CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-542Orig1s000

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: 22-542
Drug Name: Viokace (pancrelipase) Tablets
Indication(s): Exocrine Pancreatic Insufficiency
Applicant: Axcan Pharmaceutical Inc.
Review Priority: Standard
Date(s):
Stamp: October 30, 2009
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Biometrics Division: Division of Biometrics III
Statistical Team:
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Keywords: NDA review, clinical study

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

From the statistical perspective, the data from Study VIO16EPI07-01 indicate that Viokace 16 (Pancrelipase) is statistically superior to Placebo with regard to improving fat digestion as measured by the coefficient of fat absorption (CFA). Results of this study support the efficacy of this drug in adult subjects with Exocrine Pancreatic Insufficiency (EPI).

1.2 Brief Overview of Clinical Study

This submission includes one double-blind, randomized, multi-center, Placebo-controlled, parallel group study (Study # VIO16EPI07-01) to assess the efficacy and safety of Viokace 16 (Pancrelipase) in subjects with exocrine pancreatic insufficiency (EPI). A total of 218 subjects between the ages of 18-80 years from 21 centers from USA, Canada, Poland and Slovak Republic were enrolled in the screening phase, and 50 subjects were ultimately randomized (30 Viokace and 20 placebo) after a wash-out period The treatment administered phase was for 6 to 7 days.

1.3 Statistical Issues and Findings

Both the sponsor and the reviewer assessed the efficacy variables using a two-way Analysis of Covariance (ANCOVA) model, with fixed effect for pooled site and treatment group as well as Wash-Out Phase CFA as a covariate. All analyses performed by the sponsor as well as the analyses conducted by the reviewer showed consistent results indicating a statistically significant treatment effect for Pancrelipase ($p< 0.001$).

There was a disproportionate number of male to female subjects in the treatment groups, A re-analysis, adjusting for gender, showed significant treatment by gender interaction ($p<0.001$). However, the small sample size for females precludes interpretation of a possible difference in gender effects. There was no evidence of site-treatment interaction ($p>0.05$).

2. INTRODUCTION

2.1 Overview and Background

Malabsorption due to Exocrine Pancreatic Insufficiency (EPI) manifests itself as a result of the lack of exocrine pancreatic enzyme production. Clinical steatorrhea (increased fat excretion) is the most important digestive malfunction in EPI and may be associated with severe weight loss and malabsorption of the lipid-soluble vitamins A, D, E and K.

On 28 April 2004 the FDA announced that all exocrine pancreatic insufficiency (EPI) drug products are new drugs for which a new drug application (NDA) must be approved, for continued marketing. The FDA determined that prescription pancreatic enzyme products (PEPs) are medically necessary and, allowed manufacturers until 28 April 2008, to obtain approved NDAs for EPI drug products. Guidance for Industry "Exocrine Pancreatic Insufficiency Drug Products – Submitting NDAs" was published in April 2006. In October 2007 the FDA extended this date to 28 April 2010, provided that the sponsors have an active Investigational New Drug Application (IND) by 28 April 2008 and have submitted NDAs by 28 April 2009.

The applicant has submitted one (Study VIO16EPI07-01) Phase 3, double-blind, randomized, multi-center, placebo-controlled, parallel study to assess the efficacy and safety of Viokace 16 (Pancrelipase) for the correction of steatorrhea (malabsorption of dietary fats) in patients with exocrine pancreatic insufficiency (EPI).

This study was designed under a Special Protocol Assessment (SPA), submitted to IND 60,716 on November 13, 2006. A final protocol was submitted on 25 April 2007. An amendment, for the purpose of clarification, was prepared in July 2007.

2.2 Data Sources

This NDA was submitted in electronic format and is located at:
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3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 Study Design

This is a multicenter, randomized, double-blind, parallel group, placebo-controlled, Phase 3 study to assess the safety and efficacy of VIOKACE® 16 for the correction of steatorrhea in patients with Exocrine Pancreatic Insufficiency. The study involved a Screening Phase, a Wash-Out Phase, a Randomization Phase and a Treatment Phase. The Wash-Out and Treatment Phases both included an outpatient period of 2 days followed by an inpatient period of 4 to 5 days during which the primary efficacy parameter (CFA) was evaluated. A safety follow-up visit was performed 7 to 10 days after discharge.

A total of 218 male and female subjects between the ages of 18-80 years from 21 centers from USA, Canada, Poland and Slovak Republic were enrolled. Though 21 clinical study centers were selected, this study was conducted by 19 investigators at 19 sites in North America and Europe. One center (Canada) did not recruit any patients. Of the two non-participating centers, one center (US) was closed as the investigator withdrew participation, and one center (Slovak Republic) was not initiated prior to closure of study recruitment.

The study involved a Screening Phase, a Wash-Out Phase, a Randomization Phase and a Treatment Phase lasting 6 to 7 days. The Wash-Out and Treatment Phases both included an outpatient period of 2 days followed by an inpatient period of 4 to 5 days during which the primary efficacy parameter, Coefficient of Fat Absorption (CFA) was evaluated. A safety follow-up visit was performed 7 to 10 days after discharge.

Date of first enrollment was November 23, 2007 and date of last completed subject was July 2, 2009.

1. **Screening Phase**:

The Screening Phase was a period of up to 10 days in duration during which the eligibility of the patients was assessed. Each patient was given a four-digit patient number.

At Visit 1, patients were provided with a diary and received instructions about the high fat diet and on how to record in the diary all meals and snacks consumed during the outpatient Wash-Out Phase. A dietician planned menus taking into account the patients' needs and preferences as well as the high-fat content of the diet. Patients were to target consumption of 100 g of fat per day. Patients were asked to record information regarding food consumption, stool frequency and characteristics of stool, PPI treatment, adverse events and concomitant medications and to report this information to the study staff. Patients were informed of the prohibited medications and products that they could not use during the study. Finally, patients were required to continue to use their usual pancreatic enzymes and PPI treatment. For patients not on PPI therapy at screening, they were provided with and instructed to take omeprazole 20 mg QD.

2. Wash-Out Phase:

Patients who qualified for the Wash-Out Phase, i.e. patients who had a FE-1 level below 100 µ g/g of stool (< 100 µ g/g of stool), and continued to meet inclusion/exclusion criteria received notice via telephone informing them to initiate the Wash-Out Phase. The Wash-Out Phase was a period of up to 7 days in duration comprised of an Outpatient and an Inpatient Period.

Outpatient Period

The Outpatient Period lasted two days. During this period, patients refrained from taking pancreatic enzymes but continued PPI treatment. In addition, patients adhered to the high-fat diet. The amount of food and beverages as well as the PPI consumed by the patients during these two days were recorded in the patient diary. Patients were asked to record the number of bowel movements per day, the characteristics of stools as well as information regarding adverse events and concomitant medication. At the end of the Outpatient Period, any incomplete or missing information contained in the diary was verified by the study staff with the patient. The study staff also calculated the total amount of fat ingested for both days of the Outpatient Period.

Inpatient Period

The Inpatient Period lasted up to five days and immediately followed the corresponding Outpatient Period; therefore patients had to come to the facility on the previous evening or in the morning of Day 1 of the Inpatient Period. It was important to record food entries in detail, since the total amount of fat intake was used for the calculation of the CFA.

3. Randomization Phase:

Following discharge from the Wash-Out Phase, patients returned home. Since the results of the coefficient of fat absorption were expected to be available approximately one week after the analysis was performed, patients entered a Randomization Phase that lasted up to 10 days.

Calculation of the CFA was a prerequisite for randomization. The CFA at the end of the Wash-Out Phase was calculated by using the amount of fat ingested during the stool collection period relative to the amount of fat excreted during the stool collection period.

Upon confirmation of the CFA at the end of the Wash-Out Phase, patients who qualified for the Treatment Phase (i.e. CFA below 80) were contacted via telephone and returned to the facility (Visit 3) to receive either VIOKACE® 16 or Placebo according to the double-blind treatment assignment. The double-blind study medication was packaged in kits numbered from 001 to 645. The study medication was to be taken as 6 tablets with each meal and 2 tablets with two of three snacks for a total of 22 tablets per day.

4. Treatment Phase:

The Treatment Phase lasted up to 7 days in duration and was comprised of an Outpatient and an Inpatient Period.

Outpatient Period

The Outpatient Period lasted two days. During this period, patients took the assigned randomized study medication and continued PPI treatment. In addition, patients refrained from taking their usual pancreatic enzymes and adhered to the high fat diet. The amount of food and beverages consumed by the patients during these two days as well as the use of PPI were recorded in the patient diary. Patients were asked to record the number of bowel movements, characteristics of stools as well as information regarding adverse events and concomitant medication. Patients were instructed to start taking study medication with

breakfast on the first day of the Outpatient Period. At the end of the Outpatient Period, the study staff reviewed any incomplete or missing information contained in the diary with the patient. The study staff also calculated the total amount of fat ingested for both days of the Outpatient Period.

Inpatient Period
The Inpatient Period lasted up to five days. The Inpatient Period immediately followed the preceding Outpatient Period; therefore patients had to come to the facility on the previous evening or on the morning of Day 1 of the Inpatient Period. During their stay in the facility, patients took the assigned randomized study medication treatment and continued PPI treatment. During the Inpatient Period of the Treatment Phase, the patients continued to use the same bottle of double-blind study medication. Patients were instructed to continue taking the double-blind medication with breakfast on the first day of the Inpatient Period.

For a summary of protocol amendments and changes in the conduct of the study and some key (and final) criteria for inclusion, refer to the Appendix in this review.

3.1.2 Primary and Secondary Objectives

The primary objective of this study was to assess the efficacy of VIOKACE® 16 for the correction of steatorrhea (malabsorption of dietary fats) in patients with a history of exocrine pancreatic insufficiency. The efficacy was based on a comparison of the Coefficient of Fat Absorption (CFA) between VIOKACE® 16 and Placebo.

The secondary objectives were to investigate the effect of VIOKACE® 16 on stool frequency (number of bowel movements) and stool characteristics (hard, formed/normal, soft, watery). The efficacy was based on a comparison between VIOKACE® 16 and Placebo.

3.1.3 Primary Efficacy Endpoints

The primary efficacy variable was Coefficient of Fat Absorption **(**CFA).

The CFA was calculated from fat intake and fat excretion according to the following formula:
CFA (%) = 100 [fat intake – fat excretion] / fat intake

This primary efficacy parameter was evaluated at the end of the Wash-Out Phase and the Treatment Phase (Inpatient Period). Fat intake (g) was defined as the sum of fat ingested beginning with breakfast on the day the first blue dye marker was administered up to the last meal on the day preceding the administration of the second blue dye marker. Fat excretion (g) was defined as the sum of fat excreted beginning with the stool following the appearance of the first blue tinted stool (after the administration of the first blue dye marker) up to the first tinted stool following the administration of the second blue dye marker. In other words, it was the sum of fat excreted after the first blue tinted stool up to the second blue tinted stool, excluding the first blue tinted stool but including the second blue tinted stool. Fat intake and fat excretion were derived for both the Wash-Out and the Treatment Phases respectively.

3.1.4 Secondary Endpoints

The secondary efficacy parameters were stool frequency (number of bowel movements) and stool characteristics (hard, formed/normal, soft, watery) during the Treatment Phase.

3.1.5 Blinding and Randomization

Blinding was achieved using identical tablets for the two treatments and identical packaging, created in accordance with the randomization list. A 2:1 randomization scheme (2 VIOKACE® 16 : 1 Placebo) with block sizes of 3 was used.

3.1.6 Sample Size Calculation

The sponsor estimated the sample size based on the available literature and assumed a common standard deviation for CFA of 16.75% for the Viokace 16 and Placebo treatment arms. Based on a two-sided significance level of 0.05 and a power of 80% and a 2:1 ratio with a minimum clinical difference of 15%, a sample size of 48 evaluable subjects was needed. Assuming a dropout rate of approximately 20%, the sponsor used a planned sample sized of 60: 40 in Viokace and 20 in Placebo arm.

3.1.7 Analysis Populations

There are three analysis populations in this study. The classification of patients into Safety, ITT, and Per Protocol (PP) populations was conducted prior to the database lock.

The Safety population includes all randomized patients who received at least one dose of study medication.

The ITT population includes all randomized patients and represents the primary analysis population to evaluate the efficacy of the study treatment.

The PP population is comprised of all patients in the ITT population without major protocol violations. Major protocol violations included, but were not limited to the following:

- Failure to complete the Treatment Phase
- Failure to collect all bowel movements during the collection period
- Violation of inclusion/exclusion criteria
- Study drug compliance <80% or >120%
- Use of prohibited medications during the Treatment Phase
- Non-compliance with high-fat diet

3.1.8 Statistical Methodology

Both the sponsor and the reviewer assessed the efficacy variables using a two-way Analysis of Covariance (ANCOVA) model, with fixed effect for pooled site and treatment group as well as Wash-Out Phase CFA as a covariate. These parameters were analyzed by using the main effect ANCOVA model. If the assumptions underlying the ANCOVA model were not met, then a non-parametric (NP) ANCOVA was to be considered in addition to the parametric model.

Since the sample size was small, in the review, I repeated the efficacy analyses using a non-parametric method.

3.1.9 Handling of Missing Data

Dropout subjects were to be included in the data analysis to the extent that data were available. Primary and secondary efficacy parameters were to be analyzed using the observed case (OC), baseline observation carry-forward (BOCF) and Percentile Imputation (PI) types of analysis, where applicable. For BOCF analysis, missing post-baseline assessment was to be imputed using the baseline assessment on a per patient basis. For the PI analysis, missing treatment phase assessment was to be imputed using the 25th, 50th and 75th percentile of all non-missing treatment phase assessments within a treatment group.

3.1.10 Pooling the Small Sites

To obtain a sufficient and better-balanced number of patients among study sites, pooling of study sites will be applied prior to performing the statistical inference and unblinding treatment. Sites without at least twelve (12) patients in the ITT population will be incorporated into pooled sites, as follows: All such sites will be ordered from lowest to highest in terms of number of ITT patients. In case of ties, the ordering for tied sites will be determined according to the site ID number (from smallest to largest). Sites will be combined beginning at the smallest until the resulting pooled site contains at least 12 ITT patients. The sites pooled in this way will be considered as a single site in the statistical analyses. The process described above will resume for the remaining sites not meeting the criterion of at least 12 ITT patients. If the final set of pooled sites does not meet the criterion of at least 12 ITT patients, the final set will be pooled with the preceding pooled site.

3.2 Efficacy Results

3.2.1 Subjects' Disposition

Of the 218 patients enrolled at the screening phase, 50 subjects were randomized: 30 to the VIOKASE® 16 treatment and 20 to Placebo, and these groups represented the ITT population.

Fifteen of the ITT patients were not included in the Per Protocol population (10 from the VIOKASE® 16 group and 5 from the Placebo group) due to missing end-of-study CFA values, aberrant Wash-Out Phase CFA's, non-compliance with the high-fat diet or use of prohibited medications during the Treatment Phase. For a list of subjects' dispositions, refer to the Appendix.

3.2.2 Subjects' Demographics and Baseline Characteristics

The study population included more males: 22 (73.3%) on VIOKASE® 16 and 19 (95.0%) on Placebo. There were 29 Caucasians (96.7%) on VIOKASE and 19 (95%) on Placebo. The mean age was 50.9 years (range 24-70 years) for those patients randomized to VIOKASE and 50.6 years (range 37-63 years) for those patients randomized to Placebo. A total of 3 countries participated in the study: Poland with 42 subjects; Slovak Republic with 2 subjects; and USA with 6. For "Demographics and Baseline Characteristics" table refer to the Appendix.

3.2.3 Analyses of the Primary Endpoints

Primary efficacy analyses were based on CFA% in the ITT population. Fifteen ITT patients (10 from the VIOKASE® 16 group and 5 from the Placebo group) had missing post-baseline CFA values which were imputed with the baseline assessments. A statistically significant treatment effect for Viokace in CFA is shown ($p < 0.001$). Table 1a shows the results of the primary endpoint variable change from wash out period in CFA. The Sponsors' results were identical to that of the reviewer. Since the sample size was small, in the review, I repeated the analyses using ranked observations applied to the ANCOVA model. The results were consistent to those of the parametric model.

Table 1a: Reviewer's Results of the Primary Endpoint Variable, CFA (ITT population)

Treatment	CFA Mean (SD)			P-Value for CFA Change
	Baseline	EOT	Change	
Viokace (n=30)	47.6 (24.1)	85.5 (8.9)	37.9 (25.4)	
Placebo (n=20)	56.6 (22.2)	58.0 (24.2)	1.4 (13.3)	
Difference (95% CI)	-9.1 (23.4) (-22.6, 4.5)	27.5 (16.7) (17.8, 37.2)	36.6 (21.5) (24.1, 49.0)	<0.001

1) The mean and the standard deviation values are from PROC TTEST in SAS.

2) * two-way Analysis of Covariance (ANCOVA) model, with fixed effect for pooled site and treatment group as well as Wash-Out Phase CFA as a covariate. These parameters were analyzed by using the main effect ANCOVA model.

Table 1b shows the magnitude of change calculated by subtracting total fat excretion from total fact intake for the randomized portion of the study.

Table 1b: Reviewer's Results for Change between Fat Intake and Fat Excretion

Treatment	Mean (SD)		
	Total Fat Intake	**Total Fat Excretion**	**Change**
Viokace (n=30)	320.8 (28.8)	45.7 (26.7)	275.1 (43.0)
Placebo (n=20)	315.1 (19.3)	132.8 (78.8)	182.2 (76.6)
Difference (95% CI)	5.8 (25.5) (-9.0, 20.5)	-87.1 (53.7) (-118.3, -55.9)	92.9 (58.7) (58.8, 126.9)

Since the number of subjects in the ITT and the PP populations were different due to drop-outs or protocol violations, as a sensitivity analysis, I evaluated the data using the PP population. (For the reason for drop-outs by treatment arm, refer to appendix Table 1). The results are identical to the sponsors' results and statistically significant ($p<0.001$). Table 2 shows the results of the change in CFA in PP population.

Table 2: Reviewer's Results of the Primary Endpoint Variable CFA (PP Population)

Treatment	Mean (SD)				P-Value * for CFA Change
	Total Fat Intake	**Total Fat Excretion**	**Change**	**% CFA**	
Viokace (n=20)	312.4 (14.4)	43.9 (28.2)	268.5 (32.8)	85.9 (9.3)	
Placebo (n=15)	311.9 (15.3)	129.1 (66.7)	182.8 (71.4)	58.3 (21.8)	
Difference (95% CI)	0.4 (14.8) (-9.8, 10.7)	-85.2 (48.5) (-118.9, -51.5)	85.6 (52.7) (49.0, 122.3)	27.5 (15.9) (16.5, 38.6)	<0.001

* two-way Analysis of Covariance (ANCOVA) model, with fixed effect for pooled site and treatment group as well as Wash-Out Phase CFA as a covariate. These parameters were analyzed by using the main effect ANCOVA model.

3.2.4 Analyses of the Secondary Endpoints

Tables 3a and 3b show the results of the analyses for the secondary endpoint variable, total number of stools and stool characteristics.

Mean total number of stools at baseline was borderline significant between treatment groups ($p=0.07$).

Table 3a: Reviewer's Results of the Secondary Endpoint Variable, Total Number of Stools

Treatment	Mean (SD)				P-Value	
	Baseline	**EOT**	**Change**	**% Change**	**Change**	**% Change**
Viokace (n=30)	2.9 (1.2)	1.9 (1.0)	-1.0 (1.0)	-29.0 (33.1)	0.002	0.003
Placebo (n=20)	2.4 (0.8)	2.3 (1.0)	-0.1 (0.7)	1.1 (36.8)		

The quality of the data observed for the secondary endpoints is questionable, and these results should be considered exploratory only.

Table 3b: Reviewer's Results of the Secondary Endpoint Variable, % Change in Stool Characteristics

Treatment	Mean (SD)			
	Hard	Normal	Soft	Watery
Viokace (n=30)	-- (n=0)	8.5 (65.6) (n=17)	-20.6 (70.6) (n=25)	-95.8 (8.3) (n=4)
Placebo (n=20)	-100.0 (0) (n=1)	-9.9 (68.8) (n=13)	-8.8 (37.5) (n=16)	105.7 (48.5) (n=2)

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race and Age and Other Special/Subgroup Populations

The majority of the subjects were Caucasian (96%) and male (82%). Of nine female subjects, one was in the Placebo arm.

Since there was a disproportionate number of male to female subjects in the treatment groups, I re-analyzed the data, adjusting for gender. These results showed a significant treatment by gender interaction effect ($p<0.001$). However, the small sample size for females precludes interpretation of a possible difference in gender effects.

Tables 4 and 5, show the results of the subgroup analyses by gender and by age category, respectively.

Table 4: Reviewer's Analysis of Efficacy (CFA), by Gender

Gender	Mean (SD) Change from Washout Period		Difference (95% CI)
	Viokace	Placebo	
Female (n=9)	63.0 (33.5) (n=8)	-19.0 (0) (n=1)	82.0 (-1.9, 166.0)
Male (n=41)	28.8 (13.9) (n=22)	2.4 (12.8) (n=19)	26.4 (17.9, 34.9)

Age ranged between 24 to 70 years. To create an age category, I divided the subjects into two groups, 50 years old and younger and older than 50. Table 5 shows the results of the analyses for the primary endpoint by age category.

Table 5: Reviewer's Analysis of Efficacy (CFA), by Age Category

Age Category	Mean (SD) Change from Washout Period		Difference (95% CI)
	Viokace	Placebo	
50Years & Younger (n=25)	44.6 (30.7) (n=14)	6.1 (14.2) (n=11)	38.5 (17.7, 59.3)
Older than 50 (n=25)	32.1 (18.8) (n=16)	-4.4 (9.9) (n=9)	36.6 (22.5, 50.6)

4.2 Analysis of Efficacy by Region and by Site

Though 21 clinical study centers were selected, this study was conducted by 19 investigators at 19 sites in North America and Europe. One center (Canada) did not recruit any patients. Of the two non-participating centers, one center (US) was closed as the Investigator withdrew participation, and one center (Slovak

Republic) was not initiated prior to closure of study recruitment. A total of 3 countries participated in the study; Poland with 42 subjects, Slovak Republic with 2 subjects and USA with 6. The reviewer's ANCOVA analysis did not indicate the presence of site or country treatment interaction ($p>0.1$).

To obtain a sufficient and better-balanced number of patients among study sites, the sponsor pooled study sites prior to unblinding treatment. Sites without at least twelve (12) patients in the ITT population were incorporated into pooled sites, as follows: All such sites were ordered from lowest to highest in terms of number of ITT patients. In case of ties, the ordering for tied sites was determined according to the site ID number (from smallest to largest). Sites were combined beginning at the smallest until the resulting pooled site contained at least 12 ITT patients. The sites pooled in this way were considered as a single site in the statistical analyses. The process described above was resumed for the remaining sites not meeting the criterion of at least 12 ITT patients. Table 6 shows the results of the primary efficacy endpoint for each pooled center.

Table 6: Reviewer's Analysis of Efficacy (CFA), by Pooled Sites

Pooled Site	Mean (SD) Change from Washout Period		Difference (95% CI)
	Viokace	Placebo	
E01 (n=13)	32.6 (38.3) (n=8)	-3.6 (20.5) (n=5)	36.5 (-4.9, 77.9)
E02 (n=17)	37.7 (21.2) (n=9)	2.5 (13.4) (n=8)	35.2 (16.7, 53.8)
E03 (n=14)	38.3 (19.1) (n=9)	3.3 (7.4) (n=5)	35.1 (15.4, 54.8)
NA01 (n=6)	47.8 (21.0) (n=4)	4.7 (7.1) (n=2)	43.1 (-1.4, 87.6)

The analysis results by pooled centers were similar with each other. The sample sizes were too small to make meaningful comparisons of treatment effects among the North American and European sites.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

Both the sponsor and the reviewer assessed the efficacy variables using a two-way Analysis of Covariance (ANCOVA) model, with fixed effect for pooled site and treatment group as well as Wash-Out Phase CFA as a covariate. All analyses performed by the sponsor as well as the analyses conducted by the reviewer showed consistent results indicating a statistically significant treatment effect for Pancrelipase ($p< 0.001$).

Since there was a disproportionate number of male to female subjects in the treatment groups, I re-analyzed the data adjusting for gender. These results showed an interaction for treatment by gender effect ($p<0.001$). However, the small group sizes for females preclude interpretation of a possible difference in gender effects.

5.2 Conclusions and Recommendations

From the statistical perspective, the data from Study VIO16EPI07-01 indicate that Viokace 16 (Pancrelipase) is statistically superior to Placebo with regard to improving fat digestion as measured by the coefficient of fat absorption (CFA). Results of this study support the efficacy of this drug in adult subjects with Exocrine Pancreatic Insufficiency (EPI).

Appendix

Protocol Amendments and Changes in the Conduct of the Study

The current study was designed under a Special Protocol Assessment (SPA) submitted to IND 60,716 on November 13, 2006. A final protocol was submitted on April 25, 2007 and an amendment prepared for the purpose of clarification was filed in July 2007. Reasons for the amendment were as follows:

1. Update protocol approval page information
2. Updated important contacts information
3. Clarify inclusion criteria number 4 and 8.
4. Clarify exclusion criteria number 1 and 7.
5. Clarify discontinuation criteria
6. Clarify the supply and labeling of omeprazole during the study
7. Clarify the dispensing of the double-blind VIOKACE medication during the study
8. Clarify the daily administration of the double-blind VIOKACE medication
9. Clarify the reconciliation of study medication
10. Clarify study procedures
11. Update reporting requirements information
12. Correction of typos (non-tabulated)

Table 1: Subject Disposition

Parameter	Treatment	
	Viokace (n=30)	Placebo (n=20)
Total Number of Patients Enrolled = 218		
Patients Included in the ITT Population	30	20
Patients Included in the Safety Population	30	20
Patients Included in the Per Protocol Population	20	15
If Not in PP population, Reason(s) for Exclusion (Only Major Protocol Violation):*		
Failure to Complete the Treatment Phase	1 (10%)	0
Failure to Collect All Bowel Movements During the Collection Period	1 (10%)	0
Violation of Inclusion/Exclusion Criteria	1 (10%)	0
Study Drug Compliance < 80% or > 120%	0	0
Use of Prohibited Medications During the Treatment Phase	3 (30%)	1 (20%)
Non-compliance with High-Fat Diet	4 (40%)	1 (20%)
Other	4 (40%)	3 (60%)

Source: Sponsor's Study Report, Table 11.1-1 - Page 70 of 164
*patients could be in more than one category

Table 2: Subject Demographics

Parameter	Treatment	
	Viokace (n=30)	Placebo (n=20)
Sex		
Male	22 (73.3%)	19 (95.0%)
Female	8 (26.7%)	1 (5.0%)
Age (mean ± SD)	50.9 ± 9.91	50.6 ± 7.63
Race		
Caucasian	29 (96.7%)	19 (95.0%)
Black	1 (3.3%)	0
Asian	0	0
Other	0	1 (5.0%)

Source: Sponsor's Study Report, Table 11.2-1 - Page 71 of 164

Table 3: Subject Disease / Condition History

Parameter	Treatment	
	Viokace (n=30)	Placebo (n=20)
Number of Years Since Onset of CP	n=29	n=20
Mean ± SD	9.6 ± 9.74	9.4 ± 5.98
Number of Subjects with (a):		
Abnormal Secretin Test	0	0
Diffuse Calcification of the Pancreas on Plain Film of the Abdomen	5 (16.7%)	2 (10.0%)
Abnormal ERCP or Endoscopic Ultrasound	18 (60.0%)	7 (35.0%)
Abnormal CT (dilated main pancreatic duct, atrophy or calcification of the pancreas)	17 (56.7%)	11 (55.0%)
Serum Trypsin Concentration Below 20 ng/mL	2 (6.7%)	1 (5.0%)

(a) A patient could be in more than one category

Source: Sponsor's Study Report, Table 11.2-2 - Page 73 of 164

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/s/

SHAHLA S FARR
11/03/2010

MICHAEL E WELCH
11/03/2010
Concur with review.

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number: 22-542 **Applicant: Axcan Pharma US, Inc.** **Stamp Date: 10-30-2009**

Drug Name: Viokase (pancrelipase) **NDA/BLA Type: Original application** **Indication: Treatment of exocrine pancreatic insufficiency**

On **initial** overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	X			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	X			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).			X	
4	Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets).	X			

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? Yes

If the NDA/BLA is not fileable from the statistical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter. None at this time.

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	X			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	X			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.			X	
Appropriate references for novel statistical methodology (if present) are included.			X	
Safety data organized to permit analyses across clinical trials in the NDA/BLA.	X			
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	X			

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

Principal study overview

The sponsor submitted a phase 3 confirmatory study titled "A Multicenter, Randomized, Double-Blind, Parallel, Placebo-Controlled, Phase III Study to Assess the Safety and Efficacy of VIOKASE® 16 for the Correction of Steatorrhea in Patients with Exocrine Pancreatic Insufficiency."

The primary objective of this study was to assess the efficacy of VIOKASE® 16 for the correction of steatorrhea (malabsorption of dietary fats) in adult patients with a history of exocrine pancreatic insufficiency based on the comparison of the Coefficient of Fat Absorption (CFA%) between VIOKASE® 16 and placebo. Secondary endpoints included stool frequency and stool characteristics. All patients were on PPI therapy.

The study involved a screening phase (up to 10 days), a wash-out phase (6 to 7 days), a randomization phase (up to 10 days) and a treatment phase (6 to 7 days). Out of 218 patients enrolled, 50 patients met all entry criteria, including a requirement for a wash-out phase CFA less than 80%. Of these, 30 were assigned to VIOKASE and 20 to placebo.

Primary efficacy was assessed with a two-way Analysis of Covariance model with fixed effects for pooled site and treatment group as well as wash-out phase CFA% as a covariate. This analysis shows a statistically-significant difference ($p < 0.0001$) between the VIOKASE® 16 and placebo treatment groups. A review issue will be the sensitivity of study results to the sponsor's imputation methods.

M. Welch	Dec. 1, 2009
Reviewing Statistician	Date

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22542	ORIG-1	AXCAN PHARMA INC	VIOKASE (PANCRELIPASE)UNCOATED TABLETS

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/s/

MICHAEL E WELCH
12/01/2009