

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-222Orig1s000

STATISTICAL REVIEW(S)



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

Clinical Studies

NDA/Serial Number: 22-222 / 00
Drug Name: Ultrase
Indication(s): Treatment of patients with exocrine pancreatic insufficiency caused by cystic fibrosis, chronic pancreatitis, or other related conditions
Applicant: Axcan Scandipharm
Date(s): Received Dec 28, 2007; final PDUFA goal date July 1, 2008
Review Status: Priority with major amendment

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1. EXECUTIVE SUMMARY

1.1. Conclusions and Recommendations

The evidence from the clinical trials supports a conclusion of efficacy for Ultrase MT20 minitables with H55 coating in the treatment of patients with exocrine pancreatic insufficiency due to cystic fibrosis. Pancreatic insufficiency due to other causes was not studied.

1.2. Brief Overview of Clinical Studies

Ultrase is a pancreatic enzyme supplement. It is dosed as a capsule containing enteric-coated minitables of porcine pancreatic enzyme concentrates, predominantly lipase, amylase and protease. Ultrase is produced in strengths of 4,500, 12,000, and 20,000 lipase units per capsule. These capsule strengths are designated Ultrase MT4.5, MT12, and MT20, respectively.

The applicant submitted three controlled studies in support of the efficacy and safety of Ultrase in the treatment of patients with exocrine pancreatic insufficiency. Only study UMT20CF05-01 uses the to-be-marketed form, Ultrase MT20 coated with a solvent-based agent hydroxypropyl methylcellulose (H55). Two studies, 96-01 and 96-02, use Ultrase minitables coated with a water-based agent called Eudragit and can be considered supportive for registration purposes.

UMT20CF05-01 was a multicenter, randomized, double-blind, placebo-controlled, two-period crossover study. The study consisted of a screening period (up to 11 days), two treatment periods (6-7 days) each preceded by a stabilization period (4 days) and separated by a break period (3-6 days). Patients received a high-fat diet during the treatment (but not the break) periods. Thirty-one patients were randomized to treatment.

Studies 96-01 and 96-02 were carried out nearly a decade prior to submission of this NDA (last subject completed 08/24/98 in 96-01 and 8/29/99 in 96-02). They were nearly identical in design to each other, with the main difference that 96-01 used MT20 capsules while 96-02 used MT12. They were also similar in many ways to study UMT20CF05-01; however the Ultrase minitables that were used in 96-01 and 02 had a different, water-based coating.

Like Study UMT20CF05-01; studies 96-01 and 96-02 were randomized, double-blind, multicenter, placebo-controlled, crossover study designed to evaluate the safety and efficacy of ultrase in the treatment of steatorrhea in CF subjects with a history of pancreatic enzyme insufficiency. Each study consisted of a diet and enzyme stabilization period (7 days) followed by a treatment period of approximately 6 days and then, after a switch of treatments, a second treatment period of approximately 6 days. There were 31 patients randomized in study 96-01 and 26 in study 96-02.

1.3. Statistical Issues and Findings

Three placebo-controlled studies were submitted for the evaluation of the efficacy and safety of Ultrase mini-tablets. Only one study used the to-be-marketed form of the product and is considered pivotal; the other two provided supportive evidence. All three studies used a two-period crossover design. The pivotal study included a washout period between treatments.

The primary outcome was the percent of dietary fat absorbed with percent nitrogen absorption a secondary outcome. Both the CFA% and CNA% were significantly improved with treatment by Ultrase, with no apparent sequence or period effects.

2. INTRODUCTION

2.1. Overview

Ultrase is a pancreatic enzyme supplement. It is dosed as a capsule containing enteric-coated minitabets of porcine pancreatic enzyme concentrates, predominantly lipase, amylase and protease. Ultrase is produced in strengths of 4,500, 12,000, and 20,000 lipase units per capsule. These capsule strengths are designated Ultrase MT4.5, MT12, and MT20, respectively.

The applicant's proposed indication (draft label) is "treatment of patients with exocrine pancreatic insufficiency caused by cystic fibrosis, chronic pancreatitis, or other related conditions."

The applicant submitted three controlled studies in support of the efficacy and safety of Ultrase in the treatment of patients with exocrine pancreatic insufficiency. Only study UMT20CF05-01 uses the to-be-marketed form, Ultrase MT20 coated with a solvent-based agent hydroxypropyl methylcellulose (H55). Two studies, 96-01 and 96-02, use Ultrase minitabets coated with a water-based agent called Eudragit and can be considered supportive for registration purposes. All three studies enrolled patients with pancreatic insufficiency due to cystic fibrosis.

2.2. Data Sources

Data and study reports were submitted electronically in CTD format. The location in the EDR was \\CDSESUB1\EVSPROD\NDA02222\0003.

3. STATISTICAL EVALUATION

3.1. Evaluation of Efficacy

3.1.1 Study UMT20CF05-01

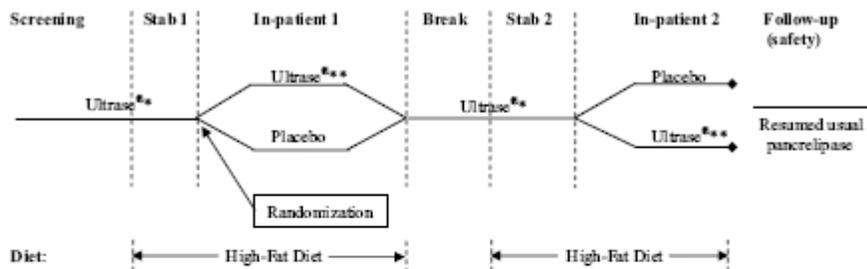
The primary objective of this study was to demonstrate the efficacy and safety of Ultrase H55-coated Ultrase MT20 for the correction of steatorrhea in cystic fibrosis (CF) patients with a history of pancreatic insufficiency.

UMT20CF05-01 was a multicenter, randomized, double-blind, placebo-controlled, two-period crossover study. The study consisted of a screening period (up to 11 days), two treatment periods (6-7 days) each preceded by a stabilization period (4 days) and separated by a break period (3-6 days). A schematic of the study design is shown below, from the clinical study report (CSR) figure 9.1, p. 26.

During the first stabilization period, all patients received Ultrase capsules and started on a high-fat diet. Patients were considered stabilized if they had three or fewer bowel movements per day

or if additional Ultrase did not cause any further reduction in their stool frequency. The stabilized dose was determined by the investigator, based upon adjustment of the patient's usual pancrelipase dose, modified in response to the high fat diet. This dose was used during the treatment periods as well as the second stabilization period. During the break period, the patient was free from high fat diet. (CSR, p. 24)

Schematic of Study Design, UMT20CF05-0



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

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

Stool specimens were collected during the treatment periods, and shipped to a central laboratory for analysis of fat and protein content (measurements to be used in the evaluation of efficacy).

Carry-over effects were not expected in this study since the treatment is a locally direct-acting pancreatic enzyme preparation. (CSR p. 30).

Efficacy Measurements:

Efficacy was based primarily on a comparison of the percent absorption of dietary fat. A secondary efficacy comparison was of the percent absorption of dietary protein.

The primary efficacy measure was the coefficient of fat absorption (CFA%), defined as

$$\text{CFA}\% = 100 \times [72\text{-hr fat intake (g)} - 72\text{-hr fat excretion (g)}] \div 72\text{-hr fat intake}$$

Note that no baseline measure of CFA% was taken.

The secondary efficacy measure was the coefficient of nitrogen absorption (CNA%), defined as

$$\text{CNA}\% = 100 \times [(72\text{-hr protein intake (g)}/6.25) - 72\text{-hr nitrogen excretion (g)}] \div (72\text{-hr protein intake (g)}/6.25)$$

Sample Size:

The results from a similar, earlier, cross-over study of Ultrase M20 showed a difference of 29% between Ultrase and the placebo group in the primary efficacy outcome (CSR, p 56). The mean CFA% was 59% with placebo and 87% with Ultrase, with n=25 patients. The treatment difference was highly significant. Based on these results, the applicant planned to have 24 completed patients. Assuming a standard deviation of 30% between placebo and Ultrase and a two-sided alpha of 0.05, a sample size of 24 would give a power of 80% to detect a minimum difference of 18%.

Planned analysis

There was a change in analysis from the protocol to the SAP and to the final analysis reported in the CSR as well. The versions are detailed below.

In the protocol, the ITT population is defined as those patients who completed one study treatment period. In the SAP and the analysis presented in the CSR, the ITT population is defined more accurately as all randomized patients.

Protocol analysis: The protocol states (section 11.5.2) that the primary and secondary efficacy variables

... will be analyzed using an analysis of variance. The model will be appropriate for a cross-over design and will include the factors of study center, treatment sequence, center-by-sequence interaction, patient within center by sequence, treatment group, treatment by sequence interaction, and treatment by center interaction. If the treatment by center interaction is found to be not statistically significant, this term will be removed from the model and the analysis will be rerun.

SAP: In contrast to the protocol, the SAP (Section 7.5) states that “because of the expected small sample size, statistical analyses will not be adjusted for study center.”

A more parsimonious model was planned for the analysis of CFA% . That is, the SAP (section 8.8.1 p 20-21) states that:

“[the two treatments would be compared] using a mixed model appropriate for a crossover design and will include the following factors:

$$Y_{ijkl} = \mu + \alpha_i + \beta_j + \gamma_k + p_l + \xi_{ijkl}$$

where:

Y_{ijkl} = CFA% for the l^{th} patient assigned to the k^{th} sequence, taking the i^{th} drug in the j^{th} period

μ = overall mean

α_i = effect of the i^{th} sequence, a fixed effect

β_j = effect of the j^{th} treatment period, a fixed effect

γ_k = effect of the k^{th} drug, a fixed effect

p_l = effect of the l^{th} patient, assumed i.i.d. $N(0, \sigma^2_p)$, a random effect

ξ_{ijkl} = random error, assumed i.i.d. $N(0, \sigma^2)$

In a first step, the best covariance structure will be determined by fitting subsequently the above model according to 3 different covariance structures (compound symmetric covariance, autoregressive order 1 and unstructured covariance). The best covariance structure will be the model with the smallest Akaike's Information Criteria Corrected (AICC).

For a 2x2 crossover trial, the multi-normality verification (multi-normality assumption underlying a crossover ANOVA model) is reduced to verify the normality of residuals from period 1 (or 2) (Chen et al, 2002). Thus, the distribution of the residuals of Treatment Period 1 from an ANOVA model will be tested for normality. If the Shapiro-Wilk's test yields to a significant p-value at a 0.10 level, a non-parametric approach will be performed: CFA% values will be rank-transformed and re-analyzed by the above mixed model....

The secondary efficacy parameter is the CNA%. ... It will be presented and analysed as for the primary efficacy parameter."

CSR: The analysis was carried out as described in the SAP. The non-parametric approach was used; in the CSR it is called "a semi-parametric approach (Iman-Conover)" and used for the following reasons: (CSR p 58)

1) violation of the normality assumption and 2) the differences between the Ultrase standard deviation (SD) and placebo SD values (e.g., placebo SD values almost 5 times Ultrase values for CFA%)

Results

Patient populations

There were 36 patients screened who were either taking Ultrase or were switched to Ultrase at the time of recruitment; these 36 constitute the safety population for the study. Of these, 32 were enrolled and 31 were randomized to treatment. These 31 patients constitute the ITT population. Of these, 24 patients completed both periods. The per-protocol population consisted of 18 patients.

All patients were 8 years of age or older with diagnosed CF and a history of pancreatic insufficiency. About half (14) were under age 18. The ITT population was predominantly Caucasian (94%; n=29), with the remainder Black (n=2) and 65% male (n=20).

Efficacy analyses

The applicant’s efficacy analyses are given below.

Table 1 (CSR table 11.4-2; p 68) shows the results for the analysis of CFA% in the ITT population.

TABLE 1 Summary and Analysis of the Coefficient of Fat Absorption (ITT Population)

| Parameter | Statistic | Treatment | | Delta |
|--|--------------|-----------------|-----------------|-----------------|
| | | Ultrase® MT20 | Placebo | |
| Number of Patients in the ITT Population | N | 30 | 31 | 30 |
| CFA% | n | 25 | 27 | 24 |
| | Mean | 88.550 | 55.614 | 34.742 |
| | STD | 4.943 | 25.104 | 25.049 |
| | Median | 89.190 | 51.950 | 40.385 |
| | (Min., Max.) | (77.36, 97.08) | (13.59, 97.12) | (-7.24, 75.22) |
| Mixed Model Fixed Effect [a] | | | | |
| Sequence | p-value | 0.9060 | | |
| Period | p-value | 0.3204 | | |
| Treatment Group | p-value | <0.0001** | | |

Note: n for CFA% includes all randomized patients who completed at least one treatment period; the delta value is the mean of the individual treatment differences in patients who completed both treatment periods.

** Indicates statistical significance at the 0.010 level.

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

Notes:

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

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

3. The fat excretion value (g/24h) transferred by the Central Lab has been multiplied by 3 before analysis in order to convert it to total fat content.

4. For each patient, Delta is the difference between CFA% Ultrase MT20 value and CFA% Placebo value.

Table 2 (CSR Table 11.4-3; p 70) shows the results for the analysis of CNA% in the ITT population.

Table 2 Summary and Analysis of the Coefficient of Nitrogen Absorption (ITT Population)

| Parameter | Statistic | Treatment | | Delta |
|--|--------------|-----------------|-----------------|-----------------|
| | | Ultrase® MT20 | Placebo | |
| Number of Patients in the ITT Population | N | 30 | 31 | 30 |
| CNA% | n | 25 | 27 | 24 |
| | Mean | 84.051 | 58.784 | 25.676 |
| | STD | 7.244 | 20.569 | 17.695 |
| | Median | 84.050 | 49.710 | 29.230 |
| | (Min., Max.) | (61.83, 95.05) | (29.98, 96.14) | (-8.86, 52.27) |
| Mixed Model Fixed Effect | | | | |
| [a] | | | | |
| Sequence | p-value | 0.5287 | | |
| Period | p-value | 0.2547 | | |
| Treatment Group | p-value | <0.0001** | | |

Note: n for CFA% includes all randomized patients who completed at least one treatment period; the delta value is the mean of the individual treatment differences in patients who completed both treatment periods.

** Indicates statistical significance at the 0.010 level.

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

Notes:

1. CNA%= Coefficient of Nitrogen Absorption

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

$$100 (72\text{-hour protein intake (g)/6.25) - 72\text{-hour nitrogen excretion (g)} \div 72\text{-hour protein intake (g)/6.25}$$

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

Based on the applicant's results, both the CFA% and CNA% were significantly improved with treatment by Ultrase, with no apparent sequence or period effects. For subjects with data from both periods (n=24) , the difference in CFA% between Ultrase and placebo was 34% and in CNA%, 26%.

Reviewer comments: In a two-period cross-over study, the compound symmetry and AR(1) covariance structures are the same. The applicant did not specify which covariance structure was used to produce the final results. In my re-analysis of the data, an unstructured covariance matrix gave the best fit to the rank transformed CFA and CNA, as judged by the AIC. My results matched the descriptive statistics but the inferential statistics differed by a small amount (less than 10%). There are many quantities and calculations to specify in the SAS procedures Proc Mixed and Proc Ranks (for example, handling ties, calculating denominator degrees of freedom) and my specifications may have differed from the applicant's.

The theory for a semi-parametric mixed model, using rank-transformed data and random effects, is not well-developed. It is not clear how the asymptotic inference in mixed models is affected by rank-transformation of the data prior to fitting the regression.

Nevertheless, fitting a variety of models, mixed-effect with patient as a random effect, or fixed-effect ANOVA, to either the raw or rank-transformed data yielded a highly significant p-value for treatment ($p < 0.0001$) and a large, insignificant p-value for sequence and period. The statistical conclusions remained the same: significant treatment effect and no effect of period or sequence.

Missing data Dropouts were not replaced and missing observations were not imputed. The efficacy analysis is thus an observed-case analysis. Five of the 30 Ultrase treated patients and 4 of the 31 placebo treated ITT patients did not provide CFA% data; 7 of the patients did not have measurements at the end of both periods and therefore were missing values of Delta, the difference between CFA% on Ultrase and on placebo (see table 1). When the smallest observed Delta (-7.24) was imputed for the 7 missing values, the mean decreased from 34.7 (table 1) to 24.3. While this value is considerably smaller than the observed mean, it is still highly significantly different from zero, implying that the missing values would be unlikely to change the conclusion of a significant treatment effect.

3.1.2 Study 96-01 and Study 96-02

Studies 96-01 and 96-02 were carried out nearly a decade prior to submission of this NDA (last subject completed 08/24/98 in 96-01; 8/29/99 in 96-02). They were nearly identical in design to each other, with the main difference that 96-01 used MT20 capsules while 96-02 used MT12. They were also similar in many ways to study UMT20CF05-01; however the Ultrase minitables that were used in 96-01 and 02 had a different, water-based coating.

Like Study UMT20CF05-01; studies 96-01 and 96-02 were randomized, double-blind, multicenter, placebo-controlled, crossover study designed to evaluate the safety and efficacy of ultrase in the treatment of steatorrhea in CF subjects with a history of pancreatic enzyme insufficiency. Each study consisted of a diet and enzyme stabilization period (7 days) followed by a treatment period of approximately 6 days and then, after a switch of treatments, a second

treatment period of approximately 6 days.

The evaluation of efficacy was based on a within–subject comparison of the percent absorption of dietary fat between Ultrase and placebo; a secondary comparison was of the percent absorption dietary protein.

The “modified intent-to-treat” population consisted of all subjects who completed at least one treatment period and for whom there was efficacy data; the “evaluable” population was all subjects who completed both treatment periods.

The CFA% was the primary efficacy variable analyzed and the CNA% was the secondary efficacy variable. Each of these variables was (96-01 CSR, p. 26)

...to be analyzed using an analysis of variance. For both the Intent-to-Treat and Efficacy populations the model was appropriate for a crossover design and included the factors of study center, treatment sequence, center by sequence interaction, subject within sequence, treatment group, treatment by sequence interaction, and treatment by center interaction. If the treatment by center interaction was found to be not statistically significant ($p>0.10$), this term would be removed from the model and the analysis would be rerun. For the Intent-to-Treat population an additional analysis would be performed using only the data from the first period of the study. The model used for this analysis was to include the factors of study center, treatment group, and the treatment by center interaction. If the treatment by center interaction was found to be not statistically significant ($p>0.10$), this term would be removed from the model and the analysis would be rerun.

(Note: I could not find in this application a Statistical Analysis Plan for these studies.)

Sample Size.

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

Results

Study 96-01

Thirty one patients were randomized. Twenty seven patients - 14 on Ultrase MT20 and 13 on placebo -- completed treatment period one and constitute what the sponsor calls the ITT population. Of these, 25 completed both treatment periods.

Patients ranged from 7 to 36 years of age, with 19 males (70%) and 8 females in the ITT population; 26 (96%) were Caucasian.

Primary efficacy results

Results for percent absorption are shown below, from the sponsor’s CSR Table 11.4.2, (p. 45). The final model included the factors of study center, treatment sequence, center by sequence interaction, subject within sequence, treatment group, treatment by sequence interaction, and treatment by center interaction.

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

Source: Table 14.8B

* Significant at .05 significance level

¹ Stool collection for subject F12 was incomplete

(CSR Table 11.4.1, p 44)

The model used for this analysis included the factors of study center, treatment group, and the treatment by center interaction.

| SUMMARY OF PERCENT ABSORPTION - INTENT-TO-TREAT SUBJECTS AT THE END OF TREATMENT PERIOD ONE | | | |
|--|-----------------------------------|-----------------------|---------------------------------------|
| Variable | Ultrase (N=14)¹ | Placebo (N=13) | Treatment Comparison (p-value) |
| Dietary Fat (g) | | | |
| Mean ± SD | 84.7 ± 13.1 | 60.6 ± 19.5 | 0.0015* |
| Range | 46.8 to 95.5 | 29.9 to 96.2 | |
| N | 13 | 13 | |
| Dietary Protein (g) | | | |
| Mean ± SD | 87.6 ± 7.3 | 63.8 ± 16.1 | 0.0001* |
| Range | 70.3 to 98.7 | 34.3 to 93.3 | |
| N | 13 | 13 | |

Source: Table 14.8B

* Significant at .05 significance level

¹ Stool collection for subject F12 was incomplete

Study 96-02

Twenty six patients were randomized. Twenty three completed treatment period one and constitute the (modified) ITT population; 12 received Ultrase MT12 and 11 placebo during treatment period one. Of these, 22 completed both treatment periods (the evaluable population).

Patients ranged from 8 to 36 years of age, with 16 males (70%) and 7 females in the ITT population; 20 (87%) were Caucasian.

Primary efficacy results

Results for percent absorption are shown below, from the sponsor's CSR Table 11.4.2, (p. 45).

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

Source: Table 14.8A

* Significant at .05 significance level

¹ Subject C02 protein/fat input was less than protein/fat output

(CSR Table 11.4.1, p 44)

| SUMMARY OF PERCENT ABSORPTION FOR INTENT-TO-TREAT SUBJECTS AT THE END OF TREATMENT PERIOD ONE | | | |
|--|-----------------------|-----------------------------------|---------------------------------------|
| Variable | Ultrase (N=12) | Placebo (N=11)¹ | Treatment Comparison (p-value) |
| Dietary Fat (g) | | | |
| Mean ± SD | 78.2 ± 11.5 | 46.6 ± 36.6 | 0.0115* |
| Range | 55.9 to 95.9 | -42.5 to 90.5 | |
| N | 12 | 11 | |
| Dietary Protein (g) | | | |
| Mean ± SD | 84.5 ± 8.3 | 55.3 ± 31.4 | 0.0071* |
| Range | 70.5 to 95.7 | -18.1 to 92.7 | |
| N | 12 | 11 | |

Source: Table 14.8B

* Significant at .05 significance level

¹ Subject C02 protein/fat input was less than protein/fat output

In both of the above analyses, treatment by center interaction was found to be non-significant and not included in the final analysis. Thus, the final model included the factors of study center, treatment sequence, center by sequence interaction, subject within sequence, treatment group, and treatment by sequence interaction.

3.2. Evaluation of Safety

The most commonly reported adverse events were gastrointestinal in nature, with more patients experiencing them while on placebo. Most of the AE's were mild or moderate. There were no deaths in these studies. For details and further discussion, see the medical officer's review.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1. Gender, Race, and Age

These data were not analyzed by race since most of the patients were Caucasian. More generally, the sample size of these studies did not allow for meaningful statistical comparisons of subgroups.

4.2. Other Special/Subgroup Populations

No other subgroups were identified.

5. SUMMARY AND CONCLUSIONS

5.1. Statistical Issues and Collective Evidence

Three placebo-controlled studies were submitted for the evaluation of the efficacy and safety of Ultrase mini-tablets. Only one study used the to-be-marketed form of the product and is considered pivotal; the other two provided supportive evidence. All three studies used a two-period crossover design. The pivotal study included a washout period between treatments.

The primary outcome was the percent of dietary fat absorbed with percent nitrogen absorption a secondary outcome. Both the CFA% and CNA% were significantly improved with treatment by Ultrase, with no apparent sequence or period effects.

5.2. Conclusions and Recommendations

The evidence from the clinical trials supports a conclusion of efficacy for this product in the treatment of patients with exocrine pancreatic insufficiency due to cystic fibrosis. Pancreatic insufficiency due to other causes was not studied.

Labeling: Results from Studies 96-01 and 96-02 should not be included in tables 2-3. That they did not use the to-be-marketed form of the product should be made clear in the text of the label.

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Stella Grosser
6/25/2008 04:52:48 PM
BIOMETRICS

Mike Welch
6/25/2008 06:52:35 PM
BIOMETRICS
Concur with review.

**Screening of New NDA for Statistical Filing
Division of Biometrics 3**

NDA #: 22-222

Applicant: Axcan Scandipharm, Inc.

Trade/Generic Name: Ultrase MT (pancrelipase, USP) capsules

Indication: Treatment of patients with exocrine pancreatic insufficiency

Type of review: Priority

Date of Submission: October 1, 2007

Filing Date: November 30, 2007

User Fee Goal Date: April 1, 2008

Project Manager (Division): Maureen Dewey (DGP)

Medical Team: Joanna Ku, MD, Anne Pariser MD (TL)

Statistical Reviewer: Stella Grosser, PhD

Filed by: M. Welch, PhD

Filing Decision: This application can be filed.

Background

ULTRASE® is a pancrelipase enzyme preparation (PEP) intended for the treatment of exocrine pancreatic Insufficiency caused by cystic fibrosis, chronic pancreatitis or other related conditions.. This product received a fast track designation on May 30, 2007 under IND 41,387. The application is submitted in eCTD format under Section 505(b)(2) and cross references COTAZYM (NDA 20580) approved for this indication. ([\\Cdsesub1\evsprod\NDA022222](#)).

Overview of studies

The sponsor's table below outlines the three principal, controlled clinical efficacy studies submitted for review.

Table 2.5.4-2 Double-Blind Placebo-Controlled Studies Providing Efficacy Data

| Study Number Location Indication Report Submission Location | Start Date Completion Date | Study Design and Type of Control/ Sample Size (n) | ULTRASE® Treatment/ Minitablet Coating Material | Duration of Treatment Periods | Treatment Periods | Efficacy Assessments |
|---|-----------------------------------|---|---|-------------------------------------|--|--|
| 96-01 3 US centers Cystic fibrosis Section 5.3.5.1 | 01-Apr-1997 to 24-Aug- 1998 | R, PC, DB, MC, XO n=31 randomized n=27 ITT | MT20 Eudragit | 2 x 6+ days in-clinic | <ul style="list-style-type: none"> 3-day pre-study screening examinations 4 days stabilization period - diet/enzymes 2 treatment periods of 6+ days in-clinic | 1° - percent of dietary fat absorbed - 72 hours sampling 2° - percent of dietary protein absorbed - 72 hours sampling |
| 96-02 4 US centers Cystic fibrosis Section 5.3.5.1 | 04-Aug-1997 to 29-Aug- 1999 | R, PC, DB, MC, XO n=26 randomized n=23 ITT | MT12 Eudragit | 2 x 6+ days in-clinic | <ul style="list-style-type: none"> 3-day pre-study screening examinations 4 days stabilization period - diet/enzymes 2 treatment periods of 6+ days in-clinic | 1° - percent of dietary fat absorbed - 72 hours sampling 2° - percent of dietary protein absorbed - 72 hours sampling |
| UMT20CF05-01 8 US centers Cystic fibrosis Section 5.3.5.1 | 30-Nov-2006 to 25-Apr- 2007 | R, PC, DB, MC, XO n=31 randomized n=31 ITT | MT20 HP55 | 2 x 6-7 days in-clinic | <ul style="list-style-type: none"> up to 11 day screening period 4-day stabilization period for each treatment period - diet/enzymes 2 treatment periods of 6 or 7 days in-clinic 3- to 6-day break period between treatment periods | 1° - percent of dietary fat absorbed (CFA%) - 72 hours sampling 2° - percent of dietary protein absorbed (CNA%) - 72 hours sampling Frequency of bowel movements Characteristics of bowel movements |

R: Randomized, PC: Placebo-controlled, DB: Double-blind, MC: Multicenter, XO: Cross-over, ITT: Intent-to-treat
Source: Section 5.3.5.1 Study 96-01, Vol. 3; Study 96-02, Vol. 7; Study UMT20CF05-01, Vol. 11

Potential Review Issues

The primary analysis method for study UMT20CF05-01 appears to have been changed at the analysis stage from a pre-specified parametric ANOVA to a "semi-parametric" method by Iman and Conover. It is not clear this method was pre-specified. This reviewer could not locate an integrated summary of efficacy addressing subgroup analyses (gender, age, and race) from the pooled studies, though an efficacy summary was submitted in Section 2. Data sets for study 96-01 include those for 96-02.

| Checklist for Filing | Remarks (NA if not applicable) |
|--|--|
| Index sufficient to locate study reports, analyses, protocols, ISE, ISS, etc. | OK, ISE in Section 2 |
| Original protocols & subsequent amendments submitted | OK |
| Study designs utilized appropriate for the indications requested | OK |
| Endpoints and methods of analysis spelled out in the protocols | OK |
| Interim analyses (if present) planned in the protocol and appropriate adjustments in significance level made | NA |
| Appropriate references included for novel statistical methodology (if present) | May need reference to method by Iman and Conover |
| Study data and definition files submitted to EDR according to eCTD Guidance | Access to EDR data files OK |
| Safety and efficacy for gender, racial, geriatric, and/or other necessary subgroups | OK |

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this page is the manifestation of the electronic signature.**

/s/

Mike Welch
10/16/2007 01:35:01 PM
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