

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
20-725

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

Clinical Pharmacology Review

NDA:	20-725
Brand Name:	Creon
Generic Name:	Pancrelipase Enzyme
Dosage form and Strength:	Delayed release capsules, 6,000, 12,000, and 24,000 Units
Route of administration:	Oral
Indication:	Adult and pediatric patients with maldigestion due to exocrine pancreatic insufficiency
Sponsor:	Solvay Pharmaceuticals
Type of submission:	Responses to Approvable Letter
Clinical Division:	Division of Gastroenterology Products (HFD-180)
OCPB Division:	DCP III
Priority:	6 months
Submission date:	06/19/08, 09/17/08
PDUFA Goal date:	12/19/08
Reviewer:	Tien-Mien Chen, Ph.D.
Team leader:	Sue-Chih Lee, Ph.D.

Background:

Creon (pancrelipase) delayed release (DR) capsule and several other pancreatic enzyme products are currently on the market without FDA approval. Creon is a pancreatic enzyme supplement of porcine origin. NDA 20-725 for Creon DR capsules was initially submitted on 07/31/97 by Solvay, but the NDA was suspended and then revoked on 04/09/03 for review. Creon was deemed not approvable on 10/09/03 mainly due to CMC (chemistry, manufacturing, and controls) deficiencies.

Sponsor undertook reformulation of their Creon product. However, the clinical trials had been completed previously using the original formulation (same as that currently on the market). As agreed upon between the Agency and the sponsor, an *in vivo* intubation bioavailability study, comparative dissolution data, and comparative analytical characterization data were used to link the to-be-marketed (TBM) formulation to the formulation used in clinical trials.

Included in the 11/17/06 resubmission was an *in vivo* intubation bioavailability study (protocol No. S245.2.003) plus comparative dissolution and analytical characterization

data. An *in vitro* stability study on Creon content when mixed with acidic foods was also submitted. No new clinical trials were conducted for this resubmission.

The results of the *in vivo* intubation study were reviewed by the Office of Clinical Pharmacology (OCP). It was concluded by OCP that the comparability between TBM formulation and the clinically tested formulation has not been demonstrated. The DSI audit report (dated 06/08/07) for the study and analytical sites of the *in vivo* intubation study (No. S245.2.003) also raised several incompliance issues. The resubmission was deemed approvable in the 08/16/07 letter. The sponsor was informed that a new clinical trial using the TBM formulation of Creon would be needed and several CMC deficiencies needed to be addressed.

The results of *in vitro* stability study on Creon content when mixed with acidic foods were also found inadequate. The use of pellets (Creon capsule content) in a bag of polypropylene cloth does not reflect the realistic contact of individual pellets with food. Furthermore, only one bag per each of 6 food types was performed which did not provide statistically meaningful data (i.e., mean \pm standard deviation, SD) per each food type. Thus, the original *in vitro* stability study is not robust enough to produce adequate results to support the claim of alternative mode of administration.

Upon request for a new *in vitro* stability study using the Agency's proposed study design, the new study results were submitted on 09/17/08 for a second cycle review.

Synopsis:

The new *in vitro* stability study using the Agency's proposed study design was submitted on 09/17/08 and therefore it is reviewed here. Please see Attachment 1 for the study procedures and results for details.

The Creon content was weighed carefully and transferred into a beaker containing the amount of food (approximately 10g) corresponding to a single application. After mixing thoroughly, the incubation was performed at 25°C for 30 or 60 minutes respectively in a thermostated water-bath. There were 6 food types tested. Per each food type and per each time point, 30 and 60 min, 5 beakers were obtained. The content of each beaker was rinsed and transferred with the aid of a sufficient amount of simulated gastric fluid onto a sieve (710 μ m).

The residual pellets collected were performed according to dissolution test procedures. The lipase activity was determined according to USP method and the recovery was compared with the actual activity of Creon capsule. The actual activity of Creon capsule was determined independently from an aliquot obtained from mixing of 20 capsules. The actual lipase activity was $\square^{(b) (4)}$ USP-u/cps with an average fill weight of $\square^{(b) (4)}$ mg. The % recovery of lipase from the *in vitro* study is shown below.

Table 1. The Recovery of Lipase Activity from *In Vitro* Stability Study

Type of Food	pH value	Recovery (n=5) Mean ± SD	
		30 min	60 min
Apple Sauce (Beech Nut)	3.6	90.2 ± 2.3	89.2 ± 1.7
Apple Sauce (Gerber Products Company)	3.6	90.8 ± 1.7	88.2 ± 3.4
Chiquita Bananas (Beech-Nut)	4.2	85.3 ± 3.1	85.9 ± 1.4
Bananas (Gerber Products Company)	4.2	86.6 ± 2.3	86.3 ± 1.6
Tender Sweet Carrots (Beech-Nut)	4.9	84.7 ± 2.4	85.9 ± 1.9
Carrots (Gerber Products Company)	5.1	85.8 ± 0.7	82.1 ± 2.3

The sponsor reported that the above dissolution data all met the proposed dissolution specification, NLT (b) (4) (Q) in 30 min.

Reviewer’s Comments:

It appears that the 60-min results were similar to those observed at 30 minutes for most of the foods tested, indicating that no more lipase was released and degraded from the enteric coated pellets after 30 min. The % recovery of lipase, however, decreased as pH of the food was greater than 4.0. The label should be modified accordingly to allow certain type of acidic food for mixing with Creon capsule contents. It should be emphasized that as stated in the proposed label, the Creon content after mixing with food should be swallowed immediately.

Recommendations:

The *in vitro* stability study on Creon content when mixed with food submitted on 09/17/08 has been reviewed by Office of Clinical Pharmacology (OCP). From OCP standpoint, the results of the *in vitro* stability study indicate that not all the foods tested may be used for mixing with Creon capsule contents and this will be reflected in the label. The following labeling comments need to be conveyed to the sponsor.

Labeling Comments: (Need to be sent to the sponsor)

The sponsor’s proposed labeling (May 2008 version) needs revision as follows: blue and underlined for addition and ~~red and strikethrough~~ for deletion by the Agency).

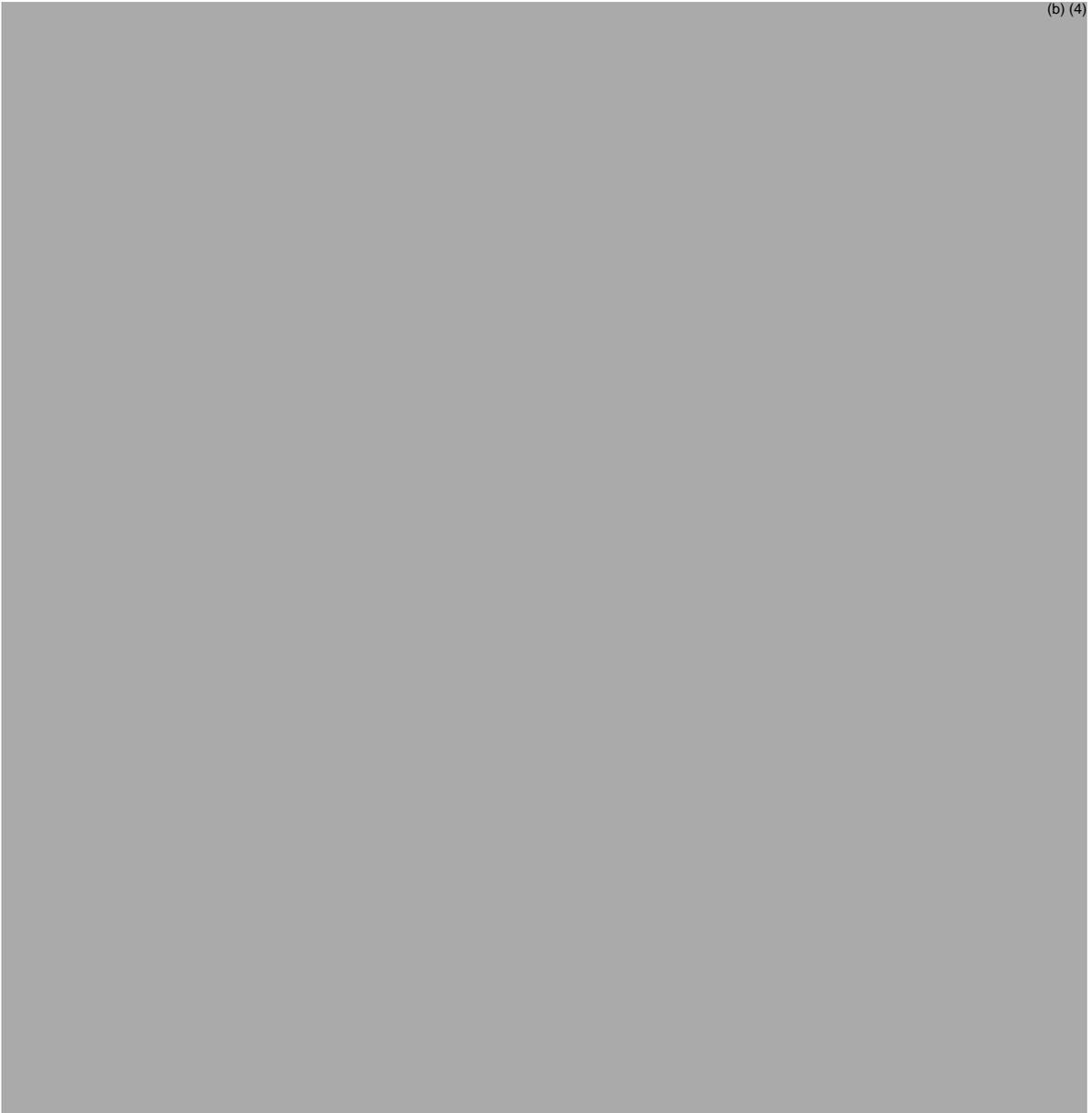


(b) (4)

2.



3.



4. Subsection **12.3 Pharmacokinetics** should be changed to Subsection 12.2.

11/10/08

Tien-Mien Chen, Ph.D.
Division of Clinical Pharmacology III

Team Leader

Sue-Chih Lee, Ph.D. 11/10/08

**NDA 20-725 for
Creon DR (Pancrelipase) Capsules**

Attachment 1

**Sponsor's Proposed Labeling
(May, 2008 Version)**

**NDA 20-725 for
Creon (Pancrelipase) DR Capsules**

Attachment 2

**In Vitro Stability Study of Creon Content
When Mixed with Food**

Study Report
Stability study of Pancrelipase delayed-release capsules used in an alternate mode of administration

1. INTRODUCTION

As an alternate mode of administration of Pancrelipase delayed-release capsules it is proposed to open the capsules and to sprinkle the capsule content, enteric-coated pellets on foods.

Considering that Pancrelipase delayed-release capsules dissolve rapidly in the stomach without release of the enzymes at pH values below pH 5.5, an alternate mode of delivery of the enteric coated pellets is being proposed. To ensure the stability of the product and particularly of the coating, Solvay Pharmaceuticals was requested by the FDA to test the stability with selected foods.

A first study was already performed and submitted earlier to the FDA. However, based on the agency's response:

“Two capsules of the to-be-marketed formulation (corresponding to approximately 24,000 USP units of lipase) were opened and transferred into a bag of polypropylene cloth. The bag was put into the food so that the pellets were very well.... After 1 hour incubation at 25°C the bag containing the pellets was removed. Residues of food were flushed from the pellets and lipase activity of the washed pellets was determined.”

The above study design is not robust enough to produce adequate results to support the claim of an alternative mode of administration. The testing of pellets (Creon capsule content) placed in a bag of polypropylene cloth may not reflect the realistic contact of individual pellets with food. Furthermore, use of only one bag per type of food did not provide statistically meaningful data (i.e., mean \pm standard deviation, SD).

The design of the study and the methodology applied for evaluation of the pellets after exposure to the food was revised with regard to the following issues, following the agency's recommendations:

- The amount of pellets represents the recommended dose of lipase for pediatric population
- Weighing of pellets and food was performed before performing the test
- For each type of food 10 beakers were prepared on five days
- The incubation was performed at 25°C
- Sampling was performed after 30 minutes for half of the beakers and after 60 minutes for the rest of the beakers
- Food was washed off with acidic solution and sieved before the pellets were transferred to the dissolution tester, starting with stage 1 (acidic stage) of the dissolution test

2. MATERIAL AND METHODS

2.1 Instruments

- Pure water installation
- Thermostatizable water bath
- Magnetic stirrer
- pH Meter

2.2 Materials

2.3 Chemicals and Reagents

- Water:
The water for all solutions is purified by filtration / ion exchange. For present purposes it is called “pure water”.
- Simulated Gastric fluid (without enzyme):
Dissolve 2.0 g of sodium chloride in 80 ml of 1 M hydrochloric acid, make up with pure water to 1,000 ml (volumetric flask).
- 0.1 M Sodium hydroxide solution

2.4 Samples

For the study a suitable aliquot from one batch (810073) of the to-be-marketed Pancrelipase delayed-release capsules 12,000 was used (cf. Table 1). This batch is used in clinical study S245.3.127. As the different strengths of Pancrelipase delayed-release capsules only differ in the fill weight of the capsules without any difference in the pellets related to composition, the results of this study are regarded representative for all strengths.

Six different exemplary foods from the US market which were already used in the former study, two of each class, i.e. carrots-, bananas-mash and apple sauce were selected. The food preparations are listed in [Table 1](#).

Table 1 Food types used for the study

Aliment / Product	Batch No.
Apple Sauce (Beech-Nut)	C0102D1428, C0102D1245
Apple Sauce (Gerber Products Company)	US 7131 5 FK
Chiquita Bananas (Beech-Nut)	C0107C1114, C0107D1421
Bananas (Gerber Products Company)	US 7135 5FK
Carrots (Beech-Nut)	C0114D1320, C0114D1321, C0114D1131
Carrots (Gerber Products Company)	US 7111 1FK

2.5 Methods

The in-vitro dissolution of lipase activity after exposure to food was tested according to the procedure in Solvay's NDA 20-725 (November 2006, Volume 5, Page 1465), SOLID000061447-Analytical Procedure: Dissolution Test Pancrelipase delayed-release Capsules and Pellets.

3. PERFORMANCE OF STUDY

For each test in the study one capsule of Pancrelipase delayed-release capsules 12,000 was used. This assumption takes into account a recommended application of 500 USP-u of lipolytic activity per kg body weight per meal (for children > 4 years) and a child aged 7 to 8 years with an assumed body weight of approximately 22 - 25 kg.¹

3.1 pH Determination of the aliments

For the alternate mode of administration of Pancrelipase delayed-release capsules the use of aliments with pH values below 5.5 is recommended to ensure maximum enzyme stability. Therefore, the pH-value of each aliment (30 mL portion) was measured at 25°C individually and the mean was calculated.

3.2 Stability testing



After 60 minutes the remaining beakers of each of 6 food types were prepared in the same way. The experimental design is shown below:

Table 2 Experimental Design

Day	1		2		3		4		5	
Pull point [minutes]	30	60	30	60	30	60	30	60	30	60
	No. of Beakers prepared									
Aliment / Product										
Carrots (Beech-Nut)	1	1	1	1	1	1	1	1	1	1
Carrots (Gerber Products Company)	1	1	1	1	1	1	1	1	1	1
Bananas (Gerber Products Company)	1	1	1	1	1	1	1	1	1	1
Bananas (Beech-Nut)	1	1	1	1	1	1	1	1	1	1
Apple Sauce (Gerber Products Company)	1	1	1	1	1	1	1	1	1	1
Apple Sauce (Beech-Nut)	1	1	1	1	1	1	1	1	1	1
Total No of beakers	6	6	6	6	6	6	6	6	6	6

The remaining pellets were transferred into the basket of the dissolution tester to perform stage 1 testing with exposure to pH 1 for two hours. The complete dissolution testing was performed but the volume of dissolution medium transferred into the titration vessel was adjusted to meet the required validated activity range for titration.

As an acceptance criterion the result of the testing should comply with the specification limit of NLT $\frac{(b)}{(4)}(Q)$, related to actual activity after 20 or 30 minutes in buffer medium.

The actual activity was determined independently from an aliquot obtained from mixing of 20 capsules.

3.3 Results

The results obtained with each type of food after 30 and 60 minutes are tabulated below as % of actual lipase activity released, reporting the highest value obtained after exposure for 20 or 30 minutes in the buffer stage, respectively. The table contains the pH-value, the actual amount of food and the weight of pellets sprinkled on the food.

The actual lipase activity was $\frac{(b)}{(4)}$ JSP-u/cps with an average fill weight of $\frac{(b)}{(4)}$ mg.

Table 3 Percentages of actual lipase activity released after exposure to food for 30 and 60 minutes (25°C)

Type of food	Apple Sauce (Beech Nut)						pH-value						3.6					
Day	1		2		3		4		5									
Time [min]	30	60	30	60	30	60	30	60	30	60	30	60	30	60	30	60		
	[% actual lipase activity released]																	
Weight [g]	91.7	88.8	86.3	87.5	90.2	90.2	91.5	91.6	91.4	88.1	mean	90.2	89.2	sd	2.27	1.66		
Weight pellets [mg]	230.11	229.80	221.85	236.63	234.61	225.44	231.91	227.61	230.73	236.16								
Type of food	Apple Sauce (Gerber Products Company)						pH-value						3.6					
Time [min]	30	60	30	60	30	60	30	60	30	60	30	60	30	60	30	60		
	[% actual lipase activity released]																	
Weight [g]	91.2	89.7	89.1	86.2	89.3	84.2	91.5	93.1	93.1	87.6	mean	90.8	88.2	sd	1.66	3.41		
Weight pellets [mg]	232.12	231.64	235.61	233.57	233.09	236.03	234.44	227.98	236.07	237.71								
Type of food	Chiquita Bananas (Beech-Nut)						pH-value						4.2					
Time [min]	30	60	30	60	30	60	30	60	30	60	30	60	30	60	30	60		
	[% actual lipase activity released]																	
Weight [g]	90.1	86.4	83.4	86.4	82.5	87.6	86.5	84.9	84.1	84.2	mean	85.3	85.9	sd	3.06	1.35		
Weight pellets [mg]	218.41	233.30	233.64	230.75	230.89	237.31	236.52	238.35	235.48	233.32								

Table 4 Percentages of actual lipase activity released after exposure to food for 30 and 60 minutes (25°C), continued

Type of food	Bananas (Gerber Products Company)						pH-value						4.2							
Day	1		2		3		4		5		6		7		8		9		10	
Time [min]	30	60	30	60	30	60	30	60	30	60	30	60	30	60	30	60	30	60	30	60
	[% actual lipase activity released]																			
Weight [g]	90.2	85.5	86.7	86.0	86.2	88.7	84.0	86.9	85.8	84.5	mean	86.6	86.3	sd	2.27	1.59				
Weight pellets [mg]	229.96	234.67	218.20	236.52	224.88	230.52	237.94	231.43	235.82	237.80										
Type of food	Tender Sweet Carrots (Beech-Nut)						pH-value						4.9							
Time [min]	30	60	30	60	30	60	30	60	30	60	30	60	30	60	30	60	30	60	30	60
	[% actual lipase activity released]																			
Weight [g]	86.1	83.2	81.4	86.2	82.7	87.9	86.7	87.1	86.4	85.0	mean	84.7	85.9	sd	2.44	1.85				
Weight pellets [mg]	234.58	229.40	235.59	221.55	233.44	236.06	229.57	233.01	230.13	238.67										
Type of food	Carrots (Gerber Products Company)						pH-value						5.1							
Time [min]	30	60	30	60	30	60	30	60	30	60	30	60	30	60	30	60	30	60	30	60
	[% actual lipase activity released]																			
Weight [g]	86.3	83.2	85.9	81.4	84.6	78.6	86.2	84.6	86.1	82.7	mean	85.8	82.1	sd	0.70	2.27				
Weight pellets [mg]	229.04	230.37	217.82	231.50	231.19	227.55	239.24	232.07	235.92	235.34										

4. DISCUSSION

For all food types investigated, the release of lipase activity was well within the specification limit of NLT $\frac{(b)}{(4)}(Q)$ after 30 and 60 minutes.. There was no major differences in the 30 to 60 minute incubation periods. However, a very slight decrease from 30 to 60 minutes was observed in Carrots (Gerber Company), where the pH value measured was 5.1. Results show excellent reproducibility over 5 days and confirm the stability and sufficient gastric resistance of the pellets under the conditions tested.

This alternate sprinkling of pellets on food mode of dosing does not affect the quality of the product and complies with the dosing of the whole capsule with respect to gastric resistance and release of the lipase activity.

**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
11/10/2008 05:56:06 PM
BIOPHARMACEUTICS

Sue Chih Lee
11/10/2008 05:59:06 PM
BIOPHARMACEUTICS

Addendum to Clinical Pharmacology Review

NDA:	20-725
Brand Name:	Creon
Generic Name:	Pancrelipase Enzyme
Dosage form and Strength:	Delayed release capsules, 6,000, 12,000, and 24,000 Units
Route of administration:	Oral
Indication:	Adult and pediatric patients with maldigestion due to exocrine pancreatic insufficiency
Sponsor:	Solvay Pharmaceuticals
Type of submission:	Resubmission
Clinical Division:	Division of Gastroenterology Products (HFD-180)
OCPB Division:	DCP III
Priority:	Standard
Submission date:	07/31/07
PDUFA Goal date:	08/17/07 (three-month extension due to a clinical major amendment)
Reviewer:	Tien-Mien Chen, Ph.D.
Team leader:	Sue-Chih Lee, Ph.D.

Resubmission of NDA 20-725 for Creon-6, -12, and -24 delayed-release capsules dated 11/17/06 included a study report of an *in vivo* intubation bioactivity Study S245.2.003. This study compared the to-be-marketed formulation (TBM) with the clinically-tested (CT) formulation used in the clinical trials. The results of the intubation study were reviewed by the Office of Clinical Pharmacology. From the clinical pharmacology standpoint, it was concluded that the sponsor did not demonstrate that TBM formulation was comparable to the CT formulation. Please see the completed clinical pharmacology review dated 07/16/07 for details.

Subsequently on 07/12/07, the sponsor submitted an amendment to the Agency (received on 07/18/07) to provide study results revised after corrections for 1) the errors found in the amount of polyethylene glycol (PEG) recovered from duodenum and 2) the amount of PEG in the capsule formulation ((b) (4) gram compared to 7 grams used in the intubation study).

After a review of the revised data provided in the sponsor's 07/12/07 amendment to this NDA, no change to the final clinical pharmacology conclusion was made. Please see OCP review addendum dated 08/01/07 for details.

Furthermore on 07/31/07, the sponsor submitted another amendment to the Agency (received on 08/01/07) to provide explanations and additional analyses for inter-subject variations on total pancreatic lipase (PL) and porcine pancreatic lipase (PPL) levels, i.e., 1). inter-subject difference in human pancreatic lipase (HPL) secretion/activities could be due to disease status, mild to severe chronic pancreatitis (CP), 2) lipase activity measurements could be related to intestinal pH values and driven by the pH activity curves, and 3) intestinal pH differences among subjects also affected the release of PPL from Creon dosage form.

Reviewer's Comments:

As indicated by the sponsor that Creon is designed to release PPL in the duodenum at pH >5.5. The lower PPL activity (U) could be related to the % of time the duodenal pH being <5.5 for two patients, Nos. 6 and 9, during the study as shown below in Table 1:

Table 1. PEG-Corrected PPL (U) Correlated with the % of Time the pH of Duodenal Aspirates being <5.5

Patient No.	TBM			CT		
	Mean pH	% Time < 5.5	PPL (unit)	Mean pH	% Time < 5.5	PPL (unit)
6	3.5	84.6	7,030	5.7	61.5	9,473
9	4.6	76.9	0.0	4.9	69.2	1,702

Mean pH values, % of time pH <5.5, and PEG-corrected PPL (U) for the rest of 7 patients are shown in Table 2. However, no clear correlations were found. The PPL (U) was from 39,764 to 190,045 for TBM formulation and from 45,905 to 287,981 for CT formulation with large inter-subject variations.

Table 2. Mean pH values, % of Time pH <5.5 and PEG corrected PPL (U) for the Rest of 7 Patients

Patient No.	TBM			CT		
	Mean pH	% Time pH <5.5	PPL (Units)	Mean pH	% Time pH <5.5	PPL (Units)
8	6.8	0.0	127067.0	5.7	38.5	47997.1
11	7	0.0	94441.4	4.5	83.3	45904.5
13	6.2	9.1	190044.7	6.5	0.0	170239.1
102	6	41.7	152417.3	6.3	33.3	287981
5	6.3	7.7	39764.2	5.8	46.2	56429.1
12	6.3	16.7	106145.6	5.7	30.8	68253.4
14	5.8	38.5	138318.2	6.5	0.0	164358.4
Overall Mean	6.3 (0.4)*	16.2 (17.3)	121,171 (47,638)	5.9 (0.7)	33.2 (28.6)	120,166 (91,381)

*. (Standard deviation)

After a review of the additional data/analyses provided in the sponsor's 07/31/07 amendment to this NDA, no change to the final clinical pharmacology conclusion is made because of the following reasons:

1. The sponsor claimed that the lower PPL activity (U) could be related to the % of time the duodenal pH being <5.5 for two patients, Nos. 6 and 9. However, no clear correlation was found between the % of time the duodenal pH being <5.5 and the porcine pancreatic enzyme activity recovered from the duodenum. Further, as commented in the original NDA review, some subjects were found to have PPL activity in duodenum which was much higher than that in the administered dose.
2. The sponsor indicated that the lipase activity (for total, HPL, and PPL) is a function of pH and it is driven by the pH activity curves. It is noted that, during the assay for lipase activity determination using tributyrin as a substrate, the pH was adjusted to 8.0. It is also true for the USP method for titrating *In vitro* PPL activity using olive oil as a substrate at pH being adjusted to 9.0. Therefore, the pH of duodenal samples is unlikely to affect the determination of total PL, HPL, and PPL activities during assays.
3. Again, an inspection of the above intubation bioactivity study and its analytical sites in France was conducted by the Division of Scientific Investigation (DSI) between 05/28/07 and 06/01/07. Several deficiencies were listed in the 483 citation which rendered the study not favorable for being accepted to support the resubmission of this NDA.

As such, the study remains unreliable for use as a tool to establish comparability between the two formulations.

08/06/07

Tien-Mien Chen, Ph.D.
Division of Clinical Pharmacology III

Team Leader

Sue-Chih Lee, Ph.D. _____ 08/07/07

**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
8/7/2007 06:12:15 PM
BIOPHARMACEUTICS

Sue Chih Lee
8/7/2007 06:36:59 PM
BIOPHARMACEUTICS

Addendum to Clinical Pharmacology Review

NDA:	20-725
Brand Name:	Creon
Generic Name:	Pancrelipase Enzyme
Dosage form and Strength:	Delayed release capsules, 6,000, 12,000, and 24,000 Units
Route of administration:	Oral
Indication:	Adult and pediatric patients with maldigestion due to exocrine pancreatic insufficiency
Sponsor:	Solvay Pharmaceuticals
Type of submission:	Resubmission
Clinical Division:	Division of Gastroenterology Products (HFD-180)
OCPB Division:	DCP III
Priority:	Standard
Submission date:	07/12/07
PDUFA Goal date:	08/17/07 (three-month extension due to a clinical major amendment)
Reviewer:	Tien-Mien Chen, Ph.D.
Team leader:	Sue-Chih Lee, Ph.D.

Resubmission of NDA 20-725 for Creon-6, -12, and -24 delayed-release capsules dated 11/17/06 included a study report of an *in vivo* intubation bioactivity Study S245.2.003. This study compared the to-be-marketed formulation (TBM) with the clinically-tested (CT) formulation used in the clinical trials. The results of the intubation study were reviewed by the Office of Clinical Pharmacology. From the clinical pharmacology standpoint, it was concluded that the sponsor did not demonstrate that TBM formulation was comparable to the CT formulation. Please see the completed clinical pharmacology review dated 07/16/07 for details.

Subsequently on 07/12/07, the sponsor submitted an amendment to the Agency (received on 07/18/07). In this amendment the sponsor provided study results revised after corrections for 1) the errors found in the amount of polyethylene glycol (PEG) recovered from duodenum and 2) the amount of PEG in the capsule formulation ((b) (4) gram compared to 7 grams used in the intubation study).

After a review of the revised data provided in the sponsor's 07/12/07 amendment to this NDA, no change to the final clinical pharmacology conclusion is made because of the following reasons:

1. Corrections for PEG amount did not reduce the inter-subject variability in the porcine pancreatic lipase (PPL) activity recovered from the duodenum. The revised data show that following oral administration of either Creon formulation, the PPL activity in duodenum as calculated from this intubation study was still highly variable among individual patients (ranged from 0 to 190,045 U for the TBM formulation and 1,702 to 287,981 U for the CT formulation with the highest activity being greater than 4-fold of the administered dose, 60,000 units) as shown below:

PEG-corrected PPL Activity (U) in the Duodenum

Parameter (unit) Statistic	TBM	Clinically Tested (CT)	TBM – CT
PPL (U)			
n	9	9	9
Mean (SD)	95,025 (66,308)	94,061 (93,393)	964 (60,727)
Range	(0 to 190,045)	(1,702 to 287,981)	-----

2. An inspection of the above intubation bioactivity study and its analytical sites in France was conducted by the Division of Scientific Investigation (DSI) between 05/28/07 and 06/01/07. Several deficiencies were listed in the 483 citation.

As such, the study remains unreliable for use as a tool to establish comparability between the two formulations.

07/25/07

Tien-Mien Chen, Ph.D.
Division of Clinical Pharmacology III

Team Leader

Sue-Chih Lee, Ph.D. _____ 07/31/07

**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
8/1/2007 11:11:05 AM
BIOPHARMACEUTICS

Sue Chih Lee
8/1/2007 11:43:47 AM
BIOPHARMACEUTICS

Clinical Pharmacology Review

NDA:	20-725
Brand Name:	Creon
Generic Name:	Pancrelipase Enzyme
Dosage form and Strength:	Delayed release capsules, 6,000, 12,000, and 24,000 Units
Route of administration:	Oral
Indication:	Adult and pediatric patients with maldigestion due to exocrine pancreatic insufficiency
Sponsor:	Solvay Pharmaceuticals
Type of submission:	Resubmission
Clinical Division:	Division of Gastroenterology Products (HFD-180)
OCPB Division:	DCP III
Priority:	Standard
Submission date:	11/17/06, 02/05/07, 03/12/07, 03/19/07, 04/11/07, 04/13/07, 04/20/07, and 05/14/07
PDUFA Goal date:	08/17/07 (three-month extension due to a clinical major amendment)
Reviewer:	Tien-Mien Chen, Ph.D.
Team leader:	Sue-Chih Lee, Ph.D.

I. Executive Summary

Creon (pancrelipase) delayed release (DR) capsule and several other pancreatic enzyme products are currently on the market without FDA approval. Creon is a pancreatic enzyme supplement of porcine origin. NDA 20-725 for Creon DR capsules was initially submitted on 07/31/97 by Solvay, but the sponsor was placed under AIP (application integrity policy). The NDA review was then suspended. The Agency revoked the AIP status for Solvay on 04/09/03 and reviewed the NDA. However, Creon was deemed not approvable on 10/09/03 mainly due to CMC (chemistry, manufacturing, and controls) deficiencies.

Subsequently, the sponsor undertook reformulation of their product. Since the clinical trials had been completed previously using the original formulation (same as that currently on the market), the sponsor proposed a two-way crossover intubation study to compare the duodenal lipase activity of the to-be-marketed (TBM) and the clinically tested formulations. The Agency agreed in the 10/21/05 meeting with the sponsor that

this study if successful in demonstrating the similarity of the two formulations, the proposed data (intubation study data, comparative dissolution data, and comparative analytical characterization data) would be sufficient to link the TBM formulation to the formulation used in clinical trials.

There are no new clinical trials submitted in this resubmission. Included in the clinical pharmacology section was an intubation study to bridge the TBM formulation to the clinically tested formulation (protocol No. S245.2.003).

A. Recommendations

NDA 20-725 for Creon-6, -12, and -24 DR capsules has been reviewed by Office of Clinical Pharmacology (OCP). From the clinical pharmacology standpoint, the sponsor has not demonstrated that the to-be-marketed formulation is comparable to the clinical formulation. The comments below should be communicated to the Medical officer and sponsor.

B. Comments:

The TBM formulation has not been shown to be comparable to the clinical formulation because of the following reasons:

The porcine pancreatic lipase (PPL) activity in duodenum following oral administration of the two formulations as determined in Study S245.2.003 was highly variable among individual patients (ranged from 0 to 201,895 U for the TBM formulation and 1,342 to 239,645 U for the clinically tested formulation). Out of a total of 18 PPL measurements (9 patients, each receiving 2 formulations), 10 were higher than the administered dose of 60,000 U with the highest activity being almost 4-fold of the administered dose. The sponsor indicated that their assay could result in higher values compared to the USP method but did not provide adequate quantitative data to relate values obtained from the two methods. On the other hand, two subjects had little or no PPL activity. These observations rendered the study unreliable for use as a tool to establish comparability between two formulations.

Note that an inspection of the study and analytical sites in France was conducted by the Division of Scientific Investigation (DSI) between 05/28/07 and 06/01/07. Their 06/08/07 inspection report listed the following deficiencies:

- 1). The inspection could not confirm the identity of the pancrelipase products dosed to subjects on each occasion.
- 2). The analytical method validations and quality control programs failed to demonstrate the performance on the analytical methods before and during the study. All the normalized study endpoints are compromised by the lack of raw data for the PEG 4000 method validation, calibration, and quality control.

After a careful evaluation of the audit report, no changes are made to the OCP conclusions, i.e., the intubation study is unreliable for use as a bridge to establish comparability between the two formulations.

C. Phase IV Commitments: None

04/10/07

07/03/07

Tien-Mien Chen, Ph.D.

Division of Clinical Pharmacology III

Team Leader

Sue-Chih Lee, Ph.D. 04/11/07, 07/15/07

II. Table of Contents

	Page
I. Executive Summary	1
II. Table of Contents	4
III. Summary of CPB Findings	4
IV. QBR	5
V. Detailed Labeling Recommendations.....	17
VI. Appendices	19

III. Summary of Clinical Pharmacology and Biopharmaceutics Findings

NDA 20-725 for Creon DR capsules was initially submitted in 1997. The NDA was reviewed by the Agency, but deemed not approvable in 2003 mainly due to CMC deficiencies. On 11/17/06, the sponsor submitted complete responses to address the deficiencies. In addition, the sponsor proposed a new formulation and included a clinical pharmacology intubation study to bridge the two formulations since the previous clinical trials had been completed using the original formulation. The formulation changes involved a new manufacturer of pancrelipase and changes in coating materials. This was a 2-way crossover intubation study (No. S245.2.003) comparing the duodenal lipase activity of the TBM and the clinically tested formulations from duodenal aspirates.

The intubation study (No. S245.2.003) was a double-blind, randomized, single-center, 2x2 crossover study conducted in France. Fifteen adult patients with chronic pancreatitis (CP) were recruited. In each study period, after an overnight fasting, each patient received with meal a dose of Creon containing 60,000 units of lipase. Aspirates were collected from duodenum continuously over a period of 3 hrs. Nine patients completed both phases (A ->B, n=4 and B ->A, n=5) of the study. The overall pancreatic lipase activity (Overall PL_{mg/mL}) and endogenous human lipase activity (HPL_{mg/mL}) were determined separately. The porcine lipase activity (PPL_{mg/mL}) was then computed as follows:

$$PPL_{mg/mL} = \text{Overall PL}_{mg/mL} - HPL_{mg/mL}$$

The results showed that the mean overall PEG-corrected PL activities for the TBM and clinically tested formulations were similar with a mean ratio of 1.06. However, the inter-subject variability for the overall PL activity (and for the HPL) was high. Apparently, some patients still had high endogenous human PL (HPL) levels.

The mean estimated PPL activity obtained from both the TBM and clinically tested formulations was similar (around 95,000 U). However, high inter-subject variability was observed. More than half of the individual PPL activity measurements were greater than the administered dose of 60,000 U while some showed little or no PPL activities detected. As such, the study is not reliable for establishing comparability of the two formulations.

IV. Question Based Review

A. General Attributes

Drug Substance:

Creon contains pancrelipase of porcine origin. The major enzymes of pancrelipase are pancreatic lipase, free proteases, and α -amylase.

Formulations:

CREON capsules contain enteric-coated pancrelipase pellets for oral administration. The enteric coating protects pancreatic enzymes against gastric acid and allows delivery of the enzymes in the duodenum, the main site of action for food digestion. The capsules are available in three strengths: CREON 6, CREON 12, and CREON 24, corresponding respectively to 6,000, 12,000, and 24,000 USP units of lipase.

Table 1. Component and Composition of Creon Formulations

Component	Theoretical quantity (mg) per capsule			Function	Reference
	6,000	12,000	24,000		
(b) (4)					
Pancrelipase	(b) (4)			Active ingredient	USP
Polyethylene glycol 4,000	(b) (4)			(b) (4)	NF
Coating					
Hypromellose phthalate	(b) (4)			(b) (4)	NF
Cetyl alcohol	(b) (4)			(b) (4)	NF
Triethyl citrate	(b) (4)			(b) (4)	NF
Dimethicone 1,000	(b) (4)			(b) (4)	NF
(b) (4)					

Activities of Three Creon Strengths

	CREON® 6 Contains	CREON® 12 Contains	CREON® 24 Contains
Lipase	6,000 USP Units	12,000 USP Units	24,000 USP Units
Free Proteases	19,000 USP Units	38,000 USP Units	76,000 USP Units
Amylase	30,000 USP Units	60,000 USP Units	120,000 USP Units

Mechanism of Action:

Chronic Pancreatitis (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 dextrans and short chain sugars.

B. General Clinical Pharmacology

Indication:

Creon (Pancrelipase DR Capsules) is indicated for adult and pediatric patients with maldigestion due to exocrine pancreatic insufficiency.

Dosing Regimen:

Doses should be taken during meals or snacks, or as prescribed by healthcare professional. Creon capsules should always be taken with food. The number of capsules and capsule strength given with meals or snacks should be estimated by assessing which dose minimizes steatorrhea and maintains good nutritional status;

1. CF patients: weight-based enzyme dosing should begin with 1,000 USP lipase units/kg/meal for patients < 4 years old, and 500 USP lipase units/kg/meal for patients ≥ 4 years old. Dosage should be adjusted according to severity of disease, control of steatorrhea and maintenance of good nutritional status. Doses in excess of 2,500 lipase 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 units/kg/meal have been associated with fibrosing colonopathy.

2.  (b) (4)

Comparative intubation (bridging) study (No. S245.2.003):

“Cross-over Pharmacology Study to Compare the Duodenal Lipase Activity of Two Creon Formulations in Duodenal Aspirates in Subjects with Pancreatic Exocrine Insufficiency Due to Chronic Pancreatitis”.

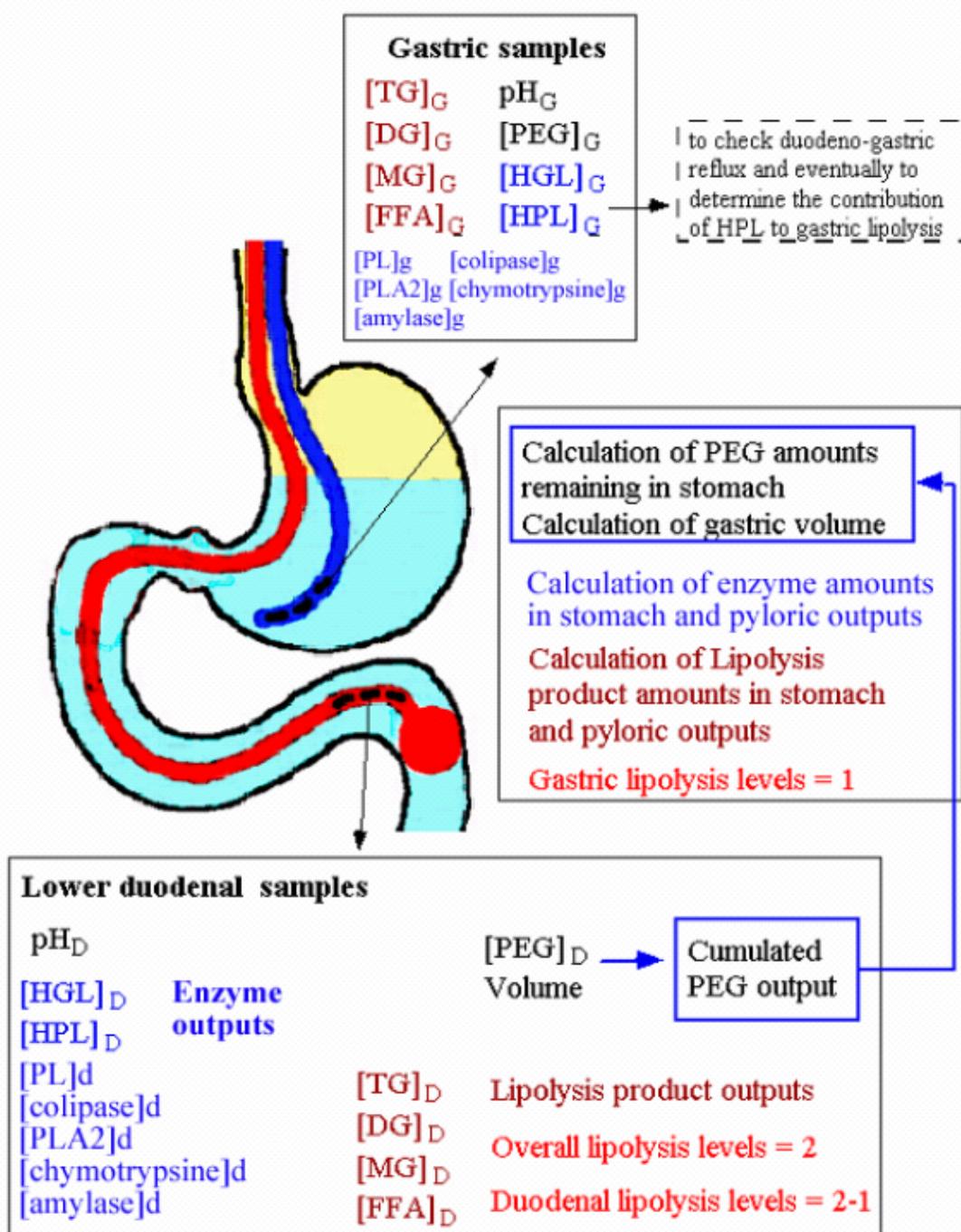
Q1. How was the study conducted?

A1. This was a double-blind, randomized, single-center, 2x2 crossover study. The study was conducted in France and 15 adult patients (14 males and one female) with CP were recruited.

After an overnight fasting, each patient was intubated with a single-lumen nasogastric tube in the stomach for giving meal and collecting gastric samples. A separate tube with the occluding balloon was placed in the duodenum. The distal end of the duodenal tube was located after the ligament of Treitz and the overall duodenal fluid was recovered due to the occluding balloon inflated after the Ligament of Treitz (see the figure below).

A non-absorbable marker was added to the meal (PEG 4000, 10 mg/mL) to monitor later the gastric emptying rate and measure the gastric volumes. The meal consisted of 80 g string beans, 90 g beef meat, 70 g pommes frites, 10 g butter, 15 mL olive oil and water to make 700 mL which contained 30 grams of fat (triglyceride; TG). A dose of Creon containing 60,000 units of lipase (the content of 5 capsules; 5 x 12,000 units) was mixed with a portion of meal and given in the first syringe via gastric tube. Nine patients completed both phases (Sequence 1: A ->B, n=4 and Sequence 2: B ->A, n=5) with a washout period of 2-10 days. Treatment A was the TBM and Treatment B was the clinically tested, i.e., currently marketed formulation. The duodenal aspirates were collected continuously over a period of 3 hrs. The lipase activities of two Creon formulations were determined. Please see individual study review in Appendix for additional details.

Figure 1 Schematic Diagram Showing the Gastric and Duodenal Tubes Used to Collect Samples During Digestion of Test Meal



Q2. How was the PPL activity in the duodenal aspirates determined?

A2. Two assay methods were used to determine separately the overall PL and HPL activities in the duodenal aspirates. One assay method determines the overall PL activity at pH 8.0, which includes only HPL and PPL activities. Another assay method determines the HPL activity. The PPL activity is thus calculated as shown below,

$$\text{PPL}_{\text{mg/mL}} = \text{Overall PL}_{\text{mg/mL}} - \text{HPL}_{\text{mg/mL}}$$

Q3. What were the overall PL and HPL activities in duodenum following oral administration of the TBM and the clinically tested formulations at the dose containing 60,000 units of lipase?

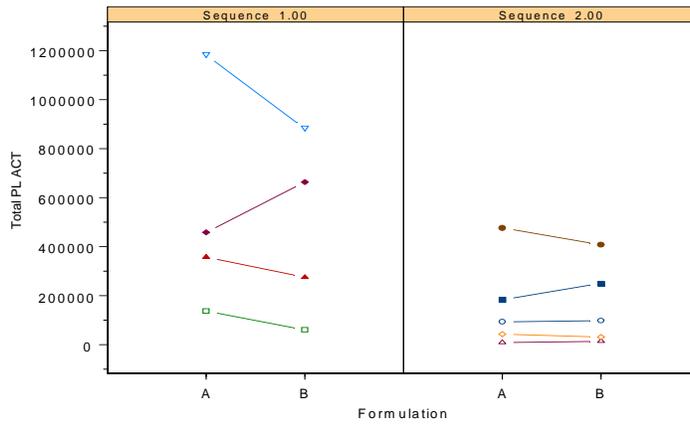
A3. The results showed that the mean overall PL activities in duodenum for the TBM and clinically tested formulations were 300,408 U and 291,259 U, respectively as shown in Table 2 and Figure 2. Mean HPL activities for the two formulations were 229,175 and 204,421 U respectively (Table 3 and Figure 3). High inter-subject variability was observed for both formulations. Although these were patients with CP, apparently some patients had high endogenous HPL levels (unlike patients with pancreatectomy).

Table 2. Overall PEG-corrected Pancreatic Lipase Activity (U) in the Duodenum

Statistic	TbMP (N = 9)	CMF (N = 9)	TbMP-CMF (N = 9)
Sample(s): Duodenal			
n	9	9	9
Mean (SD)	300408 (303597)	291259 (292227)	9149 (102588)
Median	184194	249546	4939
Min/Max	8809 / 961506	14179 / 827551	-211466 / 133955
Estimate *			1.06
95% CI *			[0.78 ; 1.44]

* Estimates and confidence intervals (CI) for the ratio TbMP/CMF based on the ANOVA model: log(value)=treatment+subject+period

Figure 2. Overall PL Activity in the Nine Patients

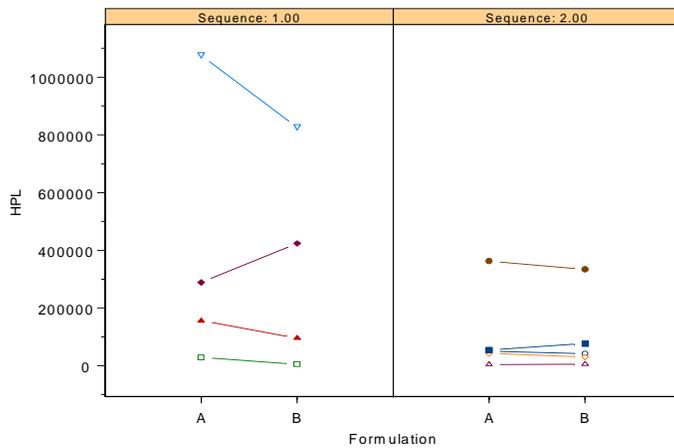


¹. Formulation A: TBM
². Formulation B: Clinically Tested

Table 3. PEG-corrected HPL Activity (U) in the Duodenum

Parameter (unit) Statistic	TBM	Clinically Tested (CT)	TBM – CT
HPL (U)			
n	9	9	9
Mean (SD)	229,175 (341,169)	204,421 (227,457)	24,754 (100,291)
Estimate	-----	-----	1.29
90% CI	-----	-----	(88.3 – 187.5)

Figure 3. HPL Activity in the Nine Patients



¹. Formulation A: TBM
². Formulation B: Clinically Tested

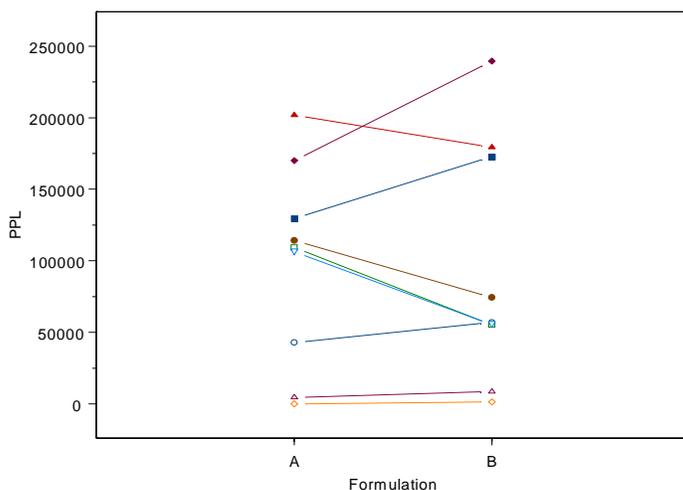
Q4. What were the PPL activities in duodenum following oral administration of the TBM and the clinically tested formulations containing 60,000 units of lipase?

A4. The results showed that the mean PPL activities in duodenum for the TBM and clinically tested formulations were 97,604 U and 93,780 U, respectively as shown in Table 4 and Figure 4. High inter-subject variability was observed for both formulations.

Table 4. PEG-corrected PPL Activity (U) in the Duodenum

Parameter (unit) Statistic	TBM	Clinically Tested (CT)	TBM – CT
PPL (U)			
n	9	9	9
Mean (SD)	97,604 (69,643)	93,780 (83,156)	3,824 (42,369)
Range	(0 to 201,895)	(1,342 to 239,645)	-----
Estimate	-----	-----	1.04
Ratio; 90% CI	-----	-----	1.06; (76.5 – 146.4)

Figure 4. PPL Activity in the Nine Patients



- ¹. Formulation A: TBM
- ². Formulation B: Clinically Tested

Note: Although the sponsor later indicated in the 05/14/07 amendment that errors were found in the calculation of Overall PEG-corrected PL values for one subject (No. 102) receiving the clinically tested formulation (second period of Sequence 1: A -> B). The previously reported mean value was 291,259 units (Table 2, p.9) and the recalculated mean value is 308,201 units (6% ↑). However, the difference is minor and thus it would not change previous OCP conclusions.

Q5. Is the TBM formulation comparable to the clinically tested formulation?

A5. No. Although the mean PPL activities in duodenum for the two formulations were similar with a geometric mean ratio of 1.06, high inter-subject variability was observed for both formulations as stated above. It is noted that out of a total of 18 PPL individual values (obtained from 9 patients, each receiving 2 formulations), 10 were higher than the administered dose of 60,000 U with the highest activity being almost 4-fold of the administered dose. The sponsor indicated that their assay could result in higher values compared to the USP method but did not provide any quantitative data to relate values obtained from the two methods. On the other hand, two subjects had no or little PPL activity as determined from their duodenum samples. These observations rendered the study unreliable for use as a tool to establish comparability between two formulations.

C. Intrinsic Factors: Data not available

D. Extrinsic Factors: Data not available

E. General Biopharmaceutics:

Q6. How does the TBM formulation differ from the clinically tested formulation?

A6. The pancrelipase of the current product in the US is produced by SPL Ltd and the pancrelipase of the new TBM product (and the marketed product in France) is produced by Solvay Pharmaceuticals GmbH.

In addition, the current Creon formulation in the US contains light mineral oil and dibutylphthalate as a (b) (4) in the delayed release coating. For the new TBM formulation those excipients have been replaced by using a (b) (4) of triethylcitrate (TEC) and cethyl alcohol (CA). Additionally, an increased amount of hydroxypropyl methylcellulose phthalate (HP 55) is used in order to achieve a comparable dissolution profile to the current formulation.

The formulations of both TBM and clinically tested are show below:

Table 5. Components and Composition of the TBM and Clinically Tested Formulations

Formulations	TBM	Clinically Tested
	mg/g of pellets	mg/g of pellets
Pancreatin/Pancrelipase (Ph. Eur./USP)	(b) (4) (Solvay Pancrelipase)	(b) (4) (SPL Pancrelipase)
Polyethylene Glycol 4,000 (Ph. Eur./USP)	(b) (4)	(b) (4)
Light Mineral Oil (USP/JP)	-----	(b) (4)
HP 55 (USP/JP)	(b) (4)	(b) (4)

Dimethicone 1,000 (USP/JPE)		(b) (4)		(b) (4)
Dibutyl Phthalate (USP/JPE)				
Triethylcitrate (Ph. Eur./USP)				-----
Cetylalcohol (Ph. Eur./USP)				-----

F. Analytical Section

Q7. Are the assay methods adequately validated?

A7. No. The sponsor has provided the assay validation data on measurements of overall PL activities and HPL activities. However, the validation data for PPL activities has not been provided. In addition, the sponsor indicated that their assay method could result in higher PPL measurement than that from the USP method, but they did not provide any quantitative data to relate values obtained from the two methods.

1. Measurement of Overall PL Activity:

The overall PL activity in duodenal aspirate included gastric PL (GPL), endogenous HPL, and PPL. The overall PL activity was determined by the absolute activity testing by determining the rate at which a suspension of pancrelipase in duodenal aspirate hydrolyzes a substrate of tributyrin emulsion at a constant temperature of 37.0°C (1 international unit = 1 µmole of butyric acid released per min). The released acid was then titrated with sodium hydroxide at pH 8.0. At pH 8.0, GPL is reported not active, therefore, under this assay condition at pH 8.0 only HPL and PPL were measured. Since these two enzymes have the same specific activity on tributyrin, name 8,000 U/mg of purified enzymes, the overall PL activity is as shown,

$$\text{Overall lipase activity } U/mL / 8000_{U/mg} = \text{Overall PL}_{mg/mL} = \text{HPL}_{mg/mL} + \text{PPL}_{mg/mL}$$

For the assay validation for overall PL activity, please see individual assay validation report in Appendix 2 for details.

The sponsor reported that the determination of lipase activity in duodenal aspirates followed ICH “Validation of Analytical Procedures”, Q2A (March, 95) and Q2B (March, 97). For validation of linearity, recombinant HPL (rHPL) which can not be differentiated from endogenous HPL, is added to a matrix as shown below.

Ingredient	Amount
Pooled Duodenal juice	1 [mL]
Verum mixture	3.5 [mg] ^a
Glycerol SigmaUltra (approx. 99% GC)	1 [mL]
Protease Inhibitor solution*	40 [μL]

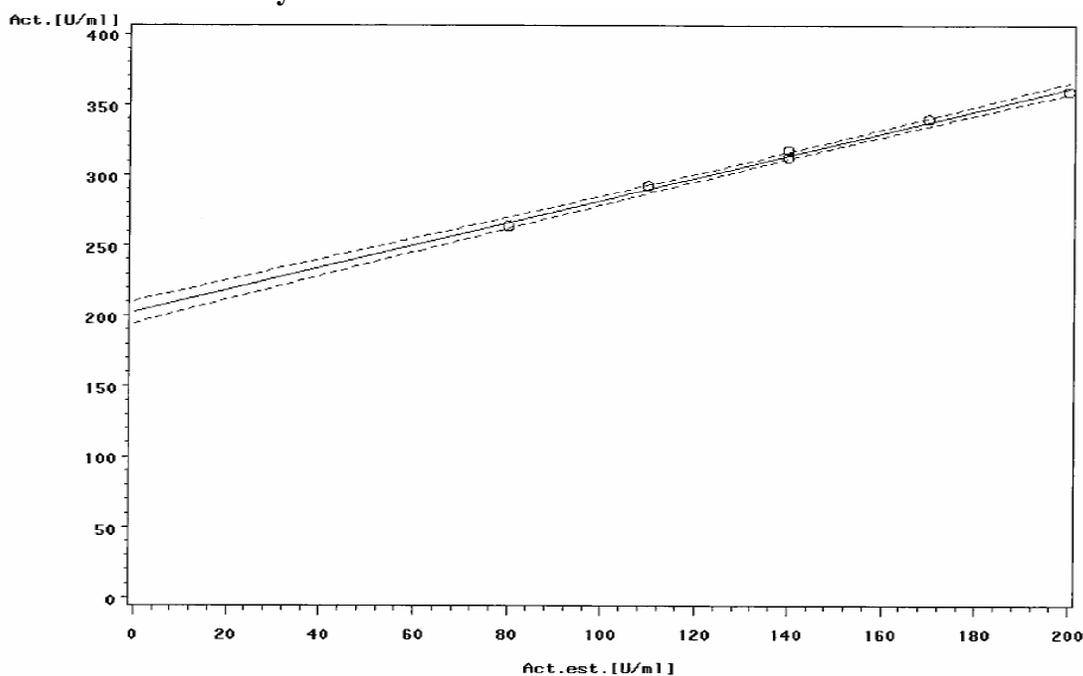
* The solution of protease inhibitors was prepared by dissolving a pellet of inhibitors (Complete™ protease inhibitor mix from Roche) into 2 mL purified water

^a added as an aliquot of a stock solution of verum mixture resulting in a final amount of 3.5 mg of verum mixture

Ten to 25 μg rHPL was added to the above matrix (with a mean PL activity of 224.5 U/mL measured). The results of rHPL activities of both the estimated and the measured (U/mL) and the regression line obtained are shown below:

level	Weight of rec. human lipase [μg]	Estimated activity [U/ml]	Measured activity [U/ml]	
LL	10	80	264	264
LL + ½(100%-LL)		110		292.55
100%	17.5	140	317.7	312.5
100%+1/2(UL-100%)		170		339.9
UL	25	200	359.37	359.37

Regression Line Calculated for Activity Recovered in U/ml vs. Activity Estimated in U/mL



The intercept obtained from the regression line was around 202.5 U/mL which was slightly smaller (10% lower) than that was measured in the matrix, 224.5 U/mL. The estimated activity for testing accuracy is the basic activity present in the matrix and the activity added by the spiked rHPL as shown below:

The Results of Accuracy Testing

level	Weight of rec. human lipase [µg]	Estimated activity [U/ml]	Measured activity [U/ml]	Recovery rate [%]
LL	10	304.5	264	86.70
		304.5	264	86.70
LI + ½(100%-LL)		334.5	292.55	87.46
100%	17.5	364.5	317.7	87.16
		364.5	312.5	85.73
100%+1/2(UL-100%)		394.5	339.9	86.16
UL	25	424.5	359.37	84.66
		424.5	359.37	84.66

Label	N	Mean	Std Dev	CV	Lower C.L. of Mean	Upper C.L. of Mean
Recovery rate [%]	8	86.153	1.067	1.2	85.261	87.045

A mean recovery of 86.15 % (with a CV of 1.2%) for the activity range of 305 to 425 U/mL was determined for the lipase activity (100% x activity found/activity estimated). Results for lipase activity obtained for precision testing are shown below:

Results for Lipase Activity for Precision Testing

Activity Level	LL	100%	UL
	Activity [U/ml]		
1	278.90	298.61	346.38
2	266.22	305.55	361.44
3	259.89	291.66	323.80
4	259.89	284.72	316.26
5	264.00	317.70	359.37
6	264.00	312.50	359.37
7	259.88	284.72	316.26
8	291.58	284.72	308.73
Mean	268.05	297.52	336.45
Variance s ²	129.64	174.74	502.49
StdDev	11.39	13.22	22.42
CV [%]	4.25	4.44	6.66

*. UL and LL designate the upper and lower limits respectively of the working range as given by the analytical procedure.

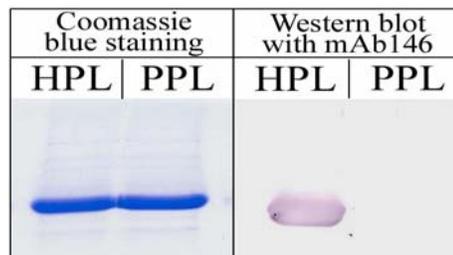
For precision testing, the estimated activity was calculated from the amount of rHPL added to the matrix with CVs being <10%.

The range as derived from the results obtained for precision, linearity and accuracy was 305 - 425 U/mL. The overall results indicate that 1) the linearity was obtained with the

range studied, 2) the above assay for accuracy leads to an underestimation of the lipolytic activity of about 14 % (recovery being 86%), and 3) the precision testing was acceptable with CVs being < 10%.

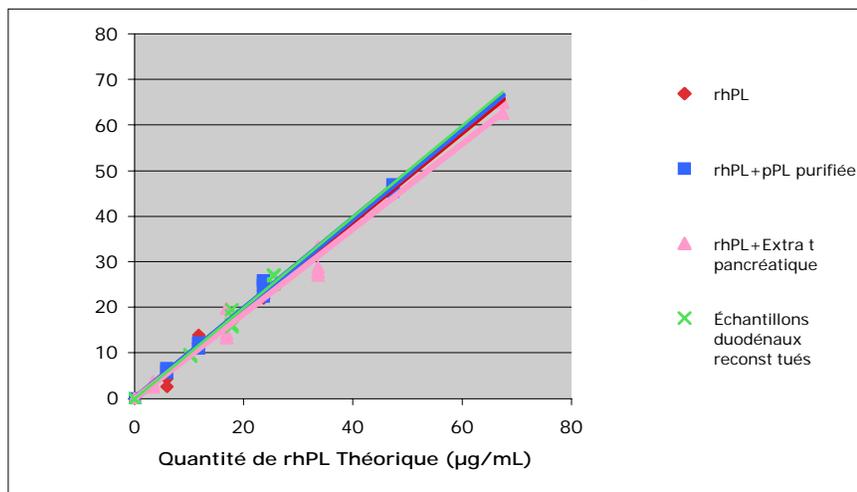
2. Measurement of HPL by Enzyme-linked Immunosorbent Assay (Double Sandwich ELISA):

By using an anti-HPL polyclonal antibody and then an anti-HPL monoclonal antibody (mAbs 146-40), the HPL and PPL, which share 86% amino acid identities, were separated by denaturing polyacrylamide gel electrophoresis. The sponsor indicated that results of immunoblotting testing showed the ELISA method being specific for rHPL not PPL.



The validation testing for the ELISA method also showed that rHPL (red diamond) when added with purified PPL (blue square), pancreatic extract (pink triangle), or reconstituted duodenal (green X) samples, they did not affect the linearity of the results.

Mass Concentration Determination of rHPL ($\mu\text{g/mL}$) by ELISA



However, in reality, the lipase activity obtained using tributyrin as the substrate, the sponsor observed a lower correlation with the results obtained for the duodenal samples. The activity in samples containing rHPL in solution with pancreatic extracts without a protease inhibitor had decreased, as expected. They observed a 50% decline in activity compared to the anticipated activity and up to a 20% decline in inter-sample activity in 90min, despite keeping the samples on ice. The sponsor explained that this difference/variation is probably due to 1) incorrect evaluation of the quantity of

endogenous HPL contained in the duodenal fluid used to produce the samples and 2) a possible decline in activity due to the proteases despite using inhibitors.

3. Measurement of PPL:

The quantity of PPL contained in each sample group has been calculated from the results of the two measurements above:

$$\text{PPL}_{\text{mg/mL}} = \text{Overall PL activity}_{\text{mg/mL}} - \text{HPL}_{\text{mg/mL}}$$

Reviewer's Comments:

Calculation of PPL in the duodenal aspirates and then comparison with Creon dose administered, however, are complicated due to different assay methods employed, i.e., 1) the labeled dose of PPL in the capsule before administration was determined using olive oil as the substrate according to the USP method, 2) determination of overall PL in the duodenal aspirates after Creon administration was based on a different method using tributyrin as the substrate (referred as tributyrin method), and 3) quantitation of HPL using ELISA method.

In order to estimate the total units of PPL appeared in the duodenal aspirates (based on the above equation) and compare it with the labeled amount (60,000 units) of PPL administered, the converting factors among each method needed to be assessed, however, they were not provided in the initial submission. The units of PPL, HPL, and overall PL reported in this NDA resubmission are in fact under the assumption that the converting factor between each assay method is identical as 1.

Upon request, the sponsor on 04/20/06 provided the mean converting factor (1.74) of the USP method (using olive oil) to the tributyrin method. However, no converting factor between tributyrin method and ELISA method was provided.

V. Detailed Labeling Recommendations

No review of sponsor's proposed labeling would be done at this review cycle.

VI. Appendices

1. Proposed Package Insert (Original and Annotated)
2. Individual Study Review
3. Cover Sheet and OCPB Filing/Review Form

**NDA 20-725 for Creon-6, -12, and -24
DR Capsules**

Appendix 1

**Sponsor's Proposed Labeling
(March, 2007 Revised Version)**

**NDA 20-725 for Creon-6, -12, and -24
DR Capsules**

Appendix 2

***In Vivo* Pharmacology Intubation (Bridging)
Study (No. S245.2.003)**

SYNOPSIS

Name of Sponsor/Company: Solvay Pharmaceuticals	Individual Study Table	(For National Authority Use only)
Name of Finished Product: To-be-marketed Creon® 12000 MMS		
Name of Active Ingredient: Pancreatin		
Title of Study: Cross-over pharmacology study to compare the duodenal lipase activity of two Creon® formulations in duodenal aspirates in subjects with pancreatic exocrine insufficiency due to chronic pancreatitis		
Investigator(s): Prof. Dr. René Laugier, Hôpital d'Adultes de la Timone, Marseille, France		
Study Center(s): The study was performed at one study center in France		
Publication (Reference): Not applicable.		
Study Period: 10 OCT 2005 (First Subject First Visit) – 19 MAY 2006 (Last Subject Last Visit)	Phase of Development: Phase II	
Objectives: Primary objective was to assess the pancreatic lipase activity of the current product (CMP) versus the to-be-marketed product (TbMP) at the site of action (in duodenal aspirate from the Ligament of Treitz). Further objectives were to assess the following parameters over time for CMP and TbMP: <ul style="list-style-type: none"> - activity of lipase (gastric and pancreatic), colipase, phospholipase A2, chymotrypsin, and amylase in the duodenal and gastric aspirates and the outputs of active enzymes at the Ligament of Treitz. - Triglycerides (TG), Diglycerides (DG), Monoglycerides (MG) and Free Fatty Acids (FFA) in gastric and duodenal outputs - gastric and duodenal pH - intragastric, duodenal and overall lipolysis levels - stability of lipase (gastric and pancreatic), colipase, phospholipase A2, chymotrypsin, and amylase activities and the evaluation of the lipolysis level in duodenal contents - endogenous (human) pancreatic lipase (HPL) and porcine pancreatic lipase (PPL) Safety and tolerability objective was to assess the safety and tolerance of the two Creon® formulations by checking the vital signs, and the occurrence of adverse events (AEs).		
Methodology: Two duodenal intubations, in a two-way cross-over design, were performed after an overnight fast (12 hours) using a double-lumen duodenal tube and a separated single-lumen naso-gastric tube. The placement of the tube was done under fluoroscopic control. The distal end with the occluding balloon was located after the ligament of Treitz. Continuous duodenal aspiration was performed over 3 hours, before and after test meal administration (single-administrations of Creon® were given with the meal in the 1st syringe into the stomach); every 15 minutes a sample was taken. Gastric samples were aspirated every 15 min via the naso-gastric tube. The		

Name of Sponsor/Company: Solvay Pharmaceuticals	Individual Study Table	(For National Authority Use only)
Name of Finished Product: To-be-marketed Creon® 12000 MMS		
Name of Active Ingredient: Pancreatin		
analytics were done in the aspirated samples and the ex-vivo duodenal pool. A specific anti-HPL ELISA was used to measure HPL concentrations and outputs independently.		
Number of Subjects (Planned, Consented, Randomized and Analyzed): The planned number of subjects was 10. Fifteen subjects consented to participate in the study, two subjects of whom consented to participate in the study for a second time. Fourteen subjects were randomized, one of them was randomized for a second time after the subject had completed the study, but pharmacological data could not be obtained. All randomized subjects were treated with study medication. For subjects who participated in the study for a second time, only the second participation was analyzed, the first participation was only listed. Fourteen subjects were analyzed in the safety population and nine subjects in the intent-to-treat population. Thirteen subjects were treated with TbMP, and 12 subjects with CMP (not counting the first study entry for subjects who entered twice).		
Diagnosis and Main Criteria for Inclusion: Male or female subjects, 18 years or older, with proven chronic pancreatitis, proven pancreatic exocrine insufficiency with steatorrhea $\geq 4\text{g/day}$ were eligible to enter the study		
Test Product, Dose and Mode of Administration, Batch Number: Name: To-be-marketed Creon® 12000 MMS in the US Dose: 5 capsules per test meal, total 60000 lipase units per test meal, corresponding to 2000 lipase per g fat intake Route: Oral (mixed in test meal) Batch: 69028		
Duration of Treatment: One single dose		
Reference Therapy, Dose and Mode of Administration, Batch Number: Name: Currently marketed Creon® 10000 MMS in the US (in France declaration of 12000 lipase units: Creon® 12000 MMS) Dose: 5 capsules per test meal, total 60000 lipase units per test meal, corresponding to 2000 lipase per g fat intake Route: Oral (mixed in test meal) Batch: 69027		
Criteria for Evaluation: <u>Pharmacology:</u> The following parameters were measured in each gastric, duodenal and ex-vivo duodenal sample: <ul style="list-style-type: none"> - volume and pH - PEG 4000 concentration - Gastric lipase, pancreatic lipase, chymotrypsin, amylase, phospholipase A2, colipase - Lipolysis product concentrations (TGs, DGs, MGs and FFAs) - HPL and PPL 		

Name of Sponsor/Company: Solvay Pharmaceuticals	Individual Study Table	(For National Authority Use only)
Name of Finished Product: To-be-marketed Creon® 12000 MMS		
Name of Active Ingredient: Pancreatin		
<u>Safety:</u> Vital signs, adverse events		
Statistical Methods: Data were analyzed descriptively. An analysis of variance (ANOVA) with factors for treatment, period and subject was performed for the pharmacological parameters. Prior to the ANOVA, the measurements were log-transformed. The estimated contrast TbMP-CMP on the logarithmic scale was back-transformed to the original scale to give a point estimate of the ratio TbMP/CMP. 95% confidence intervals for the ratio of means TbMP/CMP were calculated from the ANOVA.		
Summary – Conclusions <u>Pharmacology Results:</u> In the mean, overall pancreatic lipase activity in the duodenum was 300408 U for TbMP and 291259 U for CMP. The point estimate 1.06 for the relative lipase activity (TbMP/CMP) clearly fell into the equivalence range specified in the study protocol (0.70 - 1.43), so that equivalence of the two Creon® formulations was proven according to criteria stated in the protocol. The 95% confidence interval [0.78;1.44] for the relative lipase activity lay almost entirely within the equivalence range. In the mean, overall PPL activity at the duodenum was 97604 U for TbMP and 93780 U for CMP. The point estimate for the relative lipase activity was 1.04 with a 95% confidence interval of [0.69;1.56] <u>Safety Results:</u> No subject died during the study and no subject reported an SAE. One subject was withdrawn due to AEs after the first intubation and treatment with TbMP. Three subjects (23.1%) experienced a TEAE during treatment with TbMP. The TEAEs were vomiting (three subjects), cough, and increased bronchial secretion (one subject, each). Four subjects (33.3%) had a TEAE during CMP treatment. The TEAEs were flatulence, tracheitis, hypoglycemia, and hypertension (one subject, each). All TEAEs were unrelated to study medication in the opinion of the Investigator. No TEAE was severe, two TEAEs were mild, and all other TEAEs were moderate. <u>Conclusion:</u> The to-be-marketed Creon® formulation is equivalent to the currently marketed Creon® formulation with regard to duodenal lipase delivery. The results on the porcine pancreatic lipase at the duodenum also support the equivalence of the two formulations.		

Reviewer's Comment:

The TBM formulation has not been shown to be comparable to the clinical formulation and it rendered the study unreliable for use as a tool to establish comparability between two formulations. Please see the review in this context for details.

Analytical Methodology and Its Validation Report

I. Overall Pancreatic Lipase Activities

The matrix used for validation consisted of pooled duodenal juice mixed with glycerol and protease inhibitor. The pH of the matrix was adjusted to pH 5.0. The composition of the matrix is shown below:

Ingredient	Amount
Pooled Duodenal juice	1 [mL]
Verum mixture	3.5 [mg] ^a
Glycerol SigmaUltra (approx. 99% GC)	1 [mL]
Protease Inhibitor solution*	40 [μL]

* The solution of protease inhibitors was prepared by dissolving a pellet of inhibitors (Complete™ protease inhibitor mix from Roche) into 2 mL purified water

^a added as an aliquot of a stock solution of verum mixture resulting in a final amount of 3.5 mg of verum mixture

Aliquots of 1 mL of the duodenal juice (at pH 5.0) were mixed with the verum mixture (grinded pellets) and diluted with 1 mL glycerol. Immediately, the protease inhibitor solution was added to the matrix and the mixture was mixed thoroughly. Recombinant human pancreatic lipase with a standard activity of 8,000 U/mg using tributyrin as substrate was used for system suitability testing. The measured activity of the lipase standard has to be within the range of $\pm 10\%$ of the labeled activity.

The lipase activity was determined by the absolute activity testing by determining the rate at which a suspension of pancrelipase in duodenal aspirate hydrolyzes a substrate of tributyrin emulsion. The released carboxylic acids are titrated with sodium hydroxide at pH 8.0 when tributyrin (tributyrolyglycerol) is hydrolyzed by lipase at a constant temperature (37.0°C).

For validation of linearity, recombinant human pancreatic lipase is added to the matrix according to the scheme of trials as shown below:

Scheme for Validation of Linearity

	Number of Determinations to be performed
LL	2
LL+1/2* (100%-LL)	1
100 %	2
100% +1/2* (UL-100%)	1
UL	2

UL and LL designate the upper and lower limits respectively of the working range as given by the analytical procedure. The enzymatic activities were adjusted to obtain the responses required:

Target Responses for Evaluations of Precision and Linearity

Assay	Responses required		
	LL	100 %	UL
Lipase [μg]	10	17.5	25

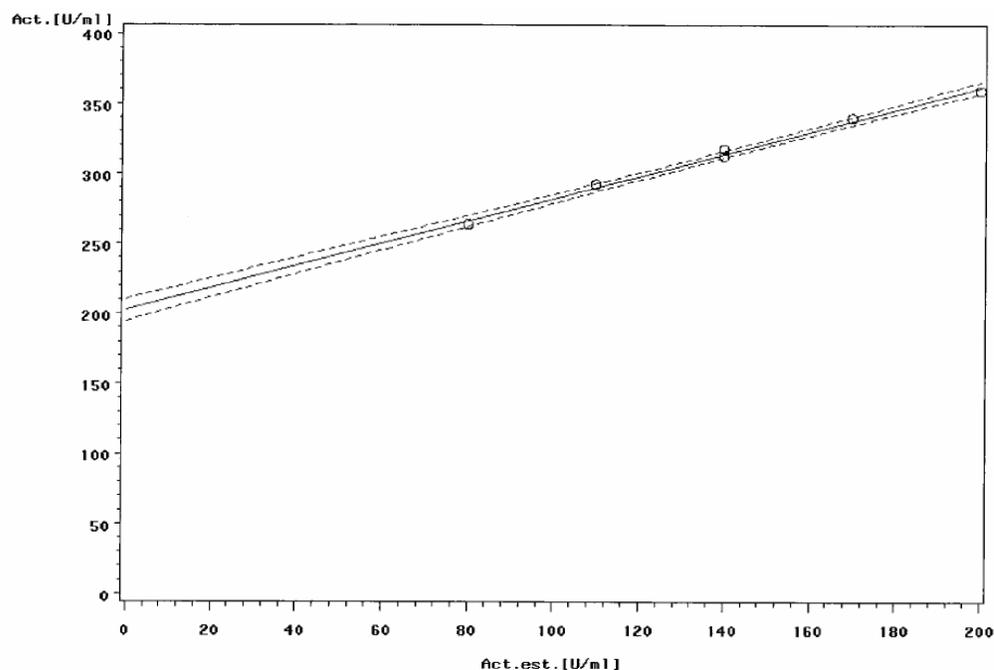
Results for lipase activity of recombinant lipase added to verum mixture with estimated activity and measured activity (U/mL) are shown below:

Table 5. Lipase activity of recombinant lipase added to verum mixture with estimated activity and measured activity (U/ml)

level	Weight of rec. human lipase [μg]	Estimated activity [U/ml]	Measured activity [U/ml]	
LL	10	80	264	264
LL + $\frac{1}{2}(100\%-\text{LL})$		110		292.55
100%	17.5	140	317.7	312.5
100% + $\frac{1}{2}(\text{UL}-100\%)$		170		339.9
UL	25	200	359.37	359.37

Regression line calculated for activity recovered in U/mL as dependent variable vs. activity estimated in U/mL as regressor variable as shown below:

Figure: Regression line calculated for Activity Recovered in U/ml vs. Activity Estimated in U/mL



The plot of residuals obtained demonstrates, that linearity is fulfilled over the whole range investigated, i.e. 80 - 200 units/mL of estimated activity of recombinant lipase added, as was demonstrated graphically and by calculating the coefficient of correlation r (0.998). This range corresponds to 305 - 425 U/mL as the matrix contains a basic lipase activity of 224.5 U/mL due to the verum mixture added.

Scheme for Validation for Precision (and Linearity)

Day	1	2	3	4
Operator	1			
	Number of Determinations performed			
LL	2	2	2	2
LL+1/2x (100%-LL)			1	
100 %	2	2	2	2
100% +1/2x (UL-100%)			1	
UL	2	2	2	2

*. UL and LL designate the upper and lower limits respectively of the working range as given by the analytical procedure.

Results for lipase activity obtained by one operator with mean, variance, SD and CV are shown below:

Table 6. Results for Lipase Activity for Precision Testing

Activity Level	LL	100%	UL
	Activity [U/ml]		
1	278.90	298.61	346.38
2	266.22	305.55	361.44
3	259.89	291.66	323.80
4	259.89	284.72	316.26
5	264.00	317.70	359.37
6	264.00	312.50	359.37
7	259.88	284.72	316.26
8	291.58	284.72	308.73
Mean	268.05	297.52	336.45
Variance s^2	129.64	174.74	502.49
StdDev	11.39	13.22	22.42
CV [%]	4.25	4.44	6.66

The estimated activity was calculated from the amount of recombinant human lipase added and the activity of lipase determined with the recovery rates calculated (100% x activity found/activity estimated). The CVs were all <10%. The estimated activity is calculated as the basic activity present in the verum matrix (p. 10) and the activity added by the spiked recombinant lipase as shown below:

Table 7. The Results of Accuracy Testing

level	Weight of rec. human lipase [µg]	Estimated activity [U/ml]	Measured activity [U/ml]	Recovery rate [%]
LL	10	304.5	264	86.70
		304.5	264	86.70
LI + ½(100%-LL)		334.5	292.55	87.46
100%	17.5	364.5	317.7	87.16
		364.5	312.5	85.73
100%+1/2(UL-100%)		394.5	339.9	86.16
UL	25	424.5	359.37	84.66
		424.5	359.37	84.66

Label	N	Mean	Std Dev	CV	Lower C.L. of Mean	Upper C.L. of Mean
Recovery rate [%]	8	86.153	1.067	1.2	85.261	87.045

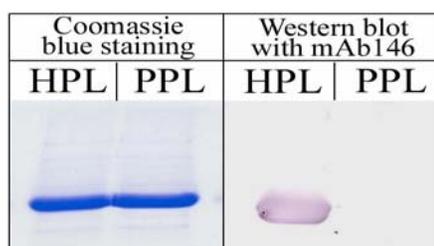
The range as derived from the results obtained for precision, linearity and accuracy is from 305 - 425 U/mL. A mean recovery of 86.15 % (with a CV of 1.2%) for the activity range of 305 to 425 U/mL was determined for the lipase activity with a confidence interval of 85.26% - 87.05% based on calculation of the individual recovery rates. This result indicates that the assay leads to an underestimation of the lipolytic activity of about 14 %.

II. Measurement of HPL Activity by Enzyme-linked Immunosorbent Assay (Double Sandwich ELISA):

The HPL and PPL share 86% amino acid identities. By using specific anti-HPL polyclonal and monoclonal (mAbs 146-40) antibodies, a specific immunological (double sandwich ELISA) test enables HPL to be measured as an indirect method of quantifying the active PPL in the digestive tract. PPL activity is equal to the difference between overall activity and PPL activity, HPL activity being deduced from ELISA.

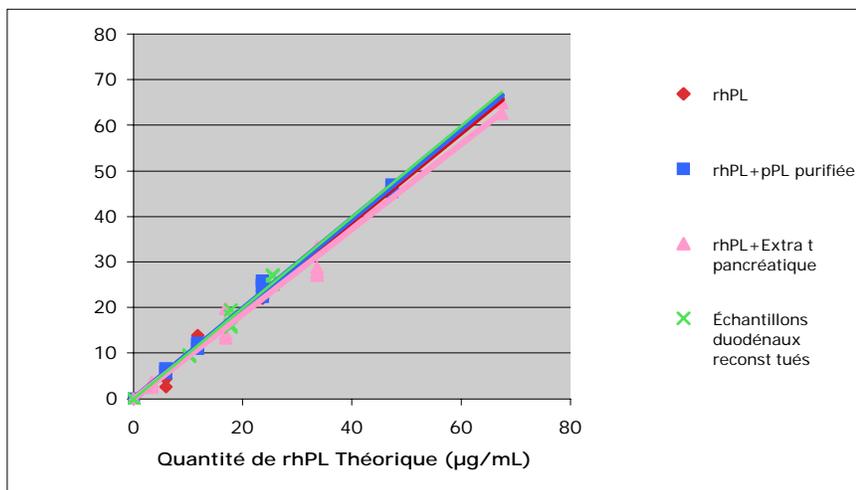
$$\text{PPL}_{\text{mg/mL}} = \text{Overall PL activity}_{\text{mg/mL}} - \text{HPL}_{\text{mg/mL}}$$

The HPL and PPL were separated by denaturing polyacrylamide gel electrophoresis. The sponsor indicated that results of immunoblotting testing showed the ELISA method being specific for rHPL not PPL.



The validation testing for the ELISA method also showed that rHPL (red diamond) when added with purified PPL (blue square), pancreatic extract (pink triangle), or reconstituted duodenal (green X) samples, they did not affect the linearity of the results.

Table 5. Mass Concentration Determination of rHPL ($\mu\text{g/mL}$) by ELISA



However, in reality, the lipase activity obtained using tributyrin as the substrate, the sponsor observed a lower correlation with the results obtained for the duodenal samples. The activity in samples containing rHPL in solution with pancreatic extracts without a protease inhibitor had decreased, as expected. They observed a 50% decline in activity compared to the anticipated activity and up to a 20% decline in inter-sample activity in 90min, despite keeping the samples on ice. The sponsor explained that this difference/variation is probably due to 1) incorrect evaluation of the quantity of endogenous HPL contained in the duodenal fluid used to produce the samples and 2) a possible decline in activity due to the proteases despite using inhibitors.

Reviewer's Comments:

Calculation of PPL in the duodenal aspirates and then comparison with Creon dose administered, however, are complicated due to different assay methods employed, i.e., 1) the labeled dose of PPL in the capsule before administration was determined using olive oil as the substrate according to the USP method, 2) determination of overall PL in the duodenal aspirates after Creon administration was based on a different method using tributyrin as the substrate (referred as tributyrin method), and 3) quantitation of HPL using ELISA method.

In order to estimate the total units of PPL appeared in the duodenal aspirates (based on the above equation) and compare it with the labeled amount (60,000 units) of PPL administered, the converting factors among each method needed to be assessed, however, they were not provided in the initial submission. The units of PPL, HPL, and overall PL reported in this NDA resubmission are in fact under the assumption that the converting factor between each assay method is identical as 1.

Upon request, the sponsor on 04/20/06 provided the mean converting factor (1.74) of the USP method (using olive oil) to the tributyrin method. However, no converting factor between tributyrin method and ELISA method was provided. The analytical method validation reports are incomplete.

**NDA 20-725 for Creon-6, -12, and -24
DR Capsules**

Appendix 3

Cover Sheet and OCPB Filing/Review Form

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number		Brand Name	Creon
OCPB Division (I, II, III)	DCP III	Generic Name	Pancrelipase
Medical Division	GI	Drug Class	Digestion Aid
OCPB Reviewer	Tien-Mien Chen, Ph.D.	Indication(s)	
OCPB Team Leader	Sue-Chih Lee, Ph.D.	Dosage Form	Delay-release capsules
		Dosing Regimen	Taken with meal or snacks
Date of Submission	11/17/06	Route of Administration	Oral
Estimated Due Date of OCPB Review	04/10/07	Sponsor	Solvay Pharmaceuticals
Medical Division Due Date	04/18/07	Priority Classification	Resubmission (6 months)
PDUFA Due Date	05/18/07		

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	X			
Reference Bioanalytical and Analytical Methods	X			Two analytical methods were provided for assay of total lipase and human lipase activities, respectively.
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-		X		
single dose:		1	1	
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 -		X		
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
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 <u>is not</u> filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?		
Comments sent to firm ?		Comments have been sent to firm (or attachment included). FDA letter date if applicable.		
QBR questions (key issues to be considered)	Did lipase bioactivities obtained from duodenal aspirates support bridging between the TBM and the clinically tested formulations?			
Other comments or information not included above				
Primary reviewer Signature and Date	Tien-Mien Chen, Ph.D. 04/10/07			
Secondary reviewer Signature and Date	Sue-Chih Lee, Ph.D. 04/10/07			

**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
7/16/2007 04:05:18 PM
BIOPHARMACEUTICS

Sue Chih Lee
7/16/2007 04:13:26 PM
BIOPHARMACEUTICS

Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	20-725	Proposed Brand Name	Creon
OCPB Division (I, II, III)	II	Generic Name	Pancrelipase
Medical Division	GI & Coagulation	Drug Class	Pancreatic Enzymes
OCPB Reviewer	Suliman Al-Fayoumi	Indication(s)	Pancreatic Insufficiency
OCPB Team Leader	Suresh Doddapaneni	Dosage Form	Delayed Release capsules
		Dosing Regimen	Individualized dosing with meals
Date of Submission	8/1/97	Route of Administration	Oral
Estimated Due Date of OCPB Review	9/18/03	Sponsor	Solvay Pharmaceuticals, Inc.
PDUFA Due Date	10/9/03	Priority Classification	Priority
Estimated Division Due Date	9/23/03		

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	X			
Reference Bioanalytical and Analytical Methods				
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:				
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:	1	1	1	
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:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:	1	1	1	
(IVVC):				
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	2	2	2	
Filability and QBR comments				
	"X" if yes	Comments		
<u>Application filable ?</u>	X			
<u>Comments sent to firm ?</u>	Not needed at this time			
QBR questions (key issues to be considered)	1. Do the results of the ¹³ CO ₂ breath test support the activity of Creon Delayed-Release Capsules in patients with exocrine pancreatic insufficiency? 2. Is the proposed dissolution test method and specifications for Creon Delayed Release Capsules acceptable?			
Other comments or information not included above	NDA 20-725 was put on AIP on 2/9/98 then was reactivated on 4/9/03			
Primary reviewer Signature and Date				
Secondary reviewer Signature and Date				

Clinical Pharmacology and Biopharmaceutics Review

NDA: 20-725

Submission Date: 8/1/97

Proposed Trade Name: Creon[®] Delayed-Release
Capsules 5, 10 & 20

ORM Division: GI & Coagulation
Drug Products

Generic Name: Pancrelipase

OCPB Division: DPE II

Sponsor: Solvay Pharmaceuticals, Inc.

Team Leader: Suresh Doddapaneni, Ph.D.

Reviewer: Suliman I. Al-Fayoumi, Ph.D.

Type of Submission: Original NDA (7 P)

Proposed Indication: Treatment of Exocrine
Pancreatic Deficiency

I. **Executive Summary**

Currently there are no delayed release pancreatic enzyme products that are approved and marketed in the US. Creon (Pancrelipase) Delayed-Release Capsule is a digestive enzyme product (containing lipase, protease & amylase) of porcine pancreatic origin. The proposed indication for Creon is the treatment of exocrine pancreatic insufficiency, which is often associated with conditions such as cystic fibrosis (CF), chronic pancreatitis, postpancreatectomy, post-GI bypass surgery and ductal obstruction of the pancreas or common bile duct. Pancreatic enzymes act by catalyzing the hydrolysis of fats to glycerol and fatty acids, protein to proteoses and derived substances and starch into dextrans and short chain sugars.

The proposed recommended starting oral dosage in CF patients is 1,000 USP lipase U/kg/meal for children < 4 yrs of age and 500 U/kg/meal for those > 4 yrs of age. There are no specific proposed dosage recommendations for other exocrine pancreatic insufficiency disorders.

Three compositionally proportional dose strengths of Creon are proposed; 5, 10 & 20, which in turn correspond to dose strengths of 5000, 10000 & 20000 USP lipase U, respectively.

The submission consists of 25 clinical studies, of which three are randomized and well-controlled pivotal trials, and one clinical pharmacology study evaluating the utility of Creon in children with cystic fibrosis using the ¹³CO₂-hiolein breath test as a biomarker for the quantitative assessment of lipase enzyme activity. In addition, dissolution test method is proposed.

In the ¹³CO₂ breath test study, a statistically significant difference on ¹³CO₂ excretion was demonstrated between Creon and placebo treatments. However, several deficiencies exist which preclude definitive conclusions including high variability, lack of assay validation, small sample size (n=11) and the absence of any documentation of the dose actually taken by patients.

The proposed dissolution test method is acceptable provided the acid stage is modified to last for 2 hrs instead of (b) (4) and an appropriate acceptance limit is set for the acid stage (e.g., Q = NLT (b) (4) after 2 hrs).

Recommendations

NDA 20-725 has been reviewed by the Office of Clinical Pharmacology and Biopharmaceutics (OCPB/DPE II), and from the view point of OCPB, the submission is acceptable provided that a satisfactory agreement is reached between the Agency and the sponsor with respect to the dissolution specifications and language in the package insert. See Appendix 1 for the Agency's proposed revisions to the Clinical Pharmacology-related sections of the package insert.

The following comments should be forwarded to the sponsor:

1. An alternate mode of administration of Creon Delayed Release Capsules such as sprinkling the pellets on soft foods should be supported by appropriate *in vitro/in vivo* data.
2. The proposed dissolution test method is acceptable provided; 1) the acid stage is modified to last for 2 hrs instead of (b) (4) and 2) an appropriate acceptance limit is set for the acid stage (e.g., Q = NLT (b) (4) after 2 hrs).
3. Study Kreo-629 has significant deficiencies and does not support the proposed language in the label. Those deficiencies have to be adequately addressed before results from the study are stated in the label. The deficiencies include,
 - High variability in the ¹³CO₂ excretion data,
 - No documentation of the dose actually taken by subjects,
 - The small number of subjects (11 CF patients and 12 healthy subjects) with stool collection done in only 7 of 11 CF patients,
 - Lack of adequate validation of the ¹³CO₂ breath test,
 - A wide range of doses were administered in pediatric subjects and CF patients only, which may have contributed to the high variability observed in the study results,
 - Discrepancy between findings of the stool fat analysis in the study and the ¹³CO₂ breath test findings.

II. Summary of CPB Findings

NDA 20-725 has been submitted under a 505(b)(1) application seeking approval for use in the treatment of adult and pediatric patients with exocrine insufficiency. In this application, the sponsor submitted data from a $^{13}\text{CO}_2$ breath study and 3 adequate and well-controlled pivotal clinical trials as well as a proposed dissolution test method.

In the $^{13}\text{CO}_2$ breath study, data on differences between Creon and placebo treatment on AUC of delta values (baseline-corrected $^{13}\text{CO}_2$ excretion) and H_2 (indicator of chymotrypsin activity) in pediatric CF patients suggest that administration of Creon in CF patients results in a statistically significant increase in $^{13}\text{CO}_2$ breath excretion relative to placebo treatment between hrs 3 & 24 post-dose. No statistically significant difference was demonstrated on H_2 test at any given time point. However, the study has the following deficiencies: high variability in the $^{13}\text{CO}_2$ excretion data, no documentation of the dose actually taken by subjects, small number of subjects (11 CF patients and 12 healthy subjects) with stool collection done in only 7 of 11 CF patients, lack of adequate validation of the $^{13}\text{CO}_2$ breath test, wide range of doses administered, and discrepancy between findings of the stool fat analysis and $^{13}\text{CO}_2$ breath test findings.

The sponsor's proposed dissolution test method is similar to the USP dissolution method for pancrelipase Delayed Release Capsules. Overall, the proposed dissolution test method is acceptable provided the acid stage is modified to last for 2 hrs instead of (b) (4) and an appropriate acceptance limit is set for the acid stage (e.g., $Q = \text{NLT } (b) (4)$ after 2 hrs).

II. Table of Contents

EXECUTIVE SUMMARY 3
SUMMARY OF CPB FINDINGS..... 5
QUESTION-BASED REVIEW..... 7
APPENDIX 1: PROPOSED PACKAGE INSERT 12
APPENDIX 2: INDIVIDUAL STUDY REVIEWS 20

III. Question-Based Review

A. Historical Overview

- **1987:** Solvay Pharmaceuticals, Inc. introduces Creon microsphere drug product (8,000 USP lipase U, 30,000 USP amylase U & 13,000 USP protease U) to the US market.
- **1991:** FDA issues Notice of Proposed Rulemaking, withdrawing the proposal for establishment of an OTC monograph for exocrine pancreatic insufficiency drug products and establishing that all exocrine pancreatic insufficiency drug products require an approved NDA for continued marketing.
- **1993:** Marketing of Creon microspheres drug product is discontinued and replaced with Creon 10 minimicrospheres capsules (10,000 USP lipase U, 33,200 USP amylase U & 37,500 USP protease U).
- **1994:** Creon 25 microspheres capsules voluntarily withdrawn from the US market in response to Agency request that all high lipase preparations (containing > 20,000 USP lipase U) be withdrawn from the market. Sponsor introduces two new dosage strengths; Creon 5 (5,000 USP lipase U, 16,600 USP amylase U & 18,75000 USP protease U) & Creon 20 (20,000 USP lipase U, 66,400 USP amylase U & 75,000 USP protease U) minimicrospheres capsules.
- **1994:** During a 6/14/94 pre-NDA meeting, the Agency requests the sponsor determine the bioavailability of the enzymes at the site of action.
- **1996:** The Agency states that the $^{13}\text{CO}_2$ breath test bioavailability study may be acceptable for submission in support of in vivo bioavailability of the Creon Minimicrospheres product (letter dated 2/27/96). The Agency recommended that the sponsor establish their own correlation between lipase output in the duodenum and post-prandial the $^{13}\text{CO}_2$ breath test.

B. General Attributes

Creon[®] (Pancrelipase) Delayed Release Capsule is a digestive enzyme product (containing lipase, protease & amylase) of porcine pancreatic origin. Pancreatic enzymes act by catalyzing the hydrolysis of fats to glycerol and fatty acids, protein to proteoses and derived substances and starch into dextrans and short chain sugars.

Pancreatic enzymes are intended for action in the GI tract, therefore formal bioavailability/bioequivalence studies are not useful. Alternative means of evaluating drug availability at the site of action have been utilized including assessing the ex vivo activity of pancreatic enzymes in gastric and duodenal aspirates as well as assessing $^{13}\text{CO}_2$ and H_2 excretion using the breath test as markers of pancreatic enzyme activity.

C. General Biopharmaceutics

1. What is the nature of the formulation?

The pancreatic enzymes in Creon are enteric-coated to resist gastric inactivation. There are three strengths of the Creon drug product currently proposed in this submission, Creon 5, 10 & 20, representing 5000, 10000 & 20000 units of labeled lipase activity, respectively. The coated minimicrospheres (pellets) used in the manufacture of these strengths of Creon are identical. The individual strengths are formulated by varying the quantity of enteric-coated pellets encapsulated in different sizes of hard gelatin capsules.

Table 1. Qualitative composition of the Creon 10 Capsule*

Ingredient	Amount (mg/capsule)
Pancreatin	(b) (4)
PEG 4,000	
LMO	
HPMCP 55	
Dibutylphthalate	
Dimethicone 1,000	
Fill weight	

* Composition of the formulation used in study Kreo-629 (¹³CO₂ breath test), which is compositionally identical to those used in the clinical trials and the proposed to-be-marketed formulation.

2. Do the results of the ¹³CO₂ breath test support the activity of Creon Delayed-Release Capsules?

Eleven male and female children with documented cystic fibrosis (4 male & 7 female, Age 10.2 ± 3.0 yrs) received single daily doses of 1,500 lipase units/kg of Creon Minimicrospheres (batch no. 042M) for 6 days followed by placebo for 6 days. The study was conducted in a double-blind, non-randomized, single center, two-period, two-period fashion. In each treatment period, the ¹³CO₂ breath test was performed following administration of a standard test meal of 1.5 g/kg rice cookies (given with 1 mg/kg ¹³C-labelled hiolin) on day 5. In addition, stool was collected on days 4, 5 and 6 and analyzed for fecal weight and fat and chymotrypsin content.

Overall, as Table 2 shows, administration of Creon in CF patients results in a statistically significant increase in ¹³CO₂ breath excretion relative to placebo treatment between hrs 3 & 24 post-dose. No statistically significant difference was demonstrated on H₂ test (indicator of chymotrypsin activity) at any time point. However, several deficiencies in

the study preclude any definitive as to the activity of Creon in exocrine pancreatic insufficiency (for a complete list of the deficiencies, see the individual study report in Appendix 2).

Given the numerous shortcomings of the study, the proposed statement in the package insert implying that Creon results (b) (4) is not substantiated by the results of this study.

Table 2. Summary of differences between Creon and placebo treatment on AUC of delta and H₂ values in CF patients

Time-interval	Difference Kreon® - placebo						p-value*
	N	Min	Max	Median	Mean	Std	
H₂-value [ppm]							
Basal - 1 hour	11	- 2280	3143	- 228	- 123	1641	0.432
Basal - 2 hours	11	- 5310	5423	- 338	- 407	3146	0.375
Basal - 3 hours	11	- 7333	6983	- 593	- 554	4060	0.322
Basal - 4 hours	11	-10063	8528	- 758	- 711	4981	0.322
Basal - 5 hours	11	-12223	10253	- 878	- 726	5844	0.322
Basal - 6 hours	11	-15328	11603	- 983	- 807	6732	0.322
Basal - 7 hours	11	-16813	13118	-1088	- 733	7329	0.322
Basal - 7.5 hours	11	-17593	13913	-1193	- 714	7678	0.322
Basal - 8 hours	8	-18463	14663	-1289	-1554	8944	0.219
Delta-value [%]							
Basal - 1 hour	11	- 111	186	- 46	8	100	0.831
Basal - 2 hours	11	- 309	465	6	70	258	0.577
Basal - 3 hours	11	- 237	1299	387	429	500	0.019
Basal - 4 hours	11	- 419	2987	1084	1130	998	0.005
Basal - 5 hours	11	- 561	6119	1952	2068	1782	0.003
Basal - 6 hours	11	- 681	10095	2568	3248	3003	0.002
Basal - 7 hours	11	- 774	13772	3772	4467	4575	0.003
Basal - 7.5 hours	11	- 777	15378	3948	5036	5446	0.003
Basal - 8 hours	11	- 736	17978	3852	5585	6282	0.005
Basal - 10 hours	11	- 826	26952	4998	7249	8919	0.010
Basal - 12 hours	11	-1197	32137	5694	8135	10401	0.007
Basal - 24 hours	10	-1938	45662	4979	10654	15135	0.010

3. Is the sprinkle mode of administration as proposed in the package insert supported by *in vivo/in vitro* data?

No data has been provided in support of administration of the enteric-coated pellets as sprinkles on soft foods. As such, administration of the enteric-coated pellets as sprinkles on soft foods is not an acceptable alternative mode of administration and should not be included in the package insert for Creon Delayed Release Capsules.

4. Is sponsor's proposed *in vitro* dissolution test method acceptable as a surrogate of *in vivo* drug release for QA/QC purposes?

The sponsor's proposed dissolution test method (See details below) is similar to the USP dissolution method.

- I. Acid Stage:** The contents of 20 capsules are placed into Apparatus I (basket) and shaken at 100 rpm in 800 ml of simulated gastric fluid without enzyme (0.1 M HCl, 0.2% NaCl, temperature not specified). After 60 minutes, the baskets are removed and the excess dissolution medium allowed to drain.
- II. Buffer Stage:** The contents of each basket are transferred to the dissolution vessels with Apparatus II (paddles) at 100 rpm in 800 ml of potassium phosphate buffer, pH 6.0 containing 1% NaCl. After 30 minutes, a 10 mL aliquot of the medium is tested for lipase activity according to the FIP/Ph.Eur. method. The acceptance limit is set at $Q = \text{[redacted]}^{(b)(4)}$ within 30 min.

The proposed dissolution test method is acceptable provided the acid stage is modified to last for 2 hrs instead of $\text{[redacted]}^{(b)(4)}$ and an appropriate acceptance limit is set for the acid stage (e.g., $Q = \text{NLT } \text{[redacted]}^{(b)(4)}$ after 2 hrs).

Appendix 1

Proposed Package Insert

7 pp withheld in full immed. after this page as (b)(4) draft labeling.

Appendix 2

Individual Study Reviews

NDA: 20-725/ Study Kreo-629**Type of Study: Lipase Activity Study**

Study Kreo-629 is entitled,

“¹³CO₂ BREATH TEST WITH ¹³C-LABELLED HIOLEIN FOR THE NON-INVASIVE DETERMINATION OF EXOCRINE PANCREATIC FUNCTION IN HEALTHY SUBJECTS AND IN PATIENTS WITH CYSTIC FIBROSIS: EFFICACY ASSESSMENT OF PANCREATIC ENZYME REPLACEMENT IN CHILDREN WITH CYSTIC FIBROSIS”.

Objectives

- To evaluate the efficacy of pancreatic enzyme replacement therapy in children with cystic fibrosis.
- To validate the ¹³CO₂-hiolein¹ breath test as a diagnostic technique for the quantitative assessment of exocrine pancreatic insufficiency.

Study Design

Eleven male and female children with documented cystic fibrosis (4 male & 7 female, Age 10.2 ± 3.0 yrs) received single daily doses of 1,500 lipase units/kg of Kreon² Minimicrospheres (batch no. 042M) for 6 days followed by placebo for 6 days. The study was conducted in a double-blind, non-randomized, single center, two-period, two-period fashion. Twelve healthy children (6 male & 6 female, Age 11.5 ± 2.4 yrs) were enrolled into the study to serve as control. Healthy children received no pancreatic enzyme treatment and only participated in the first treatment period. In each treatment period, following administration of a standard test meal of 1.5 g/kg rice cookies (given with 1 mg/kg ¹³C-labelled hiolein) on day 5, the ¹³CO₂ breath test was performed every 30 min for 8 hrs, then every hr for the next 4 hrs (up to hr 12) and finally at 24 hrs post-meal. In addition, stool was collected on days 4, 5 and 6 and analyzed for fecal weight and fat and chymotrypsin content. The Kreon capsule formulation used in this study is identical to that used in the clinical trials submitted under NDA 20-725.

Analytical Assay

All collected breath samples were assayed using the ¹³CO₂-hiolein breath test and the rice breath hydrogen (H₂) test. The ¹³CO₂-hiolein breath test allows estimation of luminal lipase activity in the form of ¹³CO₂ concentration in expired air following oral administration of the ¹³C-labelled substrate hiolein. The rice breath hydrogen (H₂) test is a useful measure of amylase activity since rice flour is believed to be completely

¹ Hiolein is a mixed triglyceride that is a specific substrate for the lipase enzyme.

² Kreon Minimicrospheres is the drug product currently approved in Germany and is identical in composition to the proposed Creon formulation.

degraded in the intestine of healthy subjects to end products including H₂ gas, which is subsequently excreted via the lungs.

Pharmacokinetics

H₂ values and the intra-individual differences between Kreon- and placebo- treated CF children (delta) were determined per time point and AUC was subsequently calculated up to each time point. Additionally, correlation between results of the ¹³CO₂-hiolein breath test and stool fat data were investigated as well as between results of the rice breath hydrogen (H₂) test and stool chymotrypsin data.

Results

Table 3. Summary of AUC data of H₂ and delta values obtained from the breath test

Time interval	Volunteers (N = 12)		Patients (N = 11)			
	Median	First-third quartile	Placebo period		Treatment period	
			Median	First-third quartile	Median	First-third quartile
H₂-value (ppm)						
Basal ^a - 1 hour	314	180-808	753	248-1828	325	145-2538
Basal - 2 hour	486	285-1299	1278	420-3538	565	273-4533
Basal - 3 hour	576	398-1678	1590	675-5113	670	393-5748
Basal - 4 hour	715	478-2015	1740	788-6568	835	528-6573
Basal - 5 hour	828	568-2230	2010	905-7513	1225	693-7683
Basal - 6 hour	888	635-2358	2523	1095-8203	1810	800-8568
Basal - 7 hour	963	725-2470	2688	1230-8638	2000	920-9363
Basal - 7.5 hour ^b	993	728-2380	2763	1335-8833	2045	980-9888
Basal - 8 hour ^c	880	640-1988	3195	1894-14683	1815	1040-9028
Delta-value (%)						
Basal ^a - 1 hour	198	122-252	94	70-190	103	48-195
Basal - 2 hour	596	459-1163	216	156-594	295	197-878
Basal - 3 hour	1498	909-2684	380	277-1339	892	316-2420
Basal - 4 hour	2966	1464-3983	588	385-2341	1932	843-4290
Basal - 5 hour	4735	2494-5597	798	434-3763	3856	1725-6082
Basal - 6 hour	6533	4117-7411	1011	492-5580	6442	3060-7773
Basal - 7 hour	7973	5902-9296	1240	532-7580	8834	3979-12194
Basal - 7.5 hour	8825	6414-10171	1362	539-8597	9537	4383-14055
Basal - 8 hour	9692	6855-11127	1482	560-9533	10081	4787-14099
Basal - 10 hour	11960	9211-14203	2149	711-10389	11287	6338-14406
Basal - 12 hour	13133	10968-15927	2893	861-10596	11862	7313-14884
Basal - 24 hour ^d	18151	14911-22004	5369	2167-11795	12868	10748-18052

^a 5 minutes before tracer application

^b N = 11 for volunteers

^c N = 7 for volunteers, N = 8 for patients during placebo period, N = 10 for patients during treatment period

^d N = 10 for patients during treatment

H₂- and delta- values were shown not to be significantly different between Kreon- and placebo- treated CF children.

Table 4. Summary of stool analysis data in patients vs. healthy subjects

	Volunteers (N = 12)	Patients	
		Placebo (N = 7)	Kreon® (N = 11)
Stool fat (g/24h)			
Geometric mean	1.8	10.9	5.6
Median	2.8	10.9	6.6
Range	0.4 - 3.5	2.1 - 33.5	1.6 - 15.8
p-value ^o	-	0.004	0.011
Stool weight (g/24h)			
Geometric mean	44.2	140.3	67.7
Median	66.2	137.7	65.7
Range	8.3 - 116.7	70.0 - 353.7	24.7 - 188.3
p-value ^o	-	0.002	0.325
Chymotrypsin^a			
Geometric mean	10.8	1.0	3.7
Median	11.9	0.6	5.1
Range	1.9 - 23.9	0.1 - 6.0	0.6 - 8.3
p-value ^o	-	0.002	0.002

^a N = 11 for volunteers

^o the p-values give the results of the two-sample Wilcoxon test comparing patients vs. volunteers

Table 5. Summary of stool analysis data for Kreon vs. placebo treatment in patients

	Geometric mean	Median	Range	p-value [*]
Stool fat (g/24h)				
Treatment period	7.8	9.3	3.1 - 15.8	0.078
Placebo period	10.9	10.9	2.1 - 33.5	
Stool weight (g/24h)				
Treatment period	86.3	98.0	42.7 - 188.3	0.031
Placebo period	140.3	137.7	70.0 - 353.7	
Chymotrypsin				
Treatment period	4.1	6.4	1.1 - 8.3	0.078
Placebo period	1.0	0.6	0.1 - 6.0	

^{*} the p-value gives the results of the one-sample Wilcoxon test for treatment differences

Table 6. Summary of differences between Creon and placebo treatment on AUC of delta and H₂ values in CF patients

Time-interval	Difference Creon® - placebo						p-value*
	N	Min	Max	Median	Mean	Std	
H₂-value [ppm]							
Basal - 1 hour	11	- 2280	3143	- 228	- 123	1641	0.432
Basal - 2 hours	11	- 5310	5423	- 338	- 407	3146	0.375
Basal - 3 hours	11	- 7333	6983	- 593	- 554	4060	0.322
Basal - 4 hours	11	-10063	8528	- 758	- 711	4981	0.322
Basal - 5 hours	11	-12223	10253	- 878	- 726	5844	0.322
Basal - 6 hours	11	-15328	11603	- 983	- 807	6732	0.322
Basal - 7 hours	11	-16813	13118	-1088	- 733	7329	0.322
Basal - 7.5 hours	11	-17593	13913	-1193	- 714	7678	0.322
Basal - 8 hours	8	-18463	14663	-1289	-1554	8944	0.219
Delta-value [%]							
Basal - 1 hour	11	- 111	186	- 46	8	100	0.831
Basal - 2 hours	11	- 309	465	6	70	258	0.577
Basal - 3 hours	11	- 237	1299	387	429	500	0.019
Basal - 4 hours	11	- 419	2987	1084	1130	998	0.005
Basal - 5 hours	11	- 561	6119	1952	2068	1782	0.003
Basal - 6 hours	11	- 681	10095	2568	3248	3003	0.002
Basal - 7 hours	11	- 774	13772	3772	4467	4575	0.003
Basal - 7.5 hours	11	- 777	15378	3948	5036	5446	0.003
Basal - 8 hours	11	- 736	17978	3852	5585	6282	0.005
Basal - 10 hours	11	- 826	26952	4998	7249	8919	0.010
Basal - 12 hours	11	-1197	32137	5694	8135	10401	0.007
Basal - 24 hours	10	-1938	45662	4979	10654	15135	0.010

Reviewer's Comments

- In the current submission, the sponsor cites two main references in support of the utility of the breath test methodology as an accurate indicator of duodenal lipase activity. The first publication (Vantrappen et al., 1989) reported an excellent correlation (r=0.89) between post-prandial ¹³CO₂ breath excretion and duodenal lipase output in both normal subjects (n=25) and patients with pancreatic disease (n=29) after oral administration of a ¹³C-labeled mixed triglyceride. The second publication (Kato et al., 1992) reported a significant correlation (p < 0.01) between measurement of ¹³CO₂ in breath and duodenal output of lipase, as determined via a traditional intubation method.

In response to an Agency request for documentation in support of assay validation of the ¹³CO₂ breath test (letter dated 10/15/97), the sponsor referenced a recent publication (Caspary et al., 1996) where a hyperbolic relationship was demonstrated between duodenal lipase activity and peak delta over baseline, which was similar to that reported by Vantrappen et al. The sponsor contended that ample evidence existed in support of the utility and value of the ¹³CO₂-hiolin breath test as an indicator of duodenal lipase activity.

- Given the high variability and scatter observed in the breath test data, a more relevant comparison appears to be the one between Creon vs. placebo treatment as opposed to treated CF patients vs. healthy subjects.

Data on differences between Kreon and placebo treatments on AUC of delta and H₂ values in CF patients (Table 3) suggest that administration of Kreon in CF patients resulted in statistically significant increase in ¹³CO₂ breath excretion relative to placebo treatment between hrs 3 & 24 post-dose. No statistically significant difference was demonstrated on H₂ test (indicator of chymotrypsin activity) at any time point.

Overall, the study has the following shortcomings:

1. High variability in data
2. No documentation of the dose actually taken by subjects.
3. Small number of subjects (11 CF patients and 12 healthy subjects) with stool collection done in only 7 of 11 CF patients.
4. Publications suggest that ¹³CO₂ breath test may be a useful measure of duodenal lipase activity. However, assay validation is still needed to insure adequate controls to allow for valid conclusions.
5. Administered dose was 1,500 lipase U/kg with patients ranging in weight from 20 to 50 kg, which may have contributed to the high variability observed in the study results.
6. Study conducted in pediatric subjects and CF patients only, which may have contributed to the high variability observed in the data.
7. Findings of the stool fat analysis in the study, considered to be a clinically relevant marker of the activity of Pancrelipase preparations in treating exocrine pancreatic insufficiency, do not appear to corroborate the mean ¹³CO₂ breath test findings as no significant differences were observed between Creon and placebo treatments. In fact, if Creon and placebo treatments were compared on medians, which might be more appropriate given the considerable variability, there are hardly any differences between the two treatments.

NDA: 20-725

Type of Study: Dissolution Test Methodology

The sponsor's proposed dissolution test method is similar to that cited in the USP monograph for Pancrelipase Delayed-Release Capsules in May 1995.

Sponsor's proposed dissolution test method

- I. **Acid Stage:** The contents of 20 capsules are placed into Apparatus I (basket) and shaken at 100 rpm in 800 ml of simulated gastric fluid without enzyme (0.1 M HCl, 0.2% NaCl, temperature not specified). After 60 minutes, the baskets are removed and the excess dissolution medium allowed to drain.
- II. **Buffer Stage:** The contents of each basket are transferred to the dissolution vessels with Apparatus II (paddles) at 100 rpm in 800 ml of potassium phosphate buffer, pH 6.0 containing 1% NaCl. After 30 minutes, a 10 mL aliquot of the medium is tested for lipase activity according to the FIP/Ph.Eur. method. The acceptance limit is set at $Q = \frac{(b)}{(A)}$ within 30 min.

Reviewer's Comments

The sponsor's proposed dissolution test method is acceptable provided the sponsor adequately addresses the following issues:

- The acid stage should be modified to last for 2 hrs instead of (b) (4)
- An acceptance limit should be set for the acid stage (e.g., $Q = \text{NLT } \frac{(b)}{(A)}$ after 2 hrs).

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

/s/

Suliman Alfayoumi
9/24/03 03:30:02 PM
BIOPHARMACEUTICS

Suresh Doddapaneni
9/24/03 03:34:24 PM
BIOPHARMACEUTICS