Clinical Pharmacology Review

NDA:	22-222
Brand Name:	Ultrase
Generic Name:	Pancrelipase Enzyme
Dosage form and Strength:	Delayed release capsules, 13,800 (MT12), 20,700 (MT18), and 23,000 Units (MT20)
Route of administration:	Oral
Indication:	Treatment of patients with exocrine pancreatic insufficiency caused by cystic fibrosis, chronic pancreatitis, or other related conditions
Sponsor:	Axcan Pharma
Type of submission:	Original Submission
Clinical Division:	Division of Gastroenterology Products (HFD-180)
OCP Division:	DCP III
Priority:	Priority (6 months)
Submission date:	10/01/07, 09/11/07, 12/20/07, and 02/01/08
PDUFA Goal date:	04/01/08
Reviewer:	Tien-Mien Chen, Ph.D.
Team leader:	Sue-Chih Lee, Ph.D.

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1. Executive Summary

1.1 Recommendations

NDA 22-222 for Ultrase MT12, MT18, MT20 delayed release capsules has been reviewed by Office of Clinical Pharmacology/Division of Clinical Pharmacology III (OCP/DCP III). From OCP standpoint, the sponsor has not demonstrated that the MT20 capsule formulation with current HP55 coating is comparable to the old MT20 capsule formulation with Eudragit LD30 coating. The medical division needs to make final decision on the approvability of the current formulation with HP55 coating based on clinical findings since there is one pivotal trial conducted using this formulation. The labeling comments on p.13 should be communicated to the Medical officer and sponsor if it is to be approved.

1.2 Comments

In the OCP Briefing held on 3/7/08 for this NDA, a discussion on the use of *in vivo* intubation studies for bioavailability/bioequivalence (BA/BE) assessment of pancreatic enzyme products was made between DCP3 and the Division of Gastroenterology Products. The following is our consensus:

Based on the experiences gathered so far on the intubation study, it is concluded that many challenges in the study design, study conduct, and assay methodology remain to be overcome before the study can be used reliably to assess BA or BE of pancreatic enzyme products. In view of the time line imposed by the Agency to the sponsors for submitting NDAs for pancreatic enzyme products, it has been decided that the intubation study for BA assessment of a pancreatic enzyme product will no longer be required for future NDA submissions.. Additionally, when demonstration of bioequivalence between formulations is necessary, the sponsor will be encouraged to conduct clinical studies for that purpose rather than utilizing the intubation studies.

1.3 Phase IV Commitments: None

02/11/08
Tien-Mien Chen, Ph.D.
Division of Clinical Pharmacology III

Team Leader

Sue-Chih Lee, Ph.D. 02/27/08

1.4 Summary of Clinical Pharmacology and Biopharmaceutics Findings

Background

Ultrase (pancrelipase) MT capsule and several other pancreatic enzyme products are currently on the market without FDA approval. Ultrase MT capsule is a pancreatic enzyme preparation of porcine origin. NDA 22-222 for Ultrase MT capsules was submitted on 10/01/07, the subject of this clinical pharmacology review. It was designated for a 6-month priority review time clock seeking approval for three strengths, MT12 (13,800 USP units), MT18 (20,700 USP units), and MT20 (23,000 USP units) for pancreatic enzyme replacement therapy. Each Ultrase MT capsule contains enteric-coated minitablets. The minitablets are composed of pancrelipase and compendial excipients in a compressed form.

Eudragit LD30 coated Ultrase MT formulation was used in early clinical studies. In 2003, the coating was changed to an HP55 base to optimize shelf-life and stability. Ultrase MT capsules (three strengths) with HP55 coating has been used in one of the pivotal clinical trials submitted for review. In order to link the previous efficacy and safety data obtained from Eudragit LD30 coated formulation to current HP55 coated formulation, an *in vivo* intubation study (No. UMT20CP05-01) was conducted to demonstrate that the above two Ultrase MT formulations with different coatings are comparable.

Additionally, upon Agency's request, an *in vitro* stability study (No. RE-071211-01) for the content of Ultrase capsule sprinkled on food at room temperature over time was conducted using the current formulation with HP55 coating to support the proposed labeling claim as shown below:

(b) (4)

Overview of Clinical Pharmacology and Biopharmaceutics:

In vivo intubation study

It was a randomized, open-label, 2x2 crossover study (No. UMT20CP05-01) to evaluate the intra-duodenal delivery of lipase of two enteric-coated capsule formulations of Ultrase MT20 (Eudragit LD30 and HP55 coatings). Chronic pacreatitis (CP) adult patients without significant pancreatic enzyme insufficiency (n=10) and CP adult patients (n=10) with pancreatic insufficiency (CPPI) were enrolled.

Patients were intubated using a modified Dreiling double-lumen intestinal tube. They received 2 capsules (total 46,000 USP units) of either Ultrase MT20 formulation in the middle of a standardized liquid meal (500 mL Ensure Plus) at each treatment arm. Continuous 15-min intraluminal aspirations were collected during 2 hrs postdosing. The activity or amount of enzymes released at the site of action (duodenum) was quantified (in terms of lipase) and compared between the above two formulations. Final data was available for analysis from a total of 11 patients (6 M+5 F); 6 with CPPI (3M+3F) and 5 with CP (3M+2F).

The results obtained from the *in vivo* intubation study showed that:

a. In primary patient population (Table 1), CPPI patients (n=6), Ultrase MT capsule with HP55 coating (current; **Test**) had higher mean % recovery (±coefficient variation; CV), i.e., 42.6% (± 154% CV), than that with old coating material, Eudragit LD30 (old: **Reference**), 27.3% (± 165% CV). Both formulations exhibited large intersubject variations. The study methodology may not reflect the bioavailability because complete duodenal aspiration can not be assured.

Table 1. Mean Activity and % Recovery of Pancrelipase in CPPI Patients

CPPI Patients (n=6)	**Eudragit LD30 (Reference)**		**HP55 (Test)**	
	Activity (IU)[1]	**% Recovery**	**Activity (IU)**	**% Recovery**
Mean	1,762.5	27.3%	2,545.50	42.6%
SD	2,907.9	CV of 165%	3,923.7	CV of 154%

[1]. one IU ≈ 7.60 USP units (conversion factor).

b. Opposite results were obtained from CP patients. Eudragit LD30 coated MT Ultrase had higher mean % recovery than the HP55 coated MT capsules (Table 2).

Therefore, for CP patients, > 100% recovery of lipase activity could be due to:

1) Their endogenous human lipase at baseline and the secretion of endogenous human lipase upon food stimulation.
2) Small no. of patients and high variability
3) Assay limitation; the assay method used could not differentiate human endogenous lipase and exogenous lipase after Ultrase MT capsule administration.

Table 2. Mean Activity and % Recovery of Pancrelipase in CP Patients

CP Patients (n=5)	**Eudragit LD30 (Reference)**		**HP55 (Test)**	
	Activity (IU)[1]	**% Recovery**	**Activity (IU)**	**% Recovery**
Mean	16,799.9	260.%	8,459.5	141.4%
SD	10,062.0	CV of 59.9%	5,918.4	CV of 70.0%

[1]. one IU ≈ 7.60 USP units (conversion factor).

c. The 90% CIs (confidence intervals) for the ratio of **Test** vs. **Ref** in primary patient population (CPPI), in patients with CP, and in combined patients was assessed and none of the above comparisons demonstrated comparable recovery from duodenal aspiration as summarized below:

Table 3. The 90% CIs for the ratio of Test vs. Reference

	Eudragit LD30 (Ref; old formulation)	**HP55 (Test;** current formulation)	**Point Estimate**	**90% CIs (Test/Ref)**
Patients	**Mean Recovery (%) of Lipase**			
CPPI* (n=6)	27.3	42.6	1.490	0.628 – 3.532
CP (n=5)	260.	141	0.540	0.180 – 1.624
Overall (n=11)	133	87.5	0.949	0.507 – 1.777

Conclusion:
Because of assay limitation, data from CP patients could not be used for the purpose of establishing comparability of Ultrase MT capsules with Eudragit LD 30 coating material and Ultrase MT capsules with HP55 coating material. On the other hand, due to small sample size, data from CPPI patients alone was inadequate for establishing comparability of the 2 formulations either.

In vitro Stability Study
Upon request by the Agency, an *in vitro* stability study (No. RE-071211-01) for Ultrase content on food was conducted to support the proposed labeling claim as shown below:

(b) (4)

The objective of this study is to demonstrate the *in vitro* stability of minitablets (the content of the current formulation of Ultrase capsules with HP55 coating material) over time when dispersed on food at room temperature. The results of *in vitro* stability of Ultrase content (minitablets) sprinkled on food (applesauce, pudding, and yogurt) showed that after 60 min of contact with foods tested, enteric coating remained function after 60-min dissolution testing in simulated gastric fluid (SGF) and afterwards, in phosphate buffer (pH 6.0) for 30 min, 92-98% of lipase was released, i.e., available for duodenum.

Thus, the above *in vitro* study supports the proposed labeling claim to sprinkle the content (minitablets) of Ultrase MT capsules on an acidic food when intact capsules could not be swallowed. The results of *in vivo* stability study are shown below:

Table 4. Mean Functionality of Ultrase MT When Sprinkled on Foods at Room Temperature

Food types	30-min Contact Time with food (Remaining activity; mean % with CV, %)	60-min Contact Time with food (Remaining activity; mean % with CV%)
Applesauce, plain	93% with CV, 3.5%	98% with CV 3.0%
Applesauce, plain	94% with CV, 0.9%	92% with CV 3.7%
Applesauce, plain	92% with CV, 4.4%	92% with CV 3.0%
Pudding chocolate	101% with CV, 0.9%	95% with CV 4.5%
Yogurt	94% with CV, 4.5%	95% with CV 1.0%

Capsules were opened (batch No. F070224D) and an amount of minitablets equivalent to 12,800 UPS units was carefully weighted, placed on about 20 grams of food in a beaker, and then minitablets and food were mixed. Applesauce (≈pH 3.5 reported), pudding (≈pH 6.4), and regular yogurt (≈pH 4.17) were chosen and tested in this study.

At the end of contact time (5, 10, 15, 30, and 60 min), the mixed sample was transferred into a small non-metal sieve and rinsed with cold 0.1N HCl. Minitablets were transferred to a dissolution basket for 60-min incubation in SGF and then for 30-min in phosphate buffer (pH 6.0±0.05). Six individual stability tests and 6 individual dissolution tests for

each contact time were performed. After contact with food samples, the functionality of the enteric coating was assessed (30 and 60 contact time points) using a 2-stage dissolution test.

Biopharmaceutics

Ultrase MT capsule is designed to release content at pH ≥5.5 and deliver enzymes to proximal part of small intestine (duodenum). Eudragit LD30 coated Ultrase MT formulation was used in early 2 pivotal clinical studies. In 2003, the coating was changed to an HP55 base to optimize shelf-life and stability. Ultrase MT capsules with HP55 coating has been used in one of the pivotal clinical trials submitted for review. Please see section 2.5 for composition/formulation for Ultrase MT capsule with Eudragit LD30 and with HP55 for details.

2. Question Based Review

2.1 General Attributes

Drug Substance:
Ultrase contains pancrelipase, a purified extract of porcine exocrine pancreatic enzymes. The major enzymes of pancrelipase are pancreatic lipase, free proteases, and α-amylase.

Formulations:
Ultrase MT contains enteric-coated pancrelipase minitablets or granules within the capsules for oral administration. The enteric coating protects pancreatic enzymes against gastric acid and is designed to dissolve at pH ≥ 5.5 which allows delivery of the enzymes to duodenum, the main site of action for food digestion. Pancreatic enzymes are not materially absorbed by the gastrointestinal tract. The Ultrase capsules are available in three strengths MT12, MT18, MT20, corresponding respectively to 13,800, 20,700, and 23,000 USP units of lipase.

Mechanism of Action:
CP is an ongoing inflammatory disorder associated with the loss of the exocrine and endocrine parenchyma and its replacement by fibrotic tissue, resulting in maldigestion subsequent to exocrine pancreatic insufficiency (EPI) and diabetes mellitus. EPI is often associated with conditions such as Cystic Fibrosis (CF), CP, postpancreatectomy, post-GI bypass surgery and ductal obstruction of the pancreas or common bile duct. In CP subjects, fat digestion is impaired as well as carbohydrate and protein digestion; steatorrhea is one of the main symptoms observed. Pancrelipase is an extract of porcine pancreatic glands. Pancreatic enzyme supplements improve digestion by catalyzing the hydrolysis of fats to glycerol and fatty acids, protein to proteoses and derived substances, and starch into dextrins and short chain sugars.

Proposed Indication:
Ultrase (Pancrelipase MT Capsules) is a pancreatic enzyme replacement therapy indicated for the treatment of patients with exocrine pancreatic insufficiency caused by cystic fibrosis, chronic pancreatitis, or other related conditions.

Proposed Dosing Regimen:
Patients with pancreatic insufficiency should consume a high-calorie diet with unrestricted fat appropriate for age and clinical status. A nutritional assessment should be performed regularly as a component of routine care and, additionally, when dosing of pancreatic enzyme replacement is altered.

Dosage should be individualized and determined by the degree of steatorrhea and the fat content of the diet. Therapy should be initiated at the lowest possible dose and gradually increased until the desired control of symptoms is obtained.

A starting dose of 500 to 1,000 lipase USP units/kg/meal with titration to less than 2,500 USP units/kg/meal or less than 4,000 lipase USP units/g fat/day is recommended. Doses in excess of 2,500 lipase USP units/kg/meal should be used with caution and only if their benefit is documented by 3-day fecal fat. Doses in excess of 6,000 lipase USP units/kg/meal have been associated with fibrosing colonopathy.

The sponsor proposed that Ultrase MT capsules should be taken orally with meal or snack. (b) (4)

2.2 General Clinical Pharmacology

Comparative Bioactivity Evaluation

"A Randomized, Open-Label Cross-Over Study to Evaluate the Intraduodenal Delivery of Total Protease and Lipase" (study No. UMT20CP05-01)

Q1. How was the study conducted?

A1. This was a randomized, open-labeled, single-center, 2x2 crossover study conducted at (b) (4) Approximately 20 adult patients (10 with CP and 10 with CPPI) were recruited to obtain 6 with CP and 6 with CPPI.

Patients were confined in the research facility for a period of 5-6 days. On Day 0, patients fasted after midnight and an intravenous (IV) infusion of 100 mL/hr of DW5% + 1/2 normal saline was to be started approximately 12 hours prior to placement of the duodenal aspirate tube.

After an overnight fasting, patients were intubated in the next morning using a modified Dreiling double-lumen intestinal tube. The tube was approximately 150

cm long with aspiration ports in the stomach and between 100 and 110 cm from the proximal end of duodenum. An oral elixir of 10 mL of metoclopromide and local anesthetics (benzocaine and lidocaine) were administered for facilitation of tube placement. The position of the tube was verified by fluoroscopy.

After the tube was in proper position, intraduodenal perfusion was initiated with normal saline at 2 mL/min, with 10 uCi/L ^{14}C polyethylene glycol (PEG) for use as a non-absorbable duodenal marker. The first half-hour of the perfusion was considered a steady-state period with no aspiration collection. Following the second half-hour of the perfusion, the aspirate collected was considered the washout. Following the third half-hour of the perfusion, the aspirate collected was considered baseline. Perfusion and aspiration was stopped for 20 minutes while subjects received a liquid meal of 500 mL of Ensure Plus. Subjects drank 250 mL of Ensure Plus and then another 250 mL with 2 capsules of either Ultrase MT20 formulation (Eudragit LD30 or HP55 coated).

The intraduodenal perfusion was restarted following completion of the Ensure Plus. Five minutes after restarting the perfusion, intraluminal aspirations were col1ected at 15-minute intervals for the next 2 hours. The pH of each sample was analyzed immediately. At the end of the study, the stomach was aspirated for residual enzymes and possible ^{14}C-PEG. Samples were kept on ice until analyzed.

After a washout period of one day, patients fasted after midnight and an IV infusion of 100 mL/hr of DW5% + 1/2 normal saline was started approximately 12 hours prior to placement of the duodenal aspirate tube for the alternative formulation not tested previously.

The primary variable was the lipase activity obtained through intraduodenal aspirates during a 2-hour period following Ultrase MT20 administration in the CPPI group. Final data was available for analysis from a total of 11 patients (6 M+5 F); 6 with CPPI (3M+3F) and 5 with CP (3M+2F).

Descriptive statistics (mean, standard deviation, range) were performed for each collection period for the CP, CPPI and CP+CPPl subjects separately.

Q2. Does Ultrase MT20 capsule with Eudragit LD30 and with HP55 enteric coatings demonstrate comparable lipase activity in duodenal aspirates?

A2. No. The results obtained from the primary patient population (CPPI; n=6) showed that Ultrase MT capsules with HP55 coating (**Test**; 42.6%) had higher mean recovery than that of Eudragit coating (**Ref**; 27.3%) in Table 5.

Table 5. Mean Activity and % Recovery of Pancrelipase from CPPI Patients

CPPI Patients (n=6)	Eudragit LD30 (Reference)		HP55 (Test)	
	Activity (IU)	% Recovery	Activity (IU)	% Recovery
Mean	1,762.50	27.3%	2,545.50	42.6%
SD	2,907.9	CV of 165%	3,923.7	CV of 154%

The results obtained from 5 CP patients showed opposite results, i.e., Ultrase MT capsules with Eudragit coating had higher mean recovery (260%) than that with HP55 coating (141%) in Table 6.

Table 6. Mean Activity and % Recovery of Pancrelipase from CP Patients

CP Patients (n=5)	Eudragit LD30 (Reference)		HP55 (Test)	
	Activity (IU)	% Recovery	Activity (IU)	% Recovery
Mean	16,799.9	260.%	8,459.5	141.4%
SD	10,062.0	CV of 59.9%	5,918.4	CV of 70.0%

The overall mean recovery in 11 patients (CP+ CPPI) was 133% for Eudragit coated and 87.5% for HP55 coated Ultrase MT capsules as shown below. The results of comparability assessment with 90% CIs are shown below.

Table 7. Results of Comparability Assessment with 90% CIs

	Eudragit LD30 (**Ref;** old formulation)	HP55 (**Test;** current formulation)	Point Estimate	90% CIs (Test/Ref)
Patients	**Mean Recovery (%) of Lipase**			
CPPI* (n=6)	27.3	42.6	1.490	0.628 – 3.532
CP (n=5)	260.	141	0.540	0.180 – 1.624
Overall (n=11)	133	87.5	0.949	0.507 – 1.777

*. Primary patient population of interests.

Therefore, for CP patients, > 100% recovery was observed which could be due to 1) their endogenous human lipase at baseline and 2) the secretion of endogenous human lipase upon food stimulation. It should be noted that the assay method used could not differentiate endogenous human lipase and exogenous lipase after administration of Ultrase MT capsules

Q3. Does the *In vitro* stability of Ultrase MT contents sprinkled on food support the proposed labeling, (b) (4)

[redacted]

A3. Yes, upon contact with foods tested at room temperature up to 60 min, the enteric coating of minitablets (content of Ultrase capsules) remained functional (stable) after 60-min in acidic SGF and in phosphate buffer at pH 6.0 for 30 min, i.e., 92-98% was released, i.e., available in duodenum as shown in Table 8. Therefore, the *in vitro* stability study on food supports the above proposed labeling claim.

Table 8. Mean Functionality of Ultrase MT When Sprinkled on Foods at Room Temperature

Food types	30-min Contact Time with food (Remaining activity; mean % with CV, %)	60-min Contact Time with food (Remaining activity; mean % with CV%)
Applesauce, plain	93% with CV, 3.5%	98% with CV 3.0%
Applesauce, plain	94% with CV, 0.9%	92% with CV 3.7%
Applesauce, plain	92% with CV, 4.4%	92% with CV 3.0%
Pudding chocolate	101% with CV, 0.9%	95% with CV 4.5%
Yogurt	94% with CV, 4.5%	95% with CV 1.0%

The objective of this study is to demonstrate the *in vitro* stability of the current formulation of Ultrase MT capsules (with HP55 coating material) over time when dispersed on food at room temperature. Capsules were opened (batch No. F070224D) and an amount of minitablets equivalent to 12,800 UPS units was carefully weighted, placed on about 20 grams of food in a beaker, and then minitablets and food were mixed. Applesauce (≈pH 3.5 reported) with 3 different flavors, pudding (≈pH 6.4) with chocolate flavor, and regular yogurt (≈pH 4.17) were chosen and tested in this study.

At the end of contact time (5, 10, 15, 30, and 60 min), the mixed sample was transferred into a small non-metal sieve and rinsed with cold 0.1N HCl. Minitablets were transferred to a dissolution basket for 60-min incubation in SGF and then for 30-min in phosphate buffer (pH 6.0±0.05). Six individual dissolution tests for each contact time were performed. The functionality of the enteric coating were assessed using a 2-stage dissolution test for samples after 60- and 30-min contact times (2 consecutive time points) with food samples.

2.3 Intrinsic Factors: Data not available

2.4 Extrinsic Factors: Data not available

2.5 General Biopharmaceutics:

Each Ultrase MT capsule contains core minitablets, each of which are enteric coated. The minitablets are composed of pancrelipase and compendial excipients, colloidal silicon dioxide, croscarmellose sodium, gelatin, hydrogenated castor oil, iron oxides, magnesium stearate, microcrystalline cellulose, talc, titanium dioxide, hydroxypropyl methylcellulose phthalate, and triethyl citrate as inactive ingredients in a (b) (4) form as shown below.

Table 9. Component and Composition of Ultrase MT Formulations (with no overage)

Component	Reference to Quality Standard	Function	13,800 USP units capsule (mg)	20,700 USP units capsule (mg)	23,000 USP units capsule (mg)
CORE MINITABLETS					
Pancrelipase	USP	Drug substance	[redacted]		
Croscarmellose sodium	USP/NF	[redacted]			
Hydrogenated Castor oil	USP/NF				
Colloidal Silicon dioxide	USP/NF				
Microcrystalline Cellulose	USP/NF				
Magnesium stearate	USP/NF				
[redacted]					
Hypromellose Phthalate (HP55)	USP/NF	[redacted]			
Triethyl Citrate	USP/NF				
Talc	USP				
[redacted]	USP				
	USP/NF				
Theoretical filling weight					
DELAYED RELEASE CAPSULES					
Gelatine	USP	[redacted]			
Titanium dioxide	USP				
Yellow iron oxide	USP/NF				
CAPSULE CAP					
Gelatine	USP	[redacted]			
Titanium dioxide	USP				
[redacted]	USP/NF				
[redacted]					
Capsule weight					
Total weight			***298.5***	***429.8***	***467.0***

Table 10. Comparison of Coating Materials between HP55 and Eudragit LD30

EUDRAGIT® COMPOSITION	
Components	**%**
Pancrelipase	[redacted]
Croscarmellose Sodium	[redacted]
Hydrogenated Castor Oil	
Colloidal Silicon Dioxide	
Microcrystalline Cellulose	
Magnesium Stearate	
[redacted]	
Methacrylic acid copolymer, Type C (Eudragit® L30D-55) 30% in water	(b) (4)
Triethyl Citrate	
Simethicone emulsion 30% in water (dry w/w)	
Talc	
	(b) (4)
Total coating membrane	(b) (4)
TOTAL	(b) (4) **100.00**

HP55 COMPOSITION	
Components	**%**
Pancrelipase	[redacted]
Croscarmellose Sodium	[redacted]
Hydrogenated Castor Oil	
Colloidal Silicon Dioxide	
Microcrystalline Cellulose	
Magnesium Stearate	
[redacted]	
Hypromellose Phthalate (HP 55)	[redacted]
Triethyl Citrate	
Talc	[redacted]
[redacted]	
Total coating membrane	[redacted]
TOTAL	[redacted] **100.00**

2.6 Analytical Section

USP Method:
A method was used to measure lipase content in the capsule *in vitro* based on that described in the USP monograph using olive oil as a substrate. Results are reported as USP U/capsule, where one USP unit of lipase activity is defined as the amount of pancreatin that liberates 1.0 microequivalent of fatty acid per minute at a pH of 9.0 and a temperature of 37°C.

Coloripase Method:
Aspirated samples were analyzed for lipase activity using the Co1oripase colorimetric assay kit utilizing colipase (NuClin Diagnostics). The Coloripase assay is an adaptation of a colorimetric procedure developed by Neoman which involves the use of the substrate, 1,2-0-dilauryl-rac-glycero-3-glutaric acid-(-6'methyl resorufin)-ester. Catalytic hydrolysis of this substrate by lipase generates 6'methyl resorufin ester (as shown below), which absorbs light at 577 nm. Generation of 6'-methyl resorufin ester in the samples is compared to that generated from known concentrations of a reference standard of porcine lipase.

Substrate	Pancreatic Lipase	
1,2-0-dilauryl-rac-glycero-3-glutaric acid-(-6'-methyl resurofin)-ester	--> OH^-	1,2-0-dilauryl-rac-gl'ycero + Glutaric acid-(-6'-methyl resurofin)-ester

	Pancreatic Lipase	
Glutaric acid-(-6'-methyl resurofin)-ester	--> OH^-	Glutaric acid + 6'-methyl resurofin ester

Lipase activity is expressed in International Units (IU), where 1 IU is defined as the amount of lipase that catalyzes 1 µmol of substrate hydrolysis per min per L at 37°C, pH 8.4. By comparing the results using the Coloripase assay with the USP method, it was determined that 1 IU/L of lipase was equivalent to 7.59 USP units/L of lipase. This conversion factor was used to compare recovery values from ingested Ultrase MT capsules.

The percentage of lipase recovered during a 2-hour period was computed by dividing the total activity recovered in IU by the total activity given (b) (4) (b) (4) (b) (4).

Q4. Is the assay methods adequately validated?

A4. The assay method was found satisfactory except for the specificity as it could not differentiate human endogenous lipase and exogenous lipase after Ultrase MT capsule administration. The Coloripase assay was validated using a lipase concentration range of 2 to 400 IU/L. The testing matrix included duodenal

washout fluid (DWF) as well as normal saline (0.85% NaCl) and water, with saline being used as a diluent for controls and samples.

Results at high lipase levels suggested non-linearity of the assay at concentrations near 400 IU/L. Lipase concentration resulting above 300 IU/L was therefore diluted to obtain a more accurate measure. The upper limit of quantitation was therefore set at 300 IU/L, and the lower limit of quantitation was determined to be 18.8 IU/L. The results of assay validation are shown below:

(b) (4)

(b) (4)

(A) 9 pages of draft labeling has been withheld in full immediately following thi... B4 CCI/TS

NDA 22-222 for Ultrase MT Delayed Release Capsules

Appendix 4.2

In Vivo Intubation (Comparability Bioactivity) Study (No. UMT20CP05-01)

And

In Vitro Stability Study of Ultrase MT on Food (No. RE-071211-01)

2.0 SYNOPSIS

<table>
<tr><td>Name of sponsor/Company:
AXCAN PHARMA INC.
Mont-Saint-Hilaire QC
Canada</td><td rowspan="3">Individual Study Table Referring to Part of the Dossier

Volume:

Page:</td><td rowspan="3">(For National Authority Use Only)</td></tr>
<tr><td>Name of Finished Product:
Ultrase MT20</td></tr>
<tr><td>Name of Active Ingredient:
Pancreatic enzymes</td></tr>
<tr><td colspan="3">Title of Study: A randomized, open-label cross-over study to evaluate the intraduodenal delivery of total protease and lipase</td></tr>
<tr><td colspan="3">Investigator: Phillip P. Toskes, M.D., Professor, Department of Medicine, University of Florida College of Medicine, Gainesville, FL</td></tr>
<tr><td colspan="3">Study Center(s): Single-center</td></tr>
<tr><td colspan="3">Publication (reference):
None</td></tr>
<tr><td>Studied period (years):
2005-2006

Date of first subject enrolled:
04 October 2005

Date of last subject visit:
28 July 2006</td><td colspan="2">Phase of development: Phase I</td></tr>
<tr><td colspan="3">Objectives:
The primary objective of this study was to evaluate 2 enteric-coated enzyme preparations, Ultrase MT20 with Eudragit LD30 coating and Ultrase MT20 with HP55 coating, in chronic pancreatitis (CP) subjects and chronic pancreatitis subjects with pancreatic insufficiency (CPPI), with respect to their in vivo delivery of protease (namely trypsin) and lipase at the site of action (duodenum).

The secondary objectives of this study were to evaluate the effects of the 2 enteric-coated formulations of Ultrase MT20 on cholecystokinin (CCK) levels, CCK releasing peptide levels, and safety.</td></tr>
</table>

Name of sponsor/Company: AXCAN PHARMA INC. Mont-Saint-Hilaire QC Canada	Individual Study Table Referring to Part of the Dossier Volume:	*(For National Authority Use Only)*
Name of Finished Product: Ultrase MT20	Page:	
Name of Active Ingredient: Pancreatic enzymes		

Methodology:
This was a single-center, randomized, open-label cross-over study to evaluate 2 enteric-coated formulations of Ultrase MT20 (Eudragit LD30 and HP55 coating) and their effect on protease and lipase *in situ* availability in subjects with CP.

Approximately 20 subjects (10 CP and 10 CPPI) were to be entered into the study, in order to obtain 12 evaluable subjects (6 per pancreatic function group). An effort was to be made to enroll equal numbers of male and female subjects and subjects of different ethnic backgrounds reflecting the approximate disease representation in the US population.

Subjects were confined in the research facility for a period of 5-6 days. Upon admission (Day 0), a medical history, surgical history, and physical examination were performed; blood and urine samples were collected for clinical laboratory evaluations and pregnancy testing; and vital signs, including height and weight, were measured. Subjects fasted after midnight and an intravenous infusion of 100 mL/hr of DW5% + 1/2 normal saline was to be started approximately 12 hours prior to placement of the duodenal aspirate tube.

On Day 1, subjects were stratified according to pancreatic function and randomly assigned to a sequence group, which specified the order that the formulations were administered. Subjects received 2 capsules of either of the Ultrase MT20 formulations (Eudragit LD30 or HP55) in the middle of a standardized meal (500 mL Ensure Plus). Duodenal aspirates obtained through a modified Dreiling double-lumen intestinal tube were collected prior to and after administration of the meal. Continuous 15-minute intraluminal aspirations were collected during 2 hours post-Ultrase MT20 administration. At the end of the period, the stomach was aspirated for residual enzyme content. During the intestinal perfusion procedure, 4 blood samples were drawn for CCK assay. Vital signs were measured after the procedure and the subject was monitored for concomitant medication use and adverse events. Two days later, the same subject received 2 capsules of the other formulation and the study procedures were repeated.

Prior to discharge from the research facility, blood and urine samples were collected for clinical laboratory evaluations and a physical examination was performed.

Number of subjects (planned and analyzed):
Number of subjects planned: 20 subjects planned in order to obtain 12 evaluable subjects
Number of subjects randomized: 16 subjects (9 CP and 7 CPPI)
Number of subjects dosed: 13 subjects (6 CP and 7 CPPI)

Diagnosis and main criteria for inclusion:
Male or non-pregnant female subjects between 21-75 years of age with a history of CP or CPPI. Evidence of CP was documented by an abnormal secretin test, diffuse calcification of the pancreas on plain film of the abdomen, an abnormal endoscopic retrograde cholangiopancreatography or endoscopic ultrasound, an abnormal computed tomography scan showing dilation of the main pancreatic duct, atrophy of the pancreas, or calcification of the pancreas, or serum trypsin <20 ng/mL. The CPPI diagnosis required evidence of steatorrhea as manifested by an elevation of quantitative fecal fat excretion. Eligible subjects were not to have received therapeutic doses of pancreatic enzyme supplementation, proton-pump inhibitors, H2-receptor antagonists, antacids, anticholinergics, antispasmodics, or octreotide within 7 days prior to study entry.

Test product, dose and mode of administration, lot number:
Ultrase MT20 (HP55 formulation), 2 capsules, lot number: H040397A

Name of sponsor/Company: AXCAN PHARMA INC. Mont-Saint-Hilaire QC Canada	**Individual Study Table Referring to Part of the Dossier** **Volume:**	***(For National Authority Use Only)***
Name of Finished Product: Ultrase MT20		
Name of Active Ingredient: Pancreatic enzymes	**Page:**	

Duration of treatment:
Single dose in each of the 2 cross-over periods.

Reference therapy, dose and mode of administration, lot number:
Ultrase MT20 (Eudragit LD30 formulation), 2 capsules, lot number: J040498C

Criteria for evaluation:
Biologic activity was measured by comparison of total protease (namely trypsin) and lipase contents in duodenal aspirates. CCK and CCK releasing peptide levels were also assessed. Safety and tolerance were assessed by clinical laboratory tests, physical examinations, vital signs, and adverse event recording.

Statistical methods:
Two populations of subjects were defined for purposes of statistical analysis: intent-to-treat and per protocol. Each population was subdivided into 2 sub-populations: the CP and the CPPI. Each test was performed on the whole population and on each sub-population individually. The intent-to-treat population included all subjects who were enrolled in the study and received Ultrase MT20 with Eudragit LD30 coating or Ultrase MT20 with HP55 coating. The intent-to-treat population was used for all safety analyses. The per protocol population included all intent-to-treat subjects who completed the study and who additionally had no major protocol violations or other events considered to potentially bias their study outcome. The per protocol population was used for all parametric analyses. The primary population of interest was *a priori* defined in the statistical analysis plan as the CPPI population because these subjects do not produce any endogenous enzymes that can blur the contribution of Ultrase MT20.

Demographic data collected for gender, race and age were summarized by descriptive statistics. Likewise, data collected at baseline on height, weight, smoking habits, alcohol consumption habits, medical history and surgical history were summarized by descriptive statistics.

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Statistical methods: (continued)

Efficacy Analysis

Primary Hypotheses: The following 2 hypotheses were tested against their alternatives:

Hypothesis 1:

H_0: The ratio of the geometric means (period 2/period 1) of the activity (measured in IU) of lipase is equal to one in the CPPI, the CP, and the CPPI + CP populations.

H_1: The ratio of the geometric means (period 2/period 1) of the activity (measured in IU) of lipase is not equal to one in the CPPI, the CP, and the CPPI + CP populations.

Hypothesis 2:

H_0: The ratio of the geometric means (period 2/period 1) of the amount (measured in μg) of trypsin is equal to one in the CPPI, the CP, and the CPPI + CP populations.

H_1: The ratio of the geometric means (period 2/period 1) of the amount (measured in μg) of trypsin is not equal to one in the CPPI, the CP, and the CPPI + CP populations.

Secondary Hypotheses: The secondary analyses tested the following hypotheses:

Secondary Hypothesis 1:

H^0: The ratio of the geometric means (CPPI subjects/CP subjects) of the activity (measured in IU) of lipase is equal to one.

H_1: The ratio of the geometric means (CPPI subjects/CP subjects) of the activity (measured in IU) of lipase is not equal to one.

Secondary Hypothesis 2:

H_0: The ratio of the geometric means (CPPI subjects/CP subjects) of the amount (measured in μg) of trypsin is equal to one.

H_1: The ratio of the geometric means (CPPI subjects/CP subjects) of the amount (measured in μg) of trypsin is not equal to one.

Method for Assessing Hypotheses: For investigating the primary and secondary hypotheses that the mean ratios were equal to 1, the following model was fitted for each of the parameters (trypsin and lipase):

Log (Period 2/Period 1) = A + BX + CY + e, where

X = +1 for subjects randomized to Eudragit LD30 coating at Period 1

X = -1 for subjects randomized to HP55 coating at Period 1

Y = +1 for CP subjects

Y = -1 for CP subjects with PI

And e = random error

The estimated values of the constants in the above equation provided the estimates of the following effects after exponentiation:

A: Carry Over Effect (Period 2/Period 1) (Intercept)

B: Treatment Effect (ratio of geometric means) (primary hypothesis)

2 x C: Covariate Effects (ratio of CPPI/CP) (secondary hypothesis)

The following SAS program for the GLM procedure was used to estimate the values of the constants in the above equation.

```
PROC GLM DATA=XXX;
MODEL LOGLIPASE LOGTRYP = X Y / SOLUTION;
RUN;
```

The point estimates for the ratios, the p-values and the 95% confidence interval for the ratios were presented as analysis results.

Name of sponsor/Company: AXCAN PHARMA INC. Mont-Saint-Hilaire QC Canada	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*
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Statistical methods (continued):

The hypotheses for the analysis of the CPPI sub-population and the CP sub-population were performed by fitting the following model:

Log (Period 2/Period 1) = A + BX + e, where

X = +1 for subjects randomized to Eudragit LD30 coating at Period 1

X = -1 for subjects randomized to HP55 coating at Period 1

e = random error

A and B are constants as explained for the full model

As a supporting analysis, the primary and the secondary hypotheses were also tested using a paired samples t-test as proposed in the protocol.

Activity or amounts for the 2 parameters (lipase, trypsin) were declared to be treatment dependent if the 95% confidence interval for the ratio of the means of the 2 formulations did not include the value 1 or the p-value for the difference in the means of the 2 formulations was <0.05 for the overall population as well as the CP and CPPI subgroups.

The total active enzyme quantities or activity delivered to the duodenum at baseline and during a 2-hour period following the administration of each of the Ultrase MT20 formulations was presented. Descriptive statistics (mean, standard deviation, range) were performed for each collection period for the CP, CPPI and CP+CPPI subjects separately.

Safety Analysis

No inferential analysis was performed for the safety parameters.

Adverse Events: The frequency and percentage of subjects with any adverse events were summarized for each formulation separately by severity and relationship to study drug. The adverse events were also summarized for the CP or CPPI subjects separately. Adverse events were described using preferred terms from the Medical Dictionary for Regulatory Activities (MedDRA) dictionary. All serious adverse events were to be presented in a listing.

Clinical Laboratory Tests: Clinical laboratory test values were summarized by descriptive statistics at each protocol-specified time point. Normal ranges were provided as part of the clinical database from the site laboratory and provided in a separate data listing.

Vital Signs: Vital sign measurements were summarized by descriptive statistics at each protocol-specified time point.

Summary and Conclusions

Efficacy results:

Both Ultrase MT20 formulations were shown to deliver lipase to the duodenum. Analyses of the activity of lipase recovered during the 2-hour post-infusion period demonstrated no statistically significant differences between the formulations for the CPPI group, as well as no statistically significant differences between the CP and CPPI subjects in the activity of lipase recovered. In addition, no statistically significant carry-over effect for lipase was observed in this cross-over study.

The results for trypsin recovery are incomplete and cannot be used for any conclusion due to limitation of the assay method.

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Safety results:
The only treatment-emergent adverse events reported during the study were vomiting (1 CP and 3 CPPI subjects) and worsening pain (1 CPPI subject). Each of these events was considered by the investigator to be moderate in intensity and unrelated to study drug administration. All of the events were noted to be resolved, with the exception of the 1 event of pain, which was noted as improved.

No subjects died or prematurely discontinued from the study due to adverse events. One subject, who was never dosed due to the inability to pass the intestinal tube, experienced a serious adverse event. The subject was hospitalized 24 days after her official withdrawal from the study with increased abdominal pain related to her CP. No other serious adverse events were reported during the study.

No clinically important changes were noted in either the CP or CPPI subjects in the analyses of laboratory values, vital signs values, or physical examinations.

Conclusion:

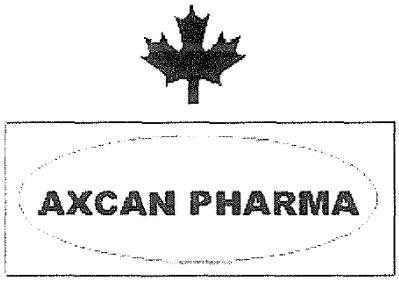
- Both Ultrase MT-20 formulations deliver lipase to the site of action with no statistically significant difference in the first 2 hours post-administration in the target population of CPPI subjects and also in all subjects with CP, regardless of their remaining pancreatic function.
- The clinical efficacy on steatorrhea of the Ultrase MT20 capsule with the HP55 coating should not be different from the efficacy of the Ultrase MT20 capsule with the Eudragit LD30 coating.
- The results for the protease release are inconclusive due to an inadequate assay kit.
- The effect on CCK and CCK releasing peptide cannot be assessed due to the lack of an adequate Good Laboratory Practice (GLP) validated method.
- Both formulations have a similar favorable safety profile when administered at single dose.

Date of the report: 16 July 2007

Reviewer's Comment:

The Ultrase MT capsule formulation with Eudragit LD30 coating has not been shown to be comparable to the current Ultrase MT capsule formulation with HP55 coating. Large intersubject variations were observed. Besides, the assay method used for this intubation study could not differentiate the exogenous lipase in the administered Ultrase MT capsules from the endogenous human lipase level. Thus, it rendered this study undesirable for use as a tool to establish comparability between two formulations or to quantify the lipase amount/activity recovered from duodenal aspirations. Please see the review in this context for details.

In Vitro Stability Study of Ultrase MT on Food



DEVELOPMENT REPORT: RE-071211-01:
***In vitro* stability testing of Ultrase MT sprinkled on food**

Prepared by:

Erick Tessier, M.Sc.
Manager, Analytical Development
and Validation
Pharmaceutical Development
Axcan Pharma Inc.

31 Jan 2008
Date

Approved by:

Carl Gauthier, Ph.D
Sr. Project Manager,
Pharmaceutical Development
Axcan Pharma Inc.

31 JAN 2008
Date

I. Background

Ultrase MT capsule is an enzymatic product that is currently under review by the FDA (NDA 22-222). Included in the NDA filing were the proposed instructions to patient that included dispersing the contents of the capsules (i.e. MiniTabs) on food. The patient instructions were written as follows:

ULTRASE® MT Capsules should be taken orally with meal or snack. Where swallowing of capsules is difficult, they may be opened and the minitablets sprinkled on a small quantity of a soft food (e.g., applesauce, gelatin, etc.), which does not require chewing, and swallowed immediately. To protect enteric coating, minitablets must not be crushed or chewed.

In order to confirm the list of compatible foods, the *in vitro* stability of the minitablets (MTs) over time in various food types have been be evaluated.

II. Objectives

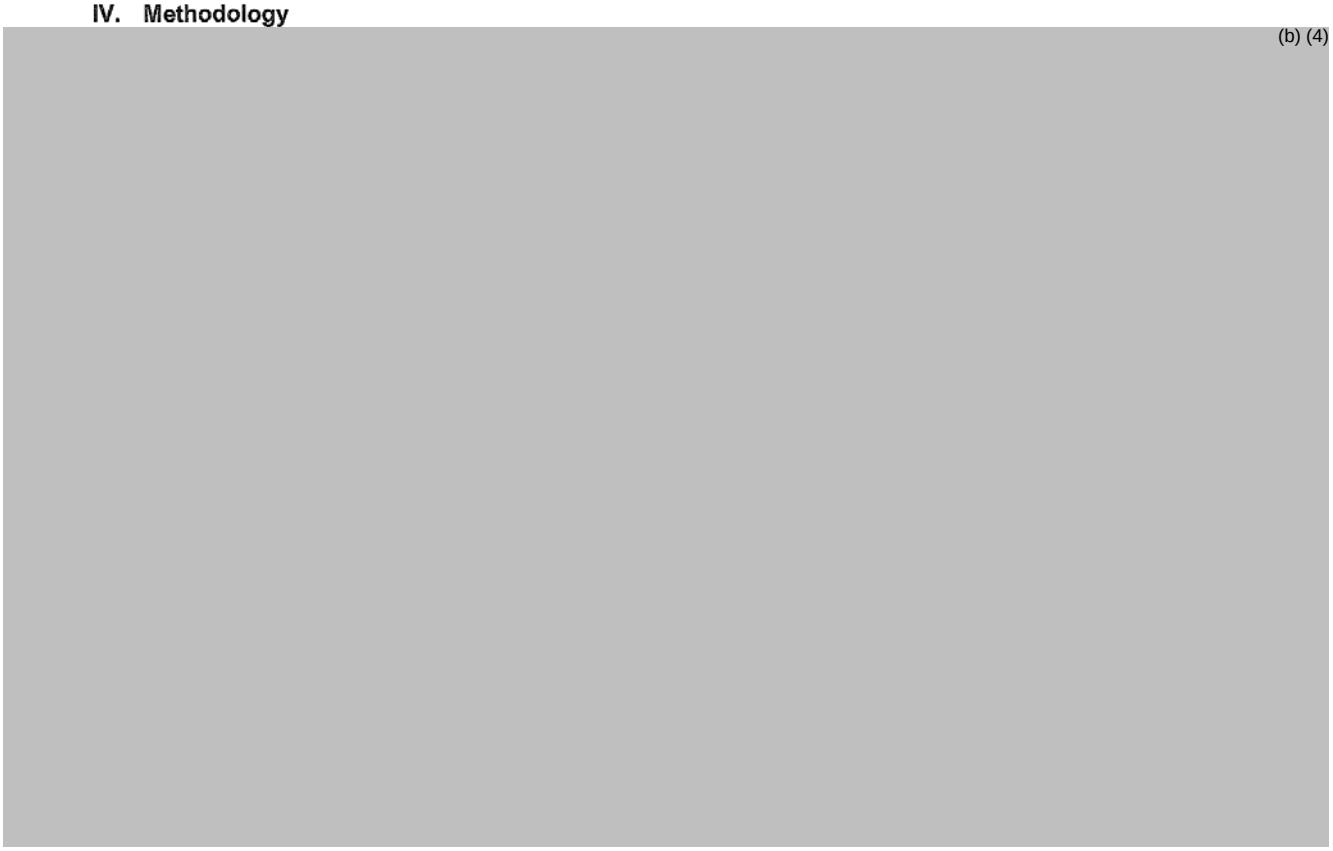
The objective of this study is to document the *in-vitro* stability of Ultrase MT over time when dispersed on applesauce, pudding and yogurt.

III. Hypothesis

MTs will be stable for up to 60 minutes in the tested food types.

IV. Methodology

(b) (4)



(b) (4)

V. Acceptance criteria

MTs samples subjected to the food contact experiment must meet the acceptance criteria of the dissolution test of Ultrase:

1. The mini-tablets show no evidence of disintegration, cracking or softening after 60 minutes in gastric fluid TS.
2. Not Less Than [redacted] USP Units of lipase activity per capsule is dissolved in 30 minutes.

VI. Results

Minitablets from Ultrase MT20 capsules lot F070224D were used in the food contact experiments. The stability of the minitablets in contact with the following three types of food was studied:

1. Apple sauce: Apple sauce is characterized by a low pH of approximately 3.5. Three different experiments were made with regular apple sauce, apple sauce with grape flavour and apple sauce with pineapple flavour.

2. Pudding: Pudding is characterized by a pH of approximately 6.4. The pudding used in the in vitro stability testing was chocolate pudding and a pH of 6.42 was reported. Three pudding flavours were tested for pH; chocolate, vanilla and butterscotch. Similar pH values were reported for each of the different flavours.

3. Yogurt: Regular (2% fat) plain yogurt was chosen for the in vitro stability testing. The pH of the yogurt tested was 4.17.

After 30 minutes or 60 minutes contact with the food sample, the functionality of the enteric-coating was assessed by subjecting the MTs samples to a 2-stage dissolution test (lipase assay) Results are summarized in table 1. Detailed data tables can be found in the certificate of analysis presented in Appendix 1.

Table 1: Results of 2-stage dissolution test of Ultrase MT sprinkled on food.

Food	Results after 30 minutes of contact time in food (% activity VS nominal)	Results after 60 minutes of contact time in food (% activity VS nominal)
Apple sauce, plain	93% with 3.5% RSD	98% with 3.0% RSD
Apple sauce, grape	94% with 0.9% RSD	92% with 3.7% RSD
Applesauce, pineapple	92% with 4.4% RSD	92% with 3.0% RSD
Pudding chocolate	101% with 0.9% RSD	95% with 4.5% RSD
Yogurt	94% with 4.5% RSD	95% with 1.0% RSD

VII. Conclusion

The stability of Ultrase MTs was demonstrated in applesauce (3 flavours), chocolate pudding and yogurt. Dissolution results showed that the enteric-coating remains functional after 30 and 60 minutes of contact with each food-type. These results support the sprinkling of minitablets on applesauce, pudding or yogurt, and therefore supports the intended administration of Ultrase MT in patients where swallowing the capsule is difficult.

Reviewer's Comment:

The above *in vitro* study was reviewed and it supports the proposed labeling claim to sprinkle the content (minitablets) of Ultrase MT capsules on food when intact capsules could not be swallowed.

NDA 22-222 for Ultrase MT Delayed Release Capsules

Appendix 4.3

Cover Sheet and OCP Filing/Review Form

Office of Clinical Pharmacology

ew Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	**22-222**	**Brand Name**	**Ultrase**
OCPB Division (I, II, III)	**DCP III**	**Generic Name**	**Pancreatic Enzyme Product**
Medical Division	**GI**	**Drug Class**	**Pancreatic enzyme**
OCPB Reviewer	**Tien-Mien Chen, Ph.D.**	**Indication(s)**	**Exocrine pancreatic insufficiency**
OCPB Team Leader	**Sue-Chih Lee, Ph.D.**	**Dosage Form**	**Delay-Release Capsules**
		Dosing Regimen	**<2,500 units/kg/meal**
Date of Submission	**10/01/07**	**Route of Administration**	**Oral**
Estimated Due Date of OCPB Review	**02/28/08**	**Sponsor**	**Axcan Pharma**
Medical Division Due Date	**03/01/08**	**Priority Classification**	**P**
PDUFA Due Date	**04/01/08**		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**			
Tabular Listing of All Human Studies	**X**			
HPK Summary	**X**			
Labeling				
Reference Bioanalytical and Analytical Methods	**X**			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:	**X**	**1**	**1**	A 2x2 crossover BE-type PK study
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				

PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:	**X**			A traditional 2 x 2 crossover in patients
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		**1**	**1**	

Filability and QBR comments

	"X" if yes	**Comments**
Application filable ?	**X**	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm ?	**X**	Comments have been sent to firm (or attachment included). FDA letter date if applicable. IRs from OCP had been sent to the sponsor.
QBR questions (key issues to be considered)	**Is the clinically tested formulation bioequivalent to the to-be-marketed formulation?**	
Other comments or information not included above		
Primary reviewer Signature and Date	**Tien-Mien Chen, Ph.D. 11/10/07**	
Secondary reviewer Signature and Date	**Sue-Chih Lee, Ph.D. 11/11/07**	

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

/s/

Tien-Mien Chen
3/10/2008 12:46:44 PM
BIOPHARMACEUTICS

Sue Chih Lee
3/10/2008 02:02:09 PM
BIOPHARMACEUTICS
Reviewer's 1st draft: 2/11/08, final copy: 3/10/08