)	2 (0.6)	2 (2.9)	2 (0.7)	3 (12.0)	3 (3.9)
Respiratory Tract Infection	13 (18.6)	15 (4.9)	7 (10.3)	7 (2.5)	1 (4.0)	1 (1.3)

(Table above is taken from Page 95 of the Applicant's 726 Study Report)

Deaths and Serious Adverse Events (SAEs)

No deaths occurred during the study period. SAEs were experience by 8.6% of the patients on liprotamase vs. 4.4% of patients on placebo. There were 14 SAEs, 12 were treatment emergent

and two occurred in patients who received no study drug. See table below for a complete listing of treatment-emergent SAEs). A brief description of the three non-respiratory SAEs follows:

- Patient 055001 was hospitalized, and the information and diagnostic data available reflect a diagnosis of renal calculi. The etiology of Patient 055001's renal calculi is unclear; however, this reviewer believes it is probably not related to study drug as causes of kidney stones are known to be multi-factorial.

- Patient 901008 randomized to liprotamase was hospitalized with a diagnosis of Distal Intestinal Obstruction Syndrome (DIOS). This condition occurred after one day of study drug administration (which immediately followed the 5-6 day off enzyme treatment). The DIOS was thought to be secondary to the discontinuation of the patient's usual PEP therapy.

- Patient 017003 was readmitted to the hospital immediately after he was discharged following the inpatient off enzyme Baseline period. The patient received one dose of study medication. A diagnosis of pulmonary embolus (PE) was made, and was thought to be secondary to the inpatient stay.

This reviewer agrees with the assessments of the Investigators as described above. The majority of non-DIOS SAEs were consistent with those commonly found in the CF population.

Table 36. Serious Treatment Emergent Adverse Events [Study 726]

SUBJECT ID	AGE (YR) SEX	TREATMENT GROUP	PREFERRED TERM / REPORTED TERM	SEVERITY	RELATIONSHIP TO STUDY DRUG
001004	36, F	ALTU-135	Respiratory Tract Infection / Pulmonary Exacerbation of CF	Moderate	Not Related
042001	20, F	ALTU-135	Respiratory Tract Infection / CF Pulmonary Exacerbation	Moderate	Not Related
			Respiratory Tract Infection / CF Pulmonary Exacerbation	Moderate	Not Related
055001	22, M	ALTU-135	Nephrolithiasis / Kidney Stone	Moderate	Unlikely
			Respiratory Tract Infection / Pulmonary Exacerbation	Moderate	Not Related
901004	25, F	ALTU-135	Upper Respiratory Tract Infection / Upper Tract Respiratory Infection	Mild	Not Related
901008	25, M	ALTU-135	DIOS / DIOS	Moderate	Unlikely
301005	31, F	ALTU-135	Respiratory Tract Infection / Pulmonay Exacerbation	Moderate	Not Related
041003	10, M	Placebo	Aspartate Aminotransferase Increased / Elevated AST	Moderate	Unlikely
901011	18, M	Placebo	Respiratory Tract Infection / Respiratory Exacerbation	Mild	Not Related
301004	16, F	Placebo	Respiratory Tract Infection / Pulmonary Exacerbation	Moderate	Not Related
017003	28, M	Not Randomized	Pulmonary Embolism / Pulmonary Embolus	Moderate	Not Related

(Table above is taken from Pages 99-100 of the Applicant's 726 Study Report)

Significant Laboratory Data: Transaminase Elevations

AST or ALT ≥ 2.5x ULN

Patients with AST or ALT ≥ 2.5x ULN are summarized below by treatment group.

Placebo arm - Nine patients:

- Six of these patients had elevated screening values; three had normal screening values
- Peak elevations ranged from 2.9x ULN - 5.2x ULN for the patients with elevated screening values and were 2.7x ULN, 3.3x ULN and 4.8x ULN for those patients with normal screening values.

Liprotamase arm - Six patients:

- Three of these patients had elevated screening values; three had normal screening values.
- Peak elevations were 2.9x ULN, 4.3x ULN and 5.7x ULN for the patients with elevated screening values, and 2.8x ULN, 7.8x ULN and 9.9x ULN for those patients with normal screening values.

Of note are the two remarkable elevations of 7.8x ULN (AST) in Patient 403005 (simultaneous elevation of 5.9x ULN for ALT) and 9.9x ULN (ALT) in Patient 002001, which both occurred in the liprotamase treatment group in patients who had normal screening values. In the placebo group, there were no elevations greater than 5.2x ULN. There were a numerically higher number of patients with elevations of ALT and/or AST ≥ 5x ULN in the liprotamase group than the placebo group; also, the magnitude of elevations appeared to be greater in the liprotamase group than the placebo group.

No patient demonstrated simultaneous elevations of ALT or AST (3x ULN) in addition to total bilirubin (2x ULN); thus, no patient met the criteria for Hy's Law.

Study TC-2A

Exposure

The study drug exposure in the dose ranging Study TC-2A (safety population), which utilized a product that is physico-chemically not comparable to the product administered in the Phase 3 trial, is shown below.

Table 37. Study Drug Exposure by Treatment Group, Safety Population (Study TC-2A)

Duration of Treatment (Days)	Liprotamase Dose Group: 6,500 U (N=41)	32,500 U (N=43)	130,000 U (N=41)	Total (N=125)
Mean (SD)	27.1 (4.32)	27.3 (4.14)	25.9 (7.29)	26.7 (5.42)
Median	28.0	28.0	28.0	28.0
Min, Max	5, 30	5, 29	1, 30	1, 30

Table above is taken from Page 34 of the Summary of Clinical Safety.

Mean (SD) duration of treatment across all 125 subjects in the Safety Population of this study was 26.7 (5.42) days and was similar across the Low, Mid and High dose groups

Common Adverse Events

During treatment, patients were most likely to experience GI-related AEs; a total of 106 patients (85%) experienced at least one GI-related AE. Of these, 93% occurred in Treatment arm 1, 80% occurred in Treatment arm 2, and 83% occurred in Treatment arm 3. In addition,

respiratory, thoracic, and mediastinal disorders were experienced by 66 patients (53%). Of these AEs, 59% occurred in Treatment arm 1, 56% occurred in Treatment arm 2, and 44% occurred in Treatment arm 3; however, the majority were thought to be related to the underlying disease of CF. No clear association between gastrointestinal AEs and treatment group (i.e., low, middle, or high dose) was found. Furthermore, there was no apparent association between respiratory AEs and treatment group (i.e., low, middle, or high dose). See Appendix 5 for a complete table of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term.

Deaths and Serious Adverse Events

There were no deaths during the study period. Treatment-emergent SAEs were experienced by 12 patients (9.6%). There were six patients (14.6%) in Treatment arm 1, two patients (4.7%) in Treatment arm 2, and four patients (9.8%) in Treatment arm 3. Most of the SAEs were related to GI disorders (three patients [2.4%]) and respiratory, thoracic, and mediastinal disorders (six patients [4.8%]). See table below. There were two cases of DIOS and one case of intestinal obstruction as described below:

- Patient 102-001 (24 year old male), randomized to Treatment arm 1, tolerated the discontinuation of his usual PEP, complaining only of increased stool frequency. However, three days after administration of liprotamase, he developed the onset of abdominal pain, cramping, and difficulty passing stool. Two days later, the patient was admitted to the hospital with persistent symptoms and a presumed diagnosis of DIOS. Study drug was discontinued at that time. The patient responded to appropriate treatment, and was discharged fours days later with resolution of symptoms.

- Patient 127-004 (21 year old female), randomized to Treatment arm 3, developed abdominal "tenderness" one day after discontinuing per usual PEP. Over the next couple of days, her abdominal "pain" increased. On the day she started treatment with study drug, she had an abdominal film that "revealed findings suggestive of meconium ileus equivalent" or DIOS. The patient's hospital course was complicated by acute renal failure presumed to be secondary to NSAID use plus dehydration. With appropriate treatment, both conditions resolved over several days.

- Patient 116-002 (15 year old male), randomized to Treatment arm 3, developed symptoms of bowel obstruction two days after discontinuation of his usual PEP. He had received 3 doses of study medication. Symptoms worsened over the next couple of days until he was treated and the symptoms resolved.

The only treatment-emergent SAE that was considered by the investigator to be related to the study drug occurred in Patient 102-001. In each of the other cases described above, since the obstructive symptoms began prior to initiation of study drug, the investigator felt that it was unlikely that the events were study drug related. This reviewer concurs with the investigator's opinion in the case of the 24 year old male; however, for the subsequent two cases, the study drug could possibly be related to the events. Both patients started to have symptoms prior to study drug, but both patients' conditions worsened after study drug.

The other non-GI treatment-emergent SAEs appeared to be secondary to the patient's underlying disease of CF, and there was one case of a food allergy. No clear association between incidence of gastrointestinal or respiratory treatment-emergent SAEs and dose group was apparent. There were two patients who had SAEs which occurred within 1 week after completion of the treatment period. Both were hospitalized for lung infiltrations, thought to be secondary to underlying lung disease. This reviewer agrees with the assessments of the investigators regarding each of the non-GI treatment-emergent SAEs relation to study drug.

Serious treatment emergent adverse events are shown in the table below.

Table 38. Patients with Treatment Emergent Serious Adverse Events

System Organ Class	Preferred Term	Site	Subj No.	Treat-ment Arm	Intensity	Relationship to Study Drug	Action Taken	Outcome	Treatment Day when event occurred
GI Disorders	DIOS	102	001	Arm 1	Moderate	Probable	Drug discontinued, hospitalization, Concomitant Med	Resolved without Sequelae	T5
	Intestinal Obstruction	116	002	Arm 3	Severe	Unlikely	Drug discontinued, Hospitalization	Resolved without Sequelae	T2
	DIOS	127	004	Arm 3	Severe	Unlikely	Concomitant Med, Hospitalization	Resolved without Sequelae	T1 (one dose)
Respiratory, Thoracic, and Mediastinal Disorders	Lung Infiltration	103	031	Arm 3	Moderate	Unlikely	Hospitalization, Concomitant Med	Resolved without Sequelae	T5
	Lung Infiltration	105	001	Arm 1	Moderate	Unlikely	Concomitant Med, Hospitalization	Resolved without Sequelae	T10
	Lung Infiltration	110	007	Arm 1	Moderate	Unlikely	Concomitant Med, Hospitalization	Resolved without Sequelae	T14
	Lung Infiltration	110	009	Arm 2	Moderate	Unlikely	Concomitant Med, Hospitalization	Resolved without Sequelae	T16
	Lung Infiltration	113	015	Arm 3	Moderate	Unlikely	Concomitant Med, Hospitalization	Resolved without Sequelae	T17
	Haemoptysis	127	001	Arm 1	Moderate	Unlikely	Hospitalization	Resolved with Sequelae	T7
Immune System Disorders	Food Allergy	105	003	Arm 2	Moderate	Unlikely	Concomitant Med	Resolved without Sequelae	T29
Infections and Infestations	Pneumonia	103	004	Arm 1	Mild	Unlikely	Hospitalization, Concomitant Med	Resolved without Sequelae	T1 (planned admission)
Investigations	Oxygen Saturation Abnormal	123	001	Arm 1	Mild	Unlikely	Hospitalization	Resolved without Sequelae	T14

(Table above is taken from Applicant's TC-2A Study Report)

Significant Laboratory Data: Transaminase Elevations

AST or ALT ≥ 2.5x ULN

Patients with AST or ALT ≥ 2.5x ULN are summarized below by treatment group.

Treatment Arm 1 (6,500 U lipase) - Ten patients:

- Nine of these patients had elevated screening values; one had a normal screening value.
- Peak elevations ranged from 2.1x ULN – 4.4x ULN for the patients with elevated screening values except one patient whose peak elevation of 7.3x ULN occurred at screening. For the patient who had a normal value at screening, the peak elevation was 2.5x ULN. In total, there was one peak elevation > 5x ULN.

Treatment Arm 2 (32,500 U lipase) - Nine patients:

- Eight of these patients had elevated screening values; one had a normal screening value
- Peak elevations ranged from 2.6x ULN – 5.8x ULN for the patients with elevated screening values. There were two patients with > 5x ULN (5.1x ULN and 5.8x ULN). For the patient who had a normal value at screening, the peak elevation was 2.6x ULN. In total, there were two peak elevations > 5x ULN.

Treatment Arm 3 (130,000 U lipase) -11 patients

- Nine of these patients had elevated screening values; two had normal screening values
- Peak elevations ranged from 2.5x ULN – 14.9x ULN for the patients with elevated screening values. Three of these patients had peak values > 5x ULN (6.0x ULN, 9.5x ULN and 14.9x ULN). For the two patients with normal values at screening, the peak elevations were 2.5x ULN and 6.0x ULN. In total, there were four peak elevations ≥ 5x ULN.

It appears from the data presented above that there exists a trend toward higher elevations of ALT and/or AST in patients with increasing dose of liprotamase.

No patient demonstrated simultaneous elevations of ALT or AST (3x ULN) in addition to total bilirubin (2x ULN), thus no patient met the criteria for Hy's Law.

Long-term studies 767 and 810

See Table below for Summary of Exposure for Studies 767 and 810 (Safety Population).

Table 39. Total Exposure for Studies 767 and 810 (Safety Population)

Exposure Category	Statistics	Study 767				Study 810 (N=39)
		Age Subgroups, years			Total (N=214)	
		7 to < 12 (N=55)	12 to < 17 (N=57)	≥ 17 (N=102)		
Average # of Capsules per Day	Mean (SD)	5.9 (1.4)	5.7 (1.8)	5.1 (2.0)	5.5 (1.8)	4.1 (2.3)
	Median	5.5	5.8	4.9	5.4	3.4
	Range	3.1, 8.8	1.7, 9.9	1.3, 10.6	1.3, 10.6	1.7, 10.5
Duration of Treatment (weeks)	Mean (SD)	43.45 (14.74)	39.73 (17.97)	35.79 (19.37)	38.81 (18.11)	24.25 (16.77)
	Median	51.00	48.29	48.29	49.07	25.14
	Range	3.14, 55.86	1.00, 53.29	0.29, 54.86	0.29, 55.86	0.14, 55.57
Person-time (years)	Mean (SD)	0.83 (0.28)	0.76 (0.34)	0.69 (0.37)	0.74 (0.35)	0.46 (0.32)
	Median	0.98	0.93	0.93	0.94	0.48
	Range	0.06, 1.07	0.02, 1.02	0.01, 1.05	0.01, 1.07	0.00, 1.07

(Table above is taken from Page 35 of the Summary of Clinical Safety.)

According to the table above, it appears that pediatric patients received a slightly higher dose of liprotamase than the adult population. Thus, it is likely that pediatric patients had a larger weight based dose assuming the pediatric patients weighed less than the adult patients.

For patient demographic data and baseline characteristics for each of the long-term studies, see Appendix 6.

Relevant Safety Data - Study 767 (Cystic Fibrosis; n=214)

This was an open-label study of approximately one year duration in CF patients ages 7 to 62 years. There was one death during this study. Patient 028101 was hospitalized and died secondary to MRSA sepsis, pneumonia and respiratory arrest. In the opinion of the investigator, the events were not related to the study drug. Since complications of respiratory infections and pneumonia are common secondary to CF, this reviewer agrees with the investigator.

The Applicant divided the population into three categories based upon what percent of study days the patient had received more than five liprotamase capsules. Low exposure was defined as $\leq$ 25%, Mid exposure was >25% to $\leq$ 75% and High exposure was ≥75%.

Overall, 61 (28.5%) of the 214 patients experienced at least one SAE; the incidence of SAEs did not increase with exposure to liprotamase based on the percent of days subjects took more than five capsules. The highest SAE incidence was observed in the Low exposure subgroup (35.2%) compared with the Mid (27.0%) and High (20.6%) exposure subgroups.

A summary of the most commonly reported SAEs in Study 767 is presented in Appendix 7. The most commonly reported SAEs were infections (24.3%); these were respiratory tract infections (18.2%), pneumonia (1.4%), bronchitis (1.4%), bronchiectasis (0.9%), and pseudomonal lung infection (0.9%). Serious GI events were reported in seven (3.3%) patients with abdominal pain, the most frequently reported serious GI event (0.9%). The most commonly reported SAEs appear to be consistent with the underlying disease of CF.

DIOS was reported in three patients (1.4%) during the course of the study, including one patient in each of the exposure subgroups. The cases are described below:

- Patient 027101 (18 year old male) developed symptoms consistent with DIOS within one week of starting study drug. The event resolved following appropriate treatment. The patient was discontinued from the study. In the investigator's opinion, the severity of this event was moderate and the relationship to study drug was probable, as the timing of symptom onset with the start of study drug indicates a causal relationship.

- Patient 021107 (21 year old male) had DIOS reported on Day 31 as moderate in severity and in the investigator's opinion probably related to study treatment. The patient resumed treatment and completed the study without recurrence of DIOS.

- Patient 201110 (13 year old male) had DIOS reported on Day 85, which was assessed as mild in severity and, in the investigator's opinion, possibly related to study treatment. The patient resumed treatment and completed the study without recurrence of DIOS.

In one of the patients (Patient 027101, 18 year old male), the event was reported as an SAE and led to treatment discontinuation. Of note, Patient 027101 had DIOS (reported as "bowel obstruction") during Study TC-2A (Patient 116002 above) two days after discontinuation of his usual PEP. He had received 3 doses of study medication. In Patient 021107 (21 year old male), the DIOS was reported on Day 31 as moderate in severity and probably related to study treatment. The event resolved following appropriate treatment. In Patient 201110 (13 year old male), the DIOS was reported on Day 85 and was assessed as mild in severity and possibly related to study treatment. The event resolved following appropriate treatment. Both of these patients resumed treatment and completed the study without recurrence of DIOS.

This reviewer believes that all three cases of DIOS could possibly or probably be related to study drug.

Relevant Safety Data - Study 810 (Chronic Pancreatitis or Pancreatectomy; n=39)

This was an open-label study of approximately one year duration in CP or pancreatectomy patients, ages 27 to 72 years. Of note, this study was terminated early for unclear reasons, thus there were 39 patients included in the safety analysis. The Applicant divided the population into three categories based upon what percent of study days the patient had received more than five liprotamase capsules. Low exposure was defined as $\leq$ 25%, Mid exposure was >25% to $\leq$ 75% and High exposure was ≥75%. There were 29, 6 and 4 patients in the Low, Mid, and High

exposure groups, respectively. Due to the small number of patients in both the Mid exposure and High exposure subgroups, it is difficult to detect any pattern of incidence based upon this exposure classification.

There was one accidental death secondary to a house fire during the study. Overall, 15 SAEs were reported in four patients (3 Low exposure, 1 Mid exposure, no High exposure). One patient in the Low exposure subgroup reported 11 serious events of "chronic pancreatitis exacerbation". All remaining SAE event terms (4 total), were reported among 3 patients. These included the above death, intervertebral disc protrusion, pseudomonas lung infection and fall.

Five patients withdrew from the study as a result of TEAEs. These events included:

- Increased creatine kinase (CK) levels (maximum level of 1980 U/L) of unknown etiology with questionable relation to chest pain with unknown diagnosis.
- Abnormal liver function test (< 2x ULN)
- Gastritis
- Multiple series of gastrointestinal, musculoskeletal, and nervous system events
- Cystic Fibrosis (discovered diagnosis of CF during study; patients with CF were excluded from study participation)

The investigator reported that all the above TEAEs could have been related to the study drug, with the exception of CF. This reviewer agrees with the investigator's assessment.

See Appendix 8 for a listing of TEAE's reported in ≥ 5% of patients.

Significant Laboratory Data: Transaminase Elevations –Studies 767 and 810

Liver function tests (LFTs) were routinely checked at Screening (≤ 4 wks prior to Baseline), Baseline, Weeks 2 and 4, Months 3, 4, 6, 8, 10, and 12, and at follow-up. The table below shows the proportion of subjects with LFT elevations in the long term studies, 767 and 810.

Table 40. Proportion of Subjects with LFT Elevations Long Term Studies 767 and 810 (Safety Population): Maximum Value Observed

Range	Number of Subjects [n (%)]			
	Baseline or Screening	Maximum Value On Liprotamase Treatment	Last Value	Discontinued Treatment Due to Elevated LFT
AST and/or ALT	**(N = 253)**	**(N = 245)***	**(N = 245)***	**(N = 253)‡**
Normal ALT and AST	200 (79)	105 (43)	167 (68)	0
AST or ALT > ULN to < 2.5*ULN	48 (19)	106 (43)	69 (28)	3 (1)
AST or ALT ≥ 2.5*ULN to < 5*ULN	4 (2)	27 (11)	7 (3)	1 (0)
AST or ALT ≥ 5*ULN to < 10*ULN	1 (0)	7 (3)	2 (1)	0
AST or ALT ≥ 10*ULN	0	0	0	0
Total Bilirubin	**(N = 253)**	**(N = 245)***	**(N = 245)***	**(N = 253)§**
Normal Bilirubin	238 (94)	224 (91)	231 (94)	4 (100)
Bilirubin > ULN to < 2.5*ULN	15 (6)	20 (8)	14 (6)	0
Bilirubin ≥ 2.5*ULN to < 5*ULN	0	1 (0)	0	0
Bilirubin ≥ 5*ULN to < 10*ULN	0	0	0	0
Bilirubin ≥ 10*ULN	0	0	0	0

Note: Summaries based on events exclusive of those occurring more than 14 days after discontinuation of treatment.
* Eight patients did not have any post-treatment laboratory values.
‡ Discontinued due to elevated transaminase.
§ Discontinued due to elevated bilirubin.

(Table above is taken from Applicant's Response to IR dated September 20, 2010)

At the start of the study, 19% of the patients had mildly elevated transaminases, 2% had moderate elevations (i.e., 2.5x to 5x ULN) and one patient had an elevation between 5x ULN and 10x ULN. During the study, 43% of the patients had mildly elevated transaminases, 11% had moderate elevations and 3% (seven patients) had elevations between 5x ULN and 10x ULN. According to the above table, for the last value, 28% of the patients had mildly elevated transaminases, 3% had moderate elevations and 2% (one patient) had an elevation between 5x ULN and 10x ULN. However, the "last value" represented in the above table may have been taken at the end of study or obtained many weeks after study completion. In summary, from the table above, it appears that although many patients had transaminase elevations at baseline or screening, the proportion of patients in each of the elevation categories was numerically higher on treatment compared to at baseline or screening.

No patient demonstrated simultaneous elevations of ALT or AST (3x ULN) in addition to total bilirubin (2x ULN), thus no patient met the criteria for Hy's Law.

Safety Discussion/Conclusions

As a non-porcine derived PEP, liprotamase does not carry the potential risk of porcine viral transmission as do the porcine derived PEPs. However, porcine derived PEPs have decades of safety data available, and there is a considerable body of evidence in the literature to support safety of porcine derived PEPs. The body of evidence to support safety of liprotamase, a new molecular entity (NME), comes only from the safety data obtained in the clinical development program. Exposure to the Phase 3 product[3] (i.e., the product used in Studies 726, 767 and 810) is limited to 138 patients for 5.5 weeks, 163 patients for 6 months, and 149 patients for 1 year.

Although there is a considerable body of evidence from the literature supporting the safety of PEPs, the collective clinical trial safety database of the approved PEPs is considerably smaller than that of liprotamase. The clinical trial of each PEP was generally limited to one short term clinical trial of approximately 30 patients.

As presented in the sections above, there are potential safety issues that have been identified during the review of the liprotamase development program.

- If liprotamase offers less efficacy than the currently marketed PEPs, treatment in children could result in growth retardation and malnutrition. The studies conducted in the liprotamase development program did not allow a determination of whether these risks are increased with liprotamase compared to PEPs.

- Seven DIOS events occurred in six patients during the liprotamase clinical trials (in the patient that had two events of DIOS, the events were separated by more than two years). It should be noted that no DIOS cases were observed in the clinical trials of the approved porcine-derived PEPs. There is the concern that the DIOS cases occurred with liprotamase because of lower efficacy than PEPs. However, DIOS is a known complication of cystic fibrosis, and it is possible that cases were not identified in the PEP trials because of the considerably smaller clinical trial safety database of the PEPs compared to that of liprotamase.

- A large proportion of the patient population developed elevations of transaminase levels although there were no Hy's Law cases. In Study TC-2A, there appeared to be a trend of a greater number of patients having transaminase elevations ≥ 5x ULN with increasing dose, and there appeared to be a trend of a higher magnitude of observed transaminase elevations with increasing dose. In Study 726, there appeared to be a higher magnitude of transaminase elevations in the liprotamase treatment group compared to the placebo group; a numerically higher number of patients had transaminase elevations ≥ 5x ULN in the liprotamase group than the placebo group. During the long-term studies 767 and 810, many patients had transaminase elevations at baseline or screening, however, the proportion of patients in each of the elevation categories (i.e., >1 to <2.5x ULN, ≥2.5 to

[3]There are only limited differences between the product in Study 726 and the to-be-marketed product (TBMP); these would be unlikely to have an impact on clinical efficacy and safety (see CMC Review).

<5x ULN, and ≥5x ULN to <10x ULN) was numerically higher on treatment compared to at baseline or screening.

APPENDIX 1: Dosing of PEPs

Dosing of PEPs for EPI is individualized based on age, body weight, fat content of the diet, and control of clinical symptoms such as steatorrhea. The major dosing guidelines for PEPs are the Consensus Conferences guidelines established by the Cystic Fibrosis Foundation (CFF); see table below.[4,5,6]

Table 41. Dosing Recommendations - Approved PEPs* (based on CFF Consensus Guidelines)

Age	Starting Lipase Dose / Meal or Snack†	Maximum Lipase Dose
Up to 12 months	2,000 to 4,000 USP units†,#	2,500 USP units/kg/meal or 10,000 USP units/kg/day
1 to 3 years	1,000 USP units/kg£	2,500 USP units/kg/meal or 10,000 USP units/kg/day or 4,000 units/gram of fat per day
4 years and older	500 USP units/kg£	

*Dosing recommendations summarized from labels for approved PEPs (Creon, Zenpep, Pancreaze)
†For infants, 2,000 to 4000 USP units per 120 mL of formula or per breast feeding
#Contents of capsule cannot be mixed directly into formula or breast milk prior to administration.
£Contents of the capsule can be mixed in soft acidic foods

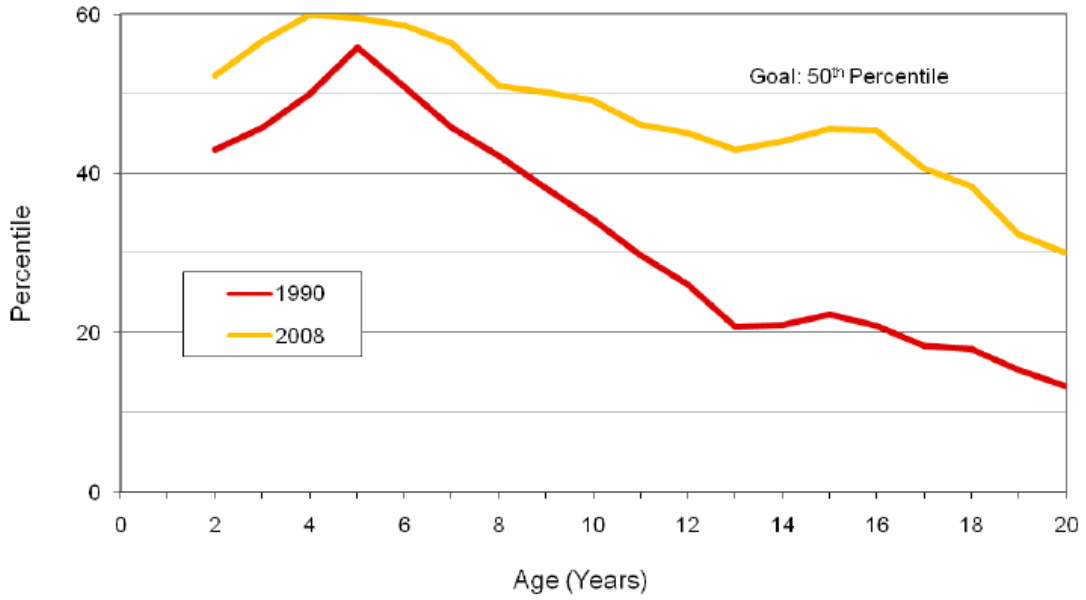
[4] Borowitz DS, Baker RD, Stallings V. Consensus Report on Nutrition for Pediatric Patients with Cystic Fibrosis. J Pediatric Gastroenterology and Nutrition. 2002 Sep; 35: 246-259.
[5] Borowitz, DS, Grand RJ, Durie PR, et al. Use of pancreatic enzyme supplements for patients with cystic fibrosis in the context of fibrosing colonopathy, J Pediatrics 1995; 127: 681-684.
[6] FitzSimmons SC, Burkhart GA, Borowitz DS, et al. High-dose pancreatic-enzyme supplements and fibrosing colonopathy in children with cystic fibrosis. NEJM 1997; 336: 1283-1289.

APPENDIX 2: CFF Registry Data (from the 2008 Annual Data Report from CFF)

BMI – CFF Registry (Annual Report 2008):

Median BMI percentiles versus age, 1990 and 2008 (from the 2008 Annual Data Report from CFF) are shown in the figure below.

Figure 8. Median BMI Percentiles vs. Age, 1990 and 2008 (2008 Annual Data Report; CFF)



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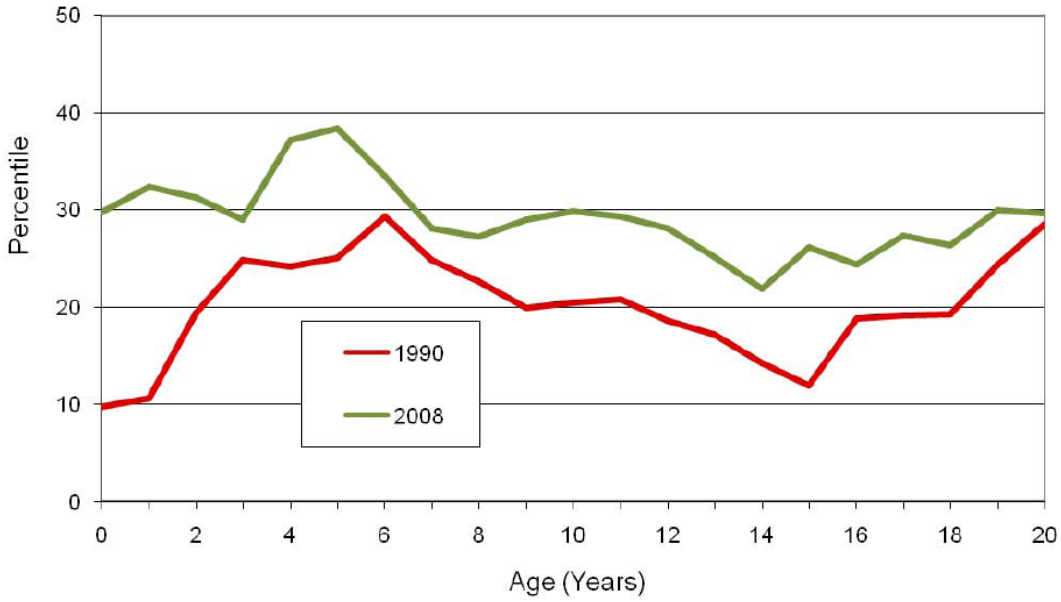
(Figure above is taken from Page 31 of the 767 Study Report.)

Height – CFF Registry (Annual Report 2008):

Median height percentiles versus age, 1990 and 2008 (from the 2008 Annual Data Report from CFF) are shown in the figure below.

Figure 9. Median Height Percentiles vs. Age, 1990 and 2008 (2008 Annual Data Report; CFF)



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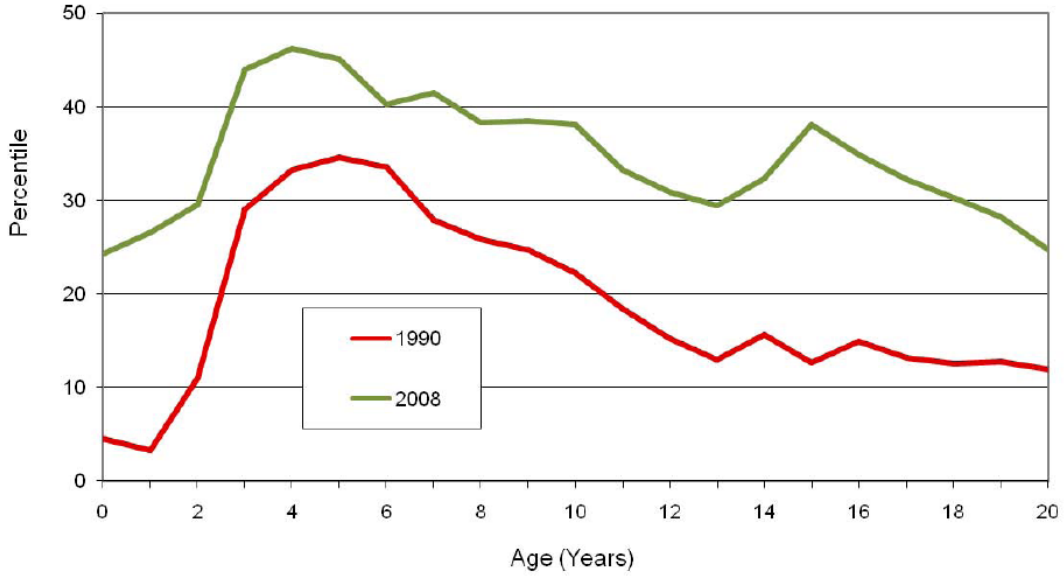
(Figure above is taken from Page 30 of the 767 Study Report.)

Weight – CFF Registry (Annual Report 2008):

Median weight percentiles versus age, 1990 and 2008 (from the 2008 Annual Data Report from CFF) are shown in the figure below.

Figure 10. Median Weight Percentiles vs. Age, 1990 and 2008 (2008 Annual Data Report; CFF)



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(Figure above is taken from Page 30 of the 767 Study Report.)

APPENDIX 3: Group Matched CFF Registry Data

Table 42. Demographic and Baseline Characteristics, Study 767 (All Treated Subjects) and the Group Matched Controls from the CFF Registry

Characteristic	Study 767 (N = 214)	CFF Registry Group Matched Controls (N = 5,660)
Age (years)		
Mean (SD)	18.6 (8.79)	19.2 (9.94)
Median	16.5	16.6
Minimum, Maximum	7.0, 62.3	7.0, 79.6
Age Subgroups (years), n (%)		
7 to < 12	55 (25.7)	1,450 (25.6)
12 to < 17	57 (26.6)	1,488 (26.3)
≥ 17	102 (47.7)	2,722 (48.1)
Age Subgroups (years), n (%)		
7 to < 20	137 (64.0)	3,674 (64.9)
≥ 20	77 (36.0)	1,986 (35.1)
Sex, n (%) Male	124 (57.9)	2,923 (51.6)
Race, n (%) Caucasian	208 (97.2)	Not Available

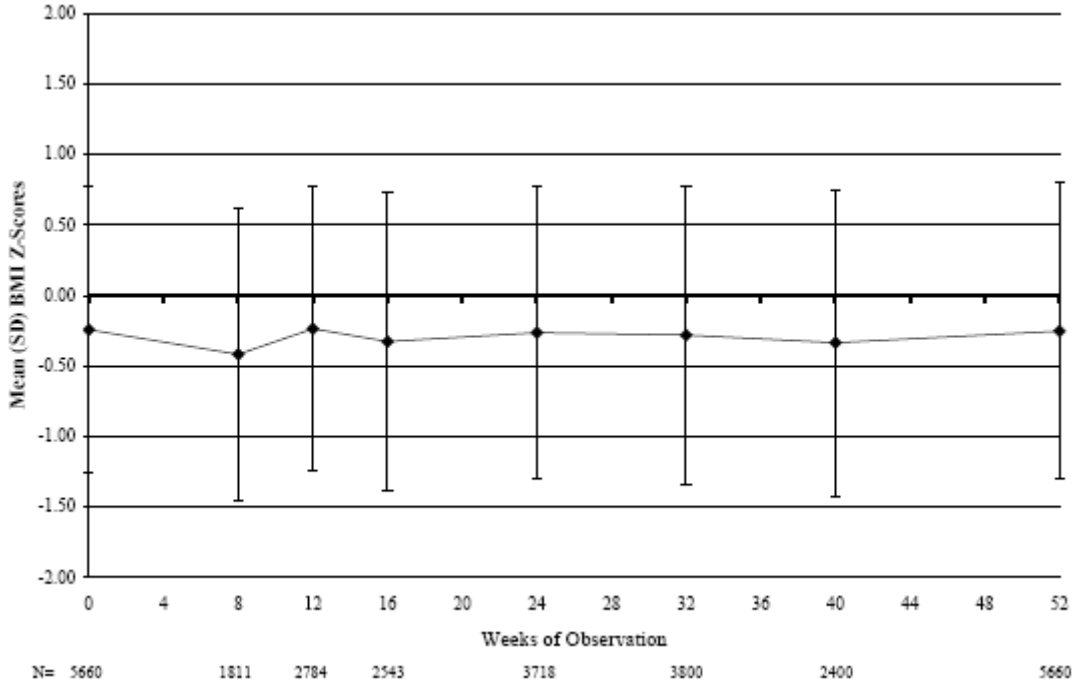
(Table above taken from Page 94 of the Summary of Clinical Efficacy.)

Table 43. Baseline BMI and BMI, Height, and Weight Z-Scores, Study 767 (All Treated Subjects) and the Group-Matched CFF Registry Patients

Characteristic	Study 767 (N = 214)			CFF Registry Group Matched Patients (N = 5,660)		
	7 to < 20 years (N = 137)	≥ 20 years (N = 77)	All subjects N = (214)	7 to < 20 years (N = 3,674)	≥ 20 years (N = 1,986)	All subjects (N = 5,660)
BMI (kg/m^2)						
Mean (SD)	17.9 (2.72)	22.4 (5.05)	19.5 (4.26)	18.7 (3.09)	22.2 (3.75)	19.9 (3.72)
Median	17.6	21.4	19.4	18.4	21.6	19.6
Min, Max	12.5, 26.0	15.4, 52.5	12.5, 52.4	11.9, 38.4	14.2, 61.0	11.9, 61.0
BMI Z-Score						
Mean (SD)	-0.541 (0.980)	-0.386 (1.042)	-0.494 (0.994)	-0.191 (0.966)	-0.339 (1.097)	-0.243 (1.016)
Median	-0.373	-0.412	-0.410	-0.173	-0.268	-0.199
Min, Max	-3.792, 1.586	-3.431, 3.150	-3.972, 3.149	-8.548, 2.620	-5.746, 3.365	-8.548, 3.365
Height Z-Score						
Mean (SD)	-0.439 (0.989)	Not	-0.490 (0.989)	-0.577 (1.026)	-0.453 (0.990)	-0.534 (1.015)
Median	-0.348	Assessed	-0.406	-0.589	-0.512	-0.538
Min, Max	-3.608, 2.240		-3.738, 2.240	-5.164, 7.707	-4.620, 3.277	-5.164, 7.707
Weight Z-Score						
Mean (SD)	-0.634 (0.975)	-0.540 (1.131)	-0.607 (1.031)	-0.457 (1.035)	-0.453 (1.113)	-0.456 (1.063)
Median	-0.611	-0.542	-0.575	-0.440	-0.395	-0.422
Min, Max	-4.245, 1.331	-3.548, 3.788	-4.378, 3.787	-9.822, 3.496	-4.799, 3.997	-9.822, 3.997

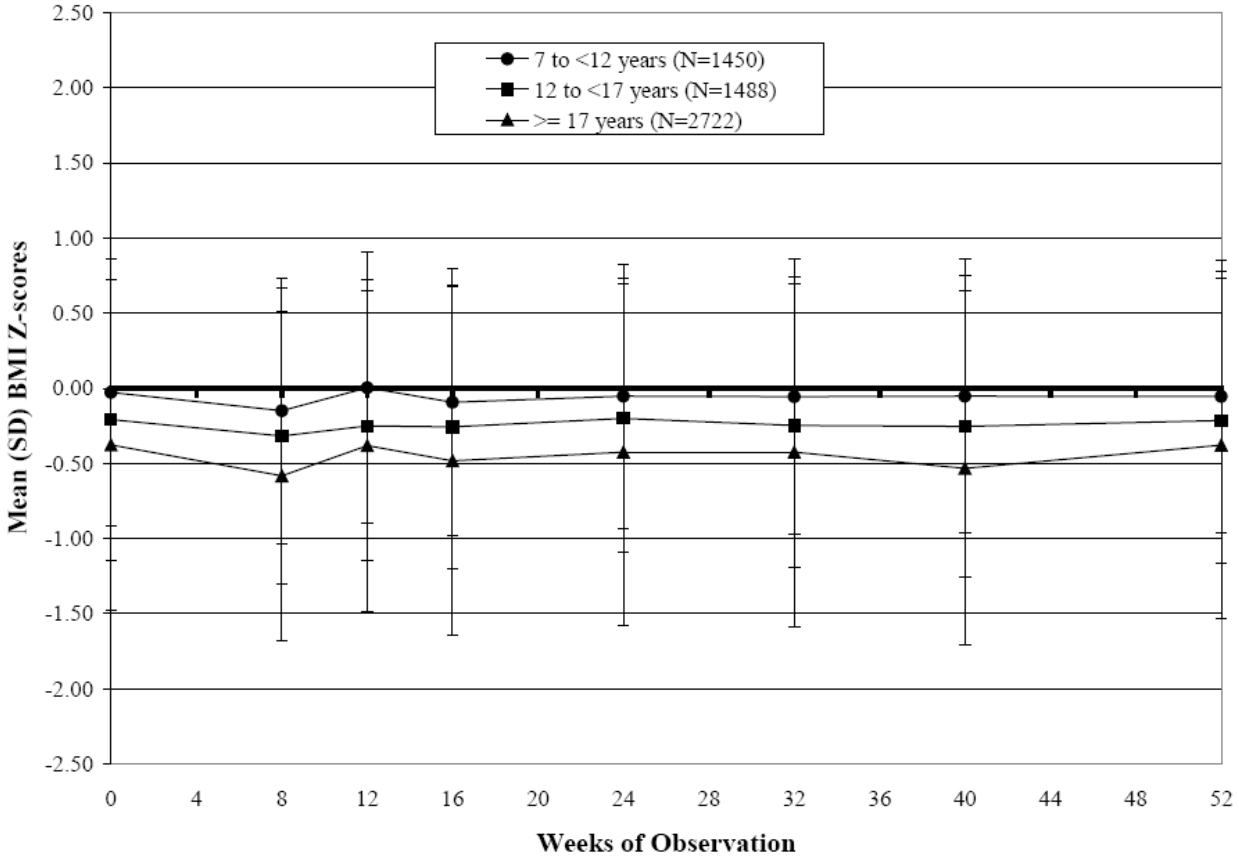
(Table above taken from Page 95 of the Summary of Clinical Efficacy.)

Figure 11. Mean (SD) BMI Z-scores Over Time, CFF Registry Population (N = 5,660)



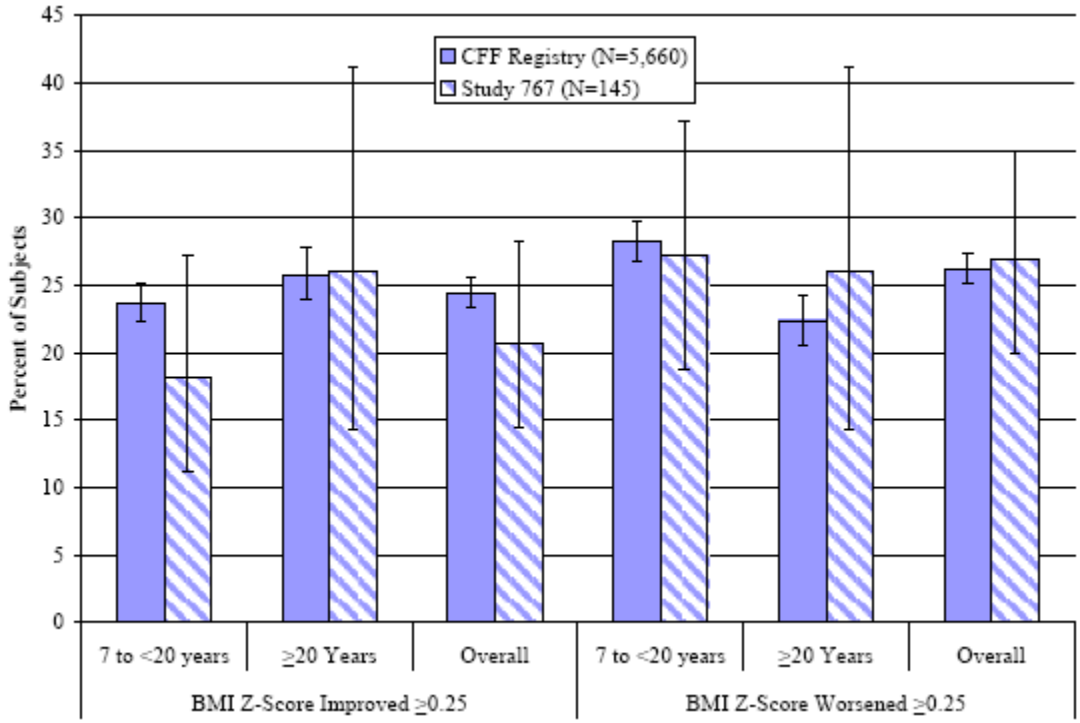
(Figure above taken from Page 105 of the Summary of Clinical Efficacy.)

Figure 12. Mean (SD) BMI Z-scores by Age Subgroups (7 to <12, 12 to <17, and ≥17 years), CFF Registry Population (N=5,660)



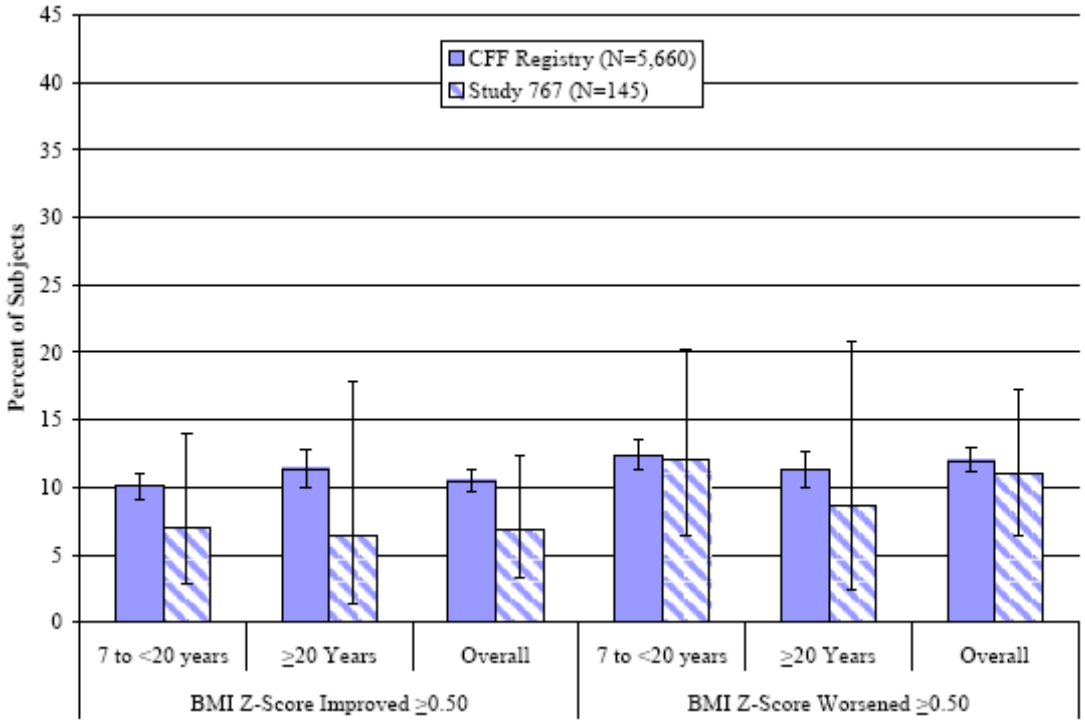
(Figure above taken from Page 26 of the Applicant's Cystic Fibrosis Foundation Registry Data Analysis.)

Figure 13. BMI Z-Score Shift Analysis (Proportion ± 95% CI): Improvements and Worsening from Baseline of ≥0.25 Overall and by Age Subgroups, Study 767 and CFF Registry Population (Subjects with Baseline and Month 12 Data)



(Figure above taken from Page 107 of the Summary of Clinical Efficacy.)

Figure 14. BMI Z-Score Shift Analysis (Proportion ± 95% CI): Improvements and Worsening from Baseline of ≥0.50 Overall and by Age Subgroups, Study 767 and CFF Registry Population (Subjects with Baseline and Month 12 Data)



(Figure above taken from Page 108 of the Summary of Clinical Efficacy.)

APPENDIX 4: BMI Classifications for Shift Analyses in Age Subgroups

Table 44. BMI Classifications for Shift Analyses in Age Subgroups

AGE	BMI	BMI CLASSIFICATION
7 to 20 years	> -0.6745 z-score	Acceptable
	-1.2822 to -0.6745 z-score	At Risk
	< -1.2822 z-score	Unacceptable
>20 years	>20 kg/m^2	Acceptable
	19 to 20 kg/ m^2	At Risk
	<19 kg/m^2	Unacceptable

(Table above taken from Page 62 of the 767 study Report.)

APPENDIX 5: TC-2A TEAE's

Table 45. Study TC-2A Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

System Organ Class/Preferred Term	All Events		
	Arm 1 (N = 41)	Arm 2 (N = 43)	Arm 3 (N = 41)
Any AE	41 (100.0%)	42 (97.7%)	39 (95.1%)
GI Disorders	38 (92.7%)	34 (79.1%)	34 (82.9%)
Abdominal Discomfort	5 (12.2%)	0 (0.0%)	2 (4.9%)
Abdominal Distension	4 (9.8%)	6 (14.0%)	6 (14.6%)
Abdominal Pain Lower	16 (39.0%)	17 (39.5%)	11 (26.8%)
Abdominal Pain Upper	10 (24.4%)	6 (14.0%)	4 (9.8%)
Abnormal Faeces	5 (12.2%)	4 (9.3%)	3 (7.3%)
Constipation	1 (2.4%)	7 (16.3%)	4 (9.8%)
Diarrhoea	5 (12.2%)	5 (11.6%)	3 (7.3%)
DIOS	1 (2.4%)	0 (0.0%)	1 (2.4%)
Dyspepsia	1 (2.4%)	1 (2.3%)	2 (4.9%)
Flatulence	11 (26.8%)	9 (20.9%)	15 (36.6%)
Frequent Bowel Movements	6 (14.6%)	4 (9.3%)	0 (0.0%)
Loose Stools	10 (24.4%)	8 (18.6%)	5 (12.2%)
Nausea	5 (12.2%)	11 (25.6%)	5 (12.2%)
Steatorrhoea	1 (2.4%)	3 (7.0%)	0 (0.0%)
Vomiting	5 (12.2%)	6 (14.0%)	5 (12.2%)
General Disorders and Administration Site Conditions	8 (19.5%)	11 (25.6%)	7 (17.1%)
Chest Pain	1 (2.4%)	1 (2.3%)	3 (7.3%)
Fatigue	3 (7.3%)	3 (7.0%)	2 (4.9%)
Pyrexia	3 (7.3%)	3 (7.0%)	4 (9.8%)
Infections and Infestations	9 (22.0%)	8 (18.6%)	8 (19.5%)
Rhinitis	1 (2.4%)	3 (7.0%)	2 (4.9%)
Investigations	13 (31.7%)	11 (25.6%)	10 (24.4%)
ALT Increased	5 (12.2%)	3 (7.0%)	6 (14.6%)
AST Increased	4 (9.8%)	0 (0.0%)	1 (2.4%)
PT Prolonged	3 (7.3%)	2 (4.7%)	1 (2.4%)
Weight Decreased	3 (7.3%)	2 (4.7%)	1 (2.4%)
Metabolism/Nutrition Disorders	5 (12.2%)	10 (23.3%)	8 (19.5%)
Decreased Appetite	2 (4.9%)	6 (14.0%)	2 (4.9%)
Hypoglycaemia	0 (0.0%)	3 (7.0%)	2 (4.9%)

(Table above is taken from Page 76 of the Applicant's TC-2A Study Report)

Table 46. Cont'd Study TC-2A Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

System Organ Class/Preferred Term	All Events		
	Arm 1 (N = 41)	Arm 2 (N = 43)	Arm 3 (N = 41)
Musculoskeletal and Connective Tissue Disorders	3 (7.3%)	4 (9.3%)	6 (14.6%)
Back Pain	1 (2.4%)	1 (2.3%)	4 (9.8%)
Nervous System Disorders	8 (19.5%)	11 (25.6%)	6 (14.6%)
Dizziness	3 (7.3%)	6 (14.0%)	1 (2.4%)
Headache	6 (14.6%)	6 (14.0%)	5 (12.2%)
Renal and Urinary Disorders	6 (14.6%)	2 (4.7%)	3 (7.3%)
Chromaturia	4 (9.8%)	2 (4.7%)	2 (4.9%)
Reproductive System and Breast Disorders	3 (7.3%)	2 (4.7%)	3 (7.3%)
Dysmennorhoea	3 (7.3%)	2 (4.7%)	2 (4.9%)
Respiratory, Thoracic, and Mediastinal Disorders	24 (58.5 %)	24 (55.8%)	18 (43.9%)
Cough	7 (17.1%)	8 (18.6%)	6 (14.6%)
Crackles Lung	7 (17.1%)	4 (9.3%)	2 (4.9%)
Dyspnoea	3 (7.3%)	1 (2.3%)	2 (4.9%)
Epistaxis	3 (7.3%)	2 (4.7%)	0 (0.0%)
Haemoptysis	4 (9.8%)	2 (4.7%)	3 (7.3%)
Lung Infiltration	4 (9.8%)	2 (4.7%)	2 (4.9%)
Nasal Congestion	4 (9.8%)	5 (11.6%)	5 (12.2%)
Pharyngolaryngeal Pain	2 (4.9%)	3 (7.0%)	2 (4.9%)
Productive Cough	1 (2.4%)	4 (9.3%)	1 (2.4%)
Rhinorrhoea	3 (7.3%)	4 (9.3%)	1 (2.4%)
Rhonci	3 (7.3%)	2 (4.7%)	4 (9.8%)
Sinus Congestion	1 (2.4%)	0 (0.0%)	3 (7.3%)
Wheezing	3 (7.3%)	0 (0.0%)	1 (2.4%)
Skin/Subcutaneous Tissue Disorders	2 (4.9%)	6 (14.0%)	1 (2.4%)
Pruritus	1 (2.4%)	1 (2.3%)	1 (2.4%)
Rash	1 (2.4%)	1 (2.3%)	1 (2.4%)

Reference: Appendix 9 (Table 26.2)
Note: Subjects with multiple AEs within a given System Organ Class and prefe
Note: The AE Coded Term "Chromaturia" was utilized for AEs associated with
marker. These events were attributed to the use of the protocol specified dye n
a true event of "Chromaturia".
* Related events are those that were classified by the Investigator as possibly, p

(Table above is taken from Applicant's TC-2A Study Report)

APPENDIX 6: Demographics and Baseline Characteristics for Studies 767 and 810

Table 47. Demographics and Baseline Characteristics for Studies 767 and 810 .

Characteristic	Study 767				Study 810 (N=39)
	Age Subgroups, years			Study 767 Total (N=214)	
	7 to < 12 (N=55)	12 to < 17 (N=57)	≥ 17 (N=102)		
Age (years)					
Mean (SD)	9.9 (1.4)	14.4 (1.3)	25.6 (7.8)	18.6 (8.79)	53.9 (14.13)
Median	10.0	14.3	24.3	16.5	53.2
Min, Max	7.0, 12.0	12.3, 16.9	17.0, 62.3	7.0, 62.3	27.2, 82.6
Gender, n (%) Male	24 (43.6)	33 (57.9)	67 (65.7)	124 (57.9)	20 (51.3)
Race, n (%) Caucasian	54 (98.2)	56 (98.2)	98 (96.1)	208 (97.2)	34 (87.2)
BMI (kg/m^2)					
Mean (SD)	16.1 (1.79)	18.4 (2.42)	21.9 (4.53)	19.5 (4.26)	22.6 (4.88)
Median	15.9	18.3	21.2	19.4	22.2
Minimum, Maximum	12.5, 21.6	14.2, 23.2	15.4, 52.5	12.5, 52.5	15.9, 37.4
Underlying Cause of EPI					
Cystic Fibrosis	55 (100)	57 (100)	102 (100)	214 (100)	0
Chronic Pancreatitis	0	0	0	0	30 (76.9)
Pancreatectomy	0	0	0	0	9 (23.1)
Baseline CFA < 40%[a], n (%)	4/23 (17.4)	8/28 (28.6)	17/37 (45.9)	29/88 (33.0)	ND
On Acid Suppression, n (%)	30 (54.5)	19 (33.3)	60 (58.8)	109 (50.9)	27 (69.2)
Have Diabetes, n (%)	ND	ND	ND	29 (13.6)	ND

Table above is taken from Page 39 of the Summary of Clinical Safety

APPENDIX 7: Study 767 SAEs and TEAEs

Table 48. Serious Treatment Emergent Adverse Events Reported in Two or More Patients

MedDRA SOC Preferred Term	Exposure Subgroups: Percent of Study Days with >5 Capsules Low (≤25%) (N=88)	Mid (>25% to <75%) (N=63)	High (≥75%) (N=63)	All Subjects (N=214)
Any Treatment-emergent SAE	*31 (35.2)*	*17 (27.0)*	*13 (20.6)*	*61 (28.5)*
Infections and Infestations	**28 (31.8)**	**13 (20.6)**	**11 (17.5)**	**52 (24.3)**
Respiratory Tract Infection	21 (23.9)	8 (12.7)	10 (15.9)	39 (18.2)
Pneumonia	3 (3.4)	0	0	3 (1.4)
Bronchitis	2 (2.2)	1 (1.6)	0	3 (1.4)
Bronchiectasis	0	1 (1.6)	1 (1.6)	2 (0.9)
Lung Infection Pseudomonal	0	1 (1.6)	1 (1.6)	2 (0.9)
Respiratory Disorders	**2 (2.3)**	**3 (4.8)**	**2 (3.2)**	**7 (3.3)**
Haemoptysis	1 (1.1)	1 (1.6)	1 (1.6)	3 (1.4)
Gastrointestinal Disorders	**3 (3.4)**	**3 (4.8)**	**1 (1.6)**	**7 (3.3)**
Abdominal Pain	1 (1.1)	1 (1.6)	0	2 (0.9)

(Table above is taken from Page 131 of the Applicant's 767 Study Report.)

Table 49. Study 767 TEAEs Reported in ≥ 5% of Patients

MedDRA SOC Preferred Term	Exposure Subgroups: Percent of Study Days with >5 Capsules Low (≤25%) (N=88) n (%)	Mid (>25% to <75%) (N=63) n (%)	High (≥75%) (N=63) n (%)	All Subjects (N=214) n (%)
Any TEAE	*86 (97.7)*	*63 (100.0)*	*62 (98.4)*	*211 (98.6)*
Gastrointestinal Disorders	**71 (80.7)**	**57 (90.5)**	**60 (95.2)**	**188 (87.9)**
Abdominal Pain	30 (34.1)	28 (44.4)	33 (52.4)	91 (42.5)
Diarrhoea	23 (26.1)	24 (38.1)	29 (46.0)	76 (35.5)
Flatulence	19 (21.6)	22 (34.9)	24 (38.1)	65 (30.4)
Abdominal Pain Upper	32 (36.4)	14 (22.2)	15 (23.8)	61 (28.5)
Frequent Bowel Movements	17 (19.3)	20 (31.7)	23 (36.5)	60 (28.0)
Steatorrhoea	9 (10.2)	21 (33.3)	22 (34.9)	52 (24.3)
Nausea	17 (19.3)	8 (12.7)	11 (17.5)	36 (16.8)
Vomiting	15 (17.0)	10 (15.9)	9 (14.3)	34 (15.9)
Abdominal Distension	9 (10.2)	4 (6.3)	8 (12.7)	21 (9.8)
Constipation	11 (12.5)	4 (6.3)	5 (7.9)	20 (9.3)
Abnormal Faeces	3 (3.4)	4 (6.3)	4 (6.3)	11 (5.1)
Infections and Infestations	**63 (71.6)**	**44 (69.8)**	**46 (73.0)**	**153 (71.5)**
Respiratory Tract Infection	38 (43.2)	22 (34.9)	22 (34.9)	82 (38.3)
Nasopharyngitis	9 (10.2)	6 (9.5)	11 (17.5)	26 (12.1)
Upper Respiratory Tract Infection	6 (6.8)	9 (14.3)	7 (11.1)	22 (10.3)
Sinusitis	7 (8.0)	4 (6.3)	9 (14.3)	20 (9.3)
Rhinitis	6 (6.8)	4 (6.3)	6 (9.5)	16 (7.5)
Pharyngitis	3 (3.4)	3 (4.8)	5 (7.9)	11 (5.1)

(Table above is taken from Page Applicant's 767 Study Report)

Table 50. Continued Study 767 TEAEs Reported in ≥ 5% of Patients

MedDRA SOC Preferred Term	Exposure Subgroups: Percent of Study Days with >5 Capsules Low (≤25%) (N=88) n (%)	Mid (>25% to <75%) (N=63) n (%)	High (≥75%) (N=63) n (%)	All Subjects (N=214) n (%)
Respiratory, Thoracic and Mediastinal Disorders	**52 (59.1)**	**33 (52.4)**	**42 (66.7)**	**127 (59.3)**
Cough	32 (36.4)	21 (33.3)	25 (39.7)	78 (36.4)
Productive Cough	11 (12.5)	7 (11.1)	9 (14.3)	27 (12.6)
Pharyngolaryngeal Pain	13 (14.8)	5 (7.9)	9 (14.3)	27 (12.6)
Rhinorrhoea	10 (11.4)	7 (11.1)	6 (9.5)	23 (10.7)
Nasal Congestion	11 (12.5)	7 (11.1)	3 (4.8)	21 (9.8)
Haemoptysis	7 (8.0)	3 (4.8)	8 (12.7)	18 (8.4)
Rales	6 (6.8)	5 (7.9)	7 (11.1)	18 (8.4)
Wheezing	7 (8.0)	3 (4.8)	6 (9.5)	16 (7.5)
Dyspnoea	6 (6.8)	4 (6.3)	2 (3.2)	12 (5.6)
Investigations	**35 (39.8)**	**28 (44.4)**	**35 (55.6)**	**98 (45.8)**
Weight Decreased	13 (14.8)	16 (25.4)	19 (30.2)	48 (22.4)
Alanine Aminotransferase Increased	8 (9.1)	6 (9.5)	7 (11.1)	21 (9.8)
Aspartate Aminotransferase Increased	3 (3.4)	6 (9.5)	4 (6.3)	13 (6.1)
Pulmonary Function Test Decreased	6 (6.8)	5 (7.9)	2 (3.2)	13 (6.1)
Prealbumin Decreased	4 (4.5)	5 (7.9)	2 (3.2)	11 (5.1)
Vitamin D Decreased	7 (8.0)	2 (3.2)	2 (3.2)	11 (5.1)
General Disorders and Administration Site Conditions	**30 (34.1)**	**16 (25.4)**	**18 (28.6)**	**64 (29.9)**
Pyrexia	18 (20.5)	10 (15.9)	11 (17.5)	39 (18.2)
Fatigue	10 (11.4)	2 (3.2)	9 (14.3)	21 (9.8)
Nervous System Disorders	**24 (27.3)**	**23 (36.5)**	**10 (15.9)**	**57 (26.6)**
Headache	17 (19.3)	17 (27.0)	7 (11.1)	41 (19.2)
Metabolism and Nutrition Disorders	**13 (14.8)**	**15 (23.8)**	**11 (17.5)**	**39 (18.2)**
Decreased Appetite	2 (2.3)	7 (11.1)	6 (9.5)	15 (7.0)
Hyperglycaemia	4 (4.5)	6 (9.5)	1 (1.6)	11 (5.1)
Skin and Subcutaneous Tissue Disorders	**13 (14.8)**	**10 (15.9)**	**16 (25.4)**	**39 (18.2)**
Rash	7 (8.0)	6 (9.5)	2 (3.2)	15 (7.0)

Source: Summary Table 14.3.1.2.1

(Table above is taken from Applicant's 767 Study Report)

APPENDIX 8: Study 810 TEAE's Reported in ≥ 5% of Patients

Table 51. Study 810 TEAE's Reported in ≥ 5% of Patients

System Organ Class Preferred Term	All Subjects (N=39) Subjects n (%)
Any TEAE	**38 (97.4)**
Gastrointestinal Disorders	**35 (89.7)**
Diarrhoea	15 (38.5)
Abdominal Pain	14 (35.9)
Nausea	13 (33.3)
Abdominal Pain Upper	10 (25.6)
Flatulence	10 (25.6)
Abdominal Distension	5 (12.8)
Constipation	5 (12.8)
Frequent Bowel Movements	4 (10.3)
Vomiting	4 (10.3)
Abdominal Discomfort	3 (7.7)
Abdominal Tenderness	3 (7.7)
Abnormal Faeces	3 (7.7)
Gastritis	3 (7.7)
Steatorrhoea	3 (7.7)
Faeces Discoloured	2 (5.1)
Haemorrhoidal Haemorrhage	2 (5.1)
Stomach Discomfort	2 (5.1)
Investigations	**20 (51.3)**
Weight Decreased	9 (23.1)
Alanine Aminotransferase Increased	4 (10.3)
Blood Glucose Increased	4 (10.3)
Aspartate Aminotransferase Increased	3 (7.7)
Blood Lactate Dehydrogenase Increased	3 (7.7)
Blood Triglycerides Increased	3 (7.7)
Blood Creatine Phophokinase Increased	2 (5.1)
Prealbumin Decreased	2 (5.1)
Infections and Infestations	**19 (48.7)**
Sinusitis	7 (17.9)
Nasopharyngitis	5 (12.8)
Lower Respiratory Tract Infection	4 (10.3)
Influenza	2 (5.1)
Upper Respiratory Tract Infection	2 (5.1)
Urinary Tract Infection	2 (5.1)
Nervous System Disorders	**15 (38.5)**
Headache	8 (20.5)
Dizziness	4 (10.3)
Sinus Headache	3 (7.7)

(Table above is taken from Page 77 of the Applicant's 810 Study Report)

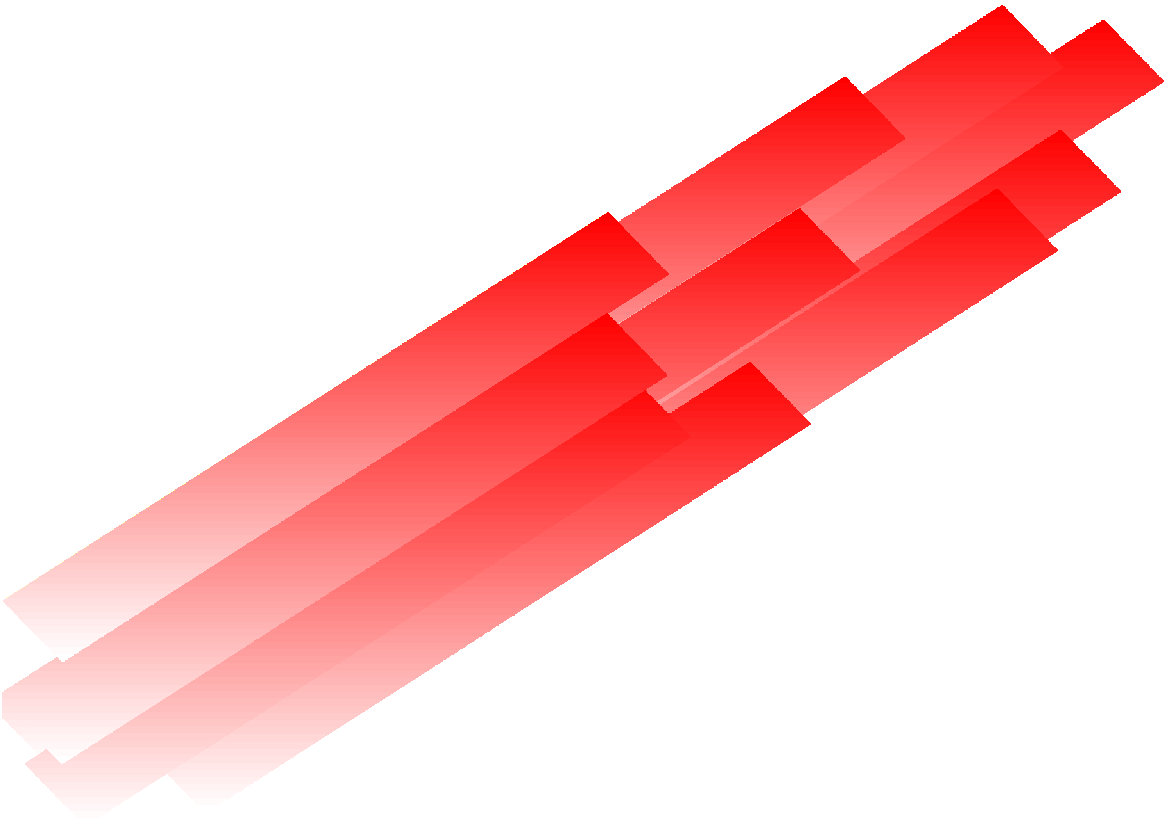
(cont.) Study 810 TEAE's Reported in ≥ 5% of Patients

System Organ Class Preferred Term	All Subjects (N=39) Subjects n (%)
Musculoskeletal and Connective Tissue Disorders	**14 (35.9)**
Back Pain	7 (17.9)
Musculoskeletal Chest Pain	3 (7.7)
Myalgia	3 (7.7)
Muscle Spasms	2 (5.1)
General Disorders and Administration Site Conditions	**11 (28.2)**
Fatigue	5 (12.8)
Pyrexia	4 (10.3)
Asthenia	3 (7.7)
Chills	2 (5.1)
Skin and Subcutaneous Tissue Disorders	**11 (28.2)**
Pruritus	3 (7.7)
Rash	2 (5.1)
Skin Burning Sensation	2 (5.1)
Respiratory, Thoracic and Mediastinal Disorders	**7 (17.9)**
Nasal Congestion	2 (5.1)
Injury, Poisoning and Procedural Complications	**6 (15.4)**
Contusion	2 (5.1)
Vascular Disorders	**2 (5.1)**
Hot Flush	2 (5.1)

(Table above is taken from Page 78 of the Applicant's 810 Study Report)

Guidance for Industry

Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
May 1998
Clinical 6

Guidance for Industry

Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
May 1998
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TABLE OF CONTENTS

GUIDANCE FOR INDUSTRY[1]

Providing Clinical Evidence of Effectiveness[2] for Human Drug and Biological Products

I. INTRODUCTION

This document is intended to provide guidance to applicants planning to file new drug applications (NDAs), biologics license applications (BLAs), or applications for supplemental indications on the evidence to be provided to demonstrate effectiveness.

This document is also intended to meet the requirements of subsections 403(b)(1) and (2) of the Food and Drug Administration Modernization Act (the Modernization Act) of 1997 for human drug and biological products (P.L. 105-115).[3] Subsection 403(b)(1) directs FDA to provide guidance on the circumstances in which published matter may be the basis for approval of a supplemental application for a new indication. Section III of this guidance satisfies this requirement by describing circumstances in which published matter may partially or entirely support approval of a supplemental application. Subsection 403(b)(2) directs FDA to provide guidance on data requirements that will avoid duplication of previously submitted data by recognizing the availability of data previously submitted in support of an original application to support approval of a supplemental application. Section II of this guidance satisfies this requirement by describing a range of circumstances in which related existing data, whether from an original application or other sources, may be used to support approval of a supplemental application.

In 1962, Congress amended the Federal Food, Drug, and Cosmetic Act to add a requirement that, to obtain marketing approval, manufacturers demonstrate the effectiveness of their products through the conduct of adequate and well-controlled studies. Since then, the issue of what constitutes sufficient evidence of effectiveness has been debated by the Agency, the scientific community, industry, and others. Sound evidence of effectiveness is a crucial component of the Agency's benefit-risk assessment of a new product or use. At the same time, the demonstration of effectiveness represents a major component of drug development time and cost; the amount

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[1] This guidance document represents the agency's current thinking on providing clinical evidence of effectiveness for human drug and biological products. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both.

[2] As used in this guidance, the term efficacy refers to the findings in an adequate and well-controlled clinical trial or the intent of conducting such a trial and the term effectiveness refers to the regulatory determination that is made on the basis of clinical efficacy and other data.

[3] The Modernization Act requirements in Section 403 also apply to animal drugs and medical devices. These products will be addressed in separate guidances.

and nature of the evidence needed can therefore be an important determinant of when and whether new therapies become available to the public. The public health is best served by the development of sound evidence of effectiveness in an efficient manner.

The science and practice of drug development and clinical evaluation have evolved significantly since the effectiveness requirement for drugs was established, and this evolution has implications for the amount and type of data needed to support effectiveness in certain cases. As a result of medical advances in the understanding of pathogenesis and disease staging, it is increasingly likely that clinical studies of drugs will be more narrowly defined to focus, for example, on a more specific disease stage or clinically distinct subpopulation. As a consequence, product indications are often narrower, the universe of possible indications is larger, and data may be available from a number of studies of a drug in closely related indications that bear on a determination of its effectiveness for a new use. Similarly, there may be studies of a drug in different populations, studies of a drug alone or in combination, and studies of different doses and dosage forms, all of which may support a particular new use of a drug. At the same time, progress in clinical evaluation and clinical pharmacology have resulted in more rigorously designed and conducted clinical efficacy trials, which are ordinarily conducted at more than one clinical site. This added rigor and scope has implications for a study's reliability, generalizability, and capacity to substantiate effectiveness.

Given this evolution, the Agency has determined that it would be appropriate to articulate its current thinking concerning the quantitative and qualitative standards for demonstrating effectiveness of drugs and biologics. FDA hopes that this guidance will enable sponsors to plan drug development programs that are sufficient to establish effectiveness without being excessive in scope. The guidance should also bring greater consistency and predictability to FDA's assessment of the clinical trial data needed to support drug effectiveness.

Another major goal of this guidance is to encourage the submission of supplemental applications to add new uses to the labeling of approved drugs. By articulating how it currently views the quantity and quality of evidence necessary to support approval of a new use of a drug, FDA hopes to illustrate that the submission of supplements for new uses need not be unduly burdensome.

II. QUANTITY OF EVIDENCE NECESSARY TO SUPPORT EFFECTIVENESS

A. Legal Standards for Drug and Biological Products

Drugs: The effectiveness requirement for drug approval was added to the Federal Food, Drug, and Cosmetic Act (the Act or the FDC Act) in 1962. Between passage of the Act in 1938 and the 1962 amendments, drug manufacturers were required to show only that their drugs were safe. The original impetus for the effectiveness requirement was Congress's growing concern about the misleading and unsupported claims being made by pharmaceutical companies about their drug products coupled with high drug prices. After two years of hearings on these issues, Congress adopted the 1962 Drug Amendments,

which included a provision requiring manufacturers of drug products to establish a drug's effectiveness by "substantial evidence." *Substantial evidence* was defined in section 505(d) of the Act as "evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof."

Since the 1962 Amendments added this provision to the statute, discussions have ensued regarding the quantity and quality of the evidence needed to establish effectiveness. With regard to quantity, it has been FDA's position that Congress generally intended to require at least two adequate and well-controlled studies, each convincing on its own, to establish effectiveness. (See e.g., Final Decision on Benylin, 44 FR 51512, 518 (August 31, 1979); *Warner-Lambert Co. V. Heckler*, 787 F. 2d 147 (3d Cir. 1986)). FDA's position is based on the language in the statute[4] and the legislative history of the 1962 amendments. Language in a Senate report suggested that the phrase "adequate and well-controlled investigations" was designed not only to describe the quality of the required data but the "quantum" of required evidence. (S. Rep. No. 1744, Part 2, 87th Cong. 2d Sess. 6 (1962))

Nevertheless, FDA has been flexible within the limits imposed by the congressional scheme, broadly interpreting the statutory requirements to the extent possible where the data on a particular drug were convincing. In some cases, FDA has relied on pertinent information from other adequate and well-controlled studies of a drug, such as studies of other doses and regimens, of other dosage forms, in other stages of disease, in other populations, and of different endpoints, to support a single adequate and well-controlled study demonstrating effectiveness of a new use. In these cases, although there is only one study of the exact new use, there are, in fact, multiple studies supporting the new use, and expert judgment could conclude that the studies together represent substantial evidence of effectiveness. In other cases, FDA has relied on only a single adequate and well-controlled efficacy study to support approval — generally only in cases in which a single multicenter study of excellent design provided highly reliable and statistically strong evidence of an important clinical benefit, such as an effect on survival, and a confirmatory study would have been difficult to conduct on ethical grounds.

In section 115(a) of the Modernization Act, Congress amended section 505(d) of the Act to make it clear that the Agency may consider "data from one adequate and well-controlled clinical investigation and confirmatory evidence" to constitute substantial

[4] Section 505(d) of the Act uses the plural form in defining "substantial evidence" as "adequate and well-controlled investigations, including clinical investigations." See also use of "investigations" in section 505(b) of the Act, which lists the contents of a new drug application.

evidence if FDA determines that such data and evidence are sufficient to establish effectiveness. In making this clarification, Congress confirmed FDA's interpretation of the statutory requirements for approval and acknowledged the Agency's position that there has been substantial progress in the science of drug development resulting in higher quality clinical trial data.

Biologics. Biological products are approved under authority of section 351 of the Public Health Service Act (PHS Act) (42 U.S.C.§ 262). Under section 351, as in effect since 1944, licenses for biologics have been issued only upon a showing that the products meet standards designed to ensure the "continued safety, purity, and potency" of the products. *Potency* has long been interpreted to include effectiveness (21 CFR 600.3(s)). In 1972, FDA initiated a review of the safety and effectiveness of all previously licensed biologics. The Agency stated then that proof of effectiveness would consist of controlled clinical investigations as defined in the provision for "adequate and well-controlled studies" for new drugs (21 CFR 314.126), unless waived as not applicable to the biological product or essential to the validity of the study when an alternative method is adequate to substantiate effectiveness (21 CFR 601.25 (d) (2)). One such adequate alternative was identified to be serological response data where a previously accepted correlation with clinical effectiveness exists. As with nonbiological drug products, FDA has approved biological products based on single, multicenter studies with strong results.

Although section 123(a) of the Modernization Act amended section 351 of the PHS Act to make it clear that separate licenses are not required for biological products and the establishments at which the products are made, the evidentiary standard for a biological product was not changed: the product must be shown to be "safe, pure, and potent" (section 351 (a)(2) of the PHS Act as amended). In the Modernization Act (section 123(f)) Congress also directed the agency to take measures to "minimize differences in the review and approval" of products required to have approved BLAs under section 351 of the PHS Act and products required to have approved NDAs under section 505(b)(1) of the FDC Act.

B. Scientific Basis for the Legal Standard

The usual requirement for more than one adequate and well-controlled investigation reflects the need for *independent substantiation* of experimental results. A single clinical experimental finding of efficacy, unsupported by other independent evidence, has not usually been considered adequate scientific support for a conclusion of effectiveness. The reasons for this include the following.

- Any clinical trial may be subject to unanticipated, undetected, systematic biases. These biases may operate despite the best intentions of sponsors and investigators, and may lead to flawed conclusions. In addition, some investigators may bring conscious biases to evaluations.

- The inherent variability in biological systems may produce a positive trial result by chance alone. This possibility is acknowledged, and quantified to some extent, in the statistical evaluation of the result of a single efficacy trial. It should be noted, however, that hundreds of randomized clinical efficacy trials are conducted each year with the intent of submitting favorable results to FDA. Even if all drugs tested in such trials were ineffective, one would expect one in forty of those trials to "demonstrate" efficacy by chance alone at conventional levels of statistical significance.[5] It is probable, therefore, that false positive findings (i.e., the chance appearance of efficacy with an ineffective drug) will occur and be submitted to FDA as evidence of effectiveness. Independent substantiation of a favorable result protects against the possibility that a chance occurrence in a single study will lead to an erroneous conclusion that a treatment is effective.

- Results obtained in a single center may be dependent on site or investigator specific factors (e.g., disease definition, concomitant treatment, diet). In such cases, the results, although correct, may not be generalizable to the intended population. This possibility is the primary basis for emphasizing the need for independence in substantiating studies.

- Rarely, favorable efficacy results are the product of scientific fraud.

Although there are statistical, methodologic, and other safeguards to address the identified problems, they are often inadequate to address these problems in a single trial. Independent substantiation of experimental results addresses such problems by providing consistency across more than one study, thus greatly reducing the possibility that a biased, chance, site-specific, or fraudulent result will lead to an erroneous conclusion that a drug is effective.

The need for independent substantiation has often been referred to as the need for replication of the finding. Replication may not be the best term, however, as it may imply that precise repetition of the same experiment in other patients by other investigators is the only means to substantiate a conclusion. Precise replication of a trial is only one of a number of possible means of obtaining independent substantiation of a clinical finding and, at times, can be less than optimal as it could leave the conclusions vulnerable to any systematic biases inherent to the particular study design. Results that are obtained from studies that are of different design and independent in execution, perhaps evaluating different populations, endpoints, or dosage forms, may provide support for a conclusion of effectiveness that is as convincing as, or more convincing than, a repetition of the same study.

[5] p-value = 0.05, two-tailed, which implies an error rate in the efficacy (false positive) tail of 0.025 or one in forty.

C. The Quantity of Evidence to Support Effectiveness

The following three sections provide guidance on the quantity of evidence needed in particular circumstances to establish substantial evidence of effectiveness. Section 1 addresses situations in which effectiveness of a new use may be extrapolated entirely from existing efficacy studies. Section 2 addresses situations in which a single adequate and well-controlled study of a specific new use can be supported by information from other related adequate and well-controlled studies, such as studies in other phases of a disease, in closely related diseases, of other conditions of use (different dose, duration of use, regimen), of different dosage forms, or of different endpoints. Section 3 addresses situations in which a single multicenter study, without supporting information from other adequate and well-controlled studies, may provide evidence that a use is effective.

In each of these situations, it is assumed that any studies relied on to support effectiveness meet the requirements for adequate and well-controlled studies in 21 CFR 314.126. It should also be appreciated that reliance on a single study of a given use, whether alone or with substantiation from related trial data, leaves little room for study imperfections or contradictory (nonsupportive) information. In all cases, it is presumed that the single study has been appropriately designed, that the possibility of bias due to baseline imbalance, unblinding, post-hoc changes in analysis, or other factors is judged to be minimal, and that the results reflect a clear prior hypothesis documented in the protocol. Moreover, a single favorable study among several similar attempts that failed to support a finding of effectiveness would not constitute persuasive support for a product use unless there were a strong argument for discounting the outcomes in the studies that failed to show effectiveness (e.g., study obviously inadequately powered or lack of assay sensitivity as demonstrated in a three-arm study by failure of the study to show efficacy of a known active agent).

Whether to rely on a single study to support an effectiveness determination is not often an issue in contemporary drug development. In most drug development situations, the need to find an appropriate dose, to study patients of greater and lesser complexity or severity of disease, to compare the drug to other therapy, to study an adequate number of patients for safety purposes, and to otherwise know what needs to be known about a drug before it is marketed will result in more than one adequate and well-controlled study upon which to base an effectiveness determination.

This guidance is not intended to provide a complete listing of the circumstances in which existing efficacy data may provide independent substantiation of related claims; rather, it provides examples of the reasoning that may be employed. The examples are applicable whether the claim arises in the original filing of an NDA or BLA, or in a supplemental application.

1. Extrapolation from Existing Studies

In certain cases, effectiveness of an approved drug product for a new indication, or effectiveness of a new product, may be adequately demonstrated without additional adequate and well-controlled clinical efficacy trials. Ordinarily, this will be because other types of data provide a way to apply the known effectiveness to a new population or a different dose, regimen or dosage form. The following are examples of situations in which effectiveness might be extrapolated from efficacy data for another claim or product.

a. Pediatric uses

The rule revising the Pediatric Use section of product labeling (21 CFR 201.57(f)(9)(iv)) makes allowance for inclusion of pediatric use information in labeling without controlled clinical trials of the use in children. In such cases, a sponsor must provide other information to support pediatric use, and the Agency must conclude that the course of the disease and the effects of the drug are sufficiently similar in the pediatric and adult populations to permit extrapolation from adult efficacy data to pediatric patients. Evidence that could support a conclusion of similar disease course and similar drug effect in adult and pediatric populations includes evidence of common pathophysiology and natural history of the disease in the adult and pediatric populations, evidence of common drug metabolism and similar concentration-response relationships in each population, and experience with the drug, or other drugs in its therapeutic class, in the disease or condition or related diseases or conditions. Examples in which pediatric use labeling information has been extrapolated from adult efficacy data include ibuprofen for pain and loratidine for seasonal allergic rhinitis.

b. Bioequivalence

The effectiveness of alternative formulations and new dosage strengths may be assessed on the basis of evidence of bioequivalence.

c. Modified-release dosage forms

In some cases, modified release dosage forms may be approved on the basis of pharmacokinetic data linking the new dosage form to a previously studied immediate-release dosage form. Because the pharmacokinetic patterns of modified-release and immediate-release dosage forms are not identical, it is generally important to have some understanding of the relationship of blood concentration to response, including an understanding of the time course of that relationship, to extrapolate the immediate-release

data to the modified-release dosage form.

d. Different doses, regimens, or dosage forms

Dose-response relationships are generally continuous such that information about the effectiveness of one dose, dosage regimen, or dosage form is relevant to the effectiveness of other doses, regimens, or dosage forms. Where blood levels and exposure are not very different, it may be possible to conclude that a new dose, regimen, or dosage form is effective on the basis of pharmacokinetic data alone. Even if blood levels are quite different, if there is a well-understood relationship between blood concentration and response, including an understanding of the time course of that relationship, it may be possible to conclude that a new dose, regimen, or dosage form is effective on the basis of pharmacokinetic data without an additional clinical efficacy trial. In this situation, pharmacokinetic data, together with the well-defined pharmacokinetic/pharmacodynamic (PK/PD) relationship, are used to translate the controlled trial results from one dose, regimen, or dosage form to a new dose, regimen, or dosage form (See also section II.C.2.a).

2. Demonstration of Effectiveness by a Single Study of a New Use, with Independent Substantiation From Related Study Data

The discussion that follows describes specific examples in which a single study of a new use, with independent substantiation from study data in related uses, could provide evidence of effectiveness. In these cases, the study in the new use and the related studies support the conclusion that the drug has the effect it is purported to have. Whether related studies are capable of substantiating a single study of a new use is a matter of judgment and depends on the quality and outcomes of the studies and the degree of relatedness to the new use.

a. Different doses, regimens, or dosage forms

As discussed in Sections II.C.1.d, it may be possible to conclude that a new dose, regimen, or dosage form is effective on the basis of pharmacokinetic data without an additional clinical efficacy trial where blood levels and exposure are not very different or, even if quite different, there is a well-understood relationship between blood concentration and response. Where the relationship between blood concentration and response is not so well understood and the pharmacokinetics of the new dose, regimen, or dosage form differ from the previous one, clinical efficacy data will likely be necessary to support effectiveness of a new regimen. In this case, a single additional efficacy study should ordinarily be sufficient. For example, a single controlled trial was needed to support the recent approval of a once

daily dose of risperidone because the once daily and twice daily regimens had different pharmacokinetics and risperidone's PK/PD relationship was not well understood.

b. Studies in other phases of the disease

In many cases, therapies that are effective in one phase of a disease are effective in other disease phases, although the magnitude of the benefit and benefit-to-risk relationship may differ in these other phases. For example, if a drug is known to be effective in patients with a refractory stage of a particular cancer, a single adequate and well-controlled study of the drug in an earlier stage of the same tumor will generally be sufficient evidence of effectiveness to support the new use.

c. Studies in other populations

Often, responses in subsets of a particular patient population are qualitatively similar to those in the whole population. In most cases, separate studies of effectiveness in demographic subsets are not needed (see also discussion of the pediatric population in section II.C.1.a) However, where further studies are needed, a single study would ordinarily suffice to support effectiveness in age, race, gender, concomitant disease, or other subsets for a drug already shown to be generally effective in a condition or to be effective in one population. For example, a single study was sufficient to support tamoxifen use in breast cancer in males.

d. Studies in combination or as monotherapy

For a drug known to be effective as monotherapy, a single adequate and well-controlled study is usually sufficient to support effectiveness of the drug when combined with other therapy (as part of a multidrug regimen or in a fixed-dose combination). Similarly, known effectiveness of a drug as part of a combination (i.e., its contribution to the effect of the combination is known) would usually permit reliance on a single study of appropriate design to support its use as monotherapy, or as part of a different combination, for the same use. For example, a single study of a new combination vaccine designed to demonstrate adequate immune response will ordinarily provide sufficient evidence of effectiveness if the new combination contains products or antigens already proven to be effective alone or in other combinations. These situations are common for oncologic and antihypertensive drugs, but occur elsewhere as well.

e. Studies in a closely related disease

Studies in etiologically or pathophysiologically related conditions, or studies of a symptom common to several diseases (e.g., pain) can support each other, allowing initial approval of several uses or allowing additional claims based on a single adequate and well-controlled study. For example, certain anti-coagulant or anti-platelet therapies could be approved for use in two different settings based on individual studies in unstable angina/acute coronary syndrome and in the postangioplasty state. Because the endpoints studied and the theoretical basis for use of an anti-coagulant or anti-platelet drug are similar, each study supports the other for each claim. Similarly, single analgesic studies in several painful conditions would ordinarily be sufficient to support either a general analgesic indication or multiple specific indications. The recent approval of lamotrigine for treatment of Lennox-Gastaut Syndrome (a rare, largely pediatric, generalized seizure disorder) was based on a single adequate and well-controlled trial, due in part to related data showing efficacy of the drug in partial-onset seizures in adults.

f. Studies in less closely related diseases, but where the general purpose of therapy is similar

Certain classes of drug therapy, such as antimicrobials and antineoplastics, are appropriate interventions across a range of different diseases. For therapies of this type, evidence of effectiveness in one disease could provide independent substantiation of effectiveness in a quite different disease. For example, it is possible to argue that evidence of effectiveness of an antimicrobial in one infectious disease setting may support reliance on a single study showing effectiveness in other settings where the causative pathogens, characteristics of the site of infection that affect the disease process (e.g., structure and immunology) and patient population are similar.[6] Similarly, for an oncologic drug, evidence of effectiveness in one or more tumor types may support reliance on a single study showing effectiveness against a different kind of tumor, especially if the tumor types have a common biological origin.

g. Studies of different clinical endpoints

Demonstration of a beneficial effect in different studies on two different clinically meaningful endpoints could cross-substantiate a claim for

[6] See Division of Anti-Infective Drug Products: Points to Consider in the Clinical Development and Labeling of Anti-Infective Drug Products, October 1992.

effectiveness for each outcome. For example, the initial claim for effectiveness of enalapril for heart failure was supported by one study showing symptom improvement over several months and a second study showing improved survival in a more severely ill population. The two different findings, each from an adequate and well-controlled study, led to the conclusion that enalapril was effective in both treating symptoms and improving survival.

h. Pharmacologic/pathophysiologic endpoints

When the pathophysiology of a disease and the mechanism of action of a therapy are very well understood, it may be possible to link specific pharmacologic effects to a strong likelihood of clinical effectiveness. A pharmacologic effect that is accepted as a validated surrogate endpoint can support ordinary approval (e.g., blood pressure effects, cholesterol-lowering effects) and a pharmacologic effect that is considered reasonably likely to predict clinical benefit can support accelerated approval under the conditions described in 21 CFR 314 Subpart H and 21 CFR 601 Subpart E (e.g., CD4 count and viral load effects to support effectiveness of anti-viral drugs for HIV infection). When the pharmacologic effect is not considered an acceptable effectiveness endpoint, but the linkage between it and the clinical outcome is strong, not merely on theoretical grounds but based on prior therapeutic experience or well-understood pathophysiology, a single adequate and well-controlled study showing clinical efficacy can sometimes be substantiated by persuasive data from a well-controlled study or studies showing the related pharmacologic effect.

For example, a single clearly positive trial can be sufficient to support approval of a replacement therapy such as a coagulation factor, when it is combined with clear evidence that the condition being treated is caused by a deficiency of that factor. Demonstration of physical replacement of the deficient factor or restoration of the missing physiologic activity provides strong substantiation of the clinical effect. The corrective treatment of an inborn error of metabolism could be viewed similarly. In the case of preventive vaccines, one adequate and well-controlled clinical trial may be supported by compelling animal challenge/protection models, human serological data, passive antibody data, or pathogenesis information. The more evidence there is linking effects on the pharmacologic endpoint to improvement or prevention of the disease, the more persuasive the argument for reliance on a single clinical efficacy study.

Note, however, that plausible beneficial pharmacologic effects have often not correlated with clinical benefit, and, therefore, caution must be observed in relying on a pharmacologic effect as contributing to evidence

of effectiveness. For example, pharmacologic effects such as arrhythmia suppression by Type 1 antiarrhythmics and increased cardiac output by phosphodiesterase inhibitors or beta adrenergic inotropes resulted in increased mortality, rather than, as was expected, decreased sudden death and improved outcome in heart failure. The reasons for the absence of an expected correlation between pharmacologic and clinical effects are diverse and can include an incompletely understood relationship between the pharmacologic effect and the clinical benefit and the presence of other pharmacologic effects attributable to a drug in addition to the effect being measured and thought to be beneficial. Generally, the utility of pharmacologic outcomes in providing independent substantiation will be greatest where there is prior experience with the pharmacologic class. Even in this case, however, it is difficult to be certain that a pharmacologic effect that correlates with a clinical benefit accounts for all the clinical benefit or that other effects are not present and relevant.

3. Evidence of Effectiveness from a Single Study

When the effectiveness requirement was originally implemented in 1962, the prevailing efficacy study model was a single institution, single investigator, relatively small trial with relatively loose blinding procedures, and little attention to prospective study design and identification of outcomes and analyses. At present, major clinical efficacy studies are typically multicentered, with clear, prospectively determined clinical and statistical analytic criteria. These studies are less vulnerable to certain biases, are often more generalizable, may achieve very convincing statistical results, and can often be evaluated for internal consistency across subgroups, centers, and multiple endpoints.

The added rigor and size of contemporary clinical trials have made it possible to rely, in certain circumstances, on a single adequate and well-controlled study, without independent substantiation from another controlled trial, as a sufficient scientific and legal basis for approval. For example, the approval of timolol for reduction of post-infarction mortality was based on a single, particularly persuasive (low p-value), internally consistent, multicenter study that demonstrated a major effect on mortality and reinfarction rate. For ethical reasons, the study was considered unrepeatable. The Center for Biologics Evaluation and Research has also approved a number of products based upon a single persuasive study. The Agency provided a general statement in 1995 describing when a single, multicenter study may suffice (60 FR 39181; August 1, 1995), but the Agency has not comprehensively described the situations in which a single adequate and well-controlled study might be considered adequate support for an effectiveness claim, or the characteristics of a single study that could make it adequate support for an effectiveness claim.

Whether to rely on a single adequate and well-controlled study is inevitably a matter of judgment. A conclusion based on two persuasive studies will always be more secure than a conclusion based on a single, comparably persuasive study. For this reason, reliance on only a single study will generally be limited to situations in which a trial has demonstrated a clinically meaningful effect on mortality, irreversible morbidity, or prevention of a disease with potentially serious outcome and confirmation of the result in a second trial would be practically or ethically impossible. For example, sequential repetition of strongly positive trials that demonstrated a decrease in post-infarction mortality, prevention of osteoporotic fractures, or prevention of pertussis would present significant ethical concerns. Repetition of positive trials showing only symptomatic benefit would generally not present the same ethical concerns.

The discussion that follows identifies the characteristics of a single adequate and well-controlled study that could make the study adequate support for an effectiveness claim. Although no one of these characteristics is necessarily determinative, the presence of one or more in a study can contribute to a conclusion that the study would be adequate to support an effectiveness claim.

a. Large multicenter study

In a large multicenter study in which (1) no single study site provided an unusually large fraction of the patients and (2) no single investigator or site was disproportionately responsible for the favorable effect seen, the study's internal consistency lessens concerns about lack of generalizability of the finding or an inexplicable result attributable only to the practice of a single investigator. If analysis shows that a single site is largely responsible for the effect, the credibility of a multicenter study is diminished.

b. Consistency across study subsets

Frequently, large trials have relatively broad entry criteria and the study populations may be diverse with regard to important covariates such as concomitant or prior therapy, disease stage, age, gender or race. Analysis of the results of such trials for consistency across key patient subsets addresses concerns about generalizability of findings to various populations in a manner that may not be possible with smaller trials or trials with more narrow entry criteria. For example, the timolol postinfarction study randomized patients separately within three severity strata. The study showed positive effects on survival in each stratum supporting a conclusion that the drug's utility was not limited to a particular disease stage (e.g., relatively low or high severity).

c. Multiple *studies* in a single study

Properly designed factorial studies may be analyzed as a series of pairwise comparisons, representing, within a single study, separate demonstrations of activity of a drug as monotherapy and in combination with another drug. This model was successfully used in ISIS II, which showed that for patients with a myocardial infarction both aspirin and streptokinase had favorable effects on survival when used alone and when combined (aspirin alone and streptokinase alone were each superior to placebo; aspirin and streptokinase in combination were superior to aspirin alone and to streptokinase alone). This represented two separate (but not completely independent) demonstrations of the effectiveness of aspirin and streptokinase.

d. Multiple endpoints involving different events

In some cases, a single study will include several important, prospectively identified primary or secondary endpoints, each of which represents a beneficial, but different, effect. Where a study shows statistically persuasive evidence of an effect on more than one of such endpoints, the internal weight of evidence of the study is enhanced. For example, the approval of beta-interferon (Betaseron) for prevention of exacerbations in multiple sclerosis was based on a single multicenter study, at least partly because there were both a decreased rate of exacerbations and a decrease in MRI-demonstrated disease activity — two entirely different, but logically related, endpoints.

Similarly, favorable effects on both death and nonfatal myocardial infarctions in a lipid-lowering, postangioplasty, or postinfarction study would, in effect, represent different, but consistent, demonstrations of effectiveness, greatly reducing the possibility that a finding of reduced mortality was a chance occurrence. For example, approval of abciximab as adjunctive treatment for patients undergoing complicated angioplasty or atherectomy was supported by a single study with a strong overall result on the combined endpoint (decreased the combined total of deaths, new infarctions, and need for urgent interventions) and statistically significant effects in separate evaluations of two components of the combined endpoint (decreased new infarctions and decreased need for urgent interventions). In contrast, a beneficial effect on multiple endpoints that evaluate essentially the same phenomenon and correlate strongly, such as mood change on two different depression scales or SGOT and CPK levels postinfarction, does not significantly enhance the internal weight of the evidence from a single trial.

Although two consistent findings within a single study usually provide reassurance that a positive treatment effect is not due to chance, they do not protect against bias in study conduct or biased analyses. For example, a treatment assignment not well balanced for important prognostic variables could lead to an apparent effect on both endpoints. Thus, close scrutiny of study design and conduct are critical to evaluating this type of study.

e. Statistically very persuasive finding

In a multicenter study, a very low p-value indicates that the result is highly inconsistent with the null hypothesis of no treatment effect. In some studies it is possible to detect nominally statistically significant results in data from several centers, but, even where that is not possible, an overall extreme result and significance level means that most study centers had similar findings. For example, the thrombolysis trials of streptokinase (ISIS II, GISSI) had very sizable treatment effects and very low p-values, greatly adding to their persuasiveness. Preventive vaccines for infectious disease indications with a high efficacy rate (e.g., point estimate of efficacy of 80% or higher and a reasonably narrow 95% confidence interval) have been approved based on a single adequate and well-controlled trial.

4. Reliance on a Single, Multicenter Study — Caveats

While acknowledging the persuasiveness of a single, internally consistent, strong multicenter study, it must be appreciated that even a strong result can represent an isolated or biased result, especially if that study is the only study suggesting efficacy among similar studies. Recently, the apparent highly favorable effect of vesnarinone, an inotropic agent, in heart failure (60% reduction of mortality in what appeared to be a well-designed, placebo-controlled, multicenter trial with an extreme p-value) has proven to be unrepeatable. In an attempt to substantiate the finding, the same dose of the drug that seemed lifesaving in the earlier study significantly increased mortality (by 26%), and a lower dose also appeared to have a detrimental effect on survival. Although the population in the second study was, on the whole, a sicker population than in the first, the outcomes in similarly sick patients in each study were inconsistent so this factor does not explain the contradictory results.

When considering whether to rely on a single multicenter trial, it is critical that the possibility of an incorrect outcome be considered and that all the available data be examined for their potential to either support or undercut reliance on a single multicenter trial. In the case of vesnarinone, there were other data that were not consistent with the dramatically favorable outcome in the multicenter study. These data seemed to show an inverse dose-response relationship, showed no suggestion

of symptomatic benefit, and showed no effect on hemodynamic endpoints. These inconsistencies led the Agency, with the advice of its Cardio-Renal Advisory Committee, to refuse approval — a decision borne out by the results of the subsequent study.

This example illustrates how inadequacies and inconsistencies in the data, such as lack of pharmacologic rationale and lack of expected other effects accompanying a critical outcome, can weaken the persuasiveness of a single trial. Although an unexplained failure to substantiate the results of a favorable study in a second controlled trial is not proof that the favorable study was in error — studies of effective agents can fail to show efficacy for a variety of reasons — it is often reason not to rely on the single favorable study.

III. DOCUMENTATION OF THE QUALITY OF EVIDENCE SUPPORTING AN EFFECTIVENESS CLAIM

When submitting the requisite quantity of data to support approval of a new product or new use of an approved product, sponsors must also document that the studies were adequately designed and conducted. Essential characteristics of adequate and well-controlled trials are described in 21 CFR 314.126. To demonstrate that a trial supporting an effectiveness claim is adequate and well-controlled, extensive documentation of trial planning, protocols, conduct, and data handling is usually submitted to the Agency, and detailed patient records are made available at the clinical sites.

From a scientific standpoint, however, it is recognized that the extent of documentation necessary depends on the particular study, the types of data involved, and the other evidence available to support the claim. Therefore, the Agency is able to accept different levels of documentation of data quality, as long as the adequacy of the scientific evidence can be assured. This section discusses the factors that influence the extent of documentation needed, with particular emphasis on studies evaluating new uses of approved drugs.

For the purposes of this section, the phrase *documentation of the quality of evidence* refers to (1) the completeness of the documentation and (2) the ability to access the primary study data and the original study-related records (e.g., subjects' medical records, drug accountability records) for the purposes of verifying the data submitted as evidence. These interrelated elements bear on a determination of whether a study is adequate and well-controlled.

In practice, to achieve a high level of documentation, studies supporting claims are ordinarily conducted in accordance with good clinical practices (GCPs). Sponsors routinely monitor all clinical sites, and FDA routinely has access to the original clinical protocols, primary data, clinical site source documents for on-site audits, and complete study reports.

However, situations often arise in which studies that evaluate the efficacy of a drug product lack the full documentation described above (for example, full patient records may not be available) or in which the study was conducted with less monitoring than is ordinarily seen in commercially sponsored trials. Such situations are more common for supplemental indications because postapproval studies are more likely to be conducted by parties other than the drug sponsor and those parties may employ less extensive monitoring and data-gathering procedures than a sponsor. Under certain circumstances, it is possible for sponsors to rely on such studies to support effectiveness claims, despite less than usual documentation or monitoring. Some of those circumstances are described below.

A. Reliance on Less Than Usual Access to Clinical Data or Detailed Study Reports

FDA's access to primary data has proven to be important in many regulatory decisions. There are also reasons to be skeptical of the conclusions of published reports of studies. Experience has shown that such study reports do not always contain a complete, or entirely accurate, representation of study plans, conduct and outcomes. Outright fraud (i.e., deliberate deception) is unusual. However, incompleteness, lack of clarity, unmentioned deviation from prospectively planned analyses, or an inadequate description of how critical endpoint judgments or assessments were made are common flaws. Typically, journal article peer reviewers only have access to a limited data set and analyses, do not see the original protocol and amendments, may not know what happened to study subjects that investigators determined to be non-evaluable, and thus may lack sufficient information to detect critical omissions and problems. The utility of peer review can also be affected by variability in the relevant experience and expertise of peer reviewers. FDA's experiences with the Anturane Reinfarction Trial, as well as literature reports of the efficacy of tacrine and the anti-sepsis HA-1A antibody, illustrate its concerns with reliance on the published medical literature.

Notwithstanding these concerns, the presence of some of the factors discussed below can make it possible for FDA to rely on studies for which it has less than usual access to data or detailed study reports to partially or entirely (the so-called *paper* filing) support an effectiveness claim. FDA's reliance on a literature report to support an effectiveness claim is more likely if FDA can obtain additional critical study details. Section 1 below describes additional information that, if available, would increase the likelihood that a study could be relied on to support an effectiveness claim. Section 2 describes factors that may make efficacy findings sufficiently persuasive to permit reliance on the published literature alone. Note that the factors outlined in Section 2 are relevant to an assessment of the reliability of literature reports generally, whether alone, or accompanied by other important information as discussed in Section 1.

1. Submission of Published Literature or Other Reports in Conjunction with Other Important Information that Enhances the Reliability of the Data

If a sponsor wishes to rely on a study conducted by another party and cannot obtain the primary data from the study, for most well-conducted studies it is possible to obtain other important information, such as a protocol documenting the prospective plans for the trial, records of trial conduct and procedures, patient data listings for important variables, and documentation of the statistical analysis. FDA has considerable experience evaluating large multicenter outcome studies sponsored by U.S. and European government agencies (NIH, British Medical Research Council) and private organizations (the ISIS studies, the SAVE study) for which there was limited access to primary study data, but for which other critical information was available. Providing as many as possible of the following important pieces of information about a study, in conjunction with the published report, can increase the likelihood that the study can be relied on to support an effectiveness claim:

a. The protocol used for the study, as well as any important protocol amendments that were implemented during the study and their relation to study accrual or randomization.

b. The prospective statistical analysis plan and any changes from the original plan that occurred during or after the study, with particular note of which analyses were performed pre- and post-unblinding.

c. Randomization codes and documented study entry dates for the subjects.

d. Full accounting of all study subjects, including identification of any subjects with on-treatment data who have been omitted from analysis and the reasons for omissions, and an analysis of results using all subjects with on-study data.

e. Electronic or paper record of each subject's data for critical variables and pertinent baseline characteristics. Where individual subject responses are a critical variable (e.g., objective responses in cancer patients, clinical cures and microbial eradications in infectious disease patients, death from a particular cause), detailed bases for the assessment, such as the case report, hospital records, and narratives, should be provided when possible.

f. Where safety is a major issue, complete information for all deaths and drop-outs due to toxicity. For postapproval supplemental uses, however, there is generally less need for the results of lab tests or for details of adverse event reports and, consequently, much more limited documentation may be sufficient (e.g., only for unexpected deaths and previously undescribed serious adverse effects). Exceptions to this

approach would include situations in which the population for the supplemental use is so different that existing safety information has limited application (e.g., thrombolysis in stroke patients versus myocardial infarction patients) or where the new population presents serious safety concerns (e.g., extension of a preventive vaccine indication from young children to infants).

2. Submission of Published Literature Reports Alone

The following factors increase the possibility of reliance on published reports alone to support approval of a new product or new use:

a. Multiple studies conducted by different investigators where each of the studies clearly has an adequate design and where the findings across studies are consistent.

b. A high level of detail in the published reports, including clear and adequate descriptions of statistical plans, analytic methods (prospectively determined), and study endpoints, and a full accounting of all enrolled patients.

c. Clearly appropriate endpoints that can be objectively assessed and are not dependent on investigator judgment (e.g., overall mortality, blood pressure, or microbial eradication). Such endpoints are more readily interpreted than more subjective endpoints such as cause-specific mortality or relief of symptoms.

d. Robust results achieved by protocol-specified analyses that yield a consistent conclusion of efficacy and do not require selected post hoc analyses such as covariate adjustment, subsetting, or reduced data sets (e.g., analysis of only responders or compliant patients, or of an "eligible" or “evaluable” subset).

e. Conduct of studies by groups with properly documented operating procedures and a history of implementing such procedures effectively.

There have been approvals based primarily or exclusively on published reports. Examples include the initial approval of secretin for evaluation of pancreatic function and recent approvals of bleomycin and talc for malignant pleural effusion and doxycycline for malaria.

B. Reliance on Studies with Alternative, Less Intensive Quality Control/On-Site Monitoring

Industry-sponsored studies typically use extensive on-site and central monitoring and auditing procedures to assure data quality. Studies supported by other sponsors may employ less stringent procedures and may use no on-site monitoring at all. An International Conference on Harmonisation guideline on good clinical practices,[7] recently accepted internationally, emphasizes that the extent of monitoring in a trial should be based on trial-specific factors (e.g., design, complexity, size, and type of study outcome measures) and that different degrees of on-site monitoring can be appropriate. In recent years, many credible and valuable studies conducted by government or independent study groups, often with important mortality outcomes, had very little on-site monitoring. These studies have addressed quality control in other ways, such as by close control and review of documentation and extensive guidance and planning efforts with investigators. There is a long history of reliance on such studies for initial approval of drugs as well as for additional indications. Factors that influence whether studies with limited or no monitoring may be relied on include the following:

1. The existence of a prospective plan to assure data quality.

2. Studies that have features that make them inherently less susceptible to bias, such as those with relatively simple procedures, noncritical entry criteria, and readily assessed outcomes.

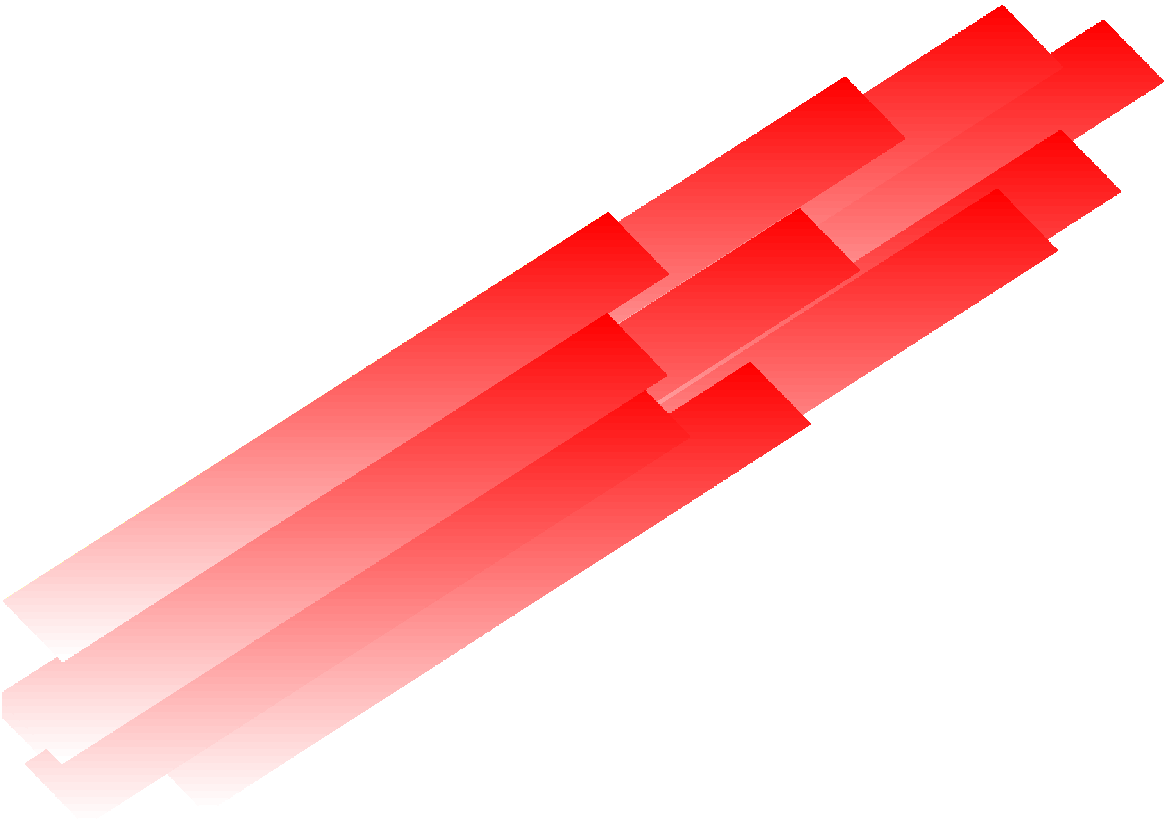
3. The ability to sample critical data and make comparisons to supporting records (e.g., hospital records).

4. Conduct of the study by a group with established operating procedures and a history of implementing such procedures effectively.

[7] International Conference on Harmonisation Guidance for Industry E6, *Good Clinical Practice: Consolidated Guideline*, April 1996.

Guidance for Industry

Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
May 1998
Clinical 6

Guidance for Industry

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GUIDANCE FOR INDUSTRY[1]

Providing Clinical Evidence of Effectiveness[2] for Human Drug and Biological Products

I. INTRODUCTION

This document is intended to provide guidance to applicants planning to file new drug applications (NDAs), biologics license applications (BLAs), or applications for supplemental indications on the evidence to be provided to demonstrate effectiveness.

This document is also intended to meet the requirements of subsections 403(b)(1) and (2) of the Food and Drug Administration Modernization Act (the Modernization Act) of 1997 for human drug and biological products (P.L. 105-115).[3] Subsection 403(b)(1) directs FDA to provide guidance on the circumstances in which published matter may be the basis for approval of a supplemental application for a new indication. Section III of this guidance satisfies this requirement by describing circumstances in which published matter may partially or entirely support approval of a supplemental application. Subsection 403(b)(2) directs FDA to provide guidance on data requirements that will avoid duplication of previously submitted data by recognizing the availability of data previously submitted in support of an original application to support approval of a supplemental application. Section II of this guidance satisfies this requirement by describing a range of circumstances in which related existing data, whether from an original application or other sources, may be used to support approval of a supplemental application.

In 1962, Congress amended the Federal Food, Drug, and Cosmetic Act to add a requirement that, to obtain marketing approval, manufacturers demonstrate the effectiveness of their products through the conduct of adequate and well-controlled studies. Since then, the issue of what constitutes sufficient evidence of effectiveness has been debated by the Agency, the scientific community, industry, and others. Sound evidence of effectiveness is a crucial component of the Agency's benefit-risk assessment of a new product or use. At the same time, the demonstration of effectiveness represents a major component of drug development time and cost; the amount

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[1] This guidance document represents the agency's current thinking on providing clinical evidence of effectiveness for human drug and biological products. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both.

[2] As used in this guidance, the term efficacy refers to the findings in an adequate and well-controlled clinical trial or the intent of conducting such a trial and the term effectiveness refers to the regulatory determination that is made on the basis of clinical efficacy and other data.

[3] The Modernization Act requirements in Section 403 also apply to animal drugs and medical devices. These products will be addressed in separate guidances.

and nature of the evidence needed can therefore be an important determinant of when and whether new therapies become available to the public. The public health is best served by the development of sound evidence of effectiveness in an efficient manner.

The science and practice of drug development and clinical evaluation have evolved significantly since the effectiveness requirement for drugs was established, and this evolution has implications for the amount and type of data needed to support effectiveness in certain cases. As a result of medical advances in the understanding of pathogenesis and disease staging, it is increasingly likely that clinical studies of drugs will be more narrowly defined to focus, for example, on a more specific disease stage or clinically distinct subpopulation. As a consequence, product indications are often narrower, the universe of possible indications is larger, and data may be available from a number of studies of a drug in closely related indications that bear on a determination of its effectiveness for a new use. Similarly, there may be studies of a drug in different populations, studies of a drug alone or in combination, and studies of different doses and dosage forms, all of which may support a particular new use of a drug. At the same time, progress in clinical evaluation and clinical pharmacology have resulted in more rigorously designed and conducted clinical efficacy trials, which are ordinarily conducted at more than one clinical site. This added rigor and scope has implications for a study's reliability, generalizability, and capacity to substantiate effectiveness.

Given this evolution, the Agency has determined that it would be appropriate to articulate its current thinking concerning the quantitative and qualitative standards for demonstrating effectiveness of drugs and biologics. FDA hopes that this guidance will enable sponsors to plan drug development programs that are sufficient to establish effectiveness without being excessive in scope. The guidance should also bring greater consistency and predictability to FDA's assessment of the clinical trial data needed to support drug effectiveness.

Another major goal of this guidance is to encourage the submission of supplemental applications to add new uses to the labeling of approved drugs. By articulating how it currently views the quantity and quality of evidence necessary to support approval of a new use of a drug, FDA hopes to illustrate that the submission of supplements for new uses need not be unduly burdensome.

II. QUANTITY OF EVIDENCE NECESSARY TO SUPPORT EFFECTIVENESS

A. Legal Standards for Drug and Biological Products

Drugs: The effectiveness requirement for drug approval was added to the Federal Food, Drug, and Cosmetic Act (the Act or the FDC Act) in 1962. Between passage of the Act in 1938 and the 1962 amendments, drug manufacturers were required to show only that their drugs were safe. The original impetus for the effectiveness requirement was Congress's growing concern about the misleading and unsupported claims being made by pharmaceutical companies about their drug products coupled with high drug prices. After two years of hearings on these issues, Congress adopted the 1962 Drug Amendments,

which included a provision requiring manufacturers of drug products to establish a drug's effectiveness by "substantial evidence." *Substantial evidence* was defined in section 505(d) of the Act as "evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof."

Since the 1962 Amendments added this provision to the statute, discussions have ensued regarding the quantity and quality of the evidence needed to establish effectiveness. With regard to quantity, it has been FDA's position that Congress generally intended to require at least two adequate and well-controlled studies, each convincing on its own, to establish effectiveness. (See e.g., Final Decision on Benylin, 44 FR 51512, 518 (August 31, 1979); *Warner-Lambert Co. V. Heckler*, 787 F. 2d 147 (3d Cir. 1986)). FDA's position is based on the language in the statute[4] and the legislative history of the 1962 amendments. Language in a Senate report suggested that the phrase "adequate and well-controlled investigations" was designed not only to describe the quality of the required data but the "quantum" of required evidence. (S. Rep. No. 1744, Part 2, 87th Cong. 2d Sess. 6 (1962))

Nevertheless, FDA has been flexible within the limits imposed by the congressional scheme, broadly interpreting the statutory requirements to the extent possible where the data on a particular drug were convincing. In some cases, FDA has relied on pertinent information from other adequate and well-controlled studies of a drug, such as studies of other doses and regimens, of other dosage forms, in other stages of disease, in other populations, and of different endpoints, to support a single adequate and well-controlled study demonstrating effectiveness of a new use. In these cases, although there is only one study of the exact new use, there are, in fact, multiple studies supporting the new use, and expert judgment could conclude that the studies together represent substantial evidence of effectiveness. In other cases, FDA has relied on only a single adequate and well-controlled efficacy study to support approval — generally only in cases in which a single multicenter study of excellent design provided highly reliable and statistically strong evidence of an important clinical benefit, such as an effect on survival, and a confirmatory study would have been difficult to conduct on ethical grounds.

In section 115(a) of the Modernization Act, Congress amended section 505(d) of the Act to make it clear that the Agency may consider "data from one adequate and well-controlled clinical investigation and confirmatory evidence" to constitute substantial

[4] Section 505(d) of the Act uses the plural form in defining "substantial evidence" as "adequate and well-controlled investigations, including clinical investigations." See also use of "investigations" in section 505(b) of the Act, which lists the contents of a new drug application.

evidence if FDA determines that such data and evidence are sufficient to establish effectiveness. In making this clarification, Congress confirmed FDA's interpretation of the statutory requirements for approval and acknowledged the Agency's position that there has been substantial progress in the science of drug development resulting in higher quality clinical trial data.

Biologics. Biological products are approved under authority of section 351 of the Public Health Service Act (PHS Act) (42 U.S.C.§ 262). Under section 351, as in effect since 1944, licenses for biologics have been issued only upon a showing that the products meet standards designed to ensure the "continued safety, purity, and potency" of the products. *Potency* has long been interpreted to include effectiveness (21 CFR 600.3(s)). In 1972, FDA initiated a review of the safety and effectiveness of all previously licensed biologics. The Agency stated then that proof of effectiveness would consist of controlled clinical investigations as defined in the provision for "adequate and well-controlled studies" for new drugs (21 CFR 314.126), unless waived as not applicable to the biological product or essential to the validity of the study when an alternative method is adequate to substantiate effectiveness (21 CFR 601.25 (d) (2)). One such adequate alternative was identified to be serological response data where a previously accepted correlation with clinical effectiveness exists. As with nonbiological drug products, FDA has approved biological products based on single, multicenter studies with strong results.

Although section 123(a) of the Modernization Act amended section 351 of the PHS Act to make it clear that separate licenses are not required for biological products and the establishments at which the products are made, the evidentiary standard for a biological product was not changed: the product must be shown to be "safe, pure, and potent" (section 351 (a)(2) of the PHS Act as amended). In the Modernization Act (section 123(f)) Congress also directed the agency to take measures to "minimize differences in the review and approval" of products required to have approved BLAs under section 351 of the PHS Act and products required to have approved NDAs under section 505(b)(1) of the FDC Act.

B. Scientific Basis for the Legal Standard

The usual requirement for more than one adequate and well-controlled investigation reflects the need for *independent substantiation* of experimental results. A single clinical experimental finding of efficacy, unsupported by other independent evidence, has not usually been considered adequate scientific support for a conclusion of effectiveness. The reasons for this include the following.

- Any clinical trial may be subject to unanticipated, undetected, systematic biases. These biases may operate despite the best intentions of sponsors and investigators, and may lead to flawed conclusions. In addition, some investigators may bring conscious biases to evaluations.

- The inherent variability in biological systems may produce a positive trial result by chance alone. This possibility is acknowledged, and quantified to some extent, in the statistical evaluation of the result of a single efficacy trial. It should be noted, however, that hundreds of randomized clinical efficacy trials are conducted each year with the intent of submitting favorable results to FDA. Even if all drugs tested in such trials were ineffective, one would expect one in forty of those trials to "demonstrate" efficacy by chance alone at conventional levels of statistical significance.[5] It is probable, therefore, that false positive findings (i.e., the chance appearance of efficacy with an ineffective drug) will occur and be submitted to FDA as evidence of effectiveness. Independent substantiation of a favorable result protects against the possibility that a chance occurrence in a single study will lead to an erroneous conclusion that a treatment is effective.

- Results obtained in a single center may be dependent on site or investigator specific factors (e.g., disease definition, concomitant treatment, diet). In such cases, the results, although correct, may not be generalizable to the intended population. This possibility is the primary basis for emphasizing the need for independence in substantiating studies.

- Rarely, favorable efficacy results are the product of scientific fraud.

Although there are statistical, methodologic, and other safeguards to address the identified problems, they are often inadequate to address these problems in a single trial. Independent substantiation of experimental results addresses such problems by providing consistency across more than one study, thus greatly reducing the possibility that a biased, chance, site-specific, or fraudulent result will lead to an erroneous conclusion that a drug is effective.

The need for independent substantiation has often been referred to as the need for replication of the finding. Replication may not be the best term, however, as it may imply that precise repetition of the same experiment in other patients by other investigators is the only means to substantiate a conclusion. Precise replication of a trial is only one of a number of possible means of obtaining independent substantiation of a clinical finding and, at times, can be less than optimal as it could leave the conclusions vulnerable to any systematic biases inherent to the particular study design. Results that are obtained from studies that are of different design and independent in execution, perhaps evaluating different populations, endpoints, or dosage forms, may provide support for a conclusion of effectiveness that is as convincing as, or more convincing than, a repetition of the same study.

[5] p-value = 0.05, two-tailed, which implies an error rate in the efficacy (false positive) tail of 0.025 or one in forty.

C. The Quantity of Evidence to Support Effectiveness

The following three sections provide guidance on the quantity of evidence needed in particular circumstances to establish substantial evidence of effectiveness. Section 1 addresses situations in which effectiveness of a new use may be extrapolated entirely from existing efficacy studies. Section 2 addresses situations in which a single adequate and well-controlled study of a specific new use can be supported by information from other related adequate and well-controlled studies, such as studies in other phases of a disease, in closely related diseases, of other conditions of use (different dose, duration of use, regimen), of different dosage forms, or of different endpoints. Section 3 addresses situations in which a single multicenter study, without supporting information from other adequate and well-controlled studies, may provide evidence that a use is effective.

In each of these situations, it is assumed that any studies relied on to support effectiveness meet the requirements for adequate and well-controlled studies in 21 CFR 314.126. It should also be appreciated that reliance on a single study of a given use, whether alone or with substantiation from related trial data, leaves little room for study imperfections or contradictory (nonsupportive) information. In all cases, it is presumed that the single study has been appropriately designed, that the possibility of bias due to baseline imbalance, unblinding, post-hoc changes in analysis, or other factors is judged to be minimal, and that the results reflect a clear prior hypothesis documented in the protocol. Moreover, a single favorable study among several similar attempts that failed to support a finding of effectiveness would not constitute persuasive support for a product use unless there were a strong argument for discounting the outcomes in the studies that failed to show effectiveness (e.g., study obviously inadequately powered or lack of assay sensitivity as demonstrated in a three-arm study by failure of the study to show efficacy of a known active agent).

Whether to rely on a single study to support an effectiveness determination is not often an issue in contemporary drug development. In most drug development situations, the need to find an appropriate dose, to study patients of greater and lesser complexity or severity of disease, to compare the drug to other therapy, to study an adequate number of patients for safety purposes, and to otherwise know what needs to be known about a drug before it is marketed will result in more than one adequate and well-controlled study upon which to base an effectiveness determination.

This guidance is not intended to provide a complete listing of the circumstances in which existing efficacy data may provide independent substantiation of related claims; rather, it provides examples of the reasoning that may be employed. The examples are applicable whether the claim arises in the original filing of an NDA or BLA, or in a supplemental application.

1. Extrapolation from Existing Studies

In certain cases, effectiveness of an approved drug product for a new indication, or effectiveness of a new product, may be adequately demonstrated without additional adequate and well-controlled clinical efficacy trials. Ordinarily, this will be because other types of data provide a way to apply the known effectiveness to a new population or a different dose, regimen or dosage form. The following are examples of situations in which effectiveness might be extrapolated from efficacy data for another claim or product.

a. Pediatric uses

The rule revising the Pediatric Use section of product labeling (21 CFR 201.57(f)(9)(iv)) makes allowance for inclusion of pediatric use information in labeling without controlled clinical trials of the use in children. In such cases, a sponsor must provide other information to support pediatric use, and the Agency must conclude that the course of the disease and the effects of the drug are sufficiently similar in the pediatric and adult populations to permit extrapolation from adult efficacy data to pediatric patients. Evidence that could support a conclusion of similar disease course and similar drug effect in adult and pediatric populations includes evidence of common pathophysiology and natural history of the disease in the adult and pediatric populations, evidence of common drug metabolism and similar concentration-response relationships in each population, and experience with the drug, or other drugs in its therapeutic class, in the disease or condition or related diseases or conditions. Examples in which pediatric use labeling information has been extrapolated from adult efficacy data include ibuprofen for pain and loratidine for seasonal allergic rhinitis.

b. Bioequivalence

The effectiveness of alternative formulations and new dosage strengths may be assessed on the basis of evidence of bioequivalence.

c. Modified-release dosage forms

In some cases, modified release dosage forms may be approved on the basis of pharmacokinetic data linking the new dosage form to a previously studied immediate-release dosage form. Because the pharmacokinetic patterns of modified-release and immediate-release dosage forms are not identical, it is generally important to have some understanding of the relationship of blood concentration to response, including an understanding of the time course of that relationship, to extrapolate the immediate-release

data to the modified-release dosage form.

d. Different doses, regimens, or dosage forms

Dose-response relationships are generally continuous such that information about the effectiveness of one dose, dosage regimen, or dosage form is relevant to the effectiveness of other doses, regimens, or dosage forms. Where blood levels and exposure are not very different, it may be possible to conclude that a new dose, regimen, or dosage form is effective on the basis of pharmacokinetic data alone. Even if blood levels are quite different, if there is a well-understood relationship between blood concentration and response, including an understanding of the time course of that relationship, it may be possible to conclude that a new dose, regimen, or dosage form is effective on the basis of pharmacokinetic data without an additional clinical efficacy trial. In this situation, pharmacokinetic data, together with the well-defined pharmacokinetic/pharmacodynamic (PK/PD) relationship, are used to translate the controlled trial results from one dose, regimen, or dosage form to a new dose, regimen, or dosage form (See also section II.C.2.a).

2. Demonstration of Effectiveness by a Single Study of a New Use, with Independent Substantiation From Related Study Data

The discussion that follows describes specific examples in which a single study of a new use, with independent substantiation from study data in related uses, could provide evidence of effectiveness. In these cases, the study in the new use and the related studies support the conclusion that the drug has the effect it is purported to have. Whether related studies are capable of substantiating a single study of a new use is a matter of judgment and depends on the quality and outcomes of the studies and the degree of relatedness to the new use.

a. Different doses, regimens, or dosage forms

As discussed in Sections II.C.1.d, it may be possible to conclude that a new dose, regimen, or dosage form is effective on the basis of pharmacokinetic data without an additional clinical efficacy trial where blood levels and exposure are not very different or, even if quite different, there is a well-understood relationship between blood concentration and response. Where the relationship between blood concentration and response is not so well understood and the pharmacokinetics of the new dose, regimen, or dosage form differ from the previous one, clinical efficacy data will likely be necessary to support effectiveness of a new regimen. In this case, a single additional efficacy study should ordinarily be sufficient. For example, a single controlled trial was needed to support the recent approval of a once

daily dose of risperidone because the once daily and twice daily regimens had different pharmacokinetics and risperidone's PK/PD relationship was not well understood.

b. Studies in other phases of the disease

In many cases, therapies that are effective in one phase of a disease are effective in other disease phases, although the magnitude of the benefit and benefit-to-risk relationship may differ in these other phases. For example, if a drug is known to be effective in patients with a refractory stage of a particular cancer, a single adequate and well-controlled study of the drug in an earlier stage of the same tumor will generally be sufficient evidence of effectiveness to support the new use.

c. Studies in other populations

Often, responses in subsets of a particular patient population are qualitatively similar to those in the whole population. In most cases, separate studies of effectiveness in demographic subsets are not needed (see also discussion of the pediatric population in section II.C.1.a) However, where further studies are needed, a single study would ordinarily suffice to support effectiveness in age, race, gender, concomitant disease, or other subsets for a drug already shown to be generally effective in a condition or to be effective in one population. For example, a single study was sufficient to support tamoxifen use in breast cancer in males.

d. Studies in combination or as monotherapy

For a drug known to be effective as monotherapy, a single adequate and well-controlled study is usually sufficient to support effectiveness of the drug when combined with other therapy (as part of a multidrug regimen or in a fixed-dose combination). Similarly, known effectiveness of a drug as part of a combination (i.e., its contribution to the effect of the combination is known) would usually permit reliance on a single study of appropriate design to support its use as monotherapy, or as part of a different combination, for the same use. For example, a single study of a new combination vaccine designed to demonstrate adequate immune response will ordinarily provide sufficient evidence of effectiveness if the new combination contains products or antigens already proven to be effective alone or in other combinations. These situations are common for oncologic and antihypertensive drugs, but occur elsewhere as well.

e. Studies in a closely related disease

Studies in etiologically or pathophysiologically related conditions, or studies of a symptom common to several diseases (e.g., pain) can support each other, allowing initial approval of several uses or allowing additional claims based on a single adequate and well-controlled study. For example, certain anti-coagulant or anti-platelet therapies could be approved for use in two different settings based on individual studies in unstable angina/acute coronary syndrome and in the postangioplasty state. Because the endpoints studied and the theoretical basis for use of an anti-coagulant or anti-platelet drug are similar, each study supports the other for each claim. Similarly, single analgesic studies in several painful conditions would ordinarily be sufficient to support either a general analgesic indication or multiple specific indications. The recent approval of lamotrigine for treatment of Lennox-Gastaut Syndrome (a rare, largely pediatric, generalized seizure disorder) was based on a single adequate and well-controlled trial, due in part to related data showing efficacy of the drug in partial-onset seizures in adults.

f. Studies in less closely related diseases, but where the general purpose of therapy is similar

Certain classes of drug therapy, such as antimicrobials and antineoplastics, are appropriate interventions across a range of different diseases. For therapies of this type, evidence of effectiveness in one disease could provide independent substantiation of effectiveness in a quite different disease. For example, it is possible to argue that evidence of effectiveness of an antimicrobial in one infectious disease setting may support reliance on a single study showing effectiveness in other settings where the causative pathogens, characteristics of the site of infection that affect the disease process (e.g., structure and immunology) and patient population are similar.[6] Similarly, for an oncologic drug, evidence of effectiveness in one or more tumor types may support reliance on a single study showing effectiveness against a different kind of tumor, especially if the tumor types have a common biological origin.

g. Studies of different clinical endpoints

Demonstration of a beneficial effect in different studies on two different clinically meaningful endpoints could cross-substantiate a claim for

[6] See Division of Anti-Infective Drug Products: Points to Consider in the Clinical Development and Labeling of Anti-Infective Drug Products, October 1992.

effectiveness for each outcome. For example, the initial claim for effectiveness of enalapril for heart failure was supported by one study showing symptom improvement over several months and a second study showing improved survival in a more severely ill population. The two different findings, each from an adequate and well-controlled study, led to the conclusion that enalapril was effective in both treating symptoms and improving survival.

h. Pharmacologic/pathophysiologic endpoints

When the pathophysiology of a disease and the mechanism of action of a therapy are very well understood, it may be possible to link specific pharmacologic effects to a strong likelihood of clinical effectiveness. A pharmacologic effect that is accepted as a validated surrogate endpoint can support ordinary approval (e.g., blood pressure effects, cholesterol-lowering effects) and a pharmacologic effect that is considered reasonably likely to predict clinical benefit can support accelerated approval under the conditions described in 21 CFR 314 Subpart H and 21 CFR 601 Subpart E (e.g., CD4 count and viral load effects to support effectiveness of anti-viral drugs for HIV infection). When the pharmacologic effect is not considered an acceptable effectiveness endpoint, but the linkage between it and the clinical outcome is strong, not merely on theoretical grounds but based on prior therapeutic experience or well-understood pathophysiology, a single adequate and well-controlled study showing clinical efficacy can sometimes be substantiated by persuasive data from a well-controlled study or studies showing the related pharmacologic effect.

For example, a single clearly positive trial can be sufficient to support approval of a replacement therapy such as a coagulation factor, when it is combined with clear evidence that the condition being treated is caused by a deficiency of that factor. Demonstration of physical replacement of the deficient factor or restoration of the missing physiologic activity provides strong substantiation of the clinical effect. The corrective treatment of an inborn error of metabolism could be viewed similarly. In the case of preventive vaccines, one adequate and well-controlled clinical trial may be supported by compelling animal challenge/protection models, human serological data, passive antibody data, or pathogenesis information. The more evidence there is linking effects on the pharmacologic endpoint to improvement or prevention of the disease, the more persuasive the argument for reliance on a single clinical efficacy study.

Note, however, that plausible beneficial pharmacologic effects have often not correlated with clinical benefit, and, therefore, caution must be observed in relying on a pharmacologic effect as contributing to evidence

of effectiveness. For example, pharmacologic effects such as arrhythmia suppression by Type 1 antiarrhythmics and increased cardiac output by phosphodiesterase inhibitors or beta adrenergic inotropes resulted in increased mortality, rather than, as was expected, decreased sudden death and improved outcome in heart failure. The reasons for the absence of an expected correlation between pharmacologic and clinical effects are diverse and can include an incompletely understood relationship between the pharmacologic effect and the clinical benefit and the presence of other pharmacologic effects attributable to a drug in addition to the effect being measured and thought to be beneficial. Generally, the utility of pharmacologic outcomes in providing independent substantiation will be greatest where there is prior experience with the pharmacologic class. Even in this case, however, it is difficult to be certain that a pharmacologic effect that correlates with a clinical benefit accounts for all the clinical benefit or that other effects are not present and relevant.

3. Evidence of Effectiveness from a Single Study

When the effectiveness requirement was originally implemented in 1962, the prevailing efficacy study model was a single institution, single investigator, relatively small trial with relatively loose blinding procedures, and little attention to prospective study design and identification of outcomes and analyses. At present, major clinical efficacy studies are typically multicentered, with clear, prospectively determined clinical and statistical analytic criteria. These studies are less vulnerable to certain biases, are often more generalizable, may achieve very convincing statistical results, and can often be evaluated for internal consistency across subgroups, centers, and multiple endpoints.

The added rigor and size of contemporary clinical trials have made it possible to rely, in certain circumstances, on a single adequate and well-controlled study, without independent substantiation from another controlled trial, as a sufficient scientific and legal basis for approval. For example, the approval of timolol for reduction of post-infarction mortality was based on a single, particularly persuasive (low p-value), internally consistent, multicenter study that demonstrated a major effect on mortality and reinfarction rate. For ethical reasons, the study was considered unrepeatable. The Center for Biologics Evaluation and Research has also approved a number of products based upon a single persuasive study. The Agency provided a general statement in 1995 describing when a single, multicenter study may suffice (60 FR 39181; August 1, 1995), but the Agency has not comprehensively described the situations in which a single adequate and well-controlled study might be considered adequate support for an effectiveness claim, or the characteristics of a single study that could make it adequate support for an effectiveness claim.

Whether to rely on a single adequate and well-controlled study is inevitably a matter of judgment. A conclusion based on two persuasive studies will always be more secure than a conclusion based on a single, comparably persuasive study. For this reason, reliance on only a single study will generally be limited to situations in which a trial has demonstrated a clinically meaningful effect on mortality, irreversible morbidity, or prevention of a disease with potentially serious outcome and confirmation of the result in a second trial would be practically or ethically impossible. For example, sequential repetition of strongly positive trials that demonstrated a decrease in post-infarction mortality, prevention of osteoporotic fractures, or prevention of pertussis would present significant ethical concerns. Repetition of positive trials showing only symptomatic benefit would generally not present the same ethical concerns.

The discussion that follows identifies the characteristics of a single adequate and well-controlled study that could make the study adequate support for an effectiveness claim. Although no one of these characteristics is necessarily determinative, the presence of one or more in a study can contribute to a conclusion that the study would be adequate to support an effectiveness claim.

a. Large multicenter study

In a large multicenter study in which (1) no single study site provided an unusually large fraction of the patients and (2) no single investigator or site was disproportionately responsible for the favorable effect seen, the study's internal consistency lessens concerns about lack of generalizability of the finding or an inexplicable result attributable only to the practice of a single investigator. If analysis shows that a single site is largely responsible for the effect, the credibility of a multicenter study is diminished.

b. Consistency across study subsets

Frequently, large trials have relatively broad entry criteria and the study populations may be diverse with regard to important covariates such as concomitant or prior therapy, disease stage, age, gender or race. Analysis of the results of such trials for consistency across key patient subsets addresses concerns about generalizability of findings to various populations in a manner that may not be possible with smaller trials or trials with more narrow entry criteria. For example, the timolol postinfarction study randomized patients separately within three severity strata. The study showed positive effects on survival in each stratum supporting a conclusion that the drug's utility was not limited to a particular disease stage (e.g., relatively low or high severity).

c. Multiple *studies* in a single study

Properly designed factorial studies may be analyzed as a series of pairwise comparisons, representing, within a single study, separate demonstrations of activity of a drug as monotherapy and in combination with another drug. This model was successfully used in ISIS II, which showed that for patients with a myocardial infarction both aspirin and streptokinase had favorable effects on survival when used alone and when combined (aspirin alone and streptokinase alone were each superior to placebo; aspirin and streptokinase in combination were superior to aspirin alone and to streptokinase alone). This represented two separate (but not completely independent) demonstrations of the effectiveness of aspirin and streptokinase.

d. Multiple endpoints involving different events

In some cases, a single study will include several important, prospectively identified primary or secondary endpoints, each of which represents a beneficial, but different, effect. Where a study shows statistically persuasive evidence of an effect on more than one of such endpoints, the internal weight of evidence of the study is enhanced. For example, the approval of beta-interferon (Betaseron) for prevention of exacerbations in multiple sclerosis was based on a single multicenter study, at least partly because there were both a decreased rate of exacerbations and a decrease in MRI-demonstrated disease activity — two entirely different, but logically related, endpoints.

Similarly, favorable effects on both death and nonfatal myocardial infarctions in a lipid-lowering, postangioplasty, or postinfarction study would, in effect, represent different, but consistent, demonstrations of effectiveness, greatly reducing the possibility that a finding of reduced mortality was a chance occurrence. For example, approval of abciximab as adjunctive treatment for patients undergoing complicated angioplasty or atherectomy was supported by a single study with a strong overall result on the combined endpoint (decreased the combined total of deaths, new infarctions, and need for urgent interventions) and statistically significant effects in separate evaluations of two components of the combined endpoint (decreased new infarctions and decreased need for urgent interventions). In contrast, a beneficial effect on multiple endpoints that evaluate essentially the same phenomenon and correlate strongly, such as mood change on two different depression scales or SGOT and CPK levels postinfarction, does not significantly enhance the internal weight of the evidence from a single trial.

Although two consistent findings within a single study usually provide reassurance that a positive treatment effect is not due to chance, they do not protect against bias in study conduct or biased analyses. For example, a treatment assignment not well balanced for important prognostic variables could lead to an apparent effect on both endpoints. Thus, close scrutiny of study design and conduct are critical to evaluating this type of study.

e. Statistically very persuasive finding

In a multicenter study, a very low p-value indicates that the result is highly inconsistent with the null hypothesis of no treatment effect. In some studies it is possible to detect nominally statistically significant results in data from several centers, but, even where that is not possible, an overall extreme result and significance level means that most study centers had similar findings. For example, the thrombolysis trials of streptokinase (ISIS II, GISSI) had very sizable treatment effects and very low p-values, greatly adding to their persuasiveness. Preventive vaccines for infectious disease indications with a high efficacy rate (e.g., point estimate of efficacy of 80% or higher and a reasonably narrow 95% confidence interval) have been approved based on a single adequate and well-controlled trial.

4. Reliance on a Single, Multicenter Study — Caveats

While acknowledging the persuasiveness of a single, internally consistent, strong multicenter study, it must be appreciated that even a strong result can represent an isolated or biased result, especially if that study is the only study suggesting efficacy among similar studies. Recently, the apparent highly favorable effect of vesnarinone, an inotropic agent, in heart failure (60% reduction of mortality in what appeared to be a well-designed, placebo-controlled, multicenter trial with an extreme p-value) has proven to be unrepeatable. In an attempt to substantiate the finding, the same dose of the drug that seemed lifesaving in the earlier study significantly increased mortality (by 26%), and a lower dose also appeared to have a detrimental effect on survival. Although the population in the second study was, on the whole, a sicker population than in the first, the outcomes in similarly sick patients in each study were inconsistent so this factor does not explain the contradictory results.

When considering whether to rely on a single multicenter trial, it is critical that the possibility of an incorrect outcome be considered and that all the available data be examined for their potential to either support or undercut reliance on a single multicenter trial. In the case of vesnarinone, there were other data that were not consistent with the dramatically favorable outcome in the multicenter study. These data seemed to show an inverse dose-response relationship, showed no suggestion

of symptomatic benefit, and showed no effect on hemodynamic endpoints. These inconsistencies led the Agency, with the advice of its Cardio-Renal Advisory Committee, to refuse approval — a decision borne out by the results of the subsequent study.

This example illustrates how inadequacies and inconsistencies in the data, such as lack of pharmacologic rationale and lack of expected other effects accompanying a critical outcome, can weaken the persuasiveness of a single trial. Although an unexplained failure to substantiate the results of a favorable study in a second controlled trial is not proof that the favorable study was in error — studies of effective agents can fail to show efficacy for a variety of reasons — it is often reason not to rely on the single favorable study.

III. DOCUMENTATION OF THE QUALITY OF EVIDENCE SUPPORTING AN EFFECTIVENESS CLAIM

When submitting the requisite quantity of data to support approval of a new product or new use of an approved product, sponsors must also document that the studies were adequately designed and conducted. Essential characteristics of adequate and well-controlled trials are described in 21 CFR 314.126. To demonstrate that a trial supporting an effectiveness claim is adequate and well-controlled, extensive documentation of trial planning, protocols, conduct, and data handling is usually submitted to the Agency, and detailed patient records are made available at the clinical sites.

From a scientific standpoint, however, it is recognized that the extent of documentation necessary depends on the particular study, the types of data involved, and the other evidence available to support the claim. Therefore, the Agency is able to accept different levels of documentation of data quality, as long as the adequacy of the scientific evidence can be assured. This section discusses the factors that influence the extent of documentation needed, with particular emphasis on studies evaluating new uses of approved drugs.

For the purposes of this section, the phrase *documentation of the quality of evidence* refers to (1) the completeness of the documentation and (2) the ability to access the primary study data and the original study-related records (e.g., subjects' medical records, drug accountability records) for the purposes of verifying the data submitted as evidence. These interrelated elements bear on a determination of whether a study is adequate and well-controlled.

In practice, to achieve a high level of documentation, studies supporting claims are ordinarily conducted in accordance with good clinical practices (GCPs). Sponsors routinely monitor all clinical sites, and FDA routinely has access to the original clinical protocols, primary data, clinical site source documents for on-site audits, and complete study reports.

However, situations often arise in which studies that evaluate the efficacy of a drug product lack the full documentation described above (for example, full patient records may not be available) or in which the study was conducted with less monitoring than is ordinarily seen in commercially sponsored trials. Such situations are more common for supplemental indications because postapproval studies are more likely to be conducted by parties other than the drug sponsor and those parties may employ less extensive monitoring and data-gathering procedures than a sponsor. Under certain circumstances, it is possible for sponsors to rely on such studies to support effectiveness claims, despite less than usual documentation or monitoring. Some of those circumstances are described below.

A. Reliance on Less Than Usual Access to Clinical Data or Detailed Study Reports

FDA's access to primary data has proven to be important in many regulatory decisions. There are also reasons to be skeptical of the conclusions of published reports of studies. Experience has shown that such study reports do not always contain a complete, or entirely accurate, representation of study plans, conduct and outcomes. Outright fraud (i.e., deliberate deception) is unusual. However, incompleteness, lack of clarity, unmentioned deviation from prospectively planned analyses, or an inadequate description of how critical endpoint judgments or assessments were made are common flaws. Typically, journal article peer reviewers only have access to a limited data set and analyses, do not see the original protocol and amendments, may not know what happened to study subjects that investigators determined to be non-evaluable, and thus may lack sufficient information to detect critical omissions and problems. The utility of peer review can also be affected by variability in the relevant experience and expertise of peer reviewers. FDA's experiences with the Anturane Reinfarction Trial, as well as literature reports of the efficacy of tacrine and the anti-sepsis HA-1A antibody, illustrate its concerns with reliance on the published medical literature.

Notwithstanding these concerns, the presence of some of the factors discussed below can make it possible for FDA to rely on studies for which it has less than usual access to data or detailed study reports to partially or entirely (the so-called *paper* filing) support an effectiveness claim. FDA's reliance on a literature report to support an effectiveness claim is more likely if FDA can obtain additional critical study details. Section 1 below describes additional information that, if available, would increase the likelihood that a study could be relied on to support an effectiveness claim. Section 2 describes factors that may make efficacy findings sufficiently persuasive to permit reliance on the published literature alone. Note that the factors outlined in Section 2 are relevant to an assessment of the reliability of literature reports generally, whether alone, or accompanied by other important information as discussed in Section 1.

1. Submission of Published Literature or Other Reports in Conjunction with Other Important Information that Enhances the Reliability of the Data

If a sponsor wishes to rely on a study conducted by another party and cannot obtain the primary data from the study, for most well-conducted studies it is possible to obtain other important information, such as a protocol documenting the prospective plans for the trial, records of trial conduct and procedures, patient data listings for important variables, and documentation of the statistical analysis. FDA has considerable experience evaluating large multicenter outcome studies sponsored by U.S. and European government agencies (NIH, British Medical Research Council) and private organizations (the ISIS studies, the SAVE study) for which there was limited access to primary study data, but for which other critical information was available. Providing as many as possible of the following important pieces of information about a study, in conjunction with the published report, can increase the likelihood that the study can be relied on to support an effectiveness claim:

a. The protocol used for the study, as well as any important protocol amendments that were implemented during the study and their relation to study accrual or randomization.

b. The prospective statistical analysis plan and any changes from the original plan that occurred during or after the study, with particular note of which analyses were performed pre- and post-unblinding.

c. Randomization codes and documented study entry dates for the subjects.

d. Full accounting of all study subjects, including identification of any subjects with on-treatment data who have been omitted from analysis and the reasons for omissions, and an analysis of results using all subjects with on-study data.

e. Electronic or paper record of each subject's data for critical variables and pertinent baseline characteristics. Where individual subject responses are a critical variable (e.g., objective responses in cancer patients, clinical cures and microbial eradications in infectious disease patients, death from a particular cause), detailed bases for the assessment, such as the case report, hospital records, and narratives, should be provided when possible.

f. Where safety is a major issue, complete information for all deaths and drop-outs due to toxicity. For postapproval supplemental uses, however, there is generally less need for the results of lab tests or for details of adverse event reports and, consequently, much more limited documentation may be sufficient (e.g., only for unexpected deaths and previously undescribed serious adverse effects). Exceptions to this

approach would include situations in which the population for the supplemental use is so different that existing safety information has limited application (e.g., thrombolysis in stroke patients versus myocardial infarction patients) or where the new population presents serious safety concerns (e.g., extension of a preventive vaccine indication from young children to infants).

2. Submission of Published Literature Reports Alone

The following factors increase the possibility of reliance on published reports alone to support approval of a new product or new use:

a. Multiple studies conducted by different investigators where each of the studies clearly has an adequate design and where the findings across studies are consistent.

b. A high level of detail in the published reports, including clear and adequate descriptions of statistical plans, analytic methods (prospectively determined), and study endpoints, and a full accounting of all enrolled patients.

c. Clearly appropriate endpoints that can be objectively assessed and are not dependent on investigator judgment (e.g., overall mortality, blood pressure, or microbial eradication). Such endpoints are more readily interpreted than more subjective endpoints such as cause-specific mortality or relief of symptoms.

d. Robust results achieved by protocol-specified analyses that yield a consistent conclusion of efficacy and do not require selected post hoc analyses such as covariate adjustment, subsetting, or reduced data sets (e.g., analysis of only responders or compliant patients, or of an "eligible" or “evaluable” subset).

e. Conduct of studies by groups with properly documented operating procedures and a history of implementing such procedures effectively.

There have been approvals based primarily or exclusively on published reports. Examples include the initial approval of secretin for evaluation of pancreatic function and recent approvals of bleomycin and talc for malignant pleural effusion and doxycycline for malaria.

B. Reliance on Studies with Alternative, Less Intensive Quality Control/On-Site Monitoring

Industry-sponsored studies typically use extensive on-site and central monitoring and auditing procedures to assure data quality. Studies supported by other sponsors may employ less stringent procedures and may use no on-site monitoring at all. An International Conference on Harmonisation guideline on good clinical practices,[7] recently accepted internationally, emphasizes that the extent of monitoring in a trial should be based on trial-specific factors (e.g., design, complexity, size, and type of study outcome measures) and that different degrees of on-site monitoring can be appropriate. In recent years, many credible and valuable studies conducted by government or independent study groups, often with important mortality outcomes, had very little on-site monitoring. These studies have addressed quality control in other ways, such as by close control and review of documentation and extensive guidance and planning efforts with investigators. There is a long history of reliance on such studies for initial approval of drugs as well as for additional indications. Factors that influence whether studies with limited or no monitoring may be relied on include the following:

1. The existence of a prospective plan to assure data quality.

2. Studies that have features that make them inherently less susceptible to bias, such as those with relatively simple procedures, noncritical entry criteria, and readily assessed outcomes.

3. The ability to sample critical data and make comparisons to supporting records (e.g., hospital records).

4. Conduct of the study by a group with established operating procedures and a history of implementing such procedures effectively.

[7] International Conference on Harmonisation Guidance for Industry E6, *Good Clinical Practice: Consolidated Guideline*, April 1996.