

**SOLVAY PHARMACEUTICALS**

**CREON<sup>®</sup> (Pancrelipase Delayed-Release Capsules)**

**Antiviral Drugs Advisory Committee  
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Open Session**

**(Appendices 1 and 2 for Closed Session under separate cover)**

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Without Redaction**

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## LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ADR	Adverse drug reaction
AE	Adverse event
AKD	Aujeszky's disease
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
AP	Acute pancreatitis
API	Active pharmaceutical ingredient
ASF	African swine fever
ASFV	African swine fever virus
BLAST	Basic local alignment search tool
BLAST	Basic local alignment search tool
BMI	Body Mass Index
BSE	Bovine spongiform encephalopathy
BVDV	Bovine viral diarrhea virus
BWP	Biotechnology Working Party
CCSI	Company core safety information
CA	Cetyl alcohol
CF	Cystic fibrosis
CFA	Coefficient of fat absorption
CFR	Code of Federal Regulations
CGI	Clinical global impression of disease
CI	Confidence interval
CMP	Currently marketed product
CNA	Coefficient of nitrogen absorption
CP	Chronic pancreatitis
DB	Double blind
DBP	Dibutyl phthalate
DM	Diabetes mellitus
EC	European community
EEC	European economic community
EEEV	Eastern equine encephalitis virus
ELISA	Enzyme-linked immunosorbent assay
EMEA	European Medicines Evaluation Agency
EMCV	Encephalomyocarditis virus
EPI	Exocrine pancreatic insufficiency
EU	European Union
FAS	Full analysis set
FC	Fibrosing colonopathy
FCV	Feline calicivirus
FDA	United States Food and Drug Administration
FFDCA	Federal Food, Drug, Cosmetic Act
FIP	Fédération International Pharmaceutique
FMD	Foot and mouth disease

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FMDV	Foot and mouth disease virus
FPV	Feline panleukopenia virus
g	Gram
GI	Gastrointestinal
GY	Gastrectomy
HEV	Hepatitis E virus
HIV	Human-Immunodeficiency-Virus
HuCV	Human caliciviruses
IBRV	Infectious bovine rhinotracheitis virus
ICH	The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IPA	Isopropyl alcohol
IU	International units
kg	Kilogram
L	Liter
LFT	Liver function test
LOD	Limit of detection
LRF	Logarithmic reduction factor
MDCK	Madin-Darby canine kidney cells
MedDRA	Medical Dictionary for Regulatory Activities
MMS	MINIMICROSPHERES®
MS	MICROSPHERES®
MTG	Mixed triglyceride
NDA	New Drug Application
NF	National Formulary
NLV	Norwalk-like viruses
NMT	No more than
NOS	Not otherwise specified
N	Number of patients
OIE	Office International des Epizooties
PARV4	Parvovirus 4
PAV	Porcine adenovirus
pCMV	Porcine cytomegalovirus
PCR	Polymerase chain reaction
PCV	Porcine circovirus
PCVAD	Porcine-Circovirus-Associated Diseases
PCV	Porcine circovirus
PDNS	Porcine dermatitis and nephropathy syndrome
PERV	Porcine endogenous retrovirus
PEV	Porcine enterovirus
PHCoV	Porcine hemagglutinating encephalomyelitis virus
PHoV	Porcine hokovirus
PLHV	Porcine lymphotropic herpesvirus
PMWS	Post-weaning multi-systemic wasting syndrome
PPV	Porcine parvovirus
PRCV	Porcine respiratory coronavirus

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PRRSV	Porcine respiratory and reproductive syndrome virus
PsRV	Pseudorabies virus
PTV	Porcine teschovirus
PY	Pancreatic surgery
Q-PCR	Quantitative polymerase chain reaction
REO III	Reovirus type III
Rota V	Porcine rotavirus
RT-PCR	Reverse transcription polymerase chain reaction
SB	Single blind
SD	Standard deviation
SE	Standard error
SHV	Suid herpesvirus
SLV	Sapporo-like virus
SMPC	Summary of product characteristic
SMQ	Standard MedDRA Query
SOC	System organ class
SVD	Swine vesicular disease
SVDV	Swine vesicular disease virus
TbMP	To-be-marketed product
TE	Treatment emergent
TEAE	Treatment-emergent adverse event
TEC	Triethyl citrate
TESAE	Treatment-emergent serious adverse event
TfR	Transferrin receptor
TGEV	Transmissible gastroenteritis virus
TSE	Transmissible spongiform encephalopathy
TTV	Torque teno virus
u/U	Units
USDA	United States Department of Agriculture
USP	United States Pharmacopeia
VES	Vesicular exanthema of swine
VESV	Vesicular exanthema of swine virus
VEV	Vesicular exanthema virus
VP2	Viral protein 2
VS	Vesicular stomatitis
VSV	Vesicular stomatitis virus
WHO	World Health Organization
WNV	West Nile virus
XMuLV	Xenotropic murine leukemia virus

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## **1.0 SUMMARY OF NDA 20-725 FOR CREON<sup>®</sup> (PANCRELIPASE DELAYED-RELEASE CAPSULES)**

### **1.1 Introduction**

This briefing document presents the efficacy and safety of NDA 20-725 for CREON<sup>®</sup> (Pancrelipase Delayed-Release Capsules) for the treatment of exocrine pancreatic insufficiency (EPI). The benefits of CREON have been demonstrated in clinical trials and over 20 years of marketing experience. EPI occurs in a number of diseases including cystic fibrosis (CF), chronic pancreatitis (CP) and pancreatic surgery (PY). Since the mid 1980's, children with CF have derived particular benefit from the treatment of their malnutrition by enzyme replacement therapy.

This document provides an overview of the regulatory history, medical need, efficacy and safety data, viral risk assessment, and mitigation strategies, as well as Solvay Pharmaceuticals' conclusions with respect to the overall benefit/risk evaluation associated with the product. The efficacy and safety data will be presented to support the use of CREON in patients with EPI stemming from underlying conditions such as cystic fibrosis (CF) and chronic pancreatitis (CP) including patients who had undergone pancreatic surgery (PY). Solvay Pharmaceuticals is seeking approval of CREON for the indication of the treatment of maldigestion due to EPI. This is applicable to the aforementioned patient populations with special attention given to data supporting the use of CREON in pediatric patients.

As will be discussed further, the efficacy of CREON was demonstrated in a number of clinical studies in which the treatment effect was measured by coefficient of fat absorption (CFA), a medically and the US Food and Drug Administration (FDA) accepted direct pharmacodynamic measure of fat malabsorption. Prior to product and process improvements made to comply with new FDA requirements for a New Drug Application (NDA), Solvay Pharmaceuticals conducted several studies with the currently marketed product (CMP). After minor changes to the product as requested by the FDA, an additional study using the to-be-marketed product (TbMP) was also requested from the FDA to support approval of this NDA. The overall clinical efficacy and safety experience with these products is presented to support the approval and labeling.

As pancreatic enzymes are porcine derived, Solvay Pharmaceuticals will discuss the steps in place to control for potential viral contaminants. Solvay Pharmaceuticals will also discuss how emerging viruses and potential mutations are monitored to ensure the continued safe use of CREON. The risk of viral contaminants will be balanced against the medical need for enzyme replacement therapy, the benefits of CREON and risk mitigation strategies for the product.

### **1.2 Regulatory History**

The availability of pancreatic enzyme supplements preceded enactment of the US Federal Food, Drug, and Cosmetic Act (FFDCA) of 1938, and thus these products had not been subject to the Act. Solvay Pharmaceuticals has over 100 years of experience producing pancreatic enzymes and more than 20 years of marketing experience with CREON in the US, in all European countries and 45 other countries around the world (in total 75 countries). CREON has been developed as an enteric-coated formulation designed to enhance the delivery of enzymes to the duodenum. The CMP was first introduced in the US in 1993.

Solvay Pharmaceuticals has conducted studies to support registration of the product worldwide. These studies with the CMP support the safe and effective use of CREON across various etiologies and patient age groups.

In response to concerns about standardization, labeling, and safety, the FDA announced in 2004 that all pancreatic enzyme products will be considered new drugs for prescription use only. In 2006, the FDA issued a guidance document titled “Exocrine Pancreatic Insufficiency Drug Products - Submitting NDAs”,<sup>1</sup> that outlined measures that must be observed to obtain approval. Thus, the CMP was modified to develop the TbMP in order to comply with the guidance using the same proven MINIMICROSPHERES (MMS) technology that is used for the CMP.

The NDA for the TbMP was submitted in November 2006. The application received an Approvable Letter in August of 2007 which included the requirement to complete one clinical study with the TbMP. The FDA had determined that the data submitted were insufficient to demonstrate the clinical comparability of the CMP and TbMP.

A complete response to the approvable letter was submitted in June 2008 with the results of study S245.3.126 demonstrating evidence of efficacy and safety with the TbMP in CF patients 12 years of age and older. The results of this study are consistent with previous data generated from clinical studies with the CMP. Supporting efficacy data are also presented in this document from the CMP trials in patients with CF, CP and PY and including pediatric patients as young as one month of age because the consistency of efficacy and safety data in studies using the CMP and TbMP confirmed the relevance of the CMP data for a complete assessment of the TbMP.

The results of study S245.3.126 with the TbMP together with the totality of efficacy and safety data collected for the CMP support approval of the TbMP as well as proposed labeling. Furthermore, evidence from 20 years of post-marketing surveillance is provided to demonstrate the safety of CREON products marketed in the US and other countries around the world with over 5 million patient-years of marketing experience.

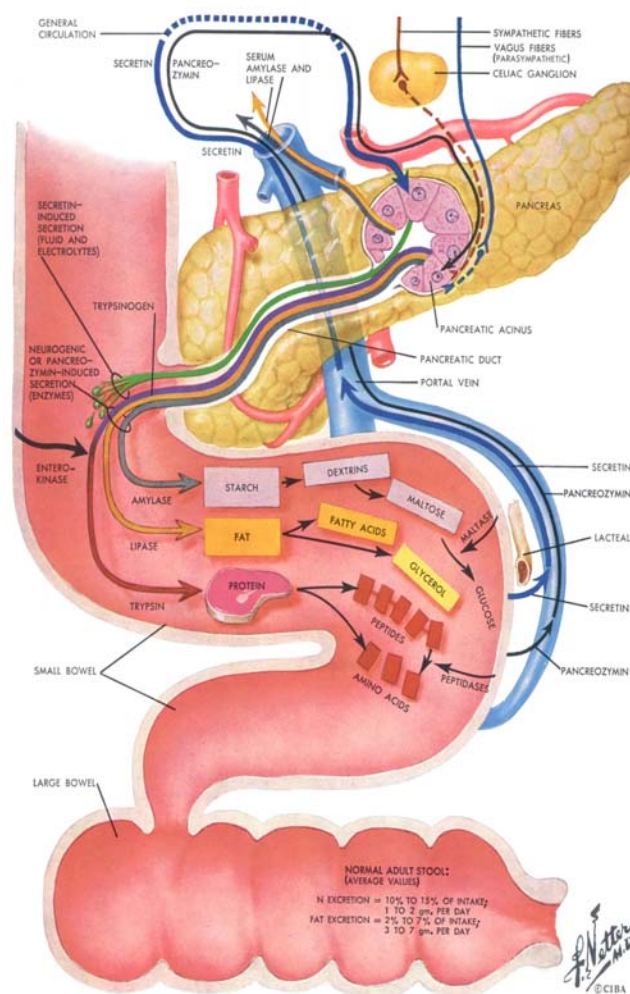
Solvay Pharmaceuticals is requesting the Agency approve the TbMP and include labeling for all CF pediatric ages, based on the totality of efficacy and safety data submitted in the NDA, which includes data from CF patients as young as one month of age. Solvay Pharmaceuticals is committed to further study the TbMP in pediatric patients less than 12 years of age with the TbMP. Solvay Pharmaceuticals currently has an ongoing study in patients 6-11 years of age (S245.3.127) and will initiate a second study in patients 0-6 years of age (S245.3.128).

The CREON NDA meets the requirements of the April 2006 guidance document “Exocrine Pancreatic Insufficiency Drug Products - Submitting NDAs”. As reviewed in the sections that follow, CREON is manufactured and controlled with state-of-the-art technology and the tightest possible specifications, including formulating the level of the three major enzyme classes to label claim with no stability overage. In addition, controls are in place to reduce the risk of viral contaminants during the manufacturing process. Assessment and mitigation strategies are also presented to ensure CREON is continued to be produced with the highest possible quality and safety.

### 1.3 Indication

Solvay Pharmaceuticals is seeking an indication for the TbMP for the treatment of maldigestion due to EPI. As detailed in the sections that follow, the TbMP can fulfill an important role for treatment of patients with EPI due to various underlying diseases.

EPI is characterized by reduced or diminished pancreatic secretion of enzymes and bicarbonate containing fluid (illustrated in Figure 1.1). The most direct consequence of EPI is the failure to properly digest fats, proteins, and carbohydrates. This in turn results in failure to absorb these components and, as a result, patients cannot digest food. Patients may experience short-term symptoms that include steatorrhea, and if left untreated, patients with chronic EPI are at risk for severe malnutrition. Enzyme replacement therapy makes up for the endogenous enzyme deficiency.



**Figure 1.1. Illustration of Exocrine Pancreatic Function**  
(Reproduced with permission from Netter, F.H. 1980. Atlas of Human Anatomy. W.B. Saunders Company)

Clinical trials typically measure treatment effects on steatorrhea in relation to fat intake (i.e., CFA) as the primary efficacy outcome and this approach simply exploits the ability of the CFA to act as a convenient surrogate marker, thereby measuring the pharmacodynamic effect of treatment on EPI.

The TbMP and CMP are formulated to contain lipases, proteases, and amylase and, therefore, can potentially aid in the digestion and absorption of fats, proteins, and carbohydrates. In the case of fat, the effects of the CMP on digestion and absorption are well established. In addition, as described in [Section 2.0](#), the TbMP also improves protein digestion and absorption as shown by effects on nitrogen absorption, and improves overall clinical symptomatology. Thus, available evidence supports the benefit of treatment for digestion and absorption of protein and for other short-term symptoms resulting from maldigestion. Given the previously demonstrated effect of amylase in pancrelipase on glucose-responsive hormones,<sup>2,3</sup> it seems highly likely that the CMP and TbMP also provides benefits on carbohydrate digestion and absorption.

#### **1.4 Medical Need for Pancreatic Enzyme Replacement Therapy**

EPI is a major corollary of diseases or conditions that affect pancreatic function, including CF, CP, or PY patients.<sup>4,5</sup> Acute effects of enzyme deficiency include maldigestion of fats, proteins, and carbohydrates, accompanied by deficiencies in fat-soluble vitamins (A, D, E, and K), and trace elements. EPI is associated with lack of appetite, steatorrhea, abdominal cramps, and flatulence. Left untreated, this leads to malnourishment and thus can contribute to an increased morbidity and mortality associated with these conditions.

In patients suffering from EPI, pancreatic enzyme replacement therapy enables the digestion and subsequently the absorption of fats, proteins, and carbohydrates. Lipid maldigestion is the main cause of fecal energy loss, leading to the major acute symptoms of EPI, although amylase and protease are also needed for adequate digestion of carbohydrates and proteins. None of the currently available treatments have been approved by the FDA.

##### **1.4.1 Exocrine Pancreatic Insufficiency in Cystic Fibrosis**

Among the conditions associated with EPI, the importance of adequate nutrition is best characterized in CF. In 2006,<sup>6</sup> more than 24,000 patients with CF were registered with the CF Foundation Patient Registry in the United States and more than 800 patients were newly diagnosed with CF in that year (median age, 6 months). Advances in treatment have improved survival in these patients from a median age of approximately 25 years in 1985 to almost 37 years in 2006.<sup>6</sup> Maintaining normal nutrition has been a key element of treatment, and marked improvements in the body mass index (BMI) of children with CF have been observed between 1990 and 2006.<sup>6</sup>

Similar to what occurs in the lungs of CF patients, mucus blocks the pancreatic duct causing irreversible damage to the pancreas. Intestinal maldigestion due to EPI in CF is detectable in most affected children within weeks of birth and in 85% to 90% of affected children by one year of age.<sup>7-9</sup> Left untreated, EPI can cause failure to thrive in children and severe weight loss in adults. While respiratory complications are the major cause of mortality in patients with CF, low body weight has been demonstrated to be closely associated with a reduced

survival.<sup>10</sup> This may be due in part to the correlation of malnourishment with loss of normal pulmonary function,<sup>6</sup> an association that becomes stronger throughout childhood.<sup>11, 12</sup> Furthermore, deficiencies in nutritional status with consequences on lung function at young age can only be partly corrected at later age.<sup>11, 12</sup> Moreover, the risk for an increased morbidity and mortality may at least be partly independent of the effects of malnourishment on lung function.<sup>13</sup>

#### **1.4.2 Exocrine Pancreatic Insufficiency in Chronic Pancreatitis and Pancreatic Surgery**

Maldigestion due to EPI may also occur as a complication of CP. Limited data are available for the incidence of CP in the US, perhaps in part due to the difficulty in distinguishing CP from recurring and remitting acute pancreatitis (AP). A recent analysis has shown a modest increase in hospital discharge with a diagnosis of CP from 7 to 8.1 per 100,000 persons over the period from 1988 to 2004.<sup>14</sup>

CP is a multifactorial disease with a variety of etiologies such as toxic events.<sup>15</sup> Alcoholism and medications are among the most frequent causes. Damage of the parenchyma can impair exocrine as well as endocrine function.<sup>16</sup> Irrespective of etiology, CP is the most frequent cause of EPI,<sup>17</sup> which may emerge 20-30 years after the onset of disease and typically presents only when postprandial secretion of pancreatic enzymes falls below 10% of normal.<sup>18, 19</sup>

Chronic maldigestion can lead to malnutrition in patients with EPI due to CP. Steatorrhea typically develops earlier in the course of CP than maldigestion of proteins and carbohydrates, and can ultimately result in weight loss and nutrient depletion.<sup>20</sup> However, steatorrhea occurs only when the patient is not avoiding food intake to diminish unpleasant symptoms and ingests food containing an adequate amount of fat to maintain or gain weight. Avoidance of nutritional intake as well as maldigestion of ingested nutrients consequently leads to malnourishment.<sup>21</sup>

Consequences of advanced disease and attendant steatorrhea are other effects that include loss of bone mineral density and bone mineral content.<sup>22</sup> In addition, altered levels of metabolites of vitamin D have been observed.<sup>23</sup> Furthermore, altered metabolism of trace elements such as zinc, copper, and selenium and vitamin deficiency have been reported in CP patients suffering from steatorrhea.<sup>24, 25</sup> In patients with CP, BMI has been shown to be associated with self-assessed quality of life,<sup>26, 27</sup> suggesting that weight loss may also negatively impact the psychological health of these patients.

#### **1.4.3 Exocrine Pancreatic Insufficiency Associated with Other Conditions**

There exist many other conditions that are associated with EPI. For example, EPI can occur as a long-term consequence of severe AP due to early activation of digestive enzymes within the pancreatic cells, resulting in self-digestion and tissue destruction.<sup>28</sup> The prevalence of EPI following severe, necrotizing AP may be as high as 70-100%.<sup>29</sup> Alternatively, pancreatic tumors may directly obstruct the duct and lead to EPI.<sup>30</sup> In addition, pancreatic surgery performed to treat either pancreatic cancer or CP can result in EPI, as can gastric or intestinal resections.<sup>30</sup>



EPI can also occur as a characteristic of other less common diseases. For example, Zollinger-Ellison Syndrome is a rare disease caused by gastrin-producing tumors of the pancreas and/or intestines. Gastrin production results in excessive gastric acid production and thereby inactivates pancreatic enzymes.<sup>30</sup> A rare genetic disease, Shwachman-Diamond syndrome, is characterized by EPI and bone marrow dysfunction.<sup>31</sup> The etiology of this disease is unknown, as is the pathogenesis underlying pancreatic involvement. Furthermore, 40-60% of patients may recover exocrine pancreatic function over time. The use of pancreatic enzyme replacement therapy may be appropriate to treat EPI when present in any or all of these conditions.

#### **1.4.4 Pancreatic Enzyme Replacement Therapy**

Pancreatic enzyme replacement therapy is recommended for EPI irrespective of underlying cause.<sup>4, 5, 17</sup> The objective of pancreatic enzyme replacement therapy is to deliver pancreatic enzymes into the duodenal lumen in sufficient quantities to normalize digestion and absorption of fats, proteins, and carbohydrates.<sup>5</sup> The lipase activity of pancreatic enzyme supplements is the primary endpoint used to gauge efficacy, which is typically measured by the CFA in accordance with the FDA 2006 guidance “Exocrine Pancreatic Insufficiency Drug Products – submitting NDAs”.<sup>1</sup> All of the commercially available preparations currently in use are derived from swine pancreas. An enteric coating is used to protect the enzymes of the TbMP and CMP from inactivation by gastric acid.

Consensus panels in the US and in Europe recommend pancreatic enzyme replacement therapy as a cornerstone of nutritional management for treatment of EPI due to CF.<sup>32, 33</sup> The CF Foundation also recommends pancreatic enzyme replacement therapy for treatment of patients with symptoms of EPI from infancy throughout adolescence,<sup>34-37</sup> and more than 90% of patients in the CF Foundation Patient Registry were using pancreatic enzyme supplements in 2006.<sup>6</sup>

Currently available pancreatic enzyme supplements are fulfilling a vital role in treatment of EPI. With the increasing lifespan of patients with CF, it seems likely that the need for pancreatic enzyme replacement therapy in that population will continue to grow, whereas there is no reason to believe that the incidences of other conditions with which EPI is associated are likely to be substantially reduced in the near future. Taken together, this provides strong support for a continued need for pancreatic enzyme replacement therapy to help ensure adequate nutrition and to optimize the outcomes for these patients.

#### **1.5 CREON (TbMP) Product**

The Agency has required all marketed pancrelipase products to be approved as NDAs to assure consistent quality and predictable effect across products in order to ensure the administration of efficacious and safe products to the applicable patient population. In response to the FDA’s 2006 guidance, Solvay Pharmaceuticals has made modifications to the TbMP such that it has:

- a well characterized drug substance;
- a robust drug substance specification which includes identity, purity, biologic activity and protein pattern of the different enzymes, microbial-viral testing, and other relevant attributes;

- a stable drug product which is formulated to its labeled claim for all enzymes (lipase, amylase, and protease) with no stability overages;
- drug product specifications, including identity, purity, protein pattern and biologic activity of the different enzymes, dissolution with extended gastric phase, and microbial testing;
- and furthermore, mineral oil has been removed from the formulation at the request of the FDA and dibutyl phthalate has been removed in response to recent global debate concerning the safety of alkyl phthalates.

## 1.6 Physical, Chemical, and Pharmaceutical Properties and Formulation

### 1.6.1 Drug Substance

Pancrelipase is an extract of porcine pancreatic glands consisting of three major enzyme classes including lipases, proteases, and amylase. Pancrelipase is a beige-white amorphous powder. It is miscible in water and practically insoluble or insoluble in alcohol and ether.

Solvay Pharmaceuticals' drug substance application has been updated to include:

- information on the animal species, tissue types, and countries of origin of the starting material-native porcine pancreas glands;
- full characterization using appropriate chemical, physical, and biologic testing. The following enzymes and co-enzymes were identified: lipase, phospholipase-A2, amylase, elastase 1 and 2, trypsin, chymotrypsin, carboxypeptidase a and b, co-lipase;
- manufacturing controls which ensure batch-to-batch consistency with respect to chemical identity, biologic activity including specific activity, identity, and purity levels;
- identity and purity by high performance liquid chromatography;
- appropriate specification limits are established and justified for lipases, amylase, and proteases;
- and a full viral risk assessment discussing viral clearance studies of the manufacturing process and controls of the drug substance.

### 1.6.2 Drug Product

The TbMP will be available in capsule strengths containing 6,000, 12,000, and 24,000 units of lipase ([Table 1.1](#)).

**Table 1.1: Units of Lipase, Free Proteases, and Amylase in CREON Capsules**

	<b>CREON 6,000</b>	<b>CREON 12,000</b>	<b>CREON 24,000</b>
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

USP, United States Pharmacopeia

CREON has enteric-coated pellets to protect the enzymes from the acidic pH of the gastric fluids. The coating is resistant to low pH and protects the enzymes from degradation and

denaturation during passage through the stomach. The coating releases the enzymes in the higher pH environment of the duodenum so that they are available for nutrient digestion.

Solvay Pharmaceuticals' drug product application has been updated to include:

- specifications which include tests for identity, biologic activity of different classes of enzymes, degradants, dissolution, and microbial testing; and
- room temperature stability that shows the product is stable for 24 months when formulated with no stability overages.

### 1.6.3 Comparability of Drug Products

Clinical efficacy data and both clinical and post-marketing safety data of the CMP are considered to be applicable for the labeling of the TbMP based on the comparability of the CMP and the TbMP for the reasons noted below.

- Solvay Pharmaceuticals has been requested by the FDA to base the enzyme activity labeling of the TbMP on the enzyme activities of batches from clinical studies of the CMP. Solvay Pharmaceuticals has evaluated the enzyme activities of 6 clinical studies of the CMP resulting in average lipase contents of approximately 120% of the current labeling (5,000/10,000 and 20,000 United States Pharmacopeia [USP]-units/capsule). Based on this finding an adaptation of the labeling to the activities found in the clinical trials was proposed (6,000/12,000 and 24,000 USP-units/capsule). The TbMP will be manufactured at 100 % of label claim, fulfilling the FDA requirement for a product with zero stability overage. A similar approach has been followed also for amylase and protease activity (Table 1.1).
- The composition changes between the CMP and TbMP are the following:
  - removal of mineral oil due to potential interference with absorption of fat soluble vitamins in the digestive tract (as required by 21 CFR 201.302)
  - the plasticizer, dibutyl phthalate, has been replaced by a plasticizer mixture of cetyl alcohol and triethyl citrate based on a general EU<sup>\*</sup> directive.
- The objective of the entire development process for the TbMP was to match the CMP as closely as possible with regard to pharmaceutical properties, mainly comparability of gastric resistance and dissolution profiles (Refer to Appendix 1). The changes to the composition of the TbMP were made in such a way that comparable gastric resistance results and dissolution profiles were obtained.
- The manufacturing process of the enteric-coated MMS was not changed between the CMP and TbMP. The pelletizing and coating processes are the same for both products and lead to the same size pellets (particle size 0.7-1.6 mm) and the same product characteristics. The manufacturing process includes steps to ensure that the proposed enzyme activity label claim is met.

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\* Directive 2003/36/EC of the European Parliament and the Council of 26 May 2003 amending for the 25<sup>th</sup> time Council Directive 76/769/EEC

- The pancrelipase of the CMP is produced by SPL Ltd and the pancrelipase of the TbMP is produced by Solvay Pharmaceuticals GmbH. The main enzymes of both active ingredients are considered comparable using currently available state-of-the-art analytical technology. Pancrelipase produced by Solvay Pharmaceuticals GmbH is used in the CREON marketed products approved in all 30 countries of European Economic Area and a further 45 countries outside Europe.

A summary of the comparison of the composition of the CMP and the TbMP is provided in [Table 1.2](#). In addition, as outlined in the sections that follow, Solvay Pharmaceuticals has evaluated clinical studies with the both the TbMP and the CMP to demonstrate consistency of the efficacy and safety of these products. Based on all of these considerations, it is concluded that the totality of efficacy and safety data are relevant for labeling and this is why CMP data are presented with TbMP data.

**Table 1.2: Comparison of CREON Currently Marketed with the To-Be-Marketed Product**

	CREON CMP	CREON TbMP
Lipase activity	5,000	6,000
Label claim [USP-u/cps]	10,000 20,000	12,000 24,000
Lipase activity Found [USP-u/cps]	CREON 10: 12,096 CREON 20: 25,225 (Mean from clinical trials)	CREON 12,000: 12,012 CREON 24,000: 24,120 (Mean from clinical trials)
Produced to 100% of labeled enzyme activity	NO	YES
Formulation	Containing DBP + mineral oil	Replacing DBP and mineral oil by TEC + CA
	Similarity of products shown by gastric resistance and dissolution comparison	
Manufacturing process	Same pelletizing and coating process	
Drug substance	Pancrelipase USP (Manufactured by SPL)	Pancrelipase USP (Manufactured by Solvay)
	Similarity of drug substance shown by analytical side-by-side characterization	

CA, cetyl alcohol; CMP, currently marketed product; DBP, dibutyl phthalate; TbMP, to be marketed product; TEC, triethyl citrate

#### 1.6.4 Viral Controls

Because CREON is produced from native porcine pancreas, the possibility of contamination of the starting material with viruses relevant to swine and capable of infecting humans has been and continues to be addressed. To determine the potential risk of viral contamination, Solvay Pharmaceuticals has performed a risk analysis. Measures were implemented to control

and reduce risk at all steps of production, from careful selection of animal materials through testing and release of the final product. A more detailed summary is provided in Appendix 2.

Pancreatic material is harvested only from animals released for human consumption. Supplier countries must have established and implemented a reliable system relating to slaughtering and food hygiene, compliance with animal health rules, and implementation of a disease surveillance system. All suppliers must meet strict criteria, including appropriate approval by competent veterinary bodies, veterinarian oversight, institution of surveillance systems, ongoing hazard analysis, and appropriate documentation. Traceability is maintained through the processes from the suppliers of pigs until distribution of finished product by Solvay Pharmaceuticals.

Solvay Pharmaceuticals' production facilities also undergo regular cleaning and disinfection to minimize any possibility of cross- contamination between batches.

In order to fully understand any potential risk, Solvay Pharmaceuticals has investigated and reviewed the range of viruses that are known to infect swine. These viruses can be broadly categorized as either enveloped or non-enveloped. Enveloped viruses are efficiently inactivated by multiple steps in the production process for CREON, whereas inactivation of non-enveloped viruses is more variable (Appendix 2). Some non-enveloped viruses can be transmissible to humans (zoonotic viruses).

Solvay Pharmaceuticals has identified four non-enveloped, potentially zoonotic viruses with relevance to human health and has developed and validated assays to test for these viruses in the drug substance as part of its release specification (Appendix 2). These process controls reflect Solvay Pharmaceuticals' commitment to produce a product with the highest possible quality and safety.

## **1.7 Preclinical**

A study in pancreatectomized and pancreatic duct-ligated pigs failed to show any evidence of absorption of pancreatic enzymes after oral administration of CREON (up to 419,528 U lipase).<sup>38</sup> Since pancreatic enzymes are not systemically available, standard pharmacokinetic studies cannot be performed.

Studies conducted in pigs with EPI induced by ligation of the pancreatic duct have demonstrated the importance of pancreatic enzymes for their growth and performance.<sup>39</sup> In these pigs, treatment with CREON partially reversed the maldigestion/malabsorption of fat and protein in a dose-dependent manner and completely reversed that of starch, demonstrating the efficacy of enzyme supplementation therapy with CREON.

A study using male mice demonstrated that the motility in the upper gastrointestinal (GI) was not affected by treatment with a single oral dose of 1.5 g/kg pancrelipase (data on file). Toxicity studies with single-dose administrations of pancrelipase in mice, rats, and dogs of both sexes have not established a lethal dose, but it can be expected to be well above 15 g of pancrelipase/kg (data on file).

Data from sub-chronic and chronic toxicity studies in dogs did not show any evidence of systemic or local GI toxicity. Indeed, under the test conditions of the chronic toxicity studies

with pancrelipase powder, no effects related to systemic toxicity or to effects in the GI tract were observed with 2 doses of 2 g pancrelipase per kg body weight per day suggesting a no adverse effect level above this dose level (data on file).

The two replacement excipients in the TbMP (cetyl alcohol and triethyl citrate) are both included in the FDA database of allowable inactive materials and there are no toxicologic objections to use of either of these excipients at the intended oral dose levels in patients.

The studies performed to assess the acute and chronic toxicity of the pancrelipase have demonstrated the absence of systemic toxicity.

## **1.8 Clinical Pharmacology**

### **1.8.1 Mechanism of Action**

CREON Capsules contain pellets which are released in the stomach. The particles of optimal size mix with the chyme in the stomach but do not dissolve due to the pH-resistant enteric coating. The pH-sensitive enteric-coated pellets have been developed to ensure the delivery of active enzymes to the small intestine. Upon entering the duodenum, the pellet coating dissolves to release the enzymes for food digestion, dependent on the pH of the duodenum.

### **1.8.2 Pharmacodynamics**

One pharmacology study (S245.2.003) was performed to investigate the release of the TbMP in the duodenum. Duodenal aspirates were evaluated in 9 subjects with exocrine pancreatic insufficiency due to CP after receiving five CREON Capsules. The overall lipase activity of the aspirates was measured and the porcine portion of this activity from CREON was calculated based on the amount of human lipase in the samples. This study showed that CREON released pancrelipase in the duodenum in accordance with the specified controlled-release characteristics of the product.

The effect of the administration schedule on the duodenal fat digestion of oral pancreatic enzyme supplements in patients with EPI was investigated in a randomized, three-way crossover study consisting of three consecutive 1-week crossover periods.<sup>40</sup> This study used a <sup>13</sup>C- mixed triglyceride breath test to monitor the effect of pancreatic enzyme replacement therapy.<sup>41</sup> A total of 24 CP patients with maldigestion due to exocrine pancreatic insufficiency were included in the study. A total of 40,000 USP lipase units were taken just before meals (Schedule A), just after the meals (Schedule B), or distributed along with meals (Schedule C). Without enzyme supplementation, the 13-CO<sub>2</sub> recovery in the breath test was 23.8 ± 15.8% (normal > 58%). During therapy, 13-CO<sub>2</sub> recovery tended to be higher when capsules were taken along with meals (61.4 ± 21.4%) or immediately following meals (60.6 ± 21.8%) than when taken just before meals (53.9 ± 20.3%). The percentage of patients who normalized fat digestion with therapy was 50, 54, and 63% with Schedules A, B, and C respectively. The optimal administration schedule for pancreatic enzyme supplements for the treatment of exocrine pancreatic insufficiency is therefore suggested to be during or just after meals.

### **1.8.3 Pharmacokinetics**

Pancrelipase consists of proteins which are digested by proteases. These digested products are then absorbed, metabolized, or excreted. Intact enzymes are not systemically available. Therefore, pharmacokinetic characterization is not possible.



## 1.9 Efficacy

This application presents substantial evidence of the effectiveness of the TbMP as demonstrated in Study S245.3.126 as well as a summary of the evidence for the comparable and substantial efficacy of the CREON CMP in patients with EPI. In total, the results of one study with the TbMP and eight clinical studies with CREON MMS conducted in 90 centers in the US, Italy, France, the UK, Japan, and the Republic of South Africa are presented. These studies were performed in patients with CF, CP, and PY, and included patients whose ages ranged from one month to more than 65 years. They were chosen because either the study designs permitted comparison with baseline or placebo, or they included efficacy data in only pediatric patients. Following is an overview of the studies, patient exposure, age groups, and the mean change in CFA, the main efficacy parameter, which was observed in each study (Table 1.3).

**Table 1.3: Summary of Efficacy in Studies with CREON**

<b>Disease</b>	<b>Study</b>	<b>Product</b>	<b>Age group</b>	<b>Mean CFA on CMP or TbMP (%)</b>	<b>Mean CFA on placebo (%)</b>	<b>Mean difference in CFA<sup>a</sup>, CMP or TbMP minus placebo (%)</b>	<b>p-value</b>
<b>CF</b>	S245.3.126	TbMP	≥ 12 years	88.6	49.8	38.8	< 0.0001
	S223.3.101	CMP	7-18 years	84.1	52.2	31.6	< 0.001
	S223.3.102	CMP	18-40 years	87.2	50.9	34.9	< 0.001
	S248.3.003	CMP	1-24 months	84.7	58.0 <sup>e</sup>	26.7 <sup>e</sup>	0.0013 <sup>e</sup>
	S245.3.118	CMP	6-36 months	77.7, 78.7 <sup>b</sup>			
<b>CP</b>	S245.3.105	CMP	< 18 years	91.3			
	S245.3.115 (CP only)	CMP	≥ 20 years	84.9 <sup>c</sup>	62.2	11.1 <sup>c,d</sup>	0.04
	223.2.01	CMP	≥ 18 years	86.6	68.0	24.6	0.0185
	K245.5005	CMP	≥ 18 years	81.5	60.3	21.2	0.004
<b>PY</b>	S245.3.115 (PY only)	CMP	≥ 20 years	82.6 <sup>c</sup>	56.3	22.7 <sup>c,d</sup>	< 0.001

CF, cystic fibrosis; CFA, coefficient of fat absorption; CMP, currently marketed product (CREON); CP, chronic pancreatitis; PY, pancreatic surgery; TbMP, to be marketed product (CREON)

<sup>a</sup>Mean difference is based on change from baseline, or change from run-in, if available, otherwise from on-treatment values

<sup>b</sup> values for CREON for Children and CREON Capsules, respectively;

<sup>c</sup> CMP 3g/day

<sup>d</sup> ANCOVA adjusted mean

<sup>e</sup> Baseline controlled study (without treatment)

The results of Study S245.3.126 assessing the efficacy and safety of the TbMP in patients with CF are a major focus of this briefing package. In this randomized, double-blind, two-

treatment period, crossover study conducted in the US, patients were randomized to the sequence TbMP followed by placebo or placebo followed by TbMP. Subjects were dosed per the CF Consensus Conferences guideline at 4,000 lipase units/g fat intake per day. The primary efficacy parameter was the CFA determined via 72-hour stool collection periods when both fat excretion and fat intake (g/day; a component of dietary data collection) were measured. Secondary efficacy measures included the coefficient of nitrogen absorption (CNA; a measure of protein absorption) and other measures of steatorrhea (stool fat, stool weight, clinical symptomatology). The mean CFA for the patients when receiving TbMP was 88.6% whereas it was 49.8% during placebo treatment, representing a clinically relevant and statistically highly significant ( $p < 0.0001$ ) mean absolute increase in CFA of 38.8% with the TbMP compared with placebo. This increase was similar in adults and in adolescents between 12 and 18 years of age. Significant increases were also observed for the CNA and other measures of steatorrhea. Furthermore, age did not affect the magnitude of the benefits observed with pancrelipase treatment as measured by CFA.

Studies of CREON CMP included three randomized trials in patients with EPI due to CF (S223.3.101, S223.3.102, and S248.3.003) in which the trial design allowed comparison of active treatment CFA values with those of either placebo treatment or baseline values. In all of these trials, which included patients ranging in age from one month to 53 years, the magnitude of active treatment values for the CFA and the significant differences from untreated values were consistent with those observed using the TbMP. CFA data in pediatric patients with CF also came from two other preference studies (S245.3.118, S245.3.105) comparing alternative preparations of the CMP. On-treatment CFA values were consistent between treatment groups and with on-treatment values observed in the other clinical trials with the CMP and the TbMP.

Furthermore, two randomized, placebo-controlled studies assessed the efficacy and safety of the CMP in patients with EPI due to CP (223.2.01, K245.5005) while a third study assessed the CMP in patients with EPI due to either CP or PY (S245.3.115). In all of these trials, the CMP significantly improved CFA compared with placebo.

In conclusion, the studies with the CMP provide substantial evidence of clinical effectiveness of the CMP in patients with EPI and likewise the data from study S245.3.126 confirms the efficacy of the TbMP. The effect sizes in the studies are consistent between the two products irrespective of the underlying condition or the patient age.

## **1.10 Safety**

### **1.10.1 Safety in Clinical Studies**

Safety data are included for completed studies only. In total, this included 51 studies with CREON, including integrated data from 29 multiple-dose studies with the CMP, the CF study with the TbMP, and 22 multiple-dose studies with a predecessor product, CREON MICROSPHERES® (MS). Over 90% of patients in studies of CF, CP, or PY completed treatment. GI disorders were the most frequent class of treatment emergent adverse



events (TEAEs) in all diseases and with both CREON and placebo. Differences between the diseases did not permit overall comparisons, but no obvious trend was observed between TEAEs and gender, age group, or increasing dose of CREON.

In CF patients from randomized, placebo-controlled trials of the CMP or the TbMP, TEAEs are generally more frequent with placebo compared with treatment with either the CMP or TbMP. This reflects the effects of untreated EPI in these patients and reinforces the symptomatic treatment benefits of CREON.

In patients with CP and PY from randomized, placebo-controlled studies, TEAEs occurred in approximately equal proportions of patients and were consistent with the underlying disease.

Thus, data from clinical trials support the safety of the CMP and the TbMP for treatment of EPI in patients with CF, CP and PY.

### **1.10.2 Post-Marketing Safety**

Solvay Pharmaceuticals also began collecting global post-marketing surveillance data for CREON in January 1984. Since that time, no data have been noted that would suggest any safety issues associated with the use of any CREON product.

### **1.11 Viral Risk Assessment and Mitigation Plan**

Because CREON is produced from native porcine pancreas, the possibility of contamination of the starting material with viruses potentially present in swine and capable of infecting humans has to be considered. In compliance with international and national guidelines concerning the viral safety of medicinal products, Solvay Pharmaceuticals has performed a risk analysis to determine the potential risk of viral contamination and has instituted measures to control and reduce risk at all steps of production. This includes careful selection of animal materials, use of a controlled and validated manufacturing process, and testing and release of the final product. A major concern regarding infection risks in treatment with animal derived drugs relates to organisms not yet known referred to as “emerging” infections. In order to ensure the high viral quality standard of Solvay Pharmaceuticals’ pancrelipase in the future, Solvay Pharmaceuticals observes the sourcing countries national animal disease surveillance programs and current state of knowledge in veterinary science with respect to emerging viruses. An ongoing risk assessment on current and future viruses relevant for Solvay Pharmaceuticals’ pancrelipase integrating all complementary measures will evaluate the appropriateness of existing procedures. Should it prove necessary, measures will be modified or introduced at each level: sourcing of raw material, processing, testing methods and procedures as well as specifications.

Solvay Pharmaceuticals is committed to develop, in cooperation with the FDA and medical community, an appropriate plan for risk identification and evaluation. Options under consideration include active surveillance and observational-type studies post approval.

## **1.12 Conclusion**

The medical need for pancreatic enzyme replacement therapy to treat maldigestion in conditions associated with EPI is clearly established and is not in dispute. In CF, the need for pancreatic enzyme replacement therapy to ensure adequate nutrition in children is recognized by the CF Foundation as well as CF consensus committees in the US and Europe. Improvements in nutrition over the past 20 years have paralleled increases in the lifespan of CF patients. In addition, pancreatic enzyme replacement therapy is also well established as a treatment for maldigestion due to CP, PY, and other diseases, to avoid potential malnutrition if EPI in these patients is left untreated.

Given the similarity in presentation and progression of CF across adult and pediatric patients, as well as the similarity of CREON products evaluated, the results of extensive clinical and in-market experience are compelling to support labeling for all age groups and all etiologies. Substantial evidence is presented herein to support the safety and efficacy of the TbMP in CF patients of all ages. Furthermore, efficacy and safety data from studies of patients with EPI due to CP or PY indicate that benefits of treatment with CREON are independent of the underlying disease.

The substantial body of evidence for the medical need for pancreatic enzyme supplements, together with the abundant evidence for the efficacy and safety of the CMP and TbMP, clearly establishes a benefit for approval of the TbMP. Approval of the TbMP for treatment of pediatric patients with CF would make available a proven therapy to improve nourishment and thereby maximize their potential lifespan. For patients of all ages with EPI due to CP or other underlying conditions, approval of the TbMP would make available a proven therapy to prevent malnourishment and improve quality of life.

In addition to the abundant evidence for benefits on fat digestion, CREON treatment also provides symptomatic relief for patients with EPI, and recent evidence also indicates improved protein digestion with the TbMP.

Because CREON is produced from native porcine pancreas, the possibility of contamination of the starting material with viruses potentially present in swine and capable of infecting humans has to be considered. To determine the potential risk of viral contamination, Solvay Pharmaceuticals has performed a risk analysis and has instituted measures to control and reduce risk at all steps of production, from careful selection of animal materials through testing and release of the final product. Based on an ongoing risk assessment on current and future viruses relevant for Solvay Pharmaceuticals' pancrelipase measures will be taken as necessary and may lead to modification or introduction of new measures on each level: sourcing of raw material, processing, testing methods and procedures as well as specifications.

To date, there are no safety data to indicate a known risk with the TbMP. Based on experience with CREON MMS, it is anticipated that that certain adverse drug reactions may occur, and these possibilities are included in the proposed label.

## **2.0 EFFICACY**

### **2.1 Overview of Efficacy Studies**

As discussed in [Section 1.4](#), it is widely accepted that pancreatic enzyme supplements can serve a valuable role to normalize digestion and thereby avert long-term consequences of malnutrition in patients with EPI. Solvay Pharmaceuticals has previously confirmed the efficacy of the CMP in clinical trials of patients with EPI due to various underlying diseases. In response to FDA regulatory requirements, an additional study was performed in patients with CF to confirm that the efficacy observed for the CMP is also applicable to the TbMP. As detailed in [Section 1.6.3](#) and demonstrated in part within this section, the similarities between the TbMP and the CMP are sufficient to warrant the inclusion of all of these data as evidence for the efficacy of CREON.

In this section, the results of nine clinical trials in patients with CF, CP, or PY are presented ([Table 2.1](#)). These trials have been performed in patients as young as 1 month old. Despite the differences in underlying diseases, patient ages, and study designs, the achieved fat absorption for patients in these studies has been remarkably consistent.

The efficacy of CREON in patients with CF is demonstrated in the first part of this section. The specific studies include study S245.3.126, a randomized, placebo-controlled study with the TbMP that formed the basis of the NDA, as well as four studies with the CMP that also include placebo and/or baseline comparator data. Two additional studies that include data on achieved fat absorption in pediatric patients are also presented.

In the second part of this section, data are shown to confirm the efficacy of the CMP in one study in patients with CP or PY, as well as two other studies that focused specifically on patients with CP.

It is important to note that these studies demonstrated benefits within time periods ranging from 5 days to 8 weeks as it would not be ethical to perform long-term placebo-controlled studies when an efficacious treatment is available. Nevertheless, in the placebo-controlled trials, the dramatic decreases in fat absorption observed in the transition of patients from the on-treatment run-in phase to the placebo phase provides substantial evidence that efficacy of treatment is normally maintained during CREON treatment. It is also important to note that the achieved on-treatment CFA was similarly high in all studies, irrespective of the CREON product, underlying disease or patient age.

Taken together, the data from studies of the TbMP and the CMP provide unambiguous evidence of the efficacy of CREON in patients with EPI irrespective of the underlying condition or patient age.

**Table 2.1: Overview of CREON Studies**

Study No/ Location	Indication	Patient Ages	Design	Treatment Duration (Days)	Study Duration	N CREON	N Placebo	CREON Product Information	Major Efficacy Results
<b>TbMP CF Baseline/Placebo-Controlled Studies</b>									
S245.3.126 USA	CF	> 12 years adolescents Adults	Randomized, double-blind Cross-over	5 days (per period)	2 weeks	32	31	24,000	Statistically significant superiority of the TbMP (88.6%) over placebo (49.78%) on the CFA (p < 0.001)
<b>CMP CF Baseline/Placebo-Controlled Studies</b>									
S223.3.101 USA	CF	7 to 17 years (Children, adolescents)	Randomized, parallel group, double-blind withdrawal design	5-7 days	2-3 weeks	18	20	20000 MMS capsule	Statistically significant difference between CREON (-3.25%) and placebo (-34.92%) for the change in CFA (p < 0.001)
S223.3.102 USA	CF	18 to 53 years (Adults)	Randomized, parallel group, double-blind withdrawal design	5-7 days	2-3 weeks	18	18	20000 MMS capsule	Statistically significant difference between CREON (-2.0%) and placebo (-36.9%) for the change in CFA (p < 0.001)
S248.3.003 Italy	CF	0.9 to 22.9 months	Single treatment, open-label	2 weeks	8 weeks	12	-	CREON for Children MMS Capsule	CFA significantly increased from baseline; after 2 weeks there was a mean increase in CFA of 26.7% (p=0.0013)
<b>Other CMP CF Studies</b>									
S245.3.118 France	CF	6 to 36 months	Randomized, reference- controlled, open label, crossover,	2 x 2 wks	30 days	40	-	CREON for Children vs 12000 MMS	CREON for Children was preferred by 20 subjects (51.3%), p=0.0662, CFA was similar for both CREON (77.7%) and CREON for Children (78.7%)
S245.3.105 UK	CF	3 to 17 years	Randomized, open-label, crossover	One month	10 weeks	57	-	10000 MMS Capsule 8000 MS	Mean CFA was comparable for both forms of CREON (93.5% and 91.3%), as was stool fat excretion (6.7 g/day and 8.4 g/day)

Study No/ Location	Indication	Patient Ages	Design	Treatment Duration (Days)	Study Duration	N CREON	N Placebo	CREON Product Information	Major Efficacy Results
<b>CMP -- CP/PY Placebo-Controlled Studies</b>									
223.2.01 USA	CP	31 to 74 years	Randomized, double-blind, placebo-controlled	14 days	28 days	13	14	10000 MMS Capsule	Statistically significant difference between CREON (36.7%) and placebo (12.1%) for the change from baseline in CFA (p=0.0185)
S245.3.115 Japan	CP PY	21 to > 65 years	Randomized, placebo-controlled double-blind, 3 parallel group	7 days	12 days	33 + 31	30	10000 MMS Sachet	CP+PY: (3.0g/d) CREON: mean change from baseline in CFA was 15.5% vs 3.9% for placebo (p=0.0148)  CP – adjusted mean CFA change from baseline: placebo (0.3), CREON 1.5g/d (9.7), p=0.07; 3.0g/d (11.4); p < 0.05  PY – adjusted mean CFA change from baseline: placebo (-1.4), CREON 1.5g/d (15.1), p=0.002; 3.0g/d (21.3); p < 0.001
K245.5005 RSA	CP	39 to 68 years	Randomized, double-blind, placebo controlled, parallel group with open run-in	21 days	6 weeks	17	16	10000 MMS	Clinically relevant and statistically significant superiority in CFA of CREON (81.5%) over placebo (60.3%); p=0.004

CFA, coefficient of fat absorption; CF=Cystic Fibrosis; CMP=Currently Marketed Product; CP=Chronic Pancreatitis; MMS, MINIMICROSPHERES; MS, MICROSPHERES; PY=Pancreatic surgery; TbMP=To-Be-Marketed Product

All completed studies using CREON CMP or TbMP that either the study designs permitted comparison with baseline or placebo, or they included efficacy data in pediatric patients

## 2.2 Study Designs

This section will discuss general principles of the design and the primary endpoint of the clinical studies that demonstrate the efficacy of CMP and TbMP. Details on the analysis conducted will be given in each of the sections that discuss the study results. Results presented were taken directly from the original study reports will be presented unless otherwise indicated.

All the studies except three were randomized and placebo-controlled. These three studies without placebo controls, S248.3.003, S245.3.118, and S245.3.105, included infants and children for which a treatment period with placebo is difficult to conduct. The study results are presented to show efficacy data in this very young age group.

Three types of design were used in the randomized, placebo-controlled efficacy studies: crossover, parallel groups, and randomized withdrawal. The efficacy study in CF patients with the TbMP (S245.3.126) employed a two-period, placebo-controlled, crossover design in which subjects were randomized to one of two sequences of treatments: TbMP followed by placebo, or placebo followed by TbMP. Before each treatment period, patients were stabilized on their existing treatment. Three studies were conducted using the parallel group design, with two treatment groups: CMP versus placebo (223.2.01, S245.3.115, K245.5005). One of those studies (S245.3.115) investigated two different doses of the CMP versus placebo in a parallel group setting. Two studies with the CMP used a randomized withdrawal design (S223.3.101, S223.3.102). In this design there were two phases: a run-in phase, and a randomized withdrawal phase. In the open-label, run-in phase, patients were treated with the CMP to achieve the desired clinical outcome. Those that responded according to pre-defined criteria were then allowed to enter the double-blind treatment period where they were randomized to either continue with the CMP or to switch to placebo. Treatment comparisons were made using results from the end of the double-blind period. All these types of design are mentioned in the “Guidance for Industry EPI Drug Products – Submitting NDAs”<sup>1</sup>.

In all randomized, placebo-controlled, efficacy studies, the pre-defined primary objective was to show superiority of the CMP or TbMP over placebo on the primary efficacy parameter. All statistical tests comparing the CMP or TbMP to placebo were two-sided and deemed statistically significant if  $p \leq 0.05$ . All these comparisons were confirmative in nature. Secondary parameters were either presented using summary statistics or using appropriate statistical models for the assessment of treatment effects.

In all of the above-mentioned efficacy studies, the CFA was used for the demonstration of efficacy (see next section). Given the designs of the studies, the primary efficacy endpoint was generally the CFA on-treatment (crossover), the change from baseline at end of treatment in CFA (parallel group), or the change from the run-in period at end of treatment in CFA (withdrawal). The only exception to this was study K245.5005, which did not assess CFA at baseline, and therefore, the achieved CFA was the primary efficacy parameter.

The primary analysis in the randomized, placebo-controlled studies was based on the full analysis set (FAS), which included all subjects that were randomized into the double-blind phase of the study, took at least one dose of double-blind study drug, and had at least one CFA measurement in the double-blind period. In study S245.3.115, the primary analysis in the study report was to be based on the per-protocol sample, but the FAS is presented herein for consistency with the rest of the efficacy study samples presented. No missing data for CFA were imputed in any of the trials.

### 2.3 Coefficient of Fat Absorption (CFA)

Pancreatic enzyme supplements act to replace the lipases, proteases, and amylase that are normally secreted by the exocrine pancreas but that are not produced in sufficient quantity in patients with EPI. As reviewed in [Section 1.4](#), the absence of these enzymes can lead to malnutrition and its long-term consequences. The more immediately evident effect of their absence is a range of symptoms that includes abdominal pain, flatulence, and diarrhea. Because of difficulties in quantifying these symptoms, the most commonly employed primary endpoint used to determine efficacy of pancreatic enzyme supplements is the measurement of the effect of the supplements on the absorption of dietary fat – the CFA.

The CFA is a surrogate marker for the efficacy of pancreatic enzyme supplements that measures absorption of fat as a percentage of fat intake according to the following equation:

**CFA Equation:**  $\text{CFA (\%)} = 100 * [\text{fat intake} - \text{fat excretion}] / \text{fat intake}$

The CFA is measured by providing subjects with a diet containing a known amount of fat that is sufficiently high to see an effect and measuring the fat in their stools. To do this, stool dye markers are given to the subject at the beginning and end of a 72-hour treatment period, and measurements of stool fat are performed for all stools collected from the appearance of the first dye marker to the appearance of the second. Thus, the CFA measures fat absorption as a gauge for the lipase activity in pancreatic enzyme supplements and, therefore, it is an FDA-accepted surrogate measure for their efficacy.

### 2.4 Exocrine Pancreatic Insufficiency Due to Cystic Fibrosis

A total of six studies supporting the efficacy of CREON in patients with CF are presented below. Four of these studies contain baseline and/or placebo data to allow a direct comparison of efficacy data in patients of ages one month to 53 years. The other two studies were performed in children (ages 3 months to 17 years) and included assessment of on-treatment CFA values. One study, S245.3.126, was performed with the TbMP in accordance with FDA regulatory requirements, whereas the other five had been performed previously with CREON MMS to address specific questions as outlined below.

As study S245.3.126 forms the basis for the NDA approval, the details of this randomized, double-blind, placebo-controlled study are presented first. This is followed by a presentation of two randomized, placebo-controlled studies with identical designs, one of which was performed in children and the other in adults. A fourth study was a single-

treatment, open-label study performed in children and measured changes from baseline in the CFA. The two final studies presented were open-label crossover studies that compared different CREON products and included measurements of achieved CFA.

#### **2.4.1 Study S245.3.126: Efficacy in Adolescents and Adults with Cystic Fibrosis**

The efficacy of the TbMP was evaluated in a two-period, randomized, placebo-controlled crossover study in 32 patients with CF in 10 study centers across the US. The study was conducted from November 15, 2007 (first subject first visit) to March 6, 2008 (last subject last visit). After stabilization on their current pancreatic enzyme treatment, patients were randomized to one of two treatment sequences –TbMP followed by placebo, or placebo followed by TbMP – with an intervening washout period. Doses were determined according to the CF Consensus Conferences guidelines at 4,000 lipase units/g fat intake.

The primary objective of this study was to demonstrate the superiority of the TbMP over placebo for improving fat digestion as measured by the effect on the CFA. Secondary measures included the coefficient of nitrogen absorption (CNA, a measure of protein absorption;  $CNA = 100[\text{nitrogen intake} - \text{nitrogen excretion}] / \text{nitrogen intake}$ ), stool fat, stool weight, clinical symptomatology (stool frequency, stool consistency, abdominal pain, flatulence), and clinical global impression of disease (CGI) assessed independently by the subject and the investigator.

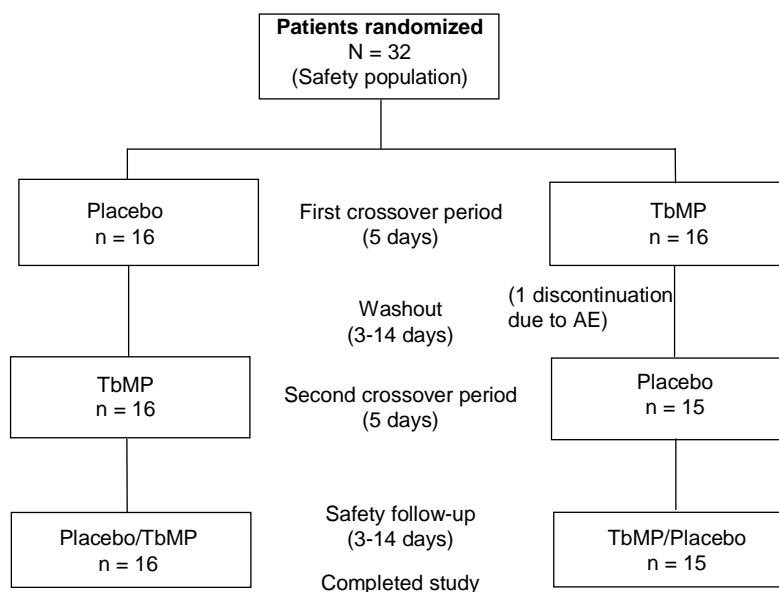
The CFA, CNA, and stool frequency were analyzed using analysis of variance (ANOVA). The model included sequence, period, and treatment as fixed effects and subject within sequence as random effect. From this model, an estimate of the treatment difference along with a 95% confidence interval and a p-value for testing the null hypothesis of equal population treatment group means were derived. A test for carry-over was not carried out. The primary analysis was performed on the full analysis sample which included all randomized subjects who took at least one dose of double-blind study medication and for whom at least one post-baseline assessment of any efficacy measurement was available.

The subjects were treated with study medication for 5 days beginning on Day 1 of each cross-over treatment period. A wash-out period of 3 to 14 days on the subject's individual pancreatic enzyme supplementation was performed until start of the second cross-over period.

The subjects received a prospectively designed, standardized diet adequate to maintain or promote body weight and growth which included 40% of calories derived from fat.<sup>32</sup> The daily meal plan was to provide a minimum daily intake of 100 grams. On Days 3-5 of both cross-over treatment periods the same diet was given to the subject.

Thirty-two subjects were randomized; 31 subjects completed both treatment sequences and were assessed for efficacy (CFA); one subject withdrew due to an adverse event (AE) and did not have any CFA evaluation during the study ([Figure 2.1](#))





**Figure 2.1. Disposition of Subjects**

During the double-blind periods, the average lipase dose on Days 3-5 was 4,189.3 units/g fat intake, and 87.5% of subjects received > 3,500 lipase units/g fat intake. This average lipase dose corresponds to 10,943 units per kg bodyweight per day. Duration of treatment was 5 days per crossover treatment period.

Subject characteristics at baseline are shown in Table 2.2. All patients were White and they ranged in age from 12 to 43 years. The placebo-pancrelipase group had a larger proportion of females.

**Table 2.2: Subject Characteristics at Baseline**

	Placebo / TbMP N=16	TbMP / Placebo N=16	Total N=32
Mean age, years (SD)	22.2 (7.8)	22.8 (6.5)	22.5 (7.1)
Female, n (%)	4 (25.0)	7 (43.8)	11 (34.4)
Race, n (%)			
White	16 (100)	16 (100)	32 (100)
Placebo CFA category, %			
≤ 50	8 (50.0)	9 (60.0)	17 (54.8)
> 50	8 (50.0)	6 (40.0)	14 (45.2)

CFA, coefficient of fat absorption; SD, standard deviation; TbMP, to be marketed product

The TbMP demonstrated statistically significant and clinically relevant superiority over placebo on the primary efficacy endpoint (Table 2.3). The treatment effect was independent of the treatment sequence (data not shown). Thus, the superiority of the TbMP over placebo for fat absorption was confirmed.

**Table 2.3: Overall Results for Coefficient of Fat Absorption**

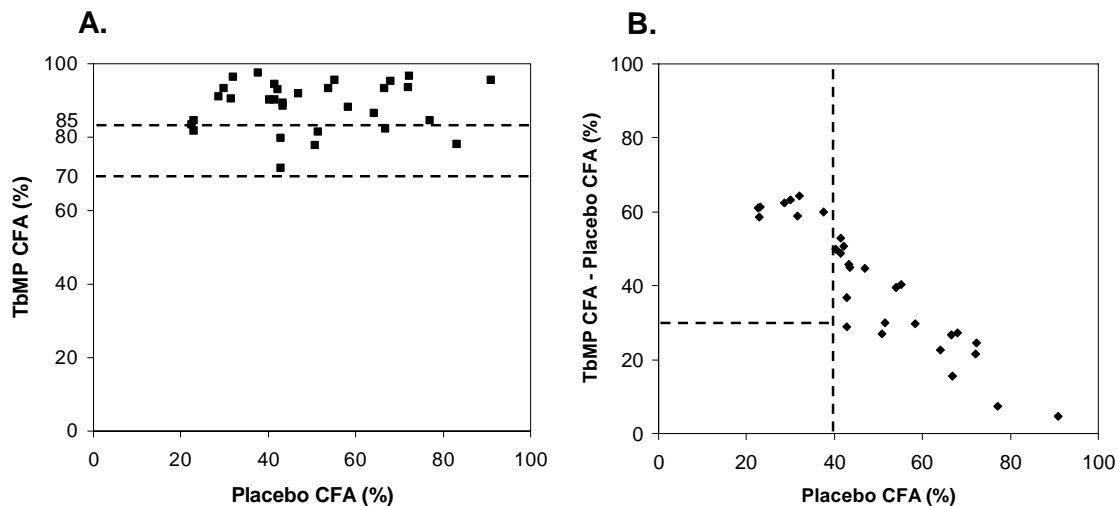
Statistic	TbMP N=32	Placebo N=31	TbMP – Placebo	p-Value <sup>a</sup>
Subjects with data	31	31	31	
Mean (SD)	88.6 (6.6)	49.8 (18.3)	38.8 (19.0)	
Median	90.2	43.4	40.3	
LS <sup>b</sup> mean (SE)	88.6 (2.3)	49.6 (2.3)	39.0 (3.3)	< 0.0001
95% CI	83.8, 93.4	44.8, 54.4	32.3, 45.8	

CFA, coefficient of fat absorption; LS, least squares; SD, standard deviation; SE, standard error; TbMP, to be marketed product

<sup>a</sup>Based on ANOVA model including treatment, sequence, and period as fixed effects and subject within sequence as a random effect.

<sup>b</sup>LS = Least Squares (derived from the statistical model)

With TbMP treatment, all subjects achieved a CFA of  $\geq 70\%$ , and 68% (21/31) achieved a CFA of  $\geq 85\%$  (Figure 2.2A). In contrast, only 16% (5/31) of all subjects had a CFA  $\geq 70\%$  during placebo treatment and only one had a CFA of  $\geq 85\%$ . Even subjects with the very low placebo CFA values clearly responded to TbMP. For example, five subjects for whom CFA values during the placebo period were  $< 30\%$  had CFA values during the TbMP treatment period ranging from 81.6% to 93.2%. All subjects with a placebo CFA of less than 40% had an on-treatment difference from placebo of over 30% (Figure 2.2). The achieved CFA did not appear to be dependent on the severity of EPI, measured by the CFA during placebo treatment (Figure 2.2A). Thus, patients whose CFA was lower during placebo treatment had correspondingly larger increases during treatment with the TbMP (Figure 2.2B).



**Figure 2.2. (A) Coefficient of Fat Absorption (CFA) of Patients on the TbMP as a Function of their CFA on Placebo. (B) Difference Between CFA of Patients on TbMP and on Placebo as a Function of their CFA on Placebo.**

When data were categorized by subject age, the superior efficacy of the TbMP compared with placebo was observed in both adolescents and adults ([Table 2.4](#)).

**Table 2.4: Results by Age for Coefficient of Fat Absorption**

Statistic	TbMP N=32	Placebo N=31	TbMP – Placebo	p-Value <sup>a</sup>
Subgroup: Age 12-18 years	n=10	n=10		
CFA LS <sup>b</sup> mean (SE)	84.2 (4.1)	40.8 (4.1)	43.4 (5.7)	< 0.001
95% CI	74.9, 93.6	31.4, 50.2	30.2, 56.7	
Subgroup: Age > 18 years	n=21	n=21		
CFA LS <sup>b</sup> mean (SE)	90.3 (3.0)	53.0 (3.0)	37.3 (4.2)	< 0.001
95% CI	84.1, 96.5	46.8, 59.2	28.5, 46.0	

CFA, coefficient of fat absorption; LS, least squares; SD, standard deviation; SE, standard error; TbMP, to be marketed product

<sup>a</sup>Based on ANOVA model including treatment, sequence, and period as fixed effects and subject within sequence as a random effect.

<sup>b</sup>LS = Least Squares (derived from the statistical model)

Secondary outcome measures also showed significant benefits of the TbMP compared to placebo. The mean CNA was greater with TbMP treatment compared with placebo treatment ([Table 2.5](#)). The average stool fat, stool nitrogen, and stool weight were lower with TbMP treatment compared with placebo treatment, while the average sum of daily fat intake and nitrogen intake recorded on Days 3-5 of each cross-over period was similar between both treatments.

**Table 2.5: Summary of Coefficient of Nitrogen Absorption**

Statistic	TbMP N=32	Placebo N=31	TbMP – Placebo	p-Value <sup>a</sup>
Subjects with data	31	31	31	
Mean (SD)	85.1 (6.4)	50.0 (17.1)	35.1 (15.5)	-
Median	85.7	53.2	32.2	-
CNA LS <sup>b</sup> mean (SE)	85.1 (1.9)	49.9 (1.9)	35.2 (2.7)	< 0.0001
95% CI	81.2, 89.0	45.9, 53.8	29.6, 40.8	-

CFA, coefficient of nitrogen absorption; LS, least squares; SD, standard deviation; SE, standard error; TbMP, to be marketed product

<sup>a</sup>Based on ANOVA model including treatment, sequence, and period as fixed effects and subject within sequence as a random effect.

<sup>b</sup>LS = Least Squares (derived from the statistical model)

Subjects with placebo CFA ≤ 50% demonstrated a greater effect of TbMP treatment on CNA compared with subjects with placebo CFA > 50% (LS mean treatment differences, 52.4 and 23.3, respectively), but both treatment differences were significant (p < 0.001).

Marked improvements were noted in the clinical symptoms. The average daily stool frequency was significantly lower with TbMP treatment compared with placebo ([Table 2.6](#)).

**Table 2.6: Average Daily Stool Frequency**

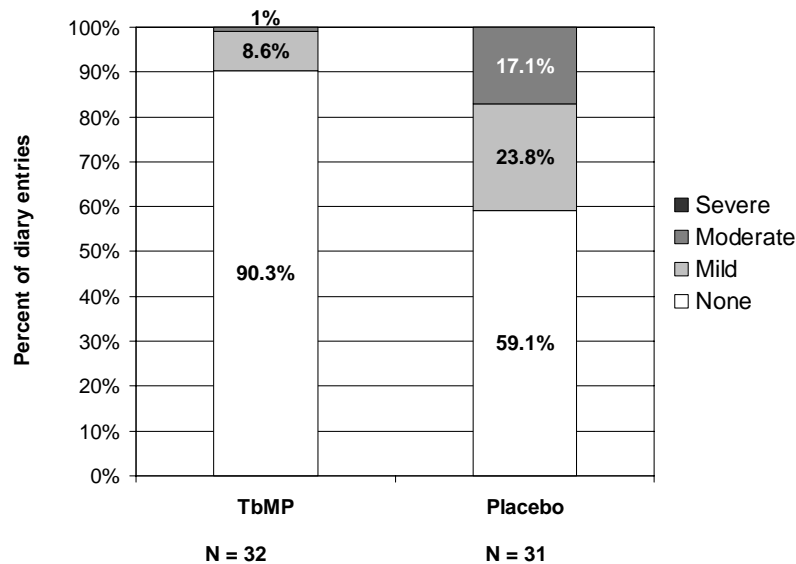
Statistic	TbMP N=32	Placebo N=31	TbMP-Placebo	p-Value <sup>a</sup>
Subjects with data	32	31	31	
Median	1.7	2.7	-1.2	-
LS <sup>b</sup> mean (SE)	1.8 (0.1)	2.8 (0.1)	-1.1 (0.2)	< 0.0001
95% CI	1.5, 2.0	2.6, 3.1	-1.4, -0.8	-

CI, confidence intervals; LS, least squares; SE, standard error; TbMP, to be marketed product

<sup>a</sup>Based on ANOVA model including treatment, sequence, and period as fixed effects and subject within sequence as a random effect.

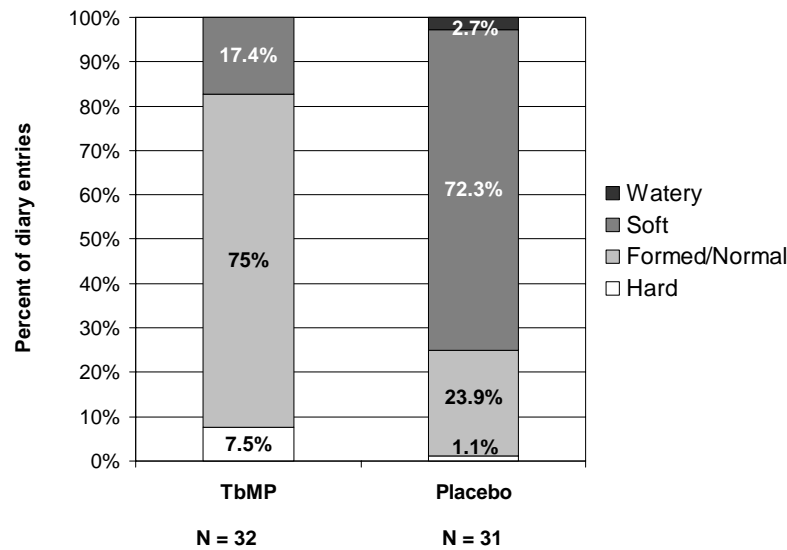
<sup>b</sup>LS = Least Squares (derived from the statistical model)

Subjects recorded daily diary entries for symptomatology, including occurrence of abdominal pain, consistency of stools, and flatulence. There were substantially more diary entries for no abdominal pain with TbMP treatment compared with placebo (Figure 2.3).



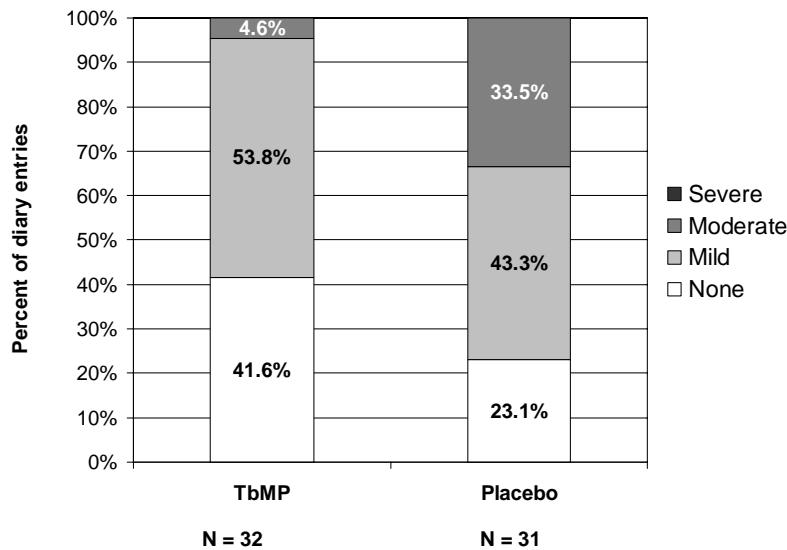
**Figure 2.3. Percentage of Diary Entries for Abdominal Pain**

With TbMP treatment, most subjects on most days reported normal stools, whereas during the placebo period, most subjects on most days reported soft stools (Figure 2.4).



**Figure 2.4. Percentage of Diary Entries for Stool Consistency**

Subjects reported substantially more days with no flatulence during the TbMP period compared with placebo, and the percentage of days with only mild or no flatulence was substantially greater during TbMP treatment compared with placebo (95.4% and 66.4%, respectively; [Figure 2.5](#)). The differences observed for each of abdominal pain, stool consistency, and flatulence were apparent on the first day of treatment and they were maintained throughout the 5 days of treatment period. As also observed for CFA and CNA scores, more severe disease (lower placebo CFA) was associated with greater improvements in the clinical symptoms (data not shown).



**Figure 2.5. Percentage of Diary Entries for Flatulence**

During treatment with the TbMP, both the subject's and the investigator's CGI reflected a stable condition with no meaningful change from baseline to the end of treatment with the TbMP. In contrast, disease symptoms during placebo treatment appeared to worsen from baseline to the end of the period as reflected by both the subject's and the investigator's assessment (data not shown).

Further analysis also showed that subgroup characteristics, disease severity and use of proton pump inhibitors, did not impact the treatment response to the TbMP.

Data collected in this study provide consistent evidence, across both primary and secondary measures, of the effectiveness of the TbMP, at a dose of about 4000 units per g of dietary fat, in the treatment of EPI in adolescent and adult subjects with CF. The mean difference of more than 38% in fat absorption between treatment with the TbMP and placebo underscores not only the study's statistical significance but also its clinical importance. Importantly, the achieved fat absorption with TbMP treatment in patients with CF was similar irrespective of the severity of EPI.

#### **2.4.2 Efficacy in Five Studies of Patients with Cystic Fibrosis**

Results of three additional double-blind, placebo/baseline-controlled studies of the CMP, deemed to be well-controlled and well-conducted, are presented here. These studies were conducted in adults (ages > 18 years), adolescents (ages 12-18 years) and pediatric patients (ages < 12 years) with CF. In addition, two studies are presented that were performed in children ages 3 months to 17 years and included on-treatment CFA values for pediatric patients.

Design details of each of the studies are reviewed and results are presented in the text and/or the tables that follow.

##### **2.4.2.1 Study S223.3.101 in Pediatric and Adolescent Cystic Fibrosis Patients and Study S223.3.102 in Adult Cystic Fibrosis Patients**

The two CF studies, S223.3.101 and S223.3.102, were designed as double-blind, parallel group, multicenter studies with an open-label run-in phase. Patients who completed the open-label phase on individualized CMP treatment with a CFA greater than 80% (determined by a 72-hour stool collection performed after open-label CMP treatment) were randomized to receive the CMP or placebo during the double-blind phase. After a minimum of 2 days of double-blind treatment, a repeat 72-hour stool collection was performed.

The primary objective of these studies was to compare the effectiveness of the CMP with placebo for the treatment of steatorrhea in CF patients (ages 7 to 18 years in study S223.3.101 and ages > 18 years in study S223.3.102) with EPI who were maintained on a high fat (approximately 100g/day) diet. The primary efficacy measure was the change from baseline (end of open-label treatment with the CMP) to final assessment in the CFA. Secondary efficacy endpoints were stool frequency, stool consistency, and CGI scores. CFA data were analyzed by ANOVA with factors for center, treatment, and their

interaction. One subject in Study S223.3.102 who was the only subject in that center was pooled with another center.

There were 40 subjects planned in Study S223.3.101 (20 per treatment arm); 38 subjects were randomized and 37 were analyzed. In Study S223.3.102, 36 subjects were analyzed (18 per treatment arm).

### Results for Studies S223.3.101 and S223.3.102

Results are presented in parallel because the protocols were similar and both studies used the same efficacy endpoints. As indicated above, patient populations were different between the studies: Study S223.3.101 recruited children and adolescent CF patients, while Study S223.3.102 recruited adult CF patients. Demographic data for patients in both studies are summarized in [Table 2.7](#).

**Table 2.7: Summary of Demographic Data Per Study in Cystic Fibrosis Patients (S223.3.101 and S223.3.102)**

Variable	Protocol No.			
	S223.3.101		S223.3.102	
	CMP (N=18)	Placebo (N=20)	CMP (N=18)	Placebo (N=18)
Gender, N (%)				
Male	7 (38.9)	11 (55.0)	10 (55.6)	12 (66.7)
Female	11 (61.1)	9 (45.0)	8 (44.4)	6 (33.3)
Age, Years				
Mean (SD)	12.1 (3.0)	12.8 (2.7)	23.3 (5.1)	24.4 (8.9)
Range	7-17	8-17	18-35	18-53
Race, N (%)				
Caucasian	16 (88.9)	20 (100.0)	18 (100.0)	18 (100.0)
Other <sup>a</sup>	2 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)

CMP, currently marketed product; SD, standard deviation

<sup>a</sup>Other than Caucasian includes black.

In these studies, the dose was individualized for each patient while on a high fat diet using clinical symptoms as a guide. The mean daily lipase dose per kg ( $\pm$  standard deviation [SD]) in the open-label and double-blind periods were comparable for both the pediatric subjects,  $7,440.4 \pm 3739.7$  units versus  $7,855.7 \pm 4381.8$  units and the adult subjects,  $4,907.2 \pm 3247.7$  units versus  $4,537.8 \pm 2648.3$  units. Adult patients required lower daily lipase doses per kg body weight to ameliorate clinical symptomatology caused by fat maldigestion than did the pediatric patients.

Fat intake during open-label treatment did not differ relevantly from that taken during the double-blind treatment in both studies. The fat intake was approximately 130 g/day in Study S223.3.101 and 150 g/day in Study S223.3.102. The mean changes from baseline in CFA were significantly smaller in the CMP group compared to placebo, indicating a significantly higher degree of maldigestion in placebo patients as compared to CMP-treated subjects ([Table 2.8](#)).

**Table 2.8: Summary of the Coefficient of Fat Absorption Per Study in Cystic Fibrosis Patients (S223.3.101 and S223.3.102)**

Protocol No.		Coefficient of Fat Absorption					
		S223.3.101			S223.3.102		
Period	Statistic	CMP	Placebo	p-Value	CMP	Placebo	p-Value
Baseline	N	18	19		18	18	
	Mean	87.4	87.1		89.2	87.8	
	SD	4.7	4.4		4.7	5.1	
Treatment	N	18	19		18	18	
	Mean	84.1	52.2		87.2	50.9	
	SD	9.3	24.4		7.2	31.0	
Change	N	18	19		18	18	
	Mean	-3.3	-34.9	< 0.001 <sup>a</sup>	-2.0	-36.9	< 0.001 <sup>a</sup>
	SD	7.6	22.2		3.8	28.4	

CMP, currently marketed product; SD, standard deviation

<sup>a</sup>p-Values based on ANOVA with factors for center, treatment, and their interaction.

In both studies, a statistically significant treatment difference ( $p < 0.001$ ) between CMP and placebo was achieved for change from baseline in the coefficient of fat absorption, as well as on frequency of bowel movements, stool consistency, and clinical global improvement.

The difference from placebo in CFA after treatment was over 30% in both studies, which represents a clear clinical relevance.

Secondary efficacy measures were also significantly improved with the CMP compared with placebo. In both studies, the stool frequency increased in the placebo group and decreased slightly in the CMP-treated group (Table 2.9). In both studies, most patients had reported formed stools most frequently during the open-label period and this was maintained after randomization to the CMP. However, most patients randomized to placebo most frequently reported soft stools (Table 2.10). Finally, for the CGI scores, most patients were rated as unchanged or improved after randomization to the CMP whereas most patients were rated as minimally or much worse after randomization to the CMP (treatment difference,  $p < 0.001$  for each study).



**Table 2.9: Summary of Stool Frequency Data over 3 Days in Cystic Fibrosis Patients (S223.3.101 and S223.3.102)**

	Open-Label Stool Collection Period <sup>a</sup>		Double-Blind Stool Collection Period		Change from Open-Label to Double-Blind	
	Placebo	CMP	Placebo	CMP	Placebo	CMP
Study S223.3.101						
N	19	18	19	18	19	18
Mean (SE) Over 3 Days	8.1 (0.8)	9.2 (0.9)	12.4 (1.3)	8.1 (0.6)	4.3 (1.0)	-1.2 (0.7)
p-Value <sup>b</sup>					0.002	
Study S223.3.102						
N	18	18	18	18	18	18
Mean (SE) Over 3 Days	7.6 (0.7)	7.2 (0.6)	14.1 (1.7)	6.6 (0.7)	6.6 (1.4)	-0.6 (0.6)
p-Value <sup>b</sup>					< 0.001	

CMP, currently marketed product; SD, standard deviation; SE, standard error

<sup>a</sup>All patients received the CMP during open-label treatment; however, sample is broken down by double-blind treatment assignment for comparison.

<sup>b</sup>p-Values based on ANOVA with factors for center, treatment, and their interaction, using center pooling (S223.3.102 only).

**Table 2.10: Summary of Stool Consistency Data in Cystic Fibrosis Patients (S223.3.101 and S223.3.102)**

Most Frequently Reported Stool Consistency Per Patient, N (%)	Open-Label CREON Stool Collection Period <sup>a</sup>		Double-Blind Stool Collection Period		p-Value <sup>b</sup>
	Placebo	CMP	Placebo	CMP	
Study S223.3.101	N=19	N=18	N=19	N=18	0.001
Hard	1 (5.3)	1 (5.6)	1 (5.3)	2 (11.1)	
Formed	13 (68.4)	15 (83.3)	1 (5.3)	16 (88.9)	
Soft	5 (26.3)	2 (11.1)	17 (89.5)	0	
Watery	0	0	0	0	
Study S223.3.102	N=18	N=18	N=18	N=18	0.001
Hard	1 (5.6)	2 (11.1)	0	0	
Formed	16 (88.9)	12 (66.7)	4 (22.2)	12 (66.7)	
Soft	1 (5.6)	4 (22.2)	14 (77.8)	4 (22.2)	
Watery	0	0	0	0	

CMP, currently marketed product

<sup>a</sup>All patients received the CMP during open-label treatment; however, sample is broken down by double-blind treatment assignment for comparison.

<sup>b</sup>p-Values based on Cochran-Mantel-Haenszel row mean scores test, controlling for center, using center pooling (S223.3.102 only). The test compares the change between treatments (from open-label to double-blind) in most frequent stool consistency.

#### 2.4.2.2 Study S248.3.003 in Infants with Cystic Fibrosis

Study S248.3.003 was an open-label, single-arm, two-center study designed to evaluate the efficacy of the CMP for children in 12 infants/children between the ages of one and 24 months with EPI due to CF. After a no-treatment baseline period of up to 10 days, subjects were treated for 8 weeks. CREON pellets were administered by spoon directly or by sprinkling on food. Stool fat was analyzed at baseline and after 2 weeks of treatment. If subjects were already on treatment (seven of 12 subjects received enzymes before the study), they had to discontinue pancreatic enzyme supplementation for 72 hours before the baseline CFA was determined. Efficacy was determined using the change from baseline in CFA, which was analyzed using a two-sided paired t-test.

Mean age of the patients was 10.4 months; the median age was 7.2 months, with an age range of 0.9 to 22.9 months. A total of 12 subjects received CREON and efficacy data were analyzed for all. The mean daily lipase dose per kg was  $8271.8 \pm 1772.5$  units of lipase CFA and stool fat at baseline and at Week 2, and the corresponding change from baseline are summarized in Table 2.11. The baseline value reflects the maldigestion status of subjects in the absence of pancreatic enzyme supplementation.

**Table 2.11: Coefficient of Fat Absorption and Stool Fat Excretion in Study S248.3.003**

Statistic	CFA (%)			Stool Fat (g/Day)		
	Baseline	Week 2	Change from Baseline	Baseline	Week 2	Change from Baseline
N	12	12	12	12	12	12
Mean	58.0 <sup>a</sup>	84.7 <sup>a</sup>	26.7	13.3	5.3	-8.0
SD	18.0	12.1	21.7	7.0	4.6	6.5
p-Value <sup>a</sup>			0.0013			0.0013

CFA, coefficient of fat absorption

<sup>a</sup>p-Value based on a two-sided paired t-test.

Although fat intake did not change between baseline and treatment, the stool weight decreased during CREON treatment. It was concluded that CREON was effective in improving the CFA, stool fat excretion, and fecal energy loss in infants with EPI due to CF.

#### 2.4.2.3 Study S245.3.118 in Infants with Cystic Fibrosis

Study S245.3.118 was an open-label, randomized, reference-controlled crossover study designed to determine parents' preference for CREON for Children (CREON pellets in a bottle) compared with the CREON capsule formulation, on a lipase-for-lipase basis in infants with EPI due to CF. CREON pellets were administered by spoon directly or by sprinkling on food. The comparability of effects of CREON for Children and CREON capsule formulation on CFA, stool weight, fecal energy, and clinical symptoms were also

examined. The mean daily lipase dose per kg was  $4310 \pm 2763$  units of lipase. Treatment duration was 12 to 15 days. Forty subjects were treated, ranging in age from 6 to 36 months (mean age, 19.5 months).

More parents preferred CREON for Children (51.3%) compared with CREON capsule formulation (23.1%), whereas 25.6% of parents had no preference (Prescott's test,  $p=0.07$ ).

Mean (SD) on-treatment CFA values were similar, irrespective of the formulation; 77.7% (13.1%) for CREON for Children and 78.7% (14.0%) for CREON capsule. Thus, both formulations of CREON provided similar efficacy, as measured by achieved CFA, fat intake and excretion, energy intake and excretion, stool weight, and clinical symptomatology.

#### **2.4.2.4 Study S245.3.105 in Infants and Adolescents with CF**

Study S245.3.105 was a randomized, open-label, multicenter crossover study designed to investigate subjects' preference for one of two CREON formulations, CREON 10000 MMS or CREON 8000 MS, in pediatric subjects with EPI due to CF. There was a 2-week run-in period with CREON 8000 followed by two crossover periods of 4 weeks each, during which the two CREON formulations were given in a randomized order. The mean capsule intake per day for CREON MMS was 23.4 capsules (235,000 lipase units) and 26.0 capsules for CREON MS (210,000 lipase units).

Patient preference was assessed upon completion of both treatment periods, and data was analyzed with respect to stool collection, clinical symptomatology, CGI symptomatology, and patient diaries.

A total of 57 subjects ranging in age from 3.9 to 17.6 years (mean age, 10.3 years) were randomized and took CREON Capsules. Of the 22 subjects with both CFA data and stool collection data, the mean achieved CFA was consistent for CREON 10000 MMS and CREON 8000 MS (91.3% and 93.5%, respectively), as was stool fat excretion (8.4 g/day and 6.7 g/day, respectively). In addition, no difference in clinical symptomatology (stool frequency, stool consistency, flatulence, and abdominal pain) was found.

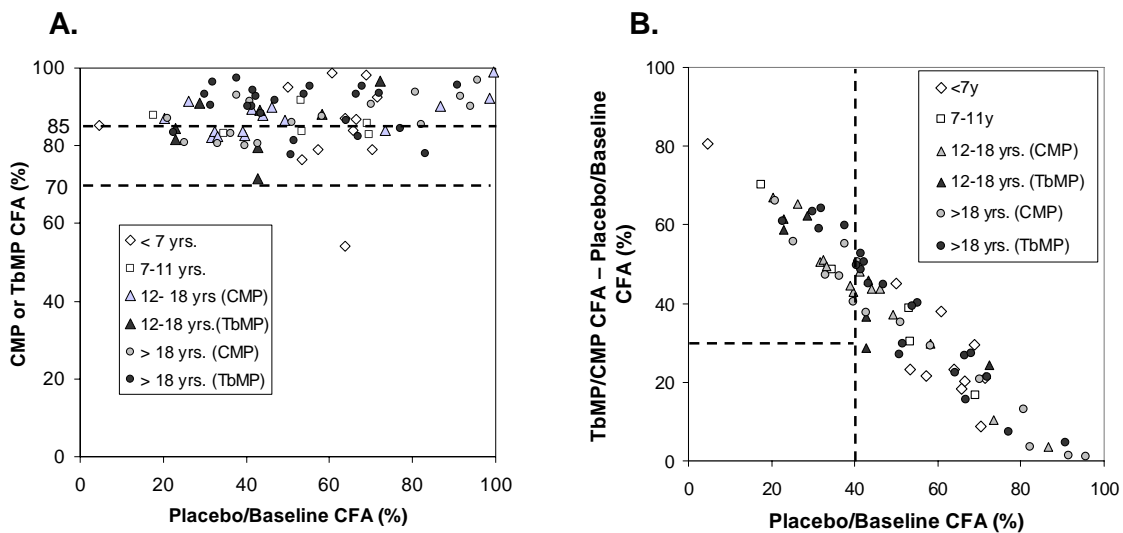
There was a greater preference for CREON 10000 MMS, which was thought to be due to the smaller size of these capsules.

#### **2.4.3 Overall Analysis of Efficacy in Cystic Fibrosis Patients**

In order to investigate whether the efficacy of CREON treatment in CF may be affected by the subjects' age, by the CREON product assessed, a graphical overlay was prepared of individual patients study results from CF trials with the TbMP or CMP that collected baseline or placebo CFA data as part of the study design. On-treatment CFA values and

changes in CFA from baseline/placebo were determined for all subjects. This approach was descriptive and no statistical inferences can be inferred.

Overall, no obvious difference was apparent between the magnitudes of effects relative to baseline for treatment with the TbMP or the CMP, irrespective of the severity of EPI as measured by the CFA during placebo treatment (Figure 2.6A). Thus, those with more severe EPI (lower CFA during placebo treatment) had correspondingly larger increases in their CFA on treatment with the TbMP or CMP (Figure 2.6B). All subjects with a placebo or baseline CFA of less than 40% had an on-treatment difference from baseline or placebo of over 30% (Figure 2.6B). No obvious differences were observed for the different products or for different age groups. CFA results from the S245.3.003 study, which enrolled infants from about 1 month to 2 years old, were not distinct from those of the other three studies, which enrolled patients from 7 to 53 years old. Overall, 99% (78/79) of subjects achieved a CFA of  $\geq 70\%$ , and 63% (50/79) achieved a CFA of  $\geq 85\%$ .



**Figure 2.6. On-Treatment Coefficient of Fat Absorption (CFA) and Differences with Treatment in Studies S245.3.126, S223.3.101, S223.3.102, and S248.3.003. (A) TbMP and CMP On-Treatment CFA as a Function of Placebo/Baseline CFA. (B) Difference Between On-Treatment CFA and Placebo/Baseline CFA as a Function of Placebo/Baseline CFA**

A summary of the efficacy data from studies of TbMP or CMP in patients with CF is presented in Table 2.12.

**Table 2.12: Summary of Efficacy in Studies with Cystic Fibrosis Patients**

Study	Product	Age group	Mean CFA on CMP or TbMP (%)	Mean CFA on Placebo (%)	Mean difference in CFA <sup>a</sup> , CMP or TbMP minus Placebo (%)	p-value
S245.3.126	TbMP	≥ 12 years	88.6	49.8	38.8	< 0.0001
S223.3.101	CMP	7-18 years	84.1	52.2	31.6	< 0.001
S223.3.102	CMP	18-40 years	87.2	50.9	34.9	< 0.001
S248.3.003	CMP	1-24 months	84.7	58.0 <sup>c</sup>	26.7 <sup>c</sup>	0.0013 <sup>c</sup>
S245.3.118	CMP	6-36 months	77.7, 78.7 <sup>b</sup>	NA	NA	
S245.3.105	CMP	< 18 years	91.3	NA	NA	

CFA, coefficient of fat absorption; CMP, currently marketed product; NA, not applicable (comparison to placebo not available); TbMP, to be marketed product

<sup>a</sup>Treatment difference is taken from change from baseline, or run-in, if available, otherwise from on-treatment values

<sup>b</sup> values for CREON for Children and CREON Capsules, respectively;

<sup>c</sup> Baseline controlled study (without treatment)

Taken together, this analysis supports labeling of CREON for patients of all ages, consistent with dosing guidelines published by the CF Foundation Consensus Conference.

## 2.4.4 Conclusions

Taken together, the data from these studies indicate the efficacy of TbMP and CMP for the treatment of maldigestion due to EPI in patients with CF. Treatment benefits are not related to patient age as appropriate dosages result in similar achieved CFA values in adults and children alike. Furthermore, the similar efficacy of the CMP and the TbMP was consistent with the only minor nature of the changes between these products.

## 2.5 Exocrine Pancreatic Insufficiency Due to Chronic Pancreatitis and in Pancreatic Surgery Patients

One study in this section assessed the efficacy of CREON in CP or PY, and two other studies focused more specifically on patients with CP.

The study in patients with CP or PY was a dose finding study of the CMP performed in Japan. In addition, the results of two double-blind, randomized, placebo-controlled, parallel-group, multicenter studies are presented of the CMP in patients with CP, one of which was performed in the US and the other in the Republic of South Africa.

### 2.5.1 Study S245.3.115: Efficacy in Adults with Chronic Pancreatitis or Pancreatic Surgery

Study S245.3.115 was a double-blind, randomized, placebo-controlled, three parallel group trial that compared placebo and the CMP at doses of 1.5 g/day and 3 g/day. This study was performed in 32 centers in Japan in adult patients with either CP or PY and was designed to show superiority of the CMP 3 g/day over placebo on the primary

efficacy measure, the change from baseline in the CFA. The comparison of the CMP 1.5 g/day with placebo was deemed secondary. Comparisons were made by specifying linear contrasts using an ANOVA model with treatment as fixed effect. Because baseline CFA values were not homogenous, the analysis was repeated using an analysis of covariance (ANCOVA) model with treatment as fixed effect and baseline CFA as covariate. This analysis was also performed separately for each of the CP and PY subgroups in the study. All patients were hospitalized for the duration of the study and were required to have a minimum fat intake of 40 grams per day. Demographic data are presented in [Table 2.13](#).

**Table 2.13: Summary of Demographic Data in Study S245.3.115**

<b>Variable</b>	<b>Placebo N=30</b>	<b>CMP 1.5 g/Day (60,000 Units Per Day) N=31</b>	<b>CMP 3.0 g/Day (120,000 Units Per Day) N=33</b>
Gender, N (%)			
Male	26 (87)	24 (77)	26 (79)
Female	4 (13)	7 (23)	7 (21)
Age, mean years (SD)	65.4 (10.2)	63.7 (9.2)	61.6 (12.4)
Diagnosis, N (%)			
Chronic Pancreatitis	12 (40)	11 (35)	12 (36)
Pancreatic Surgery	18 (60)	20 (65)	21 (64)

CMP, currently marketed product; SD, standard deviation

The FAS consisted of 94 patients. The dosage was three times 0.5 g CMP (1.5 g/day, labeled lipase activity of 60,000 units) or three times 1.0 g CMP (3.0 g/day, labeled lipase activity of 120,000 units) both with meals.

The baseline CFA values were significantly different between the treatment groups (ANOVA, FAS:  $p=0.0426$ ) – they were lowest in the placebo group and highest in the CMP 3.0 g/day. The change of the CFA between end of treatment and baseline was significantly different for the higher dose, as presented in [Table 2.14](#).

**Table 2.14: Summary of the Change of Coefficient of Fat Absorption for 3.0 g/Day and 1.5g/Day in Study S245.3.115**

<b>Statistic</b>	<b>Placebo N=30</b>	<b>CMP 1.5 g/Day N=30</b>	<b>CMP 3.0 g/Day N=33</b>
Baseline CFA, Mean (SD)	54.8 (23.6)	67.2 (19.3)	67.9 (23.7)
Treatment CFA, Mean (SD)	58.7 (19.7)	78.2 (17.8)	83.4 (11.4)
Change in CFA, Mean (SD)	3.9 (15.4)	10.9 (17.6)	15.5 (21.8)
p-Value		0.114 <sup>a</sup>	0.0148 <sup>a</sup>

CFA, coefficient of fat absorption; CMP, currently marketed product

<sup>a</sup>Comparison of CMP versus placebo: linear contrast method (ANOVA).

To adjust for heterogeneity between the treatment groups at baseline, an ANCOVA analysis was performed with the treatment group as fixed factor and the baseline CFA as a covariate (the analysis assumed a correlation between the baseline CFA and the change

in CFA). When adjusted for baseline differences, a statistically significant difference was demonstrated for both CREON groups from placebo in the FAS, as shown in [Table 2.15](#).

**Table 2.15: Results for Change in Coefficient of Fat Absorption (CFA) in the Full Analysis Set from ANCOVA with Baseline CFA in Study S245.3.115**

Statistic	Placebo N=30	CMP 1.5 g/Day N=30	CMP 3.0 g/Day N=33
Mean baseline CFA	54.8	67.2	67.9
Adjusted mean on treatment CFA	58.7	78.2	83.4
Adjusted mean change from baseline in CFA	-1.1	13.1	18.0
p-Value		0.0002	< 0.0001

CFA, coefficient of fat absorption; CMP, currently marketed product

Thirty-five patients in this study, ranging in age from 39 to 68 years (mean age, 53.4 years) had only CP. In this subset of patients, the adjusted mean change in CFA was higher in both treatment groups and the difference reached significance in the CREON 3.0 g/day group ([Table 2.16](#)). The analysis of stool fat excretion also demonstrated treatment differences. On treatment stool fat values were 22.9 g/day for placebo and 12.4 g/day for the 1.5 g dose and 9.4 g/day for the 3.0 g dose. When adjusted for baseline differences, change in stool fat for the placebo group was 1.7 g/day.

**Table 2.16: Results for Change in Coefficient of Fat Absorption (CFA) in the Full Analysis Set of Patients with Chronic Pancreatitis from ANCOVA with Baseline CFA in Study S245.3.115**

Statistics	Placebo	CMP 1.5 g/day	CMP 3.0 g/day
N	12	11	12
Mean Baseline CFA	56.7	69.8	77.9
Mean On-treatment CFA	62.2	78.7	84.9
Adjusted Mean Change from Baseline in CFA	0.3	9.7	11.4
p-Value <sup>a</sup>		0.07	0.04

CFA, coefficient of fat absorption; CMP, currently marketed product

<sup>a</sup>Comparison versus placebo; test of linear contrast from ANCOVA within the respective subgroup.

Fifty-eight subjects in this study had PY only (age range, 26-83 years). The adjusted mean change in CFA for these patients was significantly higher in both CMP treatment groups compared with placebo ([Table 2.17](#)).

**Table 2.17: Results for Change in Coefficient of Fat Absorption (CFA; %) in the Full Analysis Set of Patients with Pancreatic Surgery from ANCOVA with Baseline CFA in Study S245.3.115**

Statistics	Placebo	CMP 1.5 g/day	CMP 3.0 g/day
N	18	19	21
Mean Baseline CFA	53.5	65.1	62.2
Mean On-treatment CFA	56.3	77.8	82.6
Adjusted Mean Change from Baseline in CFA	-1.4	15.1	21.3
p-Value <sup>a</sup>		0.002	< 0.0001

CFA, coefficient of fat absorption; CMP, currently marketed product

<sup>a</sup>Comparison versus placebo; test of linear contrast from analysis of covariance within the respective subgroup.

These data indicate that the CMP is also efficacious for treatment of EPI due to CP or PY. This study also suggested a dose-dependent relationship between lipase dose and PY patients receiving a minimum amount of fat (see also [Section 2.6](#)).

#### **2.5.1.1 Efficacy in Two Studies of the CMP in Patients with Chronic Pancreatitis**

Two double-blind, randomized, placebo-controlled, parallel-group, multicenter studies were performed with the CMP (study numbers: 223.2.01 and K245.5005) in 60 patients with EPI due to CP (N=30 CMP, N=30 placebo). Study 223.2.01 was designed to show superiority of the CMP over placebo with the CFA as the primary efficacy measure. Data were analyzed by one-way ANOVA with treatment as fixed effect to test the null hypothesis of equal population means. Study K245.5005 was designed to show superiority of the CMP over placebo with the achieved CFA as the primary efficacy measure. Data were analyzed with a two sided t-test to test the null hypothesis of equal population means.

Demographic data for patients in each of these studies is shown in [Table 2.18](#).



**Table 2.18: Summary of Demographic Data Per Study in Chronic Pancreatitis Patients**

Variable	Protocol No.			
	223.2.01		K245.5005	
	CMP (N=13)	Placebo (N=14)	CMP (N=17)	Placebo (N=16)
Gender, N (%)				
Male	10 (76.9)	8 (57.1)	15 (88.2)	16 (100.0)
Female	3 (23.1)	6 (42.9)	2 (11.8)	0 (0.0)
Age, years				
Mean (SD)	51.9 (9.7)	51.0 (11.2)	50.5 (7.7)	56.3 (8.9)
Median (Range)	52 (38-74)	51 (31-69)	49 (40-66)	57 (39-68)
Race, N (%)				
Caucasian	7 (53.8)	9 (64.3)	4 (23.5)	2 (12.5)
Other	6 (46.2)	5 (35.7)	13 (76.5)	14 (87.5)

CMP, currently marketed product; SD, standard deviation

The FAS consisted of 27 patients for study 223.2.01 and of 31 patients for study K245.5005. No CFA values were assessed at baseline for study K245.5005 and so the comparison of CREON and placebo was done at the end of the treatment period.

In study 223.2.01, the mean dosage during the treatment period was comparable between the groups with 12.5 capsules per day (125,000 lipase units) in the CMP group and 14.6 capsules per day in the placebo group. The mean fat intake ( $\pm$  SD) in Study 223.2.01 was determined at baseline (CMP: 147.8 ( $\pm$  9.7) g/day, placebo 141.3 ( $\pm$  7.5) g/day) and at the end of the treatment period (CMP 141.7 ( $\pm$ 10.1) g/day, placebo 161.2 ( $\pm$  13.3) g/day).

In Study K245.5005, the mean fat intake ( $\pm$  SD) during the double-blind treatment period was 107.1 ( $\pm$  14.7) g/day in the CMP group and 110.2 ( $\pm$  10.4) g/day in the placebo group. The mean number of capsules per day in the Study K245.5005 was 15.7 (157,000 units of lipase) in the CMP group and 15.4 in the placebo group during the treatment period.

The CP studies were designed with a placebo run-in period followed by a double-blind parallel-group placebo or treatment with the CMP. In Study 223.2.01, the change from baseline for the CFA was significantly greater for the CMP compared with placebo (Table 2.19). In Study K245.5005, the difference in the CFA of the CMP treated CP subjects and placebo-treated subjects at the end of the double-blind period was statistically significant (Table 2.19).

**Table 2.19: Summary of the Coefficient of Fat Absorption (%) Per Study in Chronic Pancreatitis Patients**

		Protocol No.					
		223.2.01			K245.5005		
Period	Statistic	CMP	Placebo	p-Value	CMP	Placebo	p-Value
Baseline	N	12	14		NA	NA	
	Mean	49.9	55.9		NA	NA	
	SD	30.5	13.5		NA	NA	
Treatment	N	12	14		16	15	
	Mean	86.6	68.0		81.5	60.3	0.004 <sup>b</sup>
	SD	9.4	17.2		14.6	21.9	
Change	N	12	14		NA	NA	
	Mean	36.7	12.1	0.0185 <sup>a</sup>	NA	NA	
	SD	30.1	18.7		NA	NA	

CMP, currently marketed product; SD, standard deviation

<sup>a</sup>p-Value based on analysis of variance with treatment as fixed factor.

<sup>b</sup>p-Value based on a two-sided t-test with Satterthwaite's adjustment.

NA=not assessed.

In Study 223.2.01 the CMP presented with better results compared with placebo for stool consistency (p=0.0102), stool frequency (p=0.0015), and CGI (p=0.0435).

Thus, efficacy of the CMP for the treatment of fat maldigestion and steatorrhea secondary to EPI due to CP was confirmed in both studies, and this was accompanied by decreased stool frequency and improved stool consistency.

### 2.5.2 Overall Analysis of Efficacy Analysis in Chronic Pancreatitis and Pancreatic Surgery

The CMP effectively improved fat absorption in patients with PY or CP. An overall summary of efficacy of the TbMP and CMP in patients with CP or PY is shown in [Table 2.20](#).

**Table 2.20: Summary of Efficacy in Studies with Chronic Pancreatitis or Pancreatic Surgery Patients**

Disease	Study	Age group	Mean CFA on CMP (%)	Mean CFA on Placebo (%)	Mean difference in CFA <sup>a</sup> , CMP minus Placebo (%)	p-value
CP	S245.3.115 (CP only)	≥ 20 years	84.9 <sup>b</sup>	62.2	11.1 <sup>b,c</sup>	0.04
	223.2.01	≥ 18 years	86.6	68.0	24.6	0.0185
	K245.5005	≥ 18 years	81.5	60.3	21.2	0.004
PY	S245.3.115 (PY only)	≥ 20 years	82.6 <sup>b</sup>	56.3	22.7 <sup>b,c</sup>	< 0.001

CFA, coefficient of fat absorption; CMP, currently marketed product; CP, chronic pancreatitis; PY, pancreatic surgery;

<sup>a</sup>Treatment difference is taken from change from baseline, or run-in, if available, otherwise from on-treatment values

<sup>b</sup>CMP 3g/day

<sup>c</sup> Analysis of covariance adjusted mean

In general, and as was observed for subjects with CF, there was no obvious relationship between the baseline/placebo CFA and the CFA achieved with CMP treatment in CP and PY patients. However, baseline or placebo controlled data, particularly for patients with low placebo CFA, were not plentiful, and other differences between the studies (e.g., differences in the fat content of the diets in studies performed in different countries) did not allow a graphical representation of the independence of achieved and baseline/placebo CFA in combined study data. Nevertheless, significant increases in CFA were observed in each study despite those differences, thus supporting the generalizability of the efficacy of the CMP in patients with CP and PY.

## **2.6 Dose-Response Relationship**

Dose dependency of pancreatic enzyme replacement therapy is dependent on the dietary intake, on the severity of the EPI, and on other factors. Therefore, the existing data does not allow development of a “traditional” dose response curve.

Demonstration of dose-responsiveness for pancreatic enzyme supplements would necessarily require a focus on lipase activity, and so the fat content of the food would be of particular concern. From a physiologic standpoint, the amount of lipase enzyme provided needs to be sufficiently high to digest all fat in a meal, irrespective of variations in the nutritional content of the diet. Thus, an appropriate dose would be on the “plateau” of dose-responsiveness where the enzyme amount would be high enough to allow complete digestion of the meal.

The dose recommendations for CF subjects are based on the 2002 Consensus Conference<sup>32</sup> and the Guideline for Pancreatic Enzyme Preparations. The individual enzyme needs of patients must be taken into account for dosing. Therefore, across studies, different dietary approaches result in differences in individual fat intake.

In non-CF diseases, like in CP and in PY, doses recommendations are generally to be provided in units/meal based on literature recommendations. Layer and Holtmann<sup>42</sup> and Layer et al.<sup>43</sup> recommended a starting dose of  $\geq 25,000$ -40,000 lipase units/meal. These doses can be doubled or tripled, resulting in 75,000-80,000 units/meal, according to the patient needs.

In Study S245.3.115, a double-blind, placebo-controlled, dose-response study, two doses with standardized meals were investigated. A mean CFA of 78.2 (17.8) was reached when 20,000 units/meal were administered as compared to a mean CFA of 83.4 (11.4) when a dose of 40,000 units/meal was provided. This tends to support the dosing recommendations mentioned above and suggests that dosages  $< 40,000$  units per meal might fall into the “slope” of the dose-response curve.

In conclusion, the existing data provide some evidence of dose response for lipase activity. There are no data regarding dose response on the other enzymes (e.g., proteases, amylase).

## **2.7 Conclusion Regarding Efficacy**

Overall, the data presented indicate that the CMP and TbMP are efficacious for treatment of maldigestion in patients with EPI. The study with the TbMP in patients with CF clearly demonstrated significant superiority compared with placebo for the CFA. Furthermore, significant improvements compared with placebo were also demonstrated for the CNA, and improvements in clinical symptomatology were also evident. In addition, the treatment effects were not dependent of the age of the study subjects.

The consistent efficacy achieved in trials using the CMP or the TbMP reflects the minor nature of adjustments to the TbMP and validates the inclusion of all of these trials to support the efficacy of the TbMP. Thus, the studies with the CMP confirm the efficacy of CREON for treatment of patients with EPI due to CF and extend those findings to include patients as young as one month of age. Furthermore, the studies with the CMP extend the demonstrated efficacy of CREON to include patients with EPI due to CP or PY.

Taken together, these studies strongly suggest that the TbMP will provide an efficacious treatment option for EPI, irrespective of patients' age or underlying disease.

## **3.0 SAFETY**

This section includes safety data from clinical trials of CREON as well as comprehensive post-marketing surveillance. The clinical safety presentation includes data from both the CMP and TbMP because the products have been manufactured according to the same formulae and production process with the minor exceptions noted in [Section 1.6.3](#). A review of CREON MS safety data was performed in the subgroup of studies with CF, CP, and PY, but no different AE profile was identified. Therefore, this product will not be discussed in detail in the Clinical Safety section.

Post-marketing surveillance includes reports from the TbMP, CMP, and CREON MS. The TbMP is included, since the product has been approved in a number of non-US countries already. Furthermore, CREON MS data are provided because spontaneous reports often do not distinguish between the specific CREON products.

In addition, a discussion of fibrosing colonopathy (FC) is included.

### **3.1 Clinical Safety Database**

#### **3.1.1 Overview of Clinical Safety Database with CREON All Products**

The overall safety addressed in this section includes data from 51 studies with the TbMP, CMP, and CREON MS as of April 30, 2008, in 1532 patients. An additional ten studies, including five single-dose studies and five ongoing studies, are also included in the Supplementary tables, [Table 8.1](#), [Table 8.2](#), [Table 8.3](#), and [Table 8.4](#). As mentioned above, unless otherwise specified, discussions in the following sections are restricted to consideration of the CMP and TbMP.

The primary disease states studied were CF, CP, and PY, and tables present the data from these studies separately by etiology. Overall comparisons of disposition, demographics and TEAEs are confounded by differences in study populations (e.g., CF versus CP) and study durations, as well as by the relative paucity of placebo data in CF studies. Therefore, the focus of the discussion below is on a by-disease basis.

In the section discussing CF, the one study performed with the TbMP in CF subjects (S245.3.126) is displayed in separate columns within the tables. In the sections for each etiology, the analyses from 29 controlled multiple-dose studies with the CMP are displayed to facilitate assessment of safety data potentially attributable to the study drug. In addition, an “all CMP” group encompassed patients from all studies with the CMP for the corresponding indication.

A comprehensive overall summary on safety from all multiple-dose studies (irrespective of study design) with the CMP is also provided.

### 3.1.2 Patient Disposition

A total of 761 patients were exposed to the CMP or TbMP. Of those, 32 patients were exposed to the TbMP and a total of 761 patients were exposed to the CMP (271 in randomized, placebo-controlled trials). In the combined remaining indications (other), 136 patients were exposed in the all CMP group. Several patients received more than one product in some trials. A summary of patient disposition by disease is given in [Table 3.1](#).

**Table 3.1: Summary of Patient Disposition**

	Studies with the TbMP		Studies with the CMP		
	Placebo-Controlled		Placebo-Controlled		All Multiple-Dose Studies
	TbMP	Placebo	CMP	Placebo	All CMP
All Patients	32 <sup>a</sup>	31 <sup>a</sup>	271	241	761
Cystic Fibrosis	32 <sup>a</sup>	31 <sup>a</sup>	36	38	356
Chronic Pancreatitis	0	0	55	45	132
Pancreatic Surgery	0	0	44	22	137
Other	0	0	136	136	136

CMP, currently marketed product; TbMP, to be marketed product

<sup>a</sup>Patients were exposed to both the TbMP and placebo (crossover study)

In the sections that follow, the clinical safety evaluation is displayed separately by disease (CF, CP, and PY).

### 3.1.3 Clinical Safety in Exocrine Pancreatic Insufficiency Due to Cystic Fibrosis

#### 3.1.3.1 Patient disposition in Cystic Fibrosis Patients

The following [Table 3.2](#) presents the patient disposition for CF patients.

**Table 3.2: Patient Disposition for Cystic Fibrosis Patients**

	Studies with the TbMP		Studies with the CMP		
	Placebo controlled		Placebo controlled		All multiple dose studies
	TbMP	Placebo	CMP	Placebo	All CMP
<b>Exposed to Treatment</b>	32 (100.0) <sup>a</sup>	31 (100.0) <sup>a</sup>	36 (100.0)	38 (100.0)	356 (100.0)
<b>Completed Treatment</b>	31 (96.9) <sup>a</sup>	31 (100.0) <sup>a</sup>	35 (97.2)	35 (92.1)	325 (91.3)
<b>Withdrew under Treatment</b>	1 (3.1)	0 (0.0)	1 (2.8)	3 (7.9)	31 (8.7)
<b>Reason for Withdrawal</b>					
Adverse event	1 (3.1) <sup>b</sup>	0 (0.0)	0 (0.0)	2 (5.3)	8 (2.2)
Administrative reason	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	19 (5.3)
Withdrew consent	0 (0.0))	0 (0.0)	1 (2.8)	1 (2.6)	4 (1.1)

CMP, currently marketed product; TbMP, to be marketed product

<sup>a</sup>Patients were exposed to both the TbMP and placebo (crossover study); <sup>b</sup> one patient withdrew due to an AE after completion of the TbMP period

More than 90 % of patients completed treatment with the TbMP and CMP. The main reason for withdrawal was administrative in all CMP trials. Only a few patients withdrew due to AEs and most of those occurred in the placebo group.

### 3.1.3.2 Demographic and Other Baseline Characteristics of Cystic Fibrosis

The demographic characteristics of patients with CF are shown in [Table 3.3](#). Overall, the CREON population was male (54.5 %) with a mean age of 12 years and a mean weight of 34 kg. There were only small differences seen between the all CMP, TbMP, and placebo-treatment groups.

In all CMP studies, a substantial number of pediatric patients were exposed. One-hundred-forty-three patients (40.2%) were aged 4 to 12 years and 55 patients (15.4%) were less than 4 years. The majority of patients in the placebo-controlled studies were 12 to 30 years old.

The majority of patients in all treatment groups were Caucasian. Body weights were distributed across all lower weight ranges, which reflects the underlying disease and the young patient population.

**Table 3.3: Demographics for Patients with Cystic Fibrosis**

	Studies with the TbMP		Studies with the CMP		
	Placebo-Controlled		Placebo-Controlled		All Multiple-Dose Studies
Treatment	TbMP	Placebo	CMP	Placebo	All CMP
All Patients N (%)	32 <sup>a</sup>	31 <sup>a</sup>	36	38	356
Gender					
Male	21 (65.6)	21 (67.7)	17 (47.2)	23 (60.5)	194 (54.5)
Female	11 (34.4)	10 (32.3)	19 (52.8)	15 (39.5)	162 (45.5)
Age (years)					
Mean (SD)	23.0 (7.1)	23.2 (7.2)	17.7 (7.0)	18.3 (8.6)	12.1 (8.0)
Median	22.5	22.5	17.9	17.3	11.3
Min-Max	12.0-43.6	12.0-43.6	7.0-35.8	8.2-53.5	0.1-53.5
Age in Categories					
< 4 years	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	55 (15.4)
4-12 years	0 (0.0))	0 (0.0))	9 (25.0)	6 (15.8)	143 (40.2)
> 12-18 years	8 (25.0)	8 (25.8)	9 (25.0)	16 (42.1)	94 (26.4)
> 18-30 years	21 (65.6)	20 (64.5)	16 (44.4)	13 (34.2)	52 (14.6)
> 30-50 years	3 (9.4)	3 (9.7)	2 (5.6)	2 (5.3)	11 (3.1)
> 50-< 65 years	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.6)	1 (0.3)
≥ 65 years	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Race					
Caucasian	32 (100.0)	31 (100.0)	34 (94.4)	38 (100.0)	268 (75.3)
Black	0 (0.0)	0 (0.0)	1 (2.8)	0 (0.0)	3 (0.8)
Oriental	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	9 (2.5)
Hispanic	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Other	0 (0.0)	0 (0.0)	1 (2.8)	0 (0.0)	6 (1.7)
Unknown	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	69 (19.4)
Weight (kg)					
Mean (SD)	60.6 (12.2)	60.7 (12.4)	45.4 (12.3)	46.3 (12.8)	33.5(16.5)
Min-Max	32.7-97.8	32.7-97.8	20.8-66.2	22.4-68.0	3.3-82.4

CMP, currently marketed product; TbMP, to be marketed product

<sup>a</sup>Patients were exposed to both the TbMP and placebo (crossover study)

### 3.1.3.3 Extent of Exposure in Cystic Fibrosis Patients

The extent of exposure was assessed in terms of duration and is displayed in [Table 3.4](#). Within the all CMP treatment group, most patients were exposed to active treatment for 2 to 4 weeks. In the placebo-controlled studies, all patients were exposed for less than 2 weeks. The mean duration of exposure in CF patients was 5 - 6 days in the placebo-controlled studies for all groups. However, the mean duration in all CMP studies was more than 35 days. This difference results from the ethical consideration to avoid long-term placebo exposure in patients with EPI.

**Table 3.4: Overall Duration of Exposure in Cystic Fibrosis Patients**

	Studies with the TbMP		Studies with the CMP		
	Placebo-Controlled		Placebo-Controlled		All Multiple-Dose Studies
	TbMP	Placebo	CMP	Placebo	All CMP
<b>Exposure (Weeks)</b>					
N (%)	32 (100) <sup>a</sup>	31 (100.0) <sup>a</sup>	36 (100.0)	38 (100.0)	356 (100.0)
< 2	32 (100)	31 (100.0)	36 (100.0)	38 (100.0)	44 (12.4)
2-4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	228 (64.0)
> 4-8	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	64 (18.0)
> 8-12	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	12 (3.4)
> 12-26	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
> 26-52	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
> 52	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	8 (2.2)
Total Patient Years	0.4	0.4	0.6	0.7	35
Exposure, Mean Number of Days (SD)	5.1 (0.3)	5.1 (0.3)	6.5 (0.6)	6.4 (1.2)	35.8 (116.4)
Median	5	5	7	6	16
Min-Max	5-6	5-6	6-8	2-9	3-1509

CMP, currently marketed product; TbMP, to be marketed product

<sup>a</sup>Patients were exposed to both the TbMP and placebo (crossover study)

The mean daily lipase dose was 7659 u/day for all CMP studies and 10887 u/day for the TbMP. There were no relevant differences between the TbMP and CMP populations and the median dose for the majority of all patients and for all indications was in the range of 2,000 to 10,000 U/kg/day.

### 3.1.3.4 Summary of Adverse Events in Cystic Fibrosis Patients

Table 3.5 summarizes the overall experience of TEAEs in all studies. AEs were considered treatment emergent if they started during treatment with any study drug or worsened during treatment. Each TEAE was allocated to the treatment received by the patient at the TEAE onset.



**Table 3.5: Summary of Treatment Emergent Adverse Events in Cystic Fibrosis Patients**

	Studies with the TbMP		Studies with the CMP		
	Placebo-Controlled		Placebo-Controlled		All Multiple-Dose Studies
Treatment	TbMP	Placebo	CMP	Placebo	All CMP
No. of Patients at Risk	32 (100.0) <sup>a</sup>	31 (100.0) <sup>a</sup>	36	38	356 (100.0)
No. of TE Deaths	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
No. of Patients with at Least One TESA	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	17 (4.8)
No. of Patients with TEAE Leading to Withdrawal	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.6)	7 (2.0)
No. of Patients with at Least One TEAE	12 (37.5)	19 (61.3)	18 (50.0)	24 (63.2)	207 (58.1)

CMP, currently marketed product; TbMP, to be marketed product; TE, treatment emergent; TEAE, treatment emergent adverse event; TESA, treatment emergent serious adverse event

<sup>a</sup>Patients were exposed to both the TbMP and placebo (crossover study)

Essentially equal numbers (~2%) of patients withdrew from studies due to TEAEs in all CMP studies, although the duration of exposure was longer than for only the placebo-controlled studies. In the double-blind placebo-controlled studies, only one patient withdrew due to an AE (in the placebo group). Overall, there were no substantial differences seen in the AE profile. Treatment emergent serious AEs (TESAs) occurred in about 5% of the patients in CMP studies but no patients in any placebo-controlled trials with the CMP or TbMP. As with the difference in withdrawals, this might also be explained by the longer duration of exposure of patients in all CMP trials compared with placebo-controlled trials. One CF patient died in the open-label, long-term safety study, S245.3.117 (see [Section 3.1.6](#)).

### 3.1.3.5 Treatment Emergent Adverse Events in Cystic Fibrosis Patients

TEAEs (preferred term) that occurred in more than 5% of patients in any group with the TbMP, CMP, or placebo in all studies are displayed in [Table 3.6](#).

**Table 3.6: Treatment Emergent Adverse Events (> 5% in any group) in Cystic Fibrosis Patients**

	Studies with the TbMP		Studies with the CMP		
	Placebo-Controlled		Placebo-Controlled		All Multiple-Dose Studies
MedDRA Primary SOC/ preferred term	TbMP	Placebo	CMP	Placebo	All CMP
No. of Patients at Risk	32 (100.0) <sup>a</sup>	31 (100.0) <sup>a</sup>	36 (100.0)	38 (100.0)	356 (100.0)
Any TEAE	12 (37.5)	19 (61.3)	18 (50.0)	24 (63.2)	207 (58.1)
Gastrointestinal Disorder	6 (18.8)	12 (38.7)	10 (27.8)	22 (57.9)	92 (25.8)
Flatulence	3 (9.4)	8 (25.8)	1 (2.8)	6 (15.8)	8 (2.2)
Abdominal Pain	2 (6.3)	8 (25.8)	3 (8.3)	12 (31.6)	31 (8.7)
Vomiting	1 (3.1)	1 (3.2)	3 (8.3)	2 (5.3)	23 (6.5)
Abdominal Pain Upper	0 (0.0)	2 (6.5)	2 (5.6)	5 (13.2)	14 (3.9)
Abnormal Feces	1 (3.1)	6 (19.4)	0 (0.0)	0 (0.0)	0 (0.0)
General Disorders and Administration-Site Conditions	0 (0.0)	1 (3.2)	2 (5.6)	5 (13.2)	44 (12.4)
Pyrexia	0 (0.0)	1 (3.2)	1 (2.8)	1 (2.6)	23 (6.5)
Nervous System Disorders	4 (12.5)	6 (19.4)	3 (8.3)	3 (7.9)	44 (12.4)
Headache	2 (6.3)	6 (19.4)	3 (8.3)	3 (7.9)	42 (11.8)
Dizziness	2 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.6)
Respiratory, Thoracic, and Mediastinal Disorders	3 (9.4)	1 (3.2)	6 (16.7)	1 (2.6)	62 (17.4)
Pharyngolaryngeal Pain	1 (3.1)	0 (0.0)	3 (8.3)	0 (0.0)	10 (2.8)
Cough	1 (3.1)	0 (0.0)	1 (2.8)	0 (0.0)	43 (12.1)

CMP, currently marketed product; MedDRA, Medical Dictionary for Regulatory Activities; SOC, system organ class; TbMP, to be marketed product; TEAE, treatment emergent adverse event

<sup>a</sup>Patients were exposed to both the TbMP and placebo (crossover study)

The incidence of TEAEs in GI disorders System Organ Class (SOC) in the TbMP and CMP were much lower than in the placebo groups, demonstrating the effect of CREON on the disease-related symptomatology. In CF patients, the respiratory SOC has the second highest incidence of TEAEs, which is typical for the underlying disease. A relatively high incidence of cough was observed in all CREON trials, and again, this may be explained by the longer duration of exposure to the CMP. In general, all CF patients were suffering from chronic bronchitis with recurrent infections in the respiratory tract. No event of FC was reported.

The following [Table 3.7](#) describes the incidence of TEAEs by treatment that occurred in > 1 patient in the placebo-controlled crossover study, S245.3.126 in the TbMP treatment period, separated from the placebo treatment period as well as in both treatment periods.

**Table 3.7: Treatment Emergent Adverse Events (> 1 patient in any group) in Study S245.3.126**

	S245.3.126		
Preferred term	TbMP	Placebo	TbMP & Placebo
No. of Patients at Risk	32	31	31
Abdominal Pain	2 (6.3)	7 (22.6)	1 (3.2)
Abdominal pain upper	0 (0.0)	3 (9.7)	0 (0.0)
Abnormal faeces	0 (0.0)	5 (16.1)	1 (3.2)
Flatulence	0 (0.0)	5 (16.1)	3 (9.7)
Weight decreased	1 (3.1)	2 (6.5)	0 (0.0)
Dizziness	2 (6.3)	0 (0.0)	0 (0.0)
Headache	1 (3.1)	7 (22.6)	1 (3.2)

TbMP, to be marketed product

A higher incidence of TEAEs for GI disorders were reported by patients during the placebo period compared with TbMP.

### 3.1.3.6 Treatment Emergent Serious Adverse Events in Cystic Fibrosis Patients

All TESAEs which occurred in more than one patient in any group are displayed in [Table 3.8](#).

**Table 3.8: Summary of Treatment Emergent Serious Adverse Events (> 1 patient in any group) in Cystic Fibrosis Patients**

	Studies with the TbMP		Studies with the CMP		All Multiple-Dose Studies
	Placebo-Controlled		Placebo-Controlled		All CMP
MedDRA Primary SOC	TbMP	Placebo	CMP	Placebo	All CMP
No. of Patients at Risk	32 (100.0) <sup>a</sup>	31 (100.0) <sup>a</sup>	36 (100.0)	38 (100.0)	356 (100.0)
Any TESA	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	17 (4.8)
Gastrointestinal Disorder	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	7 (2.0)
Distal Intestinal Obstruction Syndrome	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.6)
General Disorders and Administration Site Conditions	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.8)
Pyrexia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.8)
Infections and Infestations	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	8 (2.2)
Bronchitis Acute	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.6)
Lower Respiratory Tract Infection	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.6)
Pneumonia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.6)
Respiratory, Thoracic, and Mediastinal Disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	6 (1.7)
Cough	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.8)
Bronchial Obstruction	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.6)
Productive Cough	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.6)

CMP, currently marketed product; MedDRA, Medical Dictionary for Regulatory Activities; SOC, system organ class; TbMP, to be marketed product; TESA, treatment emergent serious adverse event

<sup>a</sup>Patients were exposed to both the TbMP and placebo (crossover study)

In the CF studies, no TESAЕ occurred with the TbMP treatment or placebo. Seventeen of 356 CF patients (4.8%) reported TESAЕs with CMP in all CMP studies, and again, this might be related to the longer duration of exposure. The highest incidence of events occurred for the SOC Infections and Infestations (n=8; 2.3%) and Respiratory (n=6; 1.7%). Slightly less than 2% reported TESAЕs in the GI system. These results demonstrate that the AE profile reflects the underlying disease that affects the GI and respiratory systems.

### 3.1.3.7 Treatment Emergent Adverse Events Leading to Withdrawal in Cystic Fibrosis Patients

All TEAEs leading to withdrawal which occurred in more than one patient in any group are displayed in [Table 3.9](#).

**Table 3.9: Summary of Treatment Emergent Adverse Events Leading to Withdrawal (> 1 patient in any group) in Cystic Fibrosis Patients**

	Studies with the TbMP		Studies with the CMP		
	Placebo-Controlled		Placebo-Controlled		All Multiple-Dose Studies
MedDRA Primary SOC	TbMP	Placebo	CMP	Placebo	All CMP
No. of Patients at Risk	32 (100.0) <sup>a</sup>	31 (100.0) <sup>a</sup>	36 (100.0)	38 (100.0)	356 (100.0)
Any TEAE Leading to Withdrawal	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.6)	7 (2.0)
Gastrointestinal Disorder	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	6 (1.7)
Diarrhea	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (1.1)
Abdominal Pain	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.8)
Flatulence	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.6)
Nausea	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.6)

CMP, currently marketed product; MedDRA, Medical Dictionary for Regulatory Activities; SOC, system organ class; TbMP, to be marketed product; TEAE, treatment emergent adverse event

<sup>a</sup>Patients were exposed to both the TbMP and placebo (crossover study)

No patient had TEAEs leading to termination in the TbMP or CMP treatment groups. One patient (2.6%) in the placebo group of a CMP study and seven patients (2.0%) in the all CMP group experienced a TEAE leading to withdrawal.. The most frequent events were diarrhea (n=4; 1.1%) and abdominal pain (n=3; 0.8%). The withdrawal rate was in general very low in all CREON studies.

### 3.1.3.8 Pediatric Safety Data of Cystic Fibrosis Patients

This section describes the TEAEs by age categories with CMP and TbMP treatment in patients with CF ([Table 3.10](#)).

**Table 3.10: Treatment Emergent Adverse Events by Age in Cystic Fibrosis Patients**

	TbMP		CMP	
	Patients at Risk -	At Least One TEAE-	Patients at Risk -	At Least One TEAE-
Age Category	N	n (%)	N	n (%)
< 4 Years			55	39 (70.9)
4-12 Years			143	75 (52.4)
> 12-18 Years	8	3 (37.5)	94	54 (57.4)
> 18-30 Years	21	7 (33.3)	52	30 (57.7)
> 30-50 Years	3	2 (66.7)	11	8 (72.7)
> 50-< 65 Years			1	1 (100.0)

CMP, currently marketed product; TbMP, to be marketed product; TEAE, treatment emergent adverse event

Within the CMP group, a slightly higher incidence of TEAEs was observed in patients in age groups < 4 years old and > 10-30 years old compared with other age groups. This may be explained by more infections in these age groups, perhaps reflecting the progressing disease state of older CF patients (e.g., infections and corresponding symptoms), as well as worsening EPI (e.g., diarrhea and flatulence). The incidence of TEAEs was higher in CMP studies compared with the TbMP studies and might be explained by the longer duration of exposure in all CMP trials. The incidence of TEAEs within SOC by age in CF patients is shown in End-of-text [Table 8.5](#).

TEAEs were reviewed by gender and increasing lipase dose and no association was observed.

### 3.1.4 Clinical Safety in Exocrine Pancreatic Insufficiency Due to Chronic Pancreatitis

#### 3.1.4.1 Patient disposition in Chronic Pancreatitis Patients

The following [Table 3.11](#) describes the patient disposition for CP patients.

**Table 3.11: Patient Disposition for Chronic Pancreatitis**

	Studies with the CMP		
	Placebo controlled		All multiple dose studies
	CMP	Placebo	All CMP
Exposed to Treatment	55 (100.0)	45 (100.0)	132 (100.0)
Completed Treatment	54 (98.2)	43 (95.6)	125 (94.7)
Withdrew under Treatment	1 (1.8)	2 (4.4)	7 (5.3)
Reason for Withdrawal			
Adverse event	0 (0.0)	0 (0.0)	1 (0.8)
Administrative reason	1 (1.8)	1 (2.2)	2 (1.5)
Protocol Violations	0 (0.0)	1 (2.2)	2 (1.5)
Withdrew consent	0 (0.0)	0 (0.0)	1 (0.8)
Lost to follow-up	0 (0.0)	0 (0.0)	1 (0.8)

CMP, currently marketed product; TbMP, to be marketed product

Approximately 95 % of patients completed the treatment. Only one patient withdrew due to an AE.

### 3.1.4.2 Demographic and Other Baseline Characteristics of Chronic Pancreatitis

The demographic characteristics of patients with CP are described in Table 3.12. Overall, the populations were mainly males (87.9%) with a mean age of 54 years (only adult patients were treated) and a mean weight of 58 kg. There were only small differences seen between the TbMP, CMP, all CMP, and placebo-treatment groups. The characteristics reflected the underlying disease.

About 90% of the CP patients were male and the mean age of the patients was 55 years across all groups, which is representative for the underlying disease.

**Table 3.12: Demographics for Patients with Chronic Pancreatitis**

	Studies with the CMP		
	Placebo controlled		All Multiple-Dose Studies
Treatment	CMP	Placebo	All CMP
All Patients N (%)	55 (100.0)	45 (100.0)	132 (100.0)
Gender			
Male	49 (89.1)	39 (86.7)	116 (87.9)
Female	6 (10.9)	6 (13.3)	16 (12.1)
Age (Years)			
Mean (SD)	54.6 (9.3)	55.5 (10.3)	54.3 (9.9)
Median	53.7	54.2	54.2
Min-Max	38.9-74.9	31.0-73.0	28.8-75.0
Age in Categories			
> 18-30 yrs	0 (0.0)	0 (0.0)	3 (2.3)
> 30-50 yrs	21 (38.2)	13 (28.9)	49 (37.1)
> 50-< 65 yrs	25 (45.5)	21 (46.7)	59 (44.7)
≥ 65 yrs	9 (16.4)	11 (24.4)	21 (15.9)
Race			
Caucasian	13 (23.6)	14 (31.1)	38 (28.8)
Black	5 (9.1)	7 (15.6)	5 (3.8)
Oriental	23 (41.8)	12 (26.7)	75 (56.8)
Hispanic	0 (0.0)	0 (0.0)	0 (0.0)
Other	14 (25.5)	12 (26.7)	14 (10.6)
Weight (kg)			
Mean (SD)	60.0 (13.4)	62.8 (13.3)	57.7 (12.4)
Min-Max	32.2-116.2	43.0-96.2	32.0-116.2

CMP, currently marketed product; SD, standard deviation

### 3.1.4.3 Extent of Exposure in Patients with Chronic Pancreatitis

The extent of exposure was assessed in terms of duration of exposure and median daily lipase dose (Table 3.13). In all treatment groups, most patients were exposed to active treatment for 2 to 4 weeks. The patient exposure was 24 years for the all CMP, or 16 times higher than in the placebo-controlled studies. As with CF patients, this was due to the consideration to minimize placebo exposure in patients with EPI. Long-term data with more than 1-year treatment were available from open-label studies in a subset (~15%) of patients.

**Table 3.13: Overall Duration of Exposure in Chronic Pancreatitis Patients**

	Studies with the CMP		
	Placebo-Controlled		All Multiple-Dose Studies
Exposure (Weeks)	CMP	Placebo	All CMP
N (%)	55 (100.0)	45 (100.0)	132 (100.0)
< 2	27 (49.1)	17 (37.8)	33 (25.0)
2-4	28 (50.9)	28 (62.2)	77 (58.3)
> 4-8	0 (0.0)	0 (0.0)	0 (0.0)
> 8-12	0 (0.0)	0 (0.0)	0 (0.0)
> 12-26	0 (0.0)	0 (0.0)	4 (3.0)
> 26-52	0 (0.0)	0 (0.0)	12 (9.1)
> 52	0 (0.0)	0 (0.0)	6 (4.5)
Total Patient Years	1.7	1.5	24.3
Exposure, Mean Number of Days (SD)	11.3 (3.3)	11.9 (3.5)	67.1 (124.8)
Median	14	14	14
Min-Max	7-17	3-18	3-449

CMP, currently marketed product; SD, standard deviation

The mean daily lipase dose was 120,000 u/day for all CMP studies. The median daily lipase dose for the majority of all patients (55%) was in the range of 2,000 to 10,000 U/kg/day. For 42% of the patients, the median daily dose was < 2,000 u/kg/day in all CMP studies. There were no relevant differences between the TbMP and CMP populations.

#### 3.1.4.4 Summary of Adverse Events in Chronic Pancreatitis Patients

Table 3.14: summarizes the overall experience of TEAEs in all studies.

**Table 3.14: Summary of Treatment Emergent Adverse Events in Chronic Pancreatitis Patients**

	Studies with the CMP		
	Placebo-Controlled		All Multiple-Dose Studies
Treatment	CMP	Placebo	All CMP
No. of Patients at Risk	55 (100.0)	45 (100.0)	132 (100.0)
No. of TE Deaths	0 (0.0)	0 (0.0)	0 (0.0)
No. of Patients with at Least One TESA	1 (1.8)	2 (4.4)	4 (3.0)
No. of Patients with TEAE Leading to Withdrawal	0 (0.0)	0 (0.0)	2 (1.5)
No. of Patients with at Least One TEAE	24 (43.6)	14 (31.1)	70 (53.0)

CMP, currently marketed product; TE, treatment emergent; TEAE, treatment emergent adverse event; TESA, treatment emergent serious adverse event

TEAEs are reported for 53% of the patients of all CREON studies compared to 43% in the CMP group of placebo-controlled studies and 30% in the placebo group. This is likely due to the shorter duration of exposure of patients to placebo. In placebo-controlled studies, TESAEs occurred in 4% of the placebo patients, compared with 2 to 3% of the CMP treated patients.

### 3.1.4.5 Treatment Emergent Adverse Events in Chronic Pancreatitis Patients

TEAEs that occurred in more than 5% of patients in any group with the CMP, placebo, or in the CMP of all studies are displayed in [Table 3.15](#):

**Table 3.15: Summary of Treatment Emergent Adverse Events (> 5% in any group) in Chronic Pancreatitis Patients**

	Studies with the CMP		
	Placebo-Controlled		All Multiple-Dose Studies
	CMP	Placebo	All CMP
<b>MedDRA Primary SOC</b>			
No. of Patients at Risk	55 (100.0)	45 (100.0)	132 (100.0)
Any TEAE	24 (43.6)	14 (31.1)	70 (53.0)
Gastrointestinal Disorder	13 (23.6)	7 (15.6)	42 (31.8)
Abdominal Distension	3 (5.5)	0 (0.0)	9 (6.8)
Abdominal Pain	1 (1.8)	2 (4.4)	9 (6.8)
Constipation	5 (9.1)	1 (2.2)	9 (6.8)
Nausea	2 (3.6)	0 (0.0)	9 (6.8)
Diarrhea	1 (1.8)	1 (2.2)	7 (5.3)
General Disorders and Administration Site Conditions	4 (7.3)	5 (11.1)	23 (17.4)
Malaise	1 (1.8)	2 (4.4)	9 (6.8)
Hepatobiliary Disorders	2 (3.6)	0 (0.0)	9 (6.8)
Hepatic Function Abnormal	2 (3.6)	0 (0.0)	7 (5.3)
Infections and Infestations	0 (0.0)	1 (2.2)	9 (6.8)
Nasopharyngitis	0 (0.0)	0 (0.0)	8 (6.1)
Metabolism and Nutrition Disorders	2 (3.6)	5 (11.1)	19 (14.4)
Anorexia	0 (0.0)	0 (0.0)	7 (5.3)
Musculoskeletal and Connective-Tissue Disorders	4 (7.3)	1 (2.2)	13 (9.8)
Back Pain	1 (1.8)	1 (2.2)	8 (6.1)

CMP, currently marketed product; MedDRA, Medical Dictionary for Regulatory Activities; SOC, system organ class; TEAE, treatment emergent adverse event

The most frequently reported TEAEs occurred in the GI system. Constipation and abdominal distension were the TEAEs with the highest incidences in the CMP group in



the placebo-controlled studies. Overall, the AE profile of this patient group reflects the disease characteristics and the morbidity of these patients

### 3.1.4.6 Treatment Emergent Serious Adverse Events in Chronic Pancreatitis

An overview of all TESAEs that occurred in the placebo-controlled studies as well as all TESAEs that occurred in CP are shown in [Table 3.16](#). No TESAЕ occurred in > 1 patient in any group.

**Table 3.16: Summary of Treatment Emergent Serious Adverse Events (>1 patient in any group) in Chronic Pancreatitis Patients**

	Studies with the CMP		
	Placebo-Controlled		All Multiple-Dose Studies
MedDRA Primary SOC	CMP	Placebo	All CMP
No. of Patients at Risk	55 (100.0)	45 (100.0)	132 (100.0)
Any TESAЕ	1 (1.8)	2 (4.4)	4 (3.0)

CMP, currently marketed product; MedDRA, Medical Dictionary for Regulatory Activities; SOC, system organ class; TESAЕ, treatment emergent serious adverse event

### 3.1.4.7 Treatment Emergent Adverse Events Leading to Withdrawal in Chronic Pancreatitis Patients

No TEAE leading to withdrawal occurred in any CP patient in the placebo-controlled trials. In all CMP trials, two patients withdrew due to AE.

## 3.1.5 Clinical Safety in Exocrine Pancreatic Insufficiency in Pancreatic Surgery Patients

### 3.1.5.1 Patient Disposition in Pancreatic Surgery Patients

The following [Table 3.17](#) describes the patient disposition for PY patients.

**Table 3.17: Patient Disposition for Pancreatic Surgery Patients**

	Studies with the CMP		
	Placebo controlled		All multiple dose studies
	CMP	Placebo	All CMP
Exposed to Treatment	44 (100.0)	22 (100.0)	137 (100.0)
Completed Treatment	44 (100.0)	22 (100.0)	130 (94.9)
Withdrew under Treatment	0 (0.0)	0 (0.0)	7 (5.1)
Reason for Withdrawal			
Adverse event	0 (0.0)	0 (0.0)	5 (3.6)
Withdrew consent	0 (0.0)	0 (0.0)	2 (1.5)

CMP, currently marketed product

About 95 % of patients completed treatment. In total, five patients withdrew due to AE in all CMP trials.

### 3.1.5.2 Demographic and Other Baseline Characteristics in Pancreatic Surgery Patients

The demographic characteristics of PY patients are described in [Table 3.18](#). Overall, the CREON populations were males (> 70%) with a mean age of > 60 years (only adult patients were included in the trials) and a mean weight of about 50 kg. There were only small differences seen between the all CMP studies and the treatment groups of the placebo-controlled studies. The majority of patients in all treatment groups were Asian because the majority of patients were from studies in Japan. One trial was performed in the US.

**Table 3.18: Demographics for Patients with Pancreatic Surgery**

	Studies with the CMP		
	Placebo-Controlled	All Multiple-Dose Studies	
Treatment	CMP	Placebo	All CMP
All Patients N (%)	44	22	137
Gender			
Male	31 (70.5)	17 (77.3)	111 (81.0)
Female	13 (29.5)	5 (22.7)	26 (19.0)
Age (Years)			
Mean (SD)	65.0 (11.4)	67.9 (8.6)	59.5 (12.5)
Median	67.5	68.0	63.0
Min-Max	26.0-80.0	48.3-83.0	19.5-80.0
Age in Categories			
> 18-30 Years	1 (2.3)	0 (0.0)	4 (2.9)
> 30-50 Years	6 (13.6)	1 (4.5)	27 (19.7)
> 50-< 65 Years	6 (13.6)	6 (27.3)	43 (31.4)
≥ 65 Years	31 (70.5)	15 (68.2)	63 (46.0)
Race			
Caucasian	3 (6.8)	4 (18.2)	10 (7.3)
Black	0 (0.0)	0 (0.0)	1 (0.7)
Asian	41 (93.2)	18 (81.8)	113 (82.5)
Hispanic	0 (0.0)	0 (0.0)	0 (0.0)
Other	0 (0.0)	0 (0.0)	13 (9.5)
Unknown	0 (0.0)	0 (0.0)	0 (0.0)
Weight (kg)			
Mean (SD)	51.1 (10.2)	54.0 (12.5)	52.2 (9.7)
Min - Max	29.5-80.0	30.6-93.0	29.5-85.5

CMP, currently marketed product; SD, standard deviation

### 3.1.5.3 Extent of Exposure in Patients with Pancreatic Surgery

The extent of exposure was assessed in terms of duration of exposure and median daily lipase dose ([Table 3.19](#)). In the placebo-controlled studies, the majority of patients were exposed < 2 weeks (usually 8-9 days). As with CF and CP, the placebo exposure was limited to avoid long-term placebo exposure in patients with EPI. Among the all CMP

treatment group, most patients were exposed to active treatment for 2 to 4 weeks and about 30% of patients were treated > 26 weeks and > 52 weeks (mean, 115 days). This difference was a result of open long-term trials in Japan in this disease.

**Table 3.19: Overall Duration of Exposure in Pancreatic Surgery Patients**

Design	Studies with the CMP		
	Placebo-Controlled		All Multiple-Dose Studies
Exposure (Weeks)	CMP	Placebo	All CMP
N (%)	44 (100.0)	22 (100.0)	137 (100)
< 2	41 (93.2)	18 (81.8)	50 (36.5)
2-4	3 (6.8)	4 (18.2)	45 (32.8)
> 4-8	0 (0.0)	0 (0.0)	2 (1.5)
> 8-12	0 (0.0)	0 (0.0)	0 (0.0)
> 12-26	0 (0.0)	0 (0.0)	1 (0.7)
> 26 – 52	0 (0.0)	0 (0.0)	27 (19.7)
> 52	0 (0.0)	0 (0.0)	12 (8.8)
Total Patient Years	1.0	0.6	43.3
Exposure (Days)	8.5 (1.7)	9.2 (2.7)	115.4 (160.2)
Median	8	8	14
Min-Max	8-15	8-15	1-448

CMP, currently marketed product

The exposure for the majority of PY patients in all CREON studies (~85 %) ranged from 2,000 to 10,000 U/kg/day. The remaining 15% of patients were exposed to < 2,000 u/kg/day. The mean daily lipase dose was 150,000 u/day. There was no major difference in lipase dosing between the treatment groups.

#### 3.1.5.4 Summary of Adverse Events in Pancreatic Surgery Patients

The following [Table 3.20](#): summarizes the overall experience of TEAEs in all studies and in the placebo-controlled studies.

**Table 3.20: Summary of Treatment Emergent Adverse Events in Pancreatic Surgery Patients**

Design	Studies with the CMP		
	Placebo-Controlled		All Multiple-Dose Studies
Treatment	CMP	Placebo	All CMP
No. of Patients at Risk	44 (100.0)	22 (100.0)	137 (100.0)
No. of TE Deaths	0 (0.0)	0 (0.0)	0 (0.0)
No. of Patients with at Least One TESAE	0 (0.0)	1 (4.5)	16 (11.7)
No. of Patients with TEAE Leading to Withdrawal	0 (0.0)	0 (0.0)	3 (2.2)
No. of Patients with at Least One TEAE	29 (65.9)	13 (59.1)	91 (66.4)

CMP, currently marketed product; No., number; TbMP, to be marketed product; TE, treatment emergent; TEAE, treatment emergent adverse event; TESAE, treatment emergent serious adverse event

A similar rate of TEAEs (60-66%) occurred in patients across the studies. In total, three patients withdrew from the study because of TEAEs in all CMP studies compared with none in the placebo-controlled studies. TESAEs occurred in < 12% of patients in these trials. In the placebo-controlled studies, only one TESAe was reported in a placebo patient and no patient withdrew due to TEAEs. This is likely due to the much shorter exposure of patients to placebo (9 days versus 115 days).

### 3.1.5.5 Treatment Emergent Adverse Events in Pancreatic Surgery Patients

TEAEs that occurred in more than 5% of patients in any group with the CMP, placebo, or in the CMP of all studies are displayed in the following [Table 3.21](#):

**Table 3.21: Summary of Treatment Emergent Adverse Events (>5% in any group) in Pancreatic Surgery Patients**

	Studies with the CMP		
	Placebo-Controlled		All Multiple-Dose Studies
MedDRA Primary SOC/preferred term	CMP	Placebo	All CMP
No. of Patients at Risk	44	22	137 (100)
Any TEAE	29 (65.9)	13 (59.1)	91 (66.4)
Gastrointestinal Disorder	19 (43.2)	8 (36.4)	60 (43.8)
Abdominal Pain	5 (11.4)	2 (9.1)	20 (14.6)
Diarrhea	7 (15.9)	3 (13.6)	19 (13.9)
Abdominal Distension	2 (4.5)	3 (13.6)	14 (10.2)
Vomiting	3 (6.8)	0 (0.0)	14 (10.2)
Nausea	1 (2.3)	0 (0.0)	11 (8.0)
Flatulence	0 (0.0)	1 (4.5)	10 (7.3)
Constipation	2 (4.5)	1 (4.5)	8 (5.8)
Abdominal Tenderness	0 (0.0)	0 (0.0)	7 (5.1)
General Disorders and Administration Site Conditions	5 (11.4)	3 (13.6)	32 (23.4)
Malaise	2 (4.5)	1 (4.5)	14 (10.2)
Hepatobiliary Disorders	1 (2.3)	0 (0.0)	10 (7.3)
Hepatic Function Abnormal	0 (0.0)	0 (0.0)	8 (5.8)
Infections and Infestations	2 (4.5)	0 (0.0)	15 (10.9)
Nasopharyngitis	1 (2.3)	0 (0.0)	10 (7.3)
Metabolism and Nutrition Disorders	7 (15.9)	4 (18.2)	26 (19.0)
Hyperglycemia	5 (11.4)	0 (0.0)	13 (9.5)
Anorexia	0 (0.0)	0 (0.0)	7 (5.1)
Musculoskeletal and Connective Tissue Disorders	4 (9.1)	1 (4.5)	17 (12.4)
Back Pain	3 (6.8)	0 (0.0)	13 (9.5)
Nervous System Disorders	4 (9.1)	1 (4.5)	12 (8.8)
Headache	4 (9.1)	0 (0.0)	12 (8.8)

CMP, currently marketed product; MedDRA, Medical Dictionary for Regulatory Activities; SOC, system organ class; TbMP, to be marketed product; TEAE, treatment emergent adverse event

The most frequently affected body system in all groups was the GI system, including the symptoms typical for EPI. The incidence of TEAEs in the GI system was slightly higher in the CMP-treated patients compared with placebo and comparable to all CMP studies. Hepatic function abnormal was most frequent in all CMP trials and was probably related to the underlying diseases of CP or cancer. Hyperglycemia was the TEAE that occurred with the highest incidence in the CMP treated patients and may be explained by the presence of amylase (the enzyme responsible for starch digestion) in CREON. With PY, patients usually exhibit “brittle” diabetes due to the link between the endocrine-exocrine parts of the pancreas. The other body systems show less relevant differences in terms of TEAEs by study group. Overall, the AE profile of this patient group represents the disease characteristics and the morbidity of these patients.

### 3.1.5.6 Treatment Emergent Serious Adverse Events in Pancreatic Surgery Patients

All TESAEs (preferred term) that occurred in more than one patient in any group are displayed in [Table 3.22](#).

**Table 3.22: Summary of Treatment Emergent Serious Adverse Events (> 1 patient in any group) in Pancreatic Surgery Patients**

Design	Studies with the CMP		
	Placebo-Controlled		All Multiple-Dose Studies
	CMP	Placebo	All CMP
MedDRA Primary SOC			
No. of Patients at Risk	44 (100.0)	22 (100.0)	137 (100.0)
Any TESA	0 (0)	1 (4.5)	16 (11.7)
Gastrointestinal Disorder	0 (0.0)	0 (0.0)	6 (4.4)
Nausea	0 (0.0)	0 (0.0)	2 (1.5)
Vomiting	0 (0.0)	0 (0.0)	2 (1.5)
General Disorders and Administration Site Conditions	0 (0.0)	0 (0.0)	3 (2.2)
Pyrexia	0 (0.0)	0 (0.0)	2 (1.5)
Infections and Infestations	0 (0.0)	0 (0.0)	4 (2.9)
Liver Abscess	0 (0.0)	0 (0.0)	2 (1.5)
Neoplasm, Benign, Malignant, and Unspecified	0 (0.0)	0 (0.0)	5 (3.6)
Metastasis to Liver	0 (0.0)	0 (0.0)	2 (1.5)
Pancreatic Cancer Recurrent	0 (0.0)	0 (0.0)	2 (1.5)

CMP, currently marketed product; MedDRA, Medical Dictionary for Regulatory Activities; SOC, system organ class; TbMP, to be marketed product; TESA, treatment emergent serious adverse event

Sixteen PY patients (11.7%) reported TESAEs and the majority of those patients had pancreatic cancer in their medical history. The highest incidence of events occurring in

the GI (4.4%), Neoplasms benign, malignant and unspecified (3.7%) and Infections and infestations (2.9%) SOCs. In the placebo-controlled studies, only one patient experienced a TESA in the placebo group (hypoglycemia associated with dizziness and cold sweat).

#### **3.1.5.7 TEAEs Leading to Withdrawal in Pancreatic Surgery**

In the PY group, three (2.2%) patients discontinued CMP treatment because of TEAEs. Only anorexia was reported by more than one patient (n=3). No placebo patient withdrew from the studies due to a TEAE.

#### **3.1.6 Deaths**

In total, 9 deaths occurred in all CREON studies. Seven of these deaths were reported in open-label studies or in the compassionate use program in Japan where all patients received the CMP. Three deaths were reported in the uncontrolled trials. One patient died in Study S245.3.117 (a long-term, open-label safety study in CF patients) on Day 784 from respiratory failure after 770 days intake of the CMP. In Study S245.3.103, a patient died from respiratory failure due to side-effects of an anticancer medication 7 months after discontinuing treatment with the CMP, which had been taken for 169 days. One patient in Study S245.3.104 died 1 month after completion of the 1-year long-term safety trial. Four deaths occurred in the non-integrated data from long-term compassionate use program with the CMP in Japan.

Two additional deaths, one with CMP treatment, and one with placebo, occurred in double-blind placebo-controlled Study (S2454007) which is not yet integrated and enrolled patients with gastrectomy due to cancer. All deaths were considered unrelated to study drug.

A listing of all deaths of the clinical safety database can be found in the End-of-text [Table 8.6](#).

#### **3.1.7 Uric Acid Evaluation**

Because of the presence of purines in CREON and the risk for hyperuricemia in subjects in a catabolic status like CF,<sup>44</sup> the mean change for 24-hour urinary uric acid was investigated in two placebo-controlled CREON MMS studies in CF patients. In these trials, 5/31 adults and 2/34 children/adolescents had hyperuricosuria (> 800 mg/24 hours) during open-label CMP treatment, and the mean urinary uric acid was approximately 550 mg/24 hours ([Table 3.23](#)). During the double-blind phase, urinary uric acid decreased by 117 mg/24 hours for the placebo group and by 26 mg/24 hours for the CMP group. In the double-blind phase, hyperuricosuria was present in 3/31 adults and none of the children or adolescents in the CMP group, and in none of the patients who received placebo. Long-term data on the persistence of hyperuricosuria or the influence of the purine content of food was not available for these studies.

**Table 3.23: Urinary Uric Acid (mg/24 Hours) for Protocols S2233101 and S2233102 Combined**

	Open-Label CMP Treatment <sup>a</sup>		Double-Blind Treatment		Change from Open-Label to Double- Blind	
	Placebo	CMP	Placebo	CMP	Placebo	CMP
N	32	33	32	33	32	33
Mean	543.8	563.2	427.1	537.4	-116.7	-25.9
Standard Deviation	193.5	230.0	197.1	176.9	151.2	156.5
Minimum	101.0	124.0	8.0	205.0	-610.0	-406.0
Maximum	932.0	1077.0	790.0	872.0	125.0	259.0

CMP, currently marketed product

<sup>a</sup>all patients received the CMP during the open-label run-in period

### 3.1.8 Clinical Safety Conclusion

The safety evaluation is based on data from 51 studies with CREON, including integrated data from 29 multiple-dose studies with the CMP and the CF study with the TbMP, as well as 22 multiple-dose studies with CREON MS.

Overall comparisons of disposition, demographics, and TEAEs are confounded by differences in study populations (e.g., CF versus CP) and study durations, as well as by the relative paucity of placebo data in CF studies. Therefore, the focus of the discussion below is on a by-disease basis.

Randomized, placebo-controlled trials of CREON in patients with CF, including one study with the TbMP, have demonstrated that TEAEs are generally more frequent with placebo compared with CREON treatment. This underscores the symptomatic treatment benefits of CREON in this patient population. Over 90% of the 356 patients with CF treated with the CMP or TbMP completed treatment. Almost 60% of the CF patients reported a TEAE with any CREON product or with placebo. There were no obvious trends for TEAEs in CF patients by gender, age group, or increasing lipase dose. The most frequently affected SOC was the GI system. In the double-blind, placebo-controlled CF studies, however, GI disorders were nearly twice as frequent with placebo compared with the CMP. This pattern was driven by abdominal pain, flatulence, and stool abnormalities. GI disorders are one of the main clinical symptoms of EPI, and the higher incidence of GI disorders with placebo underscore the benefit of treatment with CREON in these patients. Other TEAEs were rare and representative for the underlying disease. Hyperuricosuria was investigated in two placebo-controlled trials in CF patients. There was some indication that the purine content of CREON may contribute to the uric acid level in CF patients. However, other sources for purines that contribute even more (e.g., food) were not investigated and no long-term data are available. Therefore, it is not possible to draw any conclusions.

Over 90% of the 132 CP patients treated with CREON MMS completed treatment. In randomized, placebo-controlled studies of patients with CP, the TEAEs occurred in approximately equal proportions of patients and were consistent with the underlying disease. More than one half of CP patients reported a TEAE with the CMP, and as was

also observed for CF, these were most frequently GI events, most predominantly constipation. However, the incidence of events such as flatulence with placebo was not as pronounced as in CF patients.

Over 90% of the 137 PY patients treated with CREON MMS completed treatment. In the double-blind, placebo-controlled studies, the proportions of PY patients treated with the CMP and placebo who reported TEAEs were approximately equal. Two-thirds of PY patients reported TEAEs with onset during the CMP and most were GI events. Hyperglycemia showed the highest incidence in the CMP group of the placebo-controlled trial and was considered related to starch digestion by amylase in these diabetes patients after pancreatic surgery.

None of the deaths were considered related to CREON treatment. TESAEs were reported in about 5% in CF patients, 3% in CP patients, and 12% in PY patients. These low rates of serious events are consistent with the low rates of withdrawal due to TEAEs. Furthermore, they are also consistent with the underlying disease and, in the case of PY patients, they reflect the fact that most were cancer patients.

In summary, the safety evaluation of 1,532 patients indicate that CREON is safe and well tolerated in infants, children, and adult patients with EPI due to CF, CP, or PY.

### **3.2 Post-Marketing Experience**

The first full year of marketing of CREON was 1984, and marketing in the US began in 1987. Therefore, this review of post-marketing safety records covers the data in Solvay Pharmaceuticals' Global Drug Safety database during the period January 1, 1984 to August 31, 2008. This database contains all case reports received from all sources worldwide (except for non-serious study cases). The AEs are coded according to the Medical Dictionary for Regulatory Activities System Organ Classes (MedDRA SOC). All AEs from clinical studies are excluded from this analysis as they are reviewed elsewhere in this document ([Section 3.1](#)).

#### **3.2.1 Patient Exposure**

In order to estimate the total patient exposure since market introduction of CREON, Solvay Pharmaceuticals calculated that each patient took an average of 2.2 g pancrelipase per day for 365 days. Based on the amount of drug sold, total exposure represents up to five million patient years.

#### **3.2.2 Summary of Adverse Drug Reaction-Reports Received**

Between January 1, 1984 and August 31, 2008, a total of 852 spontaneous, suspected adverse drug reaction (ADR)-reports were received from worldwide sources, of which 20% were considered to be serious according to the World Health Organization/International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (WHO/ICH)-criteria for seriousness. Considering the estimated exposure figures, this means that there is less than one suspected ADR-report received per 5,000 patient-years worldwide.



The overall reporting rate appears to be very low when considering the overall exposure. Most cases involve the GI tract and the skin (~60%), probably reflecting the underlying diseases involved as well as allergic and/or hypersensitivity reactions. The most frequently reported symptoms concerning the GI tract were abdominal pain (21%), diarrhea (14%), nausea (7%), flatulence (6%), and constipation (5%), while the most frequent skin reactions were rash (6%), pruritus (5%), and urticaria (3%). All other AE reports are more or less evenly distributed over the other MedDRA System Organ Classes. The majority of reports received were spontaneous reports from the market including about 45% of reports from non-healthcare professionals (consumers).

As mentioned in the clinical section above ([Section 3.1](#)), clinical trials data show that the majority of symptoms described occur with placebo treatment at comparable rates.

The issue of FC was reported in 1993 and was intensively investigated during that decade. Solvay Pharmaceuticals reviewed this issue repeatedly and found that, in all of the suspected or confirmed cases that involved CREON, other pancreatic enzyme products had also been used by the patient.

The overall review of cumulative data suggests that CREON is unlikely to be associated with the occurrence of FC. However, Solvay Pharmaceuticals continues to consider FC an important safety concern that warrants increased monitoring and a suggested warning in the label is proposed for the TbMP.

### **3.2.3 Conclusion on Post-Marketing Safety**

Post-marketing safety of CREON has been analyzed for the period from January 1, 1984 until August 31, 2008. Patient exposure to CREON during this time was estimated at about five million patient-years. The overall number of reports received (852) is remarkably low and is calculated at less than one report per 5,000 patient-years. There were no specific details that would give rise to a safety signal. FC is not considered related to CREON use.

Overall, the review of post-marketing safety data shows that CREON is safe and well tolerated. No safety signals have been detected.

### **3.3 Overall Safety Conclusion**

An analysis of 51 clinical studies of the TbMP, CREON MMS, and CREON MS in patients with EPI due to CF, CP, or PY did not reveal any serious safety issues with any CREON product. In studies of the CMP or the TbMP, more than 90% of CREON-treated patients with any of these diseases completed the studies. In all of these diseases, TEAEs usually involved the GI system. In double-blind placebo-controlled studies in CF patients, those who received placebo usually reported more frequent GI events compared with the CMP or TbMP, suggesting a relationship of these events with the underlying disease. In double-blind placebo-controlled studies of CP, there was no clear relationship of GI events with CREON treatment compared with placebo. In studies of PY, CREON-treated patients reported GI events more frequently compared with patients who received placebo.

Nevertheless, TEAEs with CREON treatment only rarely led to discontinuation from the study. Furthermore, there were no serious ADRs identified in any study.

Further analyses were also performed to look for possible associations of safety issues with age, gender, or dose. No relationship was found for any of these factors in any disease state.

The safety and tolerability indicated by clinical studies was also supported by the analysis of the post-marketing surveillance data. From a database spanning 24 years and an estimated 5 million patient-years, only 852 ADRs were reported, of which 168 were considered serious. No differences between ADR reports from US and non-US sources suggested any safety issues and no evidence was found to suggest an association of CREON with FC.

Taken together, these data indicate that CREON is safe and well tolerated in patients with EPI due to CF, CP, or PY, irrespective of patient age or gender.

## **4.0 PEDIATRICS**

### **4.1 Pediatric Labeling**

Solvay Pharmaceuticals is seeking approval of CREON with labeling that provides appropriate dosing guidance for all pediatric age groups. Pediatric labeling will be required primarily for patients with CF, which has an onset at a very young age, often at birth. CF Consensus Committees and the CF Foundation have recognized the need for initiation of pancreatic enzyme replacement therapy as soon as EPI is recognized. It is recognized that approval for these very young patients requires evidence of efficacy and safety and that has been provided in previous sections of this document ([Sections 2.0 and 3.0](#)). Moreover, it is proposed that safety information from the CMP and dosing guidelines from the CF Consensus Committees be included in the labeling.

As presented earlier in [Section 1.4.4](#), pancreatic enzyme replacement therapy is critical to achieving normal growth and development in children with CF. In the absence of pancreatic enzyme replacement therapy, approximately 90% of patients with CF would suffer from severe symptoms of maldigestion, including steatorrhea, abdominal pain, and weight loss. In children, this would ultimately result in poor growth and development, and published evidence supports the critical role of good nutritional status for the prognosis of patients with this disease. Although the age of onset of EPI may be different, the pathophysiology of pancreatic destruction and the clinical symptoms due to steatorrhea are the same for all age groups, supporting extrapolation of the need for pancreatic enzyme replacement therapy in adults to all pediatric age groups. Patients across all age groups can be effectively treated by tailoring the dose of pancreatic enzymes to their daily fat intake.

In the absence of clinical data with the TbMP for patients below the age of 12 years, Solvay Pharmaceuticals has assessed all available baseline and placebo-controlled safety and efficacy data with both the TbMP and the CMP ([Sections 2.0 and 3.0](#)). These data

demonstrate the consistency of efficacy and safety between the TbMP and the CMP in US and EU in adults and patients greater than 12 years of age. Similarly, the efficacy and safety data with both the TbMP and CMP from adults and adolescents greater than 12 years of age are comparable with safety and efficacy data with the CMP from children as young as one month of age.

There are also issues of efficacy and safety related to pediatric labeling that go beyond the demonstration of consistent efficacy and safety of the TbMP and CMP. Approval of the TbMP with limited labeling (patients 12 and older) could raise questions and concerns from physicians and parents of pediatric patients that were previously receiving the currently marketed CREON, which is labeled for all pediatric patients. Furthermore, limited labeling would mean that Solvay Pharmaceuticals would not be able to communicate information such as accepted CF Consensus Guidelines to physicians and caregivers who inquire about how to dose CREON to patients less than 12 years of age. As a result, physicians might switch CREON patients to other unapproved pancreatic enzyme products that are labeled to dose children less than 12 years of age. It is further possible that, once CREON is approved, other unapproved products may promote for use in CF regardless of age. It is well known these products have different characteristics and they perform differently. In the Federal Register Notice issued April 28, 2004, the FDA noted, "There are safety issues associated with the continued marketing of unapproved pancreatic enzyme products." Thus, diagnosed patients may be switched to or started on enzyme products that have not been evaluated for efficacy or safety and may not be pursuing approval of an NDA with due diligence.

Solvay Pharmaceuticals is requesting the Agency approve CREON with labeling for all pediatric ages based on the totality of efficacy and safety data submitted in the CREON NDA which includes data from patients as young as one month of age. It is Solvay Pharmaceuticals' position that the similarity in presentation and progression of EPI in CF between adults and pediatric patients establishes a need for pancreatic enzyme replacement therapy irrespective of age. The similarity of CREON products and the results of Study S.245.3.126 with the TbMP support the view that Solvay Pharmaceuticals' extensive clinical experience with the CMP is also applicable to the TbMP. Taken together, this provides a compelling case to support labeling for all age groups.

It is concluded that clinical and post-marketing data support the consistency of safety data between the TbMP and the CMP. Furthermore, the comparability of efficacy and safety data in patients of all ages further supports the justification to include labeling guidance for patients as young as one month of age. Solvay Pharmaceuticals recommends that reference be made in the labeling to the CF Consensus Conference Guidelines to provide prescribing physicians, patients, and their families with necessary guidance on appropriate use of pancreatic enzymes. CREON will most certainly be used by physicians in children aged as young as one month. Importantly, many patients will be transitioned to the new product and may be uncertain about dosing changes. During this transition period, it is appropriate to provide within the CREON labeling the CF Consensus

Guidelines regarding dosing of pancreatic enzymes to provide the needed guidance for physicians and caregivers of patients with CF. This guidance will help promote the appropriate use of CREON Capsules by these patients. Solvay Pharmaceuticals also recommends that all relevant safety information, including that obtained with the CMP, be incorporated into the labeling so that patients and physicians may have access to this information.

#### **4.2 Pediatric Study Commitment**

Solvay Pharmaceuticals currently has committed to generate additional pediatric data with the TbMP. One placebo-controlled study (S245.3.127) is ongoing to evaluate the efficacy and safety of the TbMP in CF patients 7-11 years of age. A second study (S245.3.128) will be initiated early next year; the TbMP will be evaluated in infants to children 6 years of age.

#### **4.3 Dosage and Administration**

CREON Capsules is orally administered and contains delayed-release, porcine-derived pancrelipase.

Patients with pancreatic insufficiency should consume a high-calorie diet with unrestricted fat, appropriate for age and clinical status. The dosage of CREON Capsules should be individualized and determined by the degree of steatorrhea present and the fat content of the diet. Therapy should be initiated at the lowest possible dose and gradually increased until the desired control of steatorrhea is obtained.

**CREON Capsules should always be taken as prescribed by your healthcare provider during meals or snacks with sufficient fluid.** 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.

When swallowing of capsules is difficult, the capsules may be carefully opened and the contents added to a small amount of low-acidic soft food with a pH less than 5.5, such as apple sauce, pudding, mashed or pureed bananas or carrots at room temperature. The soft food should be swallowed immediately without chewing and followed with water or juice to ensure the pancrelipase spheres are swallowed completely.

CREON Capsules should be swallowed immediately during regular feedings or meals. Care should be taken to ensure no enteric-coated pancrelipase spheres are retained in the mouth.

#### **Dosing in Patients with Cystic Fibrosis**

Dosage recommendations for pancreatic enzyme replacement therapy were published following the Cystic Fibrosis Foundation Consensus Conferences.<sup>1,2</sup> CREON Capsules should be administered in a manner consistent with the recommendations of the

Conferences as stated in the following paragraphs. Patients may be dosed on a fat-based or weight-based dosing scheme.

### **Infants (Up to 12 Months)**

Infants may be given 2,000 to 4,000 lipase units per 120 mL of formula or per breast-feeding.

### **Children and Older**

*< 4 Years:* Enzyme dosing should begin with 1,000 lipase units/kg per meal for children less than age 4 years to a maximum of 2,500 lipase units/kg per meal or < 4,000 lipase units/g fat per day.

*> 4 Years:* Enzyme dosing should begin with 500 lipase units/kg per meal for those older than age 4 years to a maximum of 2,500 lipase units/kg per meal or < 4,000 lipase units/g fat per day.

Enzyme doses expressed as lipase units/kg per meal should be decreased in older patients because they weigh more but tend to ingest less fat per kilogram of body weight. Usually, half the standard dose is given with snacks. The total daily dose should reflect approximately three meals and two or three snacks per day.

If symptoms and signs of malabsorption persist, the dosage may be increased by the healthcare provider. Patients should be instructed not to increase the dosage on their own. There is great inter-individual variation in response to enzymes; thus a range of doses is recommended. Changes in dosage or product may require an adjustment period of several days. If doses exceed 2,500 lipase units/kg per meal, further investigation is warranted. Doses greater than 2,500 lipase units/kg per meal should be used with caution and only if they are documented to be effective by 3-day fecal fat measures that indicate a significantly improved coefficient of absorption.

## **5.0 VIRAL RISK ASSESSMENT AND MITIGATION STRATEGY**

### **5.1 Executive Summary**

Because CREON is produced from native porcine pancreas, the possibility of contamination of the starting material with relevant viruses, i.e., potentially present in swine and capable of infecting humans has to be considered. To determine the potential risk of viral contamination, Solvay Pharmaceuticals has performed a risk analysis and has implemented measures to control and reduce the potential risk at all steps of production from careful selection of animal materials, a controlled and validated manufacturing process through testing and release of the final product.

In compliance with international and national guidelines concerning the viral safety of medicinal products animals used are only those released fit for human consumption. The selection of supplier countries strictly considers and evaluates implementation of a

reliably functioning system relating to slaughtering and food hygiene, compliance with animal health rules and implementation of a disease surveillance system. All suppliers must meet strict criteria, including appropriate approval by competent veterinary bodies, veterinarian oversight, implementation of surveillance systems, ongoing hazard analysis, and appropriate documentation. Traceability is maintained through the processes from suppliers of pigs until distribution of finished product by Solvay Pharmaceuticals.

Solvay Pharmaceuticals' production facilities also undergo regular cleaning and disinfection to minimize any possibility of the cross-contamination between batches. Further, the manufacturing process has been characterized with respect to its capability to control non-enveloped and enveloped viruses. Two distinct non-enveloped and enveloped virus inactivation mechanisms have been validated according to relevant, current guidelines.

In order to fully understand any potential risk, Solvay Pharmaceuticals has investigated and reviewed the range of viruses that are known to infect swine. These viruses can be broadly categorized as either enveloped or non-enveloped. Enveloped viruses are efficiently inactivated by multiple steps in the production process for CREON, whereas inactivation of non-enveloped viruses is more variable. However, some non-enveloped viruses can be transmissible to humans (zoonotic viruses).

Solvay Pharmaceuticals has identified a potential risk for presence of four non-enveloped, potentially or proven zoonotic viruses in the finished drug substance with relevance to human health and has developed and validated assays to test for these viruses in the drug substance as part of its release specification. Integrating the assessment of all complementary measures, the future control of viruses in the drug substance includes further viral quality risk mitigation measures. Based on this viral quality assessment and virus quality risk mitigation, the remaining theoretical risk is defined with respect to the potential level of infectious virus in the medicinal product. Thus, a clinical risk assessment of the four non-enveloped zoonotic viruses and porcine parvovirus (PPV) was performed. The assessment, which included a review of Solvay Pharmaceuticals' safety databases for confirmed zoonosis, did not reveal any evidence for a case of clinically relevant viral infection. Solvay is committed to further monitor and mitigate the remaining risk to patients.

Solvay Pharmaceuticals' process controls reflect a commitment to produce a product with the highest possible quality and safety.

## **5.2 Introduction**

Pancrelipase is a mixture of digestive enzymes extracted from porcine pancreas glands harvested only from pigs raised and slaughtered for food production. For this reason, the possibility of contamination of the starting material with swine viruses and capable of infecting humans has to be considered.

Solvay Pharmaceuticals is following international and national guidelines concerning the viral safety of medicinal products whose manufacture includes the use of materials of human or animal origin including documents on viral clearance, overall viral risk assessment, viral safety associated with plasma products, and viral safety associated with cell lines.

Detailed recommendations on viral safety are provided:

1. *Center for Drug Evaluation and Research Guidance for Industry on Exocrine Pancreatic Insufficiency Drug Products – Submitting NDAs”*
2. *ICH guideline Q5A: Viral safety evaluation of biotechnology products derived from cell lines of human or animal origin,*
3. *the Note for guidance on virus validation studies: the design, contribution and interpretation of studies validating the inactivation and removal of viruses (CPMP/BWP/268/95) of the Committee for Proprietary Medicinal Products*

In compliance with these guidelines, Solvay Pharmaceuticals has carried out a risk assessment which is provided in the following.

Porcine viruses that are relevant for pancrelipase were identified and a theoretical evaluation was performed in which the identified viruses were generally differentiated based on their physico-chemical resistance properties and based on their zoonotic potential (i.e., viruses normally found in animals but capable of infecting humans). In addition, results are presented from studies that investigated the viral quality of pancrelipase with respect to a determination of the input load of representative enveloped viruses as well as testing of non-enveloped viruses in the drug substance.

As recommended by US and international guidance documents on viral clearance and viral safety associated with plasma products, and viral safety associated with cell lines, within the following viral quality risk assessment various factors that determine the potential level of infectious virus in the medicinal product have been assessed. For this, it is summarized which measures Solvay Pharmaceuticals has established in order to ensure the virus quality of pancrelipase with respect to the identified viruses. These start with meticulous selection criteria for the sourcing of the raw material, specific measures to reduce the introduction of viruses into the raw material and include demonstrating the capacity of the manufacturing process to inactivate or remove viral contaminants. Based on the information in the subsequent sections, a rationale is provided for the selection of individual viruses, which are subject to additional control measures in the finished drug substance. Additionally, the assays which are employed in drug substance testing are described and the capability of the test assays with respect to determination of the potential level of infectious virus in the drug substance is assessed.

Based on this viral quality assessment and virus quality risk mitigation measures, the remaining theoretical risk is defined with respect to the potential level of infectious virus in the medicinal product.

Finally, the Clinical Risk Assessment integrates factors related to the use of the medicinal product that determine or influence the viral risk to the recipients.

### 5.3 Viral Quality Risk Assessment

#### 5.3.1 Identification of Porcine Viruses Relevant for Pancrelipase Viral Quality

##### 5.3.1.1 Theoretical Evaluation of Viruses Established in Swine

A total of 33 virus species from 19 virus families are well characterized in swine. Twenty species have been identified in swine within the following families, comprising enveloped viruses: *Asfarviridae*, *Arteriviridae*, *Coronaviridae*, *Flaviviridae*, *Herpesviridae*, *Orthomyxoviridae*, *Paramyxoviridae*, *Poxviridae*, *Retroviridae*, *Rhabdoviridae*, and *Togaviridae*. Of these, four have zoonotic potential (Swine Influenza virus, Vesicular Stomatitis virus, Rabies virus, and Eastern equine encephalitis virus). Further 13 species have been identified to be relevant in swine within eight non-enveloped virus families: *Adenoviridae*, *Astroviridae*, *Circoviridae*, *Caliciviridae*, *Hepeviridae*, *Picornaviridae*, *Parvoviridae*, *Reoviridae*. Of these non-enveloped viruses, three have zoonotic potential: Encephalomyocarditis virus (EMCV), Swine Vesicular Disease virus (SVDV), Porcine Rotavirus (Rota V), and two other viruses are proven zoonotic, including Hepatitis E virus (HEV) and Foot and Mouth Disease virus (FMDV).

[Table 5.1](#) and [Table 5.2](#) provide an overview of enveloped and non-enveloped swine viruses which may in general present a contamination risk using pigs as source animals. For each agent, the following topics will be covered:

- Etiology
- Host-range
- Prevalence in sourcing countries
- Disease in pigs
- Route of transmission
- Tissue/ organ tropism
- Other potential for the contamination of the raw material

Data were obtained from relevant books, review articles in scientific journals, websites and WHO documents.



**Table 5.1: Enveloped Viruses of Swine**

<i>Family/Subfamily</i>  <b>Genus</b> Species	<b>Host-range</b>	<b>Prevalence in sourcing countries</b>	<b>Disease in pigs</b>	<b>Route of transmission in pigs</b>	<b>Tissue/organ tropism</b>	<b>Other potential for raw material contamination</b>
<b><i>Arteriviridae</i>;</b> ss(+)RNA  <b>Arterivirus</b> 1) Porcine respiratory and reproductive syndrome virus (PRRSV)	Swine	endemic in EC and US	Sows: inappetence, reproductive failure (abortions or early farrowing, increased return-rates, coughing and respiratory signs) lowered fertility in boars.  In piglets diarrhea, increase in respiratory infections	contact, aerosol, venereal	differentiated macrophages such as alveolar macrophages  longlasting viremia  carriers: persistence of virus in tonsil and lymph nodes	No fecal shedding
<b><i>Asfarviridae</i> ; dsDNA</b>  <b>Asfivirus</b> 2) African swine fever virus (ASFV)	Swine  Reservoir in endemic regions (Africa): warthog, ticks	US: never reported EC: eradicated with single outbreaks; endemic in wild boar in Sardinia (Italy)	Peracute and acute with 100% mortality within 1 week  Subacute: recurrent fever over 3 weeks  Chronic form: recurrent fever, cachexia  Subclinical in reservoir hosts	oral, oronasal  indirect: arthropods iatrogenic	Initial replication site in tonsils and mandibular, less often gastric or bronchial lymph nodes; Viremia is erythrocyte- and peripheral leukocyte- associated; Replication in reticular cells, monocytes and macrophages, may also replicate in hepatocytes, endothelial cells, renal collecting duct epithelial cells, neutrophils	Fecal shedding (bloody diarrhea)

**Table 5.1: Enveloped viruses of swine (continued)**

<i>Family/Subfamily</i>  <b>Genus Species</b>	<b>Host-range</b>	<b>Prevalence in sourcing countries</b>	<b>Disease in pigs</b>	<b>Route of transmission in pigs</b>	<b>Tissue/organ tropism</b>	<b>Other potential for raw material contamination</b>
<i>Coronaviridae</i> ; ss(+)RNA						
<b>Coronavirus</b>  3) Porcine respiratory coronavirus (PRCV)	Swine	widespread in EC, lower ? prevalence in the U.S.	Usually no symptoms besides coughing	Oronasal	Initial replication in epithelial cells of nasal mucosa, lungs, tonsils, very limited infection of intestinal cells,	Nasal shedding
4) Transmissible gastroenteritis virus (TGEV)	Swine	sporadic outbreaks in Europe  Prevalent in US	rapidly spreading in naïve herds: vomiting and watery diarrhea, disease disappears spontaneously over a 3 to 5 week period, mortality is usually low  highest severity with almost 100% mortality in piglets < 7 days of age  Adult animals show varying degrees of inappetence and usually recover over a 5 to 7 day period	Oronasal	replication in enterocytes of small intestine	Fecal shedding

**Table 5.1: Enveloped viruses of swine (continued)**

<i>Family/Subfamily</i>  <b>Genus</b> Species	<b>Host-range</b>	<b>Prevalence in sourcing countries</b>	<b>Disease in pigs</b>	<b>Route of transmission in pigs</b>	<b>Tissue/organ tropism</b>	<b>Other potential for raw material contamination</b>
5) Porcine hemagglutinating encephalomyelitis virus (PHECoV)	Swine	Endemic with no clinical outbreaks in EC and US	two different disease syndromes: vomiting and wasting disease syndrome and acute encephalomyelitis, most severe in piglets around 4 days of age; in endemic regions of EC and US often subclinical	Aerosols	Initial replication in nasal mucosa, lungs, tonsils, intestinal cells?, spread from tonsillar and respiratory sites via trigeminal and vagal nerves to spinal cord and brain	
<i>Flaviviridae</i> ; ss(+)RNA <b>Pestivirus</b> 6) Classical swine fever virus (CSFV)	Swine	Eradicated from US since 1976 Eradicated in domestic pigs in EC with sporadic outbreaks Endemic in some EC regions in wild boars	acute form of CSF is highly virulent, death usually occurs within 5 to 14 days chronic form: discoloration of the abdominal skin and red splotches around the ears and extremities often occur. Pigs with chronic CSF can live for more than 100 days after the onset of infection. clinically inapparent form of CSF seldom results in noticeable clinical signs. Affected pigs suffer short periods of illness often followed by periods of recovery. Eventually, a terminal relapse occurs. The mild strain may cause small litter size, stillbirths, and other reproductive failures	oral / oronasal, transplacental	Primary replication in tonsils, spread of highly virulent strains characterized by lymphatic, viremic and visceral phases; after replication in regional lymph nodes viremic distribution proliferation in secondary target tissues of spleen, visceral lymph nodes, lymphoid tissues in the intestinal wall and bone marrow, megakaryocytes, immature granulocytes and monocytes	Shedding with all secretions and excretions (saliva, nasal and discharges, urine feces)

**Table 5.1: Enveloped viruses of swine (continued)**

<b>Family/Subfamily</b> <b>Genus</b> <b>Species</b>	<b>Host-range</b>	<b>Prevalence in sourcing countries</b>	<b>Disease in pigs</b>	<b>Route of transmission in pigs</b>	<b>Tissue/organ tropism</b>	<b>Other potential for raw material contamination</b>
7) Bovine viral diarrhoea virus (BVDV)	Artio-dactyla	low-highly prevalent in most European countries and in the U.S.	Piglets, weaners and growers: N/A  Sows: poor conception rates, abortions, fetal death, mummification, small litters	oral / oronasal,  transplacental	Primary infection of the nasal mucosa, tonsils, spread to regional lymph nodes, subsequent leukocyte-associated dissemination throughout the body	Fecal shedding
<b>Flaviviridae ;</b> ss(+)RNA  <b>Flavivirus (Arbovirus)</b>  8) West Nile Virus (WNV)	Arthropods, Birds, Equine, Humans, Rarely other mammals (sheep, dogs, pigs)	Endemic in US, EU: sporadic cases in Italy France (Rhône Delta) , Spain (Ebro Delta), Portugal	asymptomatic infection seen in pigs and dogs	Arthropod bites  <i>Enzootic life-cycle:</i> arthropod vector to birds  <i>Dead end:</i> Arthropod vector to incidental incompetent host	After subcutaneous inoculation the virus reaches regional lymph nodes and spleen; subsequent viremia and dissemination to the CNS	blood, cerebrospinal fluid  -

**Table 5.1: Enveloped viruses of swine (continued)**

<b>Family/Subfamily</b> <b>Genus</b> <b>Species</b>	<b>Host-range</b>	<b>Prevalence in sourcing countries</b>	<b>Disease in pigs</b>	<b>Route of transmission in pigs</b>	<b>Tissue/organ tropism</b>	<b>Other potential for raw material contamination</b>
9) Japanese B encephalitis virus	Mosquitos, birds, horses, rodents, pigs	Asia	No clinical effects in weaners and growers sows, boars: reproductive failure piglets : nervous symptoms	No swine to swine transmission Iatrogenic, arthropod bites, contact	viremia virus can be isolated from cerebrospinal fluids	
<b><i>Herpesviridae</i>; dsDNA</b>  <b>Alphaherpesvirinae</b>  <b>Varicellovirus</b>						
10) Pseudorabiesvirus (suid herpesvirus 1 SHV-1)	Swine, ruminants, carnivores	Eradicated in most parts of EC and in U.S.  with sporadic occurrence	Respiratory signs  Nervous signs  Reproductive failure  High mortality in piglets, low mortality in weaners and growers	oronasal	Primary replication in epithelial cells of nasopharyngeal and olfactory mucosa and tonsils with subsequent spread to regional lymph nodes and lungs. Then transport to CNS through retrograde axonal transport via olfactory and trigeminal nerves. Latency in trigeminal ganglia and tonsils	Virus may also persist in monocytes  low level viremia may lead to infection of parenchymatous organs

**Table 5.1: Enveloped viruses of swine (continued)**

<b>Family/Subfamily</b> <b>Genus</b> <b>Species</b>	<b>Host-range</b>	<b>Prevalence in sourcing countries</b>	<b>Disease in pigs</b>	<b>Route of transmission in pigs</b>	<b>Tissue/organ tropism</b>	<b>Other potential for raw material contamination</b>
<b><i>Herpesviridae</i>, dsDNA</b> <b><i>Betaherpesvirinae</i></b> <b>Roseolovirus</b> 11) Porcine cytomegalovirus (SHV-2)	Swine	endemic in US and EC, highly prevalent	Piglets/weaners: no symptoms to severe rhinitis in naïve herds; symptoms of rhinitis and pneumonia mainly in newborn pigs Naïve sows: reproductive failure	oronasal, transplacental	Primary site of infection are mucous glands of the nasal mucosa with subsequent cell-associated viremia	found in the tissues throughout the body discharges from the nose and eyes, urine and farrowing fluid
<b><i>Herpesviridae</i>, dsDNA</b> <b><i>Gammaherpesvirinae</i></b> <b>Rhadinovirus</b> 12) Porcine Lymphotropic Herpesviruses 1-3 (PLHV)	swine	endemic in pig population worldwide, highly prevalent	Unknown,  indication that co-infection with PCV-2 and PLHVs does not lead to the development of PMWS in the absence of other cofactors	oronasal,  transplacental	frequently found in the blood and in lymphoid organs; B-cells	Blood

**Table 5.1: Enveloped viruses of swine (continued)**

<i>Family/Subfamily</i>  <b>Genus</b> <b>Species</b>	<b>Host-range</b>	<b>Prevalence in sourcing countries</b>	<b>Disease in pigs</b>	<b>Route of transmission in pigs</b>	<b>Tissue/organ tropism</b>	<b>Other potential for raw material contamination</b>
<i>Orthomyxoviridae</i> ; ss(-) RNA <b>Influenzavirus A</b> 13) Swine Influenza virus	Swine	endemic in Europe: H1N1 (avian- like), H1N2, H3N2 (reassortant human- like), U.S.: classical swine H1N1, triple reassortant H3N2	in naïve herds high temperatures which cause abortions, respiratory symptoms	airborne, (nasopharyngeal route)	generally limited to the respiratory tract: lungs, nasal mucosa, tonsils trachea, tracheobronchial lymph nodes	nasal discharges
<i>Poxviridae</i> ; dsDNA <i>Chordopoxvirinae</i> 14) Suipoxvirus	Swine	endemic worldwide very low incidence	Flat macules on proximal part of limbs, ears, snout, ventral abdomen; secondary dermatitis may occur.	By arthropods (pig louse, flies)	Epidermal cells; in severe cases epithelial cells in the upper alimentary and respiratory tract may be affected	macules fluid, dry scabs

**Table 5.1: Enveloped viruses of swine (continued)**

<i>Family/Subfamily</i>  <b>Genus</b> Species	<b>Host-range</b>	<b>Prevalence in sourcing countries</b>	<b>Disease in pigs</b>	<b>Route of transmission in pigs</b>	<b>Tissue/organ tropism</b>	<b>Other potential for raw material contamination</b>
<b><i>Retroviridae</i> ; ssRNA</b>  15) Porcine endogenous retroviruses (PERV)	Swine	endemic worldwide	none	germ line	ubiquitous	-
<b><i>Rhabdoviridae</i>; ss(-)RNA</b>  <b>Vesiculovirus</b>  16) Vesicular stomatitis virus (VSV)	Cattle, horses, pigs, deer, humans, insect reservoir	endemic in South and Central America, Europe: never reported  occasion- ally in the US with sporadic outbreaks; rarely as epidemics	Clinical signs closely similar to those of FMD: lameness, fever, vesicles, mortality is usually low and most pigs recover in one to two weeks	direct contact, aerosols  arthropod vectors	epidermal cells  no viremia	vesicular fluids



**Table 5.1: Enveloped viruses of swine (continued)**

<i>Family/Subfamily</i>  <b>Genus</b> Species	<b>Host-range</b>	<b>Prevalence in sourcing countries</b>	<b>Disease in pigs</b>	<b>Route of transmission in pigs</b>	<b>Tissue/organ tropism</b>	<b>Other potential for raw material contamination</b>
<i>Rhabdoviridae</i> ; ss(-)RNA <b>Lyssavirus</b> 17) Rabies virus	Mammals	very rare in domestic pigs	nervous symptoms, paralysis 100% fatal	bite	entry of virus via sensory nerve endings of epithelial or subepithelial tissues; neuromuscular spindles; motor end plates; subsequent passive centripetal transport to CNS	saliva
<i>Paramyxoviridae</i> ; ss(-)RNA  18) Nipah virus	Swine, bats	never reported in US and EC  Single outbreaks in Southeast Asia (Malaysia)	acute febrile disease, fatal or self- limiting; morbidity is usually high but mortality is low. respiratory and /or neurological signs	Unknown/  Contact, bites	vascular endothelia, respiratory epithelia	body fluids
19) Menangle virus		single outbreaks in Australia	reproductive failure and congenital defects in pigs	respiratory? oral-fecal	Virus isolated from brain, lungs, myocardium	body fluids

**Table 5.1: Enveloped viruses of swine (continued)**

<i>Family/Subfamily</i>  <b>Genus</b> Species	<b>Host-range</b>	<b>Prevalence in sourcing countries</b>	<b>Disease in pigs</b>	<b>Route of transmission in pigs</b>	<b>Tissue/organ tropism</b>	<b>Other potential for raw material contamination</b>
<b><i>Togaviridae;</i></b> <i>ss(+)RNA</i>  <b>Alphavirus</b>  20) Eastern equine encephalitis virus (EEEV)	Mosquitoes birds, bats, reptiles, horses, human	Eastern part of the US	mosquito-borne; causes disease in humans, horses, and some bird species; high mortality rate	incidental dead end host	In horses: peripheral replication; viremia; spread to CNS probably via olfactory tract	spinal fluids

**Table 5.2: Non-Enveloped Viruses of Swine**

<i>Family/Subfamily</i> <b>Genus</b> Species	<b>Host-range</b>	<b>Prevalence in sourcing countries</b>	<b>Disease in pigs</b>	<b>Route of transmission in pigs</b>	<b>Tissue/organ tropism</b>	<b>Other potential for raw material contamination</b>
<i>Astroviridae; (+)ssRNA</i>  <b>Mamastrovirus</b>  21) Porcine astrovirus-1	Swine	unknown	gastroenteritis	fecal-oral	intestine	fecal shedding
<i>Adenoviridae; dsDNA</i>  <b>Mastadenovirus</b>  22) Porcine adenovirus (PAV)	swine	unknown, probably ubiquitous  high sero- prevalences	normally no clinically severe pathologies , single reports of pneumo-enteritis or encephalitis	(fecal)-oral  transplacental	intestine probably primary site of infection, less affinity to pulmonary epithelium	fecal shedding probably at highest titers in weaners
<i>Caliciviridae ; ss(+ )RNA</i>  <b>Vesivirus</b>  23) Vesicular exanthema virus (VEV)	swine	eradicated from world;  initial outbreak caused by virus present in fish or sea mammals fed to pigs	vesicles, similar to SVDV	oral	n/a	n/a

**Table 5.2: Non-enveloped viruses of swine (continued)**

<b>Family/Subfamily</b> <b>Genus</b> Species	<b>Host-range</b>	<b>Prevalence in sourcing countries</b>	<b>Disease in pigs</b>	<b>Route of transmission in pigs</b>	<b>Tissue/organ tropism</b>	<b>Other potential for raw material contamination</b>
<b><i>Caliciviridae</i>; ss(+)RNA</b> 24) Porcine enteric caliciviruses including Sapoviruses and Noroviruses	swine	unknown prevalence	sapoviruses infect pigs of all ages and cause diarrhea in young pigs, whereas porcine noroviruses were detected exclusively from adult pigs without clinical signs	fecal-oral	intestine	fecal shedding
<b><i>Circoviridae</i>; ssDNA</b> <b>Circovirus</b> 25) Porcine circovirus-1/-2 (PCV-1/-2)  <b>Anellovirus</b> Torque teno virus (TTV)	Swine  Humans Related viruses found in chimpanzee, African monkeys, tupaia, chickens, pigs, sheep and dogs	endemic in the U.S. and in Europe  Unknown, high sero-prevalence in European wild boar population	diarrhea, wasting in younger animals <u>PMWS</u> (Post-weaning Multi-systemic Wasting Syndrome): slow and progressive disease with a high fatality rate, starting usually at about 6 - 8 weeks of age; weaned pigs gradually become emaciated; respiratory distress and sudden death. Post weaning mortality can rise to 6 - 10% and higher. <u>PDNS</u> (Porcine Dermatitis and Nephropathy Syndrome): mainly in growers and finishers, mortality in affected pigs may be around 15%, death occurring within a few days of onset but mortality can rise much higher.  no disease known	oronasal?, direct and indirect  fecal oral?	unknown what cells are primarily infected and are permissive for the replication of PCV-2. macrophages and dendritic cells commonly contain virus in their cytoplasm but may not be the primary source of the large amounts of virus found in tissues of diseased pigs epithelial cells of lung, inguinal and mesenteric lymph nodes, tonsil and liver; macrophage-like cells  intestine	PCV-2 is presumably excreted through respiratory (nasal and tracheo-bronchial) and oral (tonsillar) secretions, urine and faeces  fecal shedding

**Table 5.2: Non-enveloped viruses of swine (continued)**

<i>Family/Subfamily</i>  <b>Genus</b> Species	<b>Host-range</b>	<b>Prevalence in sourcing countries</b>	<b>Disease in pigs</b>	<b>Route of transmission in pigs</b>	<b>Tissue/organ tropism</b>	<b>Other potential for raw material contamination</b>
<i>Hepeviridae</i> ; <i>ss(+ )RNA</i>  26) Swine Hepatitis E virus (HEV)	Swine, non-human primates, humans  cattle, dogs, rats	sero- prevalence in Europe unknown, Spain 30%, in the U.S. -80%; probably worldwide	no clinical signs	fecal-oral	primary site of replication unknown; viremia; replication in liver; virus isolated from bile, mesenteric lymph nodes, small intestine	fecal shedding viremia , bile, mesenteric lymph nodes
<i>Parvoviridae</i> ; ssDNA  <b>Parvovirus</b>  27) Porcine parvovirus (PPV)	Swine	ubiquitous worldwide; endemic in Europe and US	reproductive failure in sows, SMEDI syndrome (Stillbirth, Mummification, Embryonic Death and Infertility)  weaners/growers: none	oronasal  transplacental  (venereal)	lymphoid tissues, high mitotic activity  viremia  intestine	fecal shedding

**Table 5.2: Non-enveloped viruses of swine (continued)**

<i>Family/Subfamily</i>  <b>Genus</b> Species	<b>Host-range</b>	<b>Prevalence in sourcing countries</b>	<b>Disease in pigs</b>	<b>Route of transmission in pigs</b>	<b>Tissue/organ tropism</b>	<b>Other potential for raw material contamination</b>
<b><i>Picornaviridae</i> ; ss(+)RNA Cardiovirus</b>  28) Encephalomyo- carditis virus (EMCV)	mammals, humans, non-human primates, birds, arthropods  reservoir: rodents	sero- prevalence in Europe unknown but likely low; recent outbreaks in Italy, Greece, Cyprus, Belgium, France  US: epizootic	strains differ in pathogenicity and virulence,  particularly those in the EU tend to be less or non-pathogenic and disease in pigs is rarely diagnosed.  myocarditis, encephalitis, reproductive failure	presumably oral, (transplacental)	viremia, replication in lymphoid tissue, isolated from myocardium (highest concentrations), liver, pancreas, kidneys	fecal shedding
<b><i>Picornaviridae</i> ; ss(+)RNA Aphthovirus</b>  29) Foot and mouth disease virus (FMDV)	Bovidae, sheep, goats, swine, camelidae	eradicated in EC and U.S.  single outbreaks	Lameness, anorexia, fever, in piglets cardiac failure and sudden death is common. vesicles coronets, snouts, teats	oral  (airborne)	mucosa/lymphoid tissues of the pharynx, tonsillar region of the soft palate;  viremia;  high titers also found in pancreas without lesions	very high titers in all excretion and secretions

**Table 5.2: Non-enveloped viruses of swine (continued)**

<i>Family/Subfamily</i>  <b>Genus</b> Species	<b>Host-range</b>	<b>Prevalence in sourcing countries</b>	<b>Disease in pigs</b>	<b>Route of transmission in pigs</b>	<b>Tissue/organ tropism</b>	<b>Other potential for raw material contamination</b>
<b><i>Picornaviridae</i>;</b> ss(+)RNA <b>Enterovirus</b>  30) Swine vesicular disease virus (SVDV)	swine	eradicated in Europe with only sporadic outbreaks  U.S. never reported	clinically indistinguishable from FMD	oral; contact with vesical fluid through skin lesions,  inhalation	Primary replication at site of entry (skin, mucosa of pharynx, alimentary tract)  viremia with dissemination to sites of secondary replication (epithelia of coronary band and snout); high titers in lymph nodes draining cutaneous sites, tonsils; CNS; during viremia virus can be isolated from most organs, including pancreas	fecal shedding
31) Porcine enteroviruses (PEVs)	swine	high sero- prevalences , low disease incidence	neurological disorders, fertility disorders, and dermal lesions	oral-fecal	primary replication in intestines, lymph nodes; viremia	fecal shedding

**Table 5.2: Non-enveloped viruses of swine (continued)**

<i>Family/Subfamily</i>  <b>Genus</b> Species	<b>Host-range</b>	<b>Prevalence in sourcing countries</b>	<b>Disease in pigs</b>	<b>Route of transmission in pigs</b>	<b>Tissue/organ tropism</b>	<b>Other potential for raw material contamination</b>
<b><i>Picornaviridae</i>;</b> ss(+)RNA  <b>Teschovirus</b>  32) Porcine teschovirus 1 (PTV; formerly PEV-1)	swine	low disease incidence; sporadic outbreaks	most infections are sub-clinical and outbreaks of clinical disease are rare  partial to total paralysis, in the severe form of the disease the motor nerves are totally destroyed and the disease is irreversible.	oral-fecal	primary replication in intestines, lymph nodes; viremia; CNS	shed in large quantities in the feces
<b><i>Reoviridae ; dsRNA</i></b>  <b>Rotavirus</b>  33) Porcine rotavirus	swine	ubiquitous worldwide with up to 100% sero- conversion in adult stock endemic in the U.S. and EC	outcome of infection depends on age, virulence of virus strain, infectious dose  diarrhea in younger animals, wasting, usually persists for 3-4 days  high mortality in young piglets due to exsiccation, exacerbation	fecal-oral	primary replication in enterocytes of the tips of villi of the small intestine	fecal shedding



### **5.3.1.2 Other Potential Zoonotic Pathogens**

#### **Prion diseases**

Prion diseases or transmissible spongiform encephalopathies (TSEs) are a family of rare progressive neurodegenerative disorders that affect both humans and animals. To date, there is no published record of the natural occurrence in pigs of a transmissible spongiform encephalopathy. Because the raw materials used in production are obtained from countries with a low risk of TSEs and because sourcing is exclusively from slaughter houses that only handle swine and have appropriate controls to prevent co-mingling of raw materials, the risk for contamination of pancrelipase with prions is negligible and is not considered further.

#### **Mycoplasmas**

Mycoplasmas are a distinct class of eubacteria that lack cell walls but possess distinctive sterol-containing plasma membranes and have an exceptionally small genome. Numerous mycoplasma species appear to comprise the commensal microbial flora of healthy pigs and humans, although they may cause acute and chronic diseases and have been implicated as cofactors in disease. Mycoplasmas are efficiently inactivated by the alcohol and drying steps of the production process and so they are not considered further.

### **5.3.1.3 Exploratory Studies to Determine Initial Virus Load for Enveloped Viruses in Raw Material Used in Pancrelipase Manufacturing Process**

In addition to the theoretical evaluation as summarized before, 1 studies were conducted as requested in the CREON NDA 20-725 approvable letter with respect to a determination of the input viral load, in order to compare these data with the virus clearance capability of Solvay Pharmaceuticals' drug substance process determined in viral clearance studies. This evaluation demonstrated a robust safety margin for enveloped viruses as adventitious contaminants calculated per daily dose. Detailed information on this study is presented in Appendix 2.

### **5.3.1.4 Exploratory Studies to Determine the Virus Load for Non-enveloped Viruses in the Finished Drug Substance**

Detailed information on this study is presented in Appendix 2.

Among non-enveloped viruses, Solvay Pharmaceuticals' investigations have demonstrated a distinction between medium and high resistance with respect to physico-chemical treatment. Viral clearance study experiments could not demonstrate significant inactivation of non-enveloped viruses with high resistance like PPV, whereas medium resistant non-enveloped viruses like EMCV are significantly inactivated.

#### **5.3.1.4.1 Investigations into Presence of Porcine Parvovirus in Pancrelipase Employing Quantitative PCR Method and Infectivity Assays**

The quantitative PCR (Q-PCR) assay for PPV was established in 2002/03 and used for several investigations of PPV in pancrelipase. In the first studies conducted in co-operation with other manufacturers of pancrelipase in September 2002, approximately ten representative batches from each manufacturer were tested for the presence of PPV specific sequences in the drug substances, and all revealed positive results. More detailed information is provided in Appendix 2.

Additionally, investigations for comparison levels of DNA copies quantified using Q-PCR with the infectivity in these samples determined by cell culture assay did not allow any correlation between the level of PPV genomics and the level of infectious PPV. For that reason, infectivity assay is the most relevant assay for pancrelipase batch release testing.

#### **5.3.1.4.2 Testing of Potentially Zoonotic Viruses in Drug Substance Employing Quantitative PCR Method**

As communicated previously to the FDA, batch release testing for potential human pathogen viruses was introduced on each active pharmaceutical ingredient (API) batch between June 2005 and January 2006.

### **5.3.2 Risk Assessment for the Drug Substance**

#### **5.3.2.1 Sourcing of the Raw Material and Specific Measures to Reduce the Introduction of Viruses into the Raw Material**

For detailed information on this whole section please refer to Appendix 2.

One batch of pancrelipase drug substance requires glands from several thousand pigs, which can only be attained by the use of by-products (organs) of pigs slaughtered for food purpose. Several selection criteria and audit approval procedures are in place at Solvay Pharmaceuticals ensuring that the raw material is exclusively derived from controlled and selected sources and suppliers. These controls are summarized below.

#### Suppliers

Solvay Pharmaceuticals selects supplier countries very strictly after meticulous consideration to ensure implementation of a reliably functioning regime relating to slaughtering and food hygiene, compliance with animal health rules, and implementation of a working epizootic disease surveillance system. Only European countries and the USA are used as supplier countries. The general notifiable disease animal health status in Solvay Pharmaceuticals' supplier countries is summarized in Appendix 2.

### Slaughter of pigs and collection of pancreases

Solvay Pharmaceuticals has implemented further approval eligibility criteria for slaughterhouses that ensure that exclusively pancreas glands derived from pigs approved “fit for human consumption” are processed.

### Traceability

Traceability is maintained through the processes from suppliers of pigs until distribution of finished product by Solvay Pharmaceuticals

The compliance to these requirements is subject to regular audits Solvay Pharmaceuticals performs in order to approve and control each single supplier slaughterhouse and trading company cold-store.

### Maintenance animal medical reports and documentation of feeds

In the U.S. the use of food products is governed by the provisions of the FFDCA, and the regulations issued under its authority. The FFDCA defines food as "articles used for food or drink for man or other animals". Therefore, any product that is intended to be used as an animal feed ingredient, to become part of an ingredient or feed, or added to an animal's drinking water is considered a "food" and thus, is subject to regulation. FDA's Center for Veterinary Medicine (CVM) is responsible for the regulation of animal food (feed) products and all activities concerning animal feeding are consolidated in an Animal Feed Safety System. CVM monitors and establishes standards for feed contaminants, approves safe food additives, and manages the FDA's medicated feed and pet food programs. The Feed Contaminants Program (7371.003) builds up the framework for controlling the presence of deleterious chemicals and microorganisms in feed.

Concerning the feeding of animal protein to farmed animals, the 1997 ruminant feed final rule (21 CFR 589.2000) prohibits the use of mammalian derived proteins in ruminant feed, with the exception of certain proteins believed at that time not to pose a risk of bovine spongiform encephalopathy (BSE) transmission. Currently, the FDA is proposing to amend the agency's regulations to prohibit the use of certain cattle origin materials in the food or feed of all animals (Federal Register/ Vol.70, No. 193/ Thursday, October 6, 2005/ Proposed Rules; 21 CFR Part 589).

Since January 1, 2006, an European Community- (EC-) wide regime relating to food hygiene has been in place with a view to establishing a comprehensive and integrated policy covering all food starting at the farm level through to the point of sale to the consumer (Regulation (EC) No 178/2002). Within its integrated approach, the new regime covers all aspects of animal nutrition and animal feeding stuffs. This comprises feed additives (Regulation (EC) No 1831/2003), feed materials (Regulation (EC) No 1774/2002), undesirable substances (Directive 2002/32/EC), medicated feed, feed hygiene (approval and registration of establishments and intermediaries; Regulation EC (No) 183/2005) as well as corresponding official inspections, methods of sampling and analyses to control compliance with the regulations.

The key community legislation relating to community ban on the feeding of animal protein to farmed animals is based on Council Decision 2000/766/EC, as last amended by Commission Decision 2002/248/EC. Exclusion of all specified risk materials (Regulation (EC) No 999/2001 and amending Commission Regulation (EC) No 1292/2005) and fallen stock (Regulation (EC) No 2001/25) from any farm animal feed is ruled as well as approval of feed establishments and processing standards are (Regulation (EC) No 1774/2002, Commission Decision (EC) No 2001/9).

With regard to application of veterinary medicinal products in farmed animals, Council Directive 90/676/EWG rules prescription and documentation modalities. Special precautions must be taken by the veterinarian in order to avoid any unnecessary risk to the consumer of foodstuffs obtained from the treated animal and the veterinarian as well as the farmer is obliged to record identity of the treated animal, pharmaceutical substance, mode of administration, dose and waiting time. Records must be kept for at least 5 years. Additionally, Council Regulation (EEC) No 2377/90 (as last amended by Commission Regulation (EC) No 205/2006) classifies pharmacologically active substances used in veterinary medicinal products and establishes maximum residue limits for all pharmacologically active substances used in the Community in veterinary medicinal products administered to food-producing animals.

#### **5.3.2.2 The Capacity of the Manufacturing Process to Inactivate or Remove Viral Contaminants**

Solvay Pharmaceuticals has conducted several viral clearance studies since 1997 in order to determine the process capability of the pancrelipase manufacturing process to control adventitious enveloped and non-enveloped viruses using a very broad range of relevant and model viruses. In compliance with *ICH guideline Q5A: Viral safety evaluation of biotechnology products derived from cell lines of human or animal origin and the Note for guidance on virus validation studies: the design, contribution and interpretation of studies validating the inactivation and removal of viruses (CPMP/BWP/268/95) of the Committee for Proprietary Medicinal Products* two distinct viral clearance mechanisms have been validated in validated scale-down experiments under worst-case process parameters.

Detailed information is provided in Appendix 2.

#### **5.3.2.3 Viral Quality Measures in the Finished Drug Substance: Rationale and Testing Method**

##### **5.3.2.3.1 Rationale for Selection of Test Viruses**

##### **Enveloped viruses**

Results of virus clearance studies demonstrated that the production process of pancrelipase is highly effective in inactivating enveloped viruses. Additional studies into the worst-case initial load of the raw material porcine pancreas glands have further demonstrated that the process is capable of controlling enveloped viruses with a significant safety margin of at least 1000-fold daily dose. Thus, even in events of high

enveloped virus loads, the risk of contamination of the final drug substance with enveloped viruses, irrespective of whether they are known to be present in swine or emerging, is regarded as negligible.

### **Non-enveloped viruses**

Virus clearance studies as well as investigations into the viral contamination of pancrelipase drug substance have shown that the production process for pancrelipase does not inactivate all non-enveloped viruses to the same extent. Rather, one has to distinguish between medium resistant and very high resistant non-enveloped viruses. Non-enveloped viruses with comparably lower tenacity are moderately inactivated whereas the infectivity of very resistant viruses is not appreciably reduced.

In general, measures installed for the sourcing of the raw material pig pancreas glands reveal reasonable diligence regarding minimization of the risk of viruses being introduced into the production of pancrelipase. Where contamination with viruses still cannot be excluded, in the following section each relevant virus is dealt with individually. Particular emphasis was given to review of aspects relevant to likelihood of occurrence in pancrelipase such as prevalence in pigs; measures installed for the raw material; resistance to viral clearance steps in the manufacturing process; as well as to aspects relevant to probability of causing disease such as the route of transmission and zoonotic potential. Furthermore detailed information on the control and surveillance situation of the diseases in the supplier countries is provided.

Based on an evaluation of the process virus inactivation capability and/or measures during the sourcing process as well as on the zoonotic relevance, a conclusion was reached regarding the selection of viruses, which will be tested in the API. More detailed information is provided in Appendix 2.

### **Evaluation of individual non-enveloped porcine viruses**

#### **Porcine astrovirus-1**

Members of the family *Astroviridae* are small, non-enveloped RNA viruses. Distinct virus species exist in humans and animals. Limited data is available regarding cross-species transmissions but person-to-person spread by the faecal-oral route remains the main route of transmission in humans. Astroviruses are primarily associated with mild gastroenteritis in infants and young animals, although elderly, hospital patients and immunocompromised individuals can also be affected. These viruses display many of the epidemiologic and clinical features of rotaviruses but are not as common and not as virulent.

#### **Porcine adenoviruses**

The porcine adenoviruses belong to the family *Adenoviridae*, genus *Mastadenovirus*. The pathogen is probably distributed worldwide and most vertebrates are infected by adenovirus species. The genus *Mastadenovirus* presently contains, among others, 51 human adenovirus and 5 porcine adenovirus (PAV) species. In spite of the existence of

reported cases of pneumo-enteritis or encephalitis, PAVs do not normally produce clinically severe pathologies in swine.<sup>45</sup> To date, no case of inter-species transmission has been reported.

### **Porcine circovirus-1 and -2**

The porcine circovirus (PCV) belongs to the family *Circoviridae*. In 1974, porcine circovirus type 1 (PCV-1) was isolated from a line of swine kidney cells used for laboratory research purposes. To this date, no clinical significance has been demonstrated for PCV-1. Serological surveys for PCV-1 indicate the virus is widespread throughout swine herds and most pigs have been exposed. Another distinct swine porcine circovirus, PCV-2, was identified and associated with post-weaning multi-systemic wasting syndrome (PMWS) and porcine dermatitis and nephropathy syndrome (PDNS), now collectively known as Porcine-Circovirus-Associated Diseases (PCVAD).<sup>46</sup> However, because this organism is so common, it is believed some additional triggering mechanism is required for the infection to result in the full spectrum of clinical symptoms PCVAD (PMWS or PDNS).

PCV is shed in feces and nasal secretions of recently infected pigs. Like PPV, PCV virions are resistant to inactivation and are difficult to remove from the environment.

Porcine circoviruses appear to be host specific for swine. There are no reports of human disease associated with porcine circovirus infection according to current knowledge:

Tischer et al. reported the prevalence of PCV-1 specific antibodies in human sera, mice sera and bovine sera.<sup>47</sup> However, it was concluded that the antibodies were related with high probability to species-specific viruses sharing antigenic epitopes with PCV. Further, other studies did not find antibodies to PCV in serum samples from a range of domestic animal species and humans. Another study was conducted in 50 veterinarians in swine practice in the US who had reported having blood-to-blood contact with swine as well as from laboratory workers who had contact to PCV-2.<sup>48</sup> With three different enzyme-linked immunosorbent assays (ELISAs), antibodies to PCV-1 or PCV-2 could not be detected in any of the samples tested in the study. Therefore, the available evidence does not support the notion that PCV may be zoonotic.

### **Porcine enteric caliciviruses**

Within the family *Caliciviridae*, four genera have been distinguished: Vesivirus, Lagovirus, Norwalk-like viruses (NLV), and Sapporo-like viruses (SLV). The genera Vesivirus and Lagovirus contain a broad range of animal caliciviruses that are suspected or confirmed to cause a wide spectrum of diseases, including gastroenteritis (pigs, calves, cats, dogs, and chickens), and vesicular lesions and reproductive failure in pigs and sea lions. Viruses in the NLV and SLV genera until recently have been found only in humans. In recent years, human caliciviruses (HuCV; also known as small round-structured viruses), have emerged as one of the leading causes of epidemic, nonbacterial gastroenteritis in humans of all ages.<sup>49</sup> Also, Norwalk-like virus genes were detected in the cecal contents of slaughtered pigs without clinical signs<sup>50</sup> and certain porcine norovirus strains were shown to be genetically and antigenically related to human

noroviruses. These findings show that genetically related viruses are commonly found in different species without resulting in apparent widespread interspecies transmission.<sup>51</sup>

### **Vesicular exanthema of swine virus**

Vesicular exanthema of swine virus (VESV) belongs to the *Caliciviridae* family which has been described in and can cause vesicular disease in susceptible mammals. Vesicular exanthema of swine (VES) is a disease that has been eradicated from the world. It is now believed that the initial outbreak was caused when a closely related virus present in fish or sea mammals was fed to pigs, became adapted to pigs, and then spread among them.<sup>52</sup>

### **Porcine parvovirus**

Porcine Parvovirus is a member of the subfamily *Parvovirinae* of the family *Parvoviridae* that exhibit remarkable high physico-chemical stability. Parvoviruses are widespread pathogens that cause a wide range of diseases in animals. PPV is ubiquitous in the swine population worldwide, causing reproductive failure in pregnant females and fetal death. Vaccines against PPV are used successfully worldwide to prevent reproductive problems. Seroprevalence of anti-PPV antibodies within the pig population is very high (60 and 90%), and pigs may be infected and shed infectious virus without showing any symptoms. Despite a distinct humoral immunity parvovirus infections are often persistent, with chronic shedding of virus. Therefore, it is very likely that PPV genome can be detected in porcine serum or tissue specimens. In healthy pigs, PPV can be detected in 80% of the lymph nodes and in 45% serum samples. In sick as well as in apparently healthy animals the fecal detection of PPV is 10%.

Human parvoviruses are known within two distinct parvoviridae genera. The human parvovirus B19 which belongs to the genus *Erythrovirus*, causes “fifth disease” in children although it is more benign in adults and it is widespread globally. In industrialized countries, a seroprevalence rate up to 80% has been found by ages 60 to 70. Recently, a second human parvovirus 4 (PARV4), was identified from the plasma sample of a homeless, daily injection drug user who presented with an acute viral infection.<sup>53</sup> Subsequently, PARV4 and its variants were identified in 4–5% of pooled human plasma used in the manufacture of plasma-derived medical products and in individual plasma samples with an increased incidence in febrile patients and intravenous drug users.

Recently, a surveillance study in Hong Kong for PARV4-like viruses in animal samples from swine and cattle revealed the presence of swine parvoviruses closely related to human parvovirus PARV4, suggesting the presence of a novel parvovirus in pigs. It is proposed to be named porcine hokovirus (PHoV), under the genus *Hokovirus*.<sup>54</sup>

The emergence of canine parvovirus from feline parvovirus (Feline panleukopenia virus, FPV) is a well documented case of host-range shifts of parvoviruses. In the 1970s, canine parvovirus (CPV) evolved from FPV, switching from the feline to the canine host. CPV then further evolved in a variant which is able to infect both, cats and dogs. The original evolution of CPV was a result of stepwise adaptation to canine hosts involving multiple rapid amino acid changes (some of which have arisen in the recipient host species) which

led to the transferrin receptor (TfR) binding and efficient usage of the canine TfR as central events in the evolution and pathogenesis of CPV.

Thus, public health issues concerning the potential of porcine parvoviruses crossing the species barrier have to be addressed. This is supported by a report by Soares et al.<sup>55</sup> who found that, despite the overall conservation of viral protein 2- (VP2-) encoding sequences, there is some evidence that distinct genotypes in PPV exist between PPV strains and protein data may indicate the existence of changes in the antigenic make-up of PPV. This genetic drift might cause generation of new variant strains that may influence the epidemiology of PPV infection.

However, with respect to the probability of comparable events in the evolution of PPV, differences between PPV and CPV/FPV should be clarified. For example, it was demonstrated that the original evolution of CPV was a result of stepwise adaptation to canine hosts involving multiple rapid amino acid changes (some of which have arisen in the recipient host species) which led to the TfR binding and efficient usage of the canine TfR as central events in the evolution and pathogenesis of CPV. Therefore, this event was facilitated by an extraordinary intrinsically high rate of mutation without recombinational event and further facilitated by the fact that host ranges of CPV and FPV are controlled by receptor binding.

In contrast, the cell tropisms of PPV appear to be at least partially determined by a combination of intracellular mechanisms during viral replication rather than by cell surface receptor expression. Ridpath and Mengeling<sup>56</sup> suggest host specificity is determined by intracellular factors investigated the uptake of PPV by both permissive and non-permissive cell-lines *in vitro*. They determined that both cell types took up PPV as a result of specific binding but PPV was unable to replicate in the non-permissive bovine cell-line after transfection, indicating that factors operating following absorption and uncoating of the virus cause PPV to be limited to the porcine host. Similarly, Oraveerakul et al.<sup>57</sup> demonstrated that in non-permissive canine Madin-Darby canine kidney (MDCK) cells, PPV was able to bind to the cell surface and to some extent enter the cells but neither viral polypeptides nor progeny virus was detected.

The results discussed above, indicate that although the same structural element of viruses is involved in several host and tissue tropisms, each appears to be affecting a different mechanism.

### **Porcine teschovirus 1**

Porcine Teschovirus-1 (PTV; formerly porcine enterovirus type 1, PEV-1) belongs to the family *Picornaviridae* and recently has been assigned based on sequence analyses to the genus *Teschovirus*. Susceptibility for teschovirus-infections is exclusively known for swine. The reasons for a significant decrease of clinical cases during the last years may be based on the circulation of non- or low-pathogenic serotypes (Teschovirus 2 to 7 and 11 to 13) which cause a seroprevalence rate of up to 60% within the pig population. Although human enteroviruses have been isolated from various environmental sources,



man is thought to be the only important natural reservoir. There is no known non-human reservoir for human enteroviruses.<sup>58</sup>

### **Swine vesicular disease virus**

The Swine vesicular disease virus (SVDV) belongs to the genus *Enterovirus* within the *Picornaviridae* family. The SVDV is antigenically closely related to the human enterovirus coxsackievirus B5 and genetic studies of a number of SVDV strains and epidemiologic information strongly suggest that a human coxsackie B5 was specifically introduced into swine several decades ago. During infection, enteroviruses can be isolated from both the lower and upper alimentary tract and can be transmitted by fecal-oral and respiratory routes. Cross-species infection with SVDV does not result in clinical signs or only mild “influenza-like” symptoms in man. In lab personnel handling SVDV, seroconversion was observed in some cases without any signs of disease. SVDV is exotic in the United States and most European countries.

### **Encephalomyocarditis virus**

Encephalomyocarditis virus (EMCV), which is classified in the family *Picornaviridae*, genus *Cardiovirus*, is ubiquitously distributed worldwide. The natural history, epidemiology, and transmission of EMCV are poorly understood, however, rodents are thought to be the primary reservoir. It is suspected that susceptible animals acquire infection by consuming feed or water contaminated with EMCV by rats or other rodents or by consuming rodent carcasses containing virus. Virus concentration is much higher in tissues of infected rodents than in their excretions. In swine, which are the most commonly and severely infected domestic animals, the oral transmission of EMCV was shown to be highly dose dependent.<sup>59</sup> The virus causes acute myocarditis and sudden death in pre-weaned pigs and in surviving animals, the virus may persist in the heart tissue for some period after the acute disease.<sup>60</sup> Transplacental infection of sows causes fetal mummification, abortion, stillbirth, and neonatal death whereas infections in older pigs are asymptomatic. Studies indicate that EMCV can cause interspecies infections.<sup>61, 62</sup> Further, it has been reported that porcine EMCV can infect human myocardial cells under experimental conditions.<sup>63</sup> A sero-epidemiologic study in Austrian hunters revealed the prevalence of anti-EMCV antibodies in 15% which was significantly higher than in the control group without animal contact.<sup>64</sup> However, the few documented cases of EMCV infection in humans have not been scientifically authenticated allocated to pigs. In Australia, the human cases merely have been reported in an area with a high incidence of the pig EMCV disease.<sup>65</sup> Additionally, a recent study that describes the identification of a new human *Cardiovirus* supports the inference that human *Cardioviruses* are bona fide human viruses and not the products of sporadic viral cross-over events from rodents to humans 1870 total clinical specimens.<sup>66</sup>

### **Foot-and-mouth-disease virus**

Foot-and-mouth-disease virus (FMDV) is the type species of the *Aphthovirus* genus of the *Picornaviridae* family. Seven serotypes (A, O, C, Asia 1, and South African Territories 1, 2, and 3) have been identified serologically, and multiple subtypes occur

within each serotype. FMD is one of the most highly contagious livestock diseases in the world with detrimental economic consequences. Countries that are free of the disease have introduced a number of measures to retain this status. The disease affects domestic cloven-hoofed animals, including cattle, swine, sheep, and goats, as well as more than 70 species of wild animals, including deer, and is characterized by fever, lameness, and vesicular lesions on the tongue, feet, snout, and teats. In addition, other vesicular diseases, such as swine vesicular disease and vesicular exanthema of swine, cause signs so similar to those of FMD that they are clinically indistinguishable from FMD in swine. Strict quarantine and slaughter methods are employed to control outbreaks. Vaccination may also be used to control outbreaks. In general, the FMDV is not considered to be a human health hazard. Infection in humans is extremely rare and requires direct exposure to massive amounts of the virus. There are few scientifically authenticated cases of FMD in humans and people are considered to be quite unsusceptible to infection. When it does occur, infection with FMDV in humans causes a transient low-grade fever with vesicles on the lips and in the mouth, on the hands, and occasionally on the feet. Recovery is rapid and uneventful.

### **Porcine rotaviruses**

Rotaviruses represent a genus within the *Reoviridae* family. Rotaviruses are the most significant cause of severe gastroenteritis in young children and animals. Among rotaviruses, seven distinct groups (A-G) can be distinguished, and the rotaviruses that affect pigs are differentiated as group A, B, and C on the basis of the group-specific inner capsid protein.<sup>67</sup> Group A rotaviruses cause diarrhea in pigs, both before and after weaning, and are reported to account for 89% of all rotavirus diarrhea in commercial pig operations.<sup>68</sup>

In humans, human rotavirus group A is endemic worldwide and is detected in the majority of cases. Group B rotavirus, also called adult diarrhea rotavirus, has caused major epidemics of severe diarrhea affecting thousands of persons of all ages in China while group C rotavirus has been associated with rare and sporadic cases of diarrhea in children in many countries. The full significance of human infections with group B and C rotaviruses remains to be established.<sup>69</sup> Although rotavirus diarrhea occurs with high frequency in developed countries, mortality is low and symptomatic infection is usually restricted to young humans or animals. In developing countries, however, rotaviruses are the leading cause of life-threatening diarrhea in children. Rotaviruses are transmitted via the fecal-oral route, although speculation continues whether rotaviruses are transmitted also by the respiratory route. There has been speculation on the role of animal rotaviruses in human infections. These concerns have been intensified by the observations that certain animal rotaviruses share a neutralization antigen with human rotaviruses and certain naturally occurring animal rotavirus strains may infect humans or form reassortants with human rotaviruses.<sup>70</sup> During dual infections of cells *in vitro*, RNA segments of different viruses can reassort at high frequency and rotavirus gene reassortment in nature is evident from the phylogenetic analyses of the VP4, VP7, and NSP4 genes.<sup>71</sup> By analysis of the 10th and 11th genome segments, several human strains were shown to contain a NSP4B genogroup and a NSP5/6 gene of porcine origin. These findings suggest interspecies transmission of rotavirus strains and/or genes, and may

indicate the occurrence of at least 3 separate rotavirus transmission events between pigs and humans, providing evidence that evolution of human rotaviruses is tightly intermingled with the evolution of animal rotaviruses.<sup>72</sup> In spite of these findings, a genotyping study of human and animal fecal samples between 1997 and 2001 in The Netherlands did not reveal evidence for rotavirus group A interspecies transmissions and all bovine, porcine, and equine rotaviruses were within genotypes previously reported for these animal species.<sup>73</sup> In summary, the fecal-oral transmission among humans remains the main route of infection of humans and inter-species transmission plays a minor part in epidemiology.

### **Hepatitis E virus**

Due to its physico-chemical and morphological similarities, Hepatitis E virus (HEV) was formerly classified into the family of *Caliciviridae* but is now classified as *Hepevirus* genus under the separate family *Hepeviridae* based on genome analyses.<sup>74</sup>

Although merely one single serotype is recognized with HEV, extensive genomic diversity has been observed among HEV isolates. The most accepted classification scheme clusters HEV into at least four distinct genotypes. Genotype 1, 2, 3 and 4 are represented by the prototype Burmese isolates, the Mexican isolate, the US isolates and the new Chinese isolates, respectively. The newly identified avian HEV from chickens likely represents a separate genus. Additional genotypes may exist as other novel strains that have not been completely sequenced and so cannot be definitively assigned to a genotype at this time. Overall, all HEV strains isolated thus far are genetically related and molecular studies of human and swine HEV isolates from around the world have found that, in general, swine and human isolates from the same geographic region are more similar to each other than they are to swine or human HEV isolates from other regions. Only genotype 3 and genotype 4 swine HEV strains have been associated with human transmission and are considered as zoonotic, whereas genotypes 1 and 2 HEV are restricted to humans.

With regards to the infection dynamics of HEV in commercial pig industry, pigs can be infected at any age with infection peaking at 1 to 3 months of age. The maximum prevalence rates of HEV excretion and prevalence in serum was detected in pigs 5 to 12 weeks old. However, in several herds HEV was still present in feces.<sup>75</sup> Persistent carriage of HEV has not been excluded yet. Hepatitis E virus infection does not cause clinical illness in swine and thus can remain undetected during fattening and slaughter which significantly hampers eradication of the virus. There are four documented routes of transmission of HEV in humans. Waterborne, foodborne consuming raw or under-cooked meat infected wild animals such as boars and wild deer and domestic pigs (zoonotic transmission), bloodborne (parenteral transmission) and perinatal transmission from mother to child (vertical transmission).

#### **5.3.2.3.2 Drug Substance Testing**

Based on the identification of relevant viruses and their evaluation regarding the prevalence, zoonotic potential and probability of presence in the raw material as well as

the potential of the process to control these viruses as demonstrated in viral clearance studies, Solvay Pharmaceuticals has instituted monitoring for potentially zoonotic porcine viruses that may not be inactivated by the manufacturing process.

Details on the selection of the test viruses and the employed methods are provided in Appendix 2.

#### **5.3.2.3.3 Development and Validation of Quantitative PCR Assays in Drug Substance**

Detailed information is provided in Appendix 2.

#### **5.3.2.3.4 Development and Validation of Quantitative Infectivity Assays in the Drug Substance**

Detailed information is provided in Appendix 2.

### **5.4 Risk Estimation: Conclusion from the Viral Quality Risk Assessment**

For the reason of the natural origin of the starting material a priori, the likelihood of contamination with swine viruses has to be considered.

Solvay Pharmaceuticals has instituted numerous selection criteria, approval procedures and controls for the sourcing and handling of the raw material ensuring that the pancreas glands are derived exclusively from pigs certified as “fit for human consumption”. Thus, in compliance with national and international guidances on viral safety of medicinal products, the sourcing of the raw material pig pancreas glands reveals reasonable diligence regarding minimization of the risk of viruses being introduced into the production of pancrelipase.

Viral clearance studies which have been conducted since 1997 according to the requirements of ICH guidelines, have demonstrated highly efficient inactivation of enveloped viruses and exploratory studies in the determination of the potential initial enveloped virus load of the raw material has further demonstrated a safety margin for the process’ capability to control enveloped viruses. Non-enveloped viruses with comparably low tenacity were shown to be reduced to significant degree, while reduction of the highly resistant non-enveloped viruses is limited. Due to exclusive sourcing from “pig only” slaughterhouses from countries categorized by the European Commission Scientific Steering Committee as Geographical BSE risk level III and IV (Note for Guidance EMEA 410/01 rev. 2) and strict controls of storage conditions the commingling of the raw material with other animals’ materials and in particular, the risk of any contamination with material from other species, in particular with TSE risk material is negligible.

Integrating all measures implemented with regard to sourcing of raw material and the production process’ capacity to inactivate viruses, the contamination likelihood for drug substance pancrelipase is negligible concerning enveloped viruses. The likelihood of

contamination of the drug substance with non-enveloped viruses is considered moderate for medium-resistant non-enveloped viruses or high with regard to highly resistant non-enveloped viruses, respectively

Where contamination with and inactivation of viruses still cannot be excluded, each hazard was assessed individually. Particular emphasis was given to review aspects relevant to likelihood of occurrence in pancrelipase such as prevalence in pigs, status in supplier countries, measures installed for the raw material; resistance to physical-chemical factors; and results from virological monitoring as well as to aspects relevant to probability of causing disease like host range and zoonotic potential.

As a consequence thereof, the drug substance is routinely tested for the presence of specific non-enveloped viruses.

## **5.5 Viral Quality Risk Mitigation**

Solvay Pharmaceuticals' viral quality risk mitigation foresees the rejection of batches that tested positive for specific viruses.

More detailed information is provided in Appendix 2.

### **5.5.1 Virological Batch Release Testing**

### **5.5.2 Justification of Specification for Porcine Parvovirus in Pancrelipase**

Detailed information is provided in Appendix 2.

### **5.5.3 Justification of Specifications for Zoonotic and Potentially Zoonotic Viruses in Pancrelipase**

As indicated above, a value of PPV testing may be attributable to its role as a model virus for the highly resistant non-enveloped viruses. On the other hand, no direct link can be established for the presence of PPV to the presence or absence of other highly resistant non-enveloped viruses. For that reason, Solvay Pharmaceuticals tests for additional viruses that have the potential to infect humans and are therefore more relevant to patients' safety.

More detailed information is provided in Appendix 2.

## **5.6 Ongoing Risk-Assessment on Viruses Relevant for CREON**

A major concern regarding infection risks in treatment with animal derived drugs relates to organisms not yet known referred to as "emerging" infections. As defined by the 1992 Institute of Medicine Report, *Emerging Infectious Diseases: Microbial Threats to Health in the United States*, emerging infections are those whose incidence have increased within the past two decades or threaten to increase in the near future. The emergence may be due to:

- a) the spread of a genuinely new agent, for example as a result of variation of existing organisms thus having broadened their host range
- b) the recognition of an infection that has been present in the population but has gone undetected, or
- c) the realization that an established disease has an infectious origin.

Emergence may also be used to describe the reappearance (or "reemergence") of a known infection after a decline in incidence.

In order to ensure the high viral quality standard of Solvay Pharmaceuticals' pancrelipase in the future, Solvay Pharmaceuticals observes the sourcing countries national animal disease surveillance programs and current state of knowledge in veterinary science with respect to emerging viruses as defined before. An ongoing risk assessment on current and future viruses relevant for Solvay Pharmaceuticals' pancrelipase integrating all complementary measures will evaluate the appropriateness of existing procedures. In case of inappropriateness, measures will be taken as necessary and may lead to modification or introduction of new measures on each level: sourcing of raw material, processing, testing methods and procedures as well as specifications.

## **5.7 Conclusion Regarding CMC Risk Assessment and Mitigation**

For detailed information please refer to Appendix 2

In general, the possibility of viral contamination of animal tissues used for production of pancrelipase cannot be excluded. Solvay Pharmaceuticals has investigated the potential for viral contamination of starting materials and the capacity of the manufacturing process to inactivate those contaminants. Enveloped viruses are sufficiently inactivated during at least 2 steps in the production process, whereas more variability exists with respect to inactivation of non-enveloped viruses.

Solvay Pharmaceuticals has identified resistant viruses with relevance to human health. This clinical risk is addressed in the following section.

## **5.8 Clinical Risk Assessment**

### **5.8.1 Porcine Parvovirus in Human Pathogenesis**

None of the known PPV is considered as a human pathogen. To date there is no report of PPV being transmitted to humans by pig-derived medicinal products. Moreover, no specific antibody production to PPV was found to be induced in humans. A study of long-term pig farm staff reported that no PPV antibodies were detected in any of the 56 study subjects' sera.<sup>76, 77</sup> Soucie et al.<sup>78</sup> investigated the presence of PPV antibodies in serum specimens from 98 patients who had received Hyate:C, a porcine factor VIII product, that had been contaminated by PPV. As it is known that the production process of factor VIII is not capable of inactivating PPV significantly, it can be assumed that at least part of the viral load represented infectious virus. However, none of the specimens from the individuals who received the contaminated product tested positive for anti-PPV

IgG antibodies. In another study Giangrande et al.<sup>79</sup> examined sera from 81 Hyate:C recipients for the presence of antibodies to several porcine viruses including PPV. As in the previous study, none of the sera tested had detectable antibodies to PPV. These data indicate that there is no evidence of human infections in patients who received PPV-contaminated products.

### 5.8.2 Potential Zoonotic Viruses for Humans

As noted above, from the list of viruses which have been identified to occur in swine, in total 4 viruses, namely HEV, SVDV, EMCV and Rotavirus A have been identified to be of special interest with regard to pancrelipase products and their potential of transmission from swine to human. The risk of each virus is assessed as follows noting its potential to transmit to humans, the disease characteristics and biomarker for determination of a potential infection.

#### 5.8.2.1 Porcine Hepatitis E Virus (HEV)

**Assessment:** During the last decades HEV infection in human has been judged as a travel-related waterborne disease which occurred in developing countries with poor sanitation standards. However, it is currently recognized that there may exist other pathways in particular zoonotic transmission in the industrialized world. A search of the literature has revealed that HEV can be transmitted to man by eating undercooked or grilled swine livers and intestines.

Epidemiological data from blood donors in the US and Western Europe show a seroprevalence for anti HEV of 2.2 to 18 %. Therefore; HEV needs to be considered to be a confirmed zoonosis.<sup>80</sup>

**Human Disease Characteristic:** In general, HEV causes a self-limiting disease and patients typically recover without sequelae within a period of 2-4 weeks. Hepatitis E can present with the typical symptoms of viral hepatitis very similar to Hepatitis A, e.g., jaundice (yellow discoloration of the skin and sclera of the eyes, dark urine and pale stools), anorexia, enlarged tender liver (hepatomegaly), elevated liver function test (LFT; specifically, alanine aminotransferase [ALT]), abdominal pain, tenderness, nausea, vomiting, and fever. Other less common symptoms include arthralgia, diarrhea, pruritus, and urticarial rash. The severity of the clinical course ranges from sub-clinical to fulminant disease. However, fulminant hepatitis may occur in certain high-risk populations, which to date include pregnant women and immune-compromised patients. It has been postulated that the pathogenesis of HEV may be due to direct liver cell injury (caused by immunological mechanisms and/or direct cytopathic effects) or to viral antigen-antibody complex mediated vasculitis. In contrast to Hepatitis B and C, there is no evidence of persistence or increased risk of hepatocellular carcinoma.<sup>81, 82</sup>

Mortality ranges from 0.5 – 4 %, which is higher than Hepatitis A (0.2 %).<sup>83</sup> In pregnancy fulminant course of the disease is described in the third trimester with mortality rates around 20 % due to acute liver failure.<sup>84</sup> It remains unclear if this poor outcome is associated with poor standards of medical care, or certain virus genotypes occurring in particular geographic regions and their typical pathway of transmission.



**Biomarkers:** Biomarkers to determine an HEV infection include serology: anti HEV IgM, anti HEV IgG. HEV RNA

#### 5.8.2.2 Swine Vesicular Disease Virus (SVDV)

**Assessment:** An extensive literature search showed evidence for seroconversion of SVDV in only a single case in a laboratory worker, who in retrospect had probably direct contact with infectious material.<sup>85</sup> Cases of food-borne transmission have not been reported, since there are highly effective control mechanisms in place with regard to food production. Due to the natural course of the disease and veterinary assessments, it is highly unlikely that SVDV contamination of the drug product occurs. Although, SVDV is considered to be potentially zoonotic, it is a low risk to humans because of the veterinary procedures in place to control for this virus.

**Disease Characteristics:** SVDV can cause a mild flu-like illness in humans. Laboratory personnel may seroconvert. Cell-culture virus isolation SVD virus is related to human Coxsackie B-5 virus,<sup>86</sup> and respiratory illness possibly due to the virus have been reported in people working with it in the laboratory. There have been no cases with vesicular eruption.

**Biomarkers:** Biomarkers to determine an SVDV infection include ELISA, virus neutralization and direct complement fixation test.

#### 5.8.2.3 Encephalomyocarditis Virus (EMCV)

**Assessment:** An extended search and review of the veterinary and medical literature showed only evidence for human infection with EMCV by detection of specific antibodies in human 30 years ago.<sup>87</sup> Cases of human heart disease caused by porcine EMCV have never been reported. EMCV is considered to be a potential zoonosis.

**Disease characteristics:** The EMC viruses have rarely been recognized as the cause of human illness, and the severe myocarditis and acute fatal infections seen in many other species have not been reported in humans. Serosurveys indicate that human EMCV infections are relatively common in certain areas of the world, but most cases are asymptomatic or unrecognized. Clinical signs in humans have varied from mild febrile illness to severe encephalomyelitis.<sup>88</sup>

**Biomarkers:** RNA isolation. Reverse Transcription- (RT-) PCR.

#### 5.8.2.4 Porcine Rotavirus A

**Assessment:** There is evidence that zoonotic transmission of rotaviruses, or at least their genes (via co-infection with human strains), can occur. Nevertheless rotaviruses are generally species-specific, and cross-species transmission remains under discussion as it has only been demonstrated experimentally.<sup>89, 90</sup> Only two case reports have been identified that raised suspicion regarding human infection via porcine Rotavirus C.<sup>91</sup> However, an extensive literature search did not reveal any well documented evidence for the transmission of Rotavirus A, which occur endemically in swine. Rotavirus A is



considered to be a potential zoonosis. Populations at risk for porcine Rotavirus A include children, the elderly, and immunosuppressed patients.

**Disease characteristics:** Acute gastroenteritis including watery diarrhea (> 3 episodes per day), fever, vomiting, abdominal pain, and nausea.

**Biomarkers:** Qualitative determination of rotaviruses in stool samples by enzyme immunoassay. Virus characterization by RT-PCR, nested PCR. Viral RNA extraction.

### 5.8.3 Conclusion

Based on the extensive literature searches and reviews, as well as the assessment outlined above, contamination with three of the four porcine viruses (SVDV, EMCV, and rotavirus) can be considered to have a low potential for affecting the safety of pancrelipase. For these three viruses, serologic evidence of infection and/or documented porcine exposure has been reported only in individual cases, and in particular only in persons with documented contact with infective materials, i.e., laboratory personnel handling serum samples. Therefore porcine SVDV, EMCV, and rotaviruses will be under continued surveillance with regard to genetic variability and reports of clinically relevant human cases in the literature, including the respective pathways of exposure, but will otherwise be considered minimal risk to the safe use of pancrelipase.

The fourth virus, HEV, in contrast, is able to cause symptomatic illness. In order to mitigate the residual risk, Solvay Pharmaceuticals has implemented appropriate mitigation steps in the production process to control the risk as described in [Section 5.5](#). Because of this potential risk, Solvay Pharmaceuticals has reviewed the clinical databases for any signals suggestive of HEV infection in patients in clinical trials or in post marketing experience.

## 5.9 Risk Assessments on Safety Databases

In addition to the safety evaluation in Section 3, the following section provides information about the results of specific database searches for any ADR reports from Solvay Pharmaceuticals' postmarketing safety database as well as serious and non-serious AEs from the clinical trials database, in order to detect any Hepatitis E related reporting.

In order to detect potential cases of Hepatitis E, the Standard MedDRA Query (SMQ) for Hepatic Disorders (broad search, version 11.0) was applied on the databases. This search strategy was applied to the clinical and the postmarketing database. In the following section, clinical study data and postmarketing data will be presented and evaluated separately.

### 5.9.1 Review of Clinical Database

The SMQ for Hepatic Disorders was applied to the clinical study database including 1532 patients. For all CREON MMS studies (CMP and TbMP) a search of the clinical database (N=793) identified the preferred terms with the following frequencies: hyperbilirubinemia (n=1; 0.1%), hypoalbuminemia (n=2; 0.3%), jaundice (n=1; 0.1%),

liver abscess (n=2; 0.3%), liver disorder (n=1; 0.1%), hepatic function abnormal (n=21; 2.6%), Hepatitis B (n=1; 0.1%) and hepatomegaly (n=1; 0.1%). For the CREON MS patients, a similar pattern of preferred terms was observed at lower frequency.

The following preferred terms were selected for medical review: hepatic function abnormal, Hepatitis B, hyperbilirubinemia and jaundice. These terms have the most specificity for a potential clinical hepatitis. The review focused on liver function test (LFT) abnormalities and particular attention was given to parameters indicating hepatocellular injury and the duration of CREON exposure.

For preferred term hepatic function abnormal, patients either had no ALT elevation or had a cholestatic pattern in liver function test results. Those patients with a LFT pattern indicating hepatocellular damage had ALTs less than 200 IU/L. The LFT abnormalities observed were considered unrelated to treatment and were caused by other etiologies.

In one patient, jaundice was reported and was associated with a common bile duct stricture.

Hyperbilirubinemia occurred in one patient. This patient had ALT abnormalities less than 100 IU/L. The event was unrelated to study drug.

One patient having an abnormal ALT value was diagnosed with Hepatitis B sixteen weeks after start of CREON treatment.

The current evaluation did not reveal any evidence of viral infection due to administration of CREON; however the short observation period of the clinical trials limits the ability to draw a definitive conclusion.

### **5.9.2 Review of Adverse Drug Reaction-Reports from Post-Marketing (Spontaneous Reporting)**

As per August 21, 2008, Solvay Pharmaceuticals' postmarketing safety database contained 21 reports which included any kind of liver related preferred terms; this represents about 2.2% of all reports concerning pancrelipase from a total exposure of about 5 million patient years. Of those 21 reports 12 were clinical study cases and these were evaluated in [section 5.9.1](#) above, Risk Assessment on Clinical Databases. The remaining nine cases are spontaneous reports from the market (healthcare professionals, authorities, consumers, literature, others) which were medically evaluated in detail.

In summary, features of these nine cases are as follows:

There were

- 2 spontaneous cases from the US: jaundice, hepatic pain (both non-serious)
- 1 spontaneous case from Germany: hepatic enzymes increased (not serious)
- 1 spontaneous case from Japan: cirrhosis (serious) (from study extension that time (1999) considered not to be a study patient)
- 5 authority cases from France: hepatomegaly, hepatitis, cholestatic hepatitis (2x), hypoalbuminemia (all serious).

It was concluded that no cases of confirmed or suspected Hepatitis E have been detected by this evaluation and an association of the cases summarized above to CREON intake is unlikely.

It is important to recognize that the major indications for enzyme substitution are exocrine insufficiency due to CP and CF. Both diseases carry a high risk of liver disorders by themselves. CP is induced in 70%-80% by chronic alcohol abuse. Thirty percent of these patients develop hepatic disorders including all symptoms which were reported in above mentioned cases. In addition, 10% of CF patients who survive to adulthood have a form of biliary cirrhosis characterized by cholestatic enzyme abnormalities and the development of chronic liver disease. In light of these findings, which indicate a high background prevalence of liver abnormalities among patients who take CREON, the marginal risk, if any, of acquiring liver disease due to HEV infection is very low.

Beside liver diseases inherent to the underlying disease as described above, there are a variety of liver diseases that need to be considered in the differential diagnosis, including drug-induced toxic liver damage, viral hepatitis (A, B, C, and D), other viral diseases affecting the liver (mononucleosis, herpes, adenovirus hepatitis), cryptogenic hepatitis, immune and autoimmune liver diseases, genetic liver diseases, liver involvement in systemic diseases, cholestatic syndromes, vascular injuries and mass lesions.

Major risk factors for liver disease that should be sought in the clinical history include details of alcohol use, medications (including herbal compounds, birth control pills, and over-the-counter medications), personal habits, sexual activity, travel, exposure to jaundiced or other high-risk persons, injection drug use, recent surgery, remote or recent transfusion with blood and blood products, occupation, accidental exposure to blood or needlestick, and familial history of liver disease.

The nine cases which include different signs or symptoms of liver disease do not provide sufficient information for proper diagnosis or an assessment of the causal relationship to CREON intake. However, considering the high incidence of liver disease associated to the underlying disease as well as the multiplicity of differential diagnosis, it is reasonable to state for all nine cases that an involvement of Hepatitis E with any of the hepatic ADRs on database is highly unlikely.

As pregnant women carry a higher risk for fulminant hepatitis in case of HEV infections, Solvay Pharmaceuticals' safety database has also been searched for all reported pregnancies in association with the use of CREON. The safety database contains two cases of reported pregnancy without any reported adverse drug reaction. These pregnancy reports are being followed up according to specific procedures. One pregnancy is due in November 2008, the second one (dated from 2004, a CF patient) was lost to follow-up. None of the hepatic disorder cases include a pregnant patient.

### **5.9.3 Conclusion for Risk Assessment in Humans**

Taken together, no clinically relevant risk could be identified in terms of CREON intake and any liver diseases. In particular, no association between CREON and potential HEV

infections could be established based on the review of the clinical databases. Both databases have limitations in risk detection, but given that Hepatitis E is not found in pancreatic cells and the implementation of appropriate mitigation steps for Hepatitis E contamination in the CREON production process, it is considered unlikely that a causal relationship between CREON intake and Hepatitis E exists.

Nevertheless, further diligence is required to determine whether there is an increased risk. Therefore Solvay Pharmaceuticals is committed to develop, in cooperation with the FDA and medical community, an appropriate plan for risk identification and evaluation.

## **5.10 Post-Marketing Risk Assessment Plan**

As per the FDA guidance for Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment, Solvay Pharmaceuticals' will conduct ongoing safety signal identification, evaluation and develop an appropriate pharmacovigilance plan to assess potential risks.

### **5.10.1 Signal Identification**

Beyond case analysis and developing case series, systematic data monitoring and signal detection based on data mining techniques will:

- Monitor the company's safety database
- Monitor large adverse event databases, such as FDA's Adverse Event Reporting System.
- Investigate event reporting frequency over time
- Generate event disproportionality statistic (e.g., compare the fraction of all reports for the particular event for the drug with the fraction of reports for the same particular event for all drugs)

Data monitoring and analysis will specifically focus on:

- Adverse events associated with infectious diseases
- Identification of a previously unrecognized at-risk population
- Other concerns identified by Solvay Pharmaceuticals or FDA

### **5.10.2 Pharmacovigilance Plan**

Solvay Pharmaceuticals may perform actions to enhance and expedite safety information. This may include:

- Submission of specific serious adverse event reports in an expedited manner beyond routine required reporting (i.e., as 15-day reports)
- Submission of adverse event report summaries at more frequent, prespecified intervals (e.g., quarterly rather than annually)

Solvay Pharmaceuticals is committed to develop, in cooperation with the FDA and medical community, an appropriate plan for risk identification and evaluation. Options under consideration include active surveillance and observational-type studies post approval.

A sentinel surveillance concept is proposed below for post marketing monitoring of viral risk.

#### **5.10.2.1 Sentinel surveillance of potential virus risks**

Sentinel surveillance can provide an alternative to population-based surveillance for the pro-active collection and analysis of individual patient-related information and monitoring of trends. Sentinel surveillance systems involve a limited number of selected sites, from which the information collected may be extended to the general population. A concentration of resources in defined sites produces information that is considered to provide more accurate estimates than those normally available from broader surveillance programs.

Sentinel sites for patients taking CREON could include:

- CF centers
- specialized hospitals
- selected medical prescribers.

In order to facilitate recruitment of patients and controls, co-operation can be sought with official bodies and/or non-governmental organizations like CF Foundation and the Therapeutic Development Network.

The following elements could be considered as part of a surveillance program conducted in patients with CF:

#### **Clinical data collection and assessment (patient based approach)**

- Adverse Events of Special Interest (sign/symptoms associated with infectious diseases; to be defined).
- Tools/Education: physicians and patients could be asked to complete dedicated forms during a regular patient visit (“study-like” recording of specific AEs, this could have an interventional character). Patients could be educated to visit the sentinel site when particular symptoms occur (to be defined).
- Blood samples: taken at baseline (start of the surveillance) and in pre-determined time intervals; additional testing as needed on an individual patient level.

#### **Investigation of viral exposure (population based approach)**

- Specific antibody tests could be used (as available) to determine and compare the incidence of viral exposure on the population level (“epidemiological risk assessment”)

The outline below proposes a viral exposure investigation (“model approach”) that could be expanded or adapted to specific viral exposure determination as appropriate.

#### Proposal to Investigate Viral Exposure

The presence of anti-viral IgG in blood samples indicates viral exposure. Anti-viral IgG may persist for as long as 2-3 years and possibly longer.<sup>92</sup> Therefore, measurement of these antibodies is a useful method to determine viral exposure.

A possible study design could include:

- Baseline assessment (“screening”)
  - Collect blood samples from CREON-users (naïve or pre-treated)
  - Collect blood samples from non-users, e.g. sibling living with the patient
  - Compare positive rates
- Follow-up assessment (e.g., after 1 year), baseline test-negative subjects only
  - Collect blood samples from CREON-users
  - Collect blood samples from non-users
  - Compare positive rates

The outline described above could provide an estimate regarding the group at risk compared to a matched (i.e., age, diet, region) control population. Nevertheless, it should be recognized that this estimate might be confounded by uncontrolled competing sources of viral contamination because all relevant viruses have a number of host species, which could complicate identification of an appropriate control group. In addition, the size of these studies would be highly dependent on the assumptions about the incidence of viral infections in human.

Details and feasibility of the proposed surveillance are under development.

## **6.0 BENEFIT/RISK ASSESSMENT**

### **6.1 Benefits of CREON TbMP for the Treatment of Exocrine Pancreatic Insufficiency**

As discussed in more detail in [Section 1.4](#), pancreatic enzyme supplements are a cornerstone of nutritional management for the treatment of EPI due to CF. In turn, nutrition is a critically important factor for survival of these patients, as overall increases in the BMI of CF patients over the past 20 years are strongly associated with increases in lifespan. With adequate nutrition, children with CF demonstrate improved growth and development, improved lung function, and increased life expectancy. Thus, perhaps the most compelling benefit that would result from approval of CREON TbMP for treatment of EPI in patients of all ages is that it would mean the availability of an approved and proven therapy to maximize the opportunity for children with CF to reach adulthood.

Approval of CREON TbMP would also benefit patients with EPI due to other conditions such as CP. The availability of an approved and proven therapy to treat maldigestion

would mean that these patients might be better able to avert weight loss and nutrient depletion so that they may enjoy an improved quality of life.

The consistently high quality of various formulations of CREON over the past 24 years, which have been manufactured and controlled with state-of-the-art technologies, has yielded reproducible efficacy and safety. This has helped to make CREON the market leader for pancreatic enzyme supplements. The S245.3.126 Study has demonstrated that the efficacy of the CMP is also applicable to the TbMP.

The amended label of the TbMP to eliminate overfill would also provide a benefit by allowing patients and healthcare workers to more accurately determine dosages. Furthermore, Solvay Pharmaceuticals controls for the content of all three enzyme components of the TbMP – lipase, protease, and amylase – and so patients and healthcare workers will be able to determine actual dosages of all three enzymes with considerable precision. In addition, dibutyl phthalate has been removed from the formulation in response to recent global debate concerning the safety of alkyl phthalates, and mineral oil has been removed to avoid the possibility that it might inhibit absorption of key nutrients. Solvay Pharmaceuticals constantly strives to improve this product according to available information, and these modifications reflect the efforts toward that end.

The consistency of CREON benefits demonstrated in short-term clinical trials has primarily focused on its effects on fat absorption. However, the observed clinical improvement in CNA also indicates a benefit of treatment with the TbMP for protein digestion and strongly suggests that the protease component of CREON has clinical relevance. It is also plausible that the amylase component of CREON aids in digestion of carbohydrates, although that possibility has not yet been directly tested. In addition, substantial evidence has also been presented that CREON also provides benefits on clinical symptomatology and thereby provides symptomatic relief for patients with EPI. Solvay Pharmaceuticals is not able to compare long-term benefits of CREON treatment against placebo or no treatment because long-term deprivation of a proven therapy would be unethical. Randomized withdrawal studies have demonstrated that stopping treatment results in unacceptably low fat absorption by patients within 5 days. Nevertheless, the improvements in digestion afforded by CREON treatment are highly likely to provide a benefit by protecting against malnourishment of patients with EPI, irrespective of the underlying disease.

It follows then that the primary benefit resulting from approval of CREON TbMP is that it would mean the availability of an approved and proven therapy for EPI. Thus, approval of the TbMP would ensure that CREON continues to fulfill an important need for these patients.

## **6.2 Risks of CREON TbMP for the Treatment of Exocrine Pancreatic Insufficiency**

The risks associated with the TbMP can be broadly categorized into those that are known, those that are anticipated, and those for which a potential exists. Known risks are defined as risks that have been observed and reasonably established as associated with CREON

administration. Anticipated risks are defined as those that have not yet been observed or established, but are anticipated based on knowledge of the class of drug or known pharmacologic properties. Potential risks are defined as risks that have not been observed or established for CREON or other products in its class but for which there are reasons to suspect they might occur.

### **6.2.1 Known Risks**

Known risks of any drug include any adverse drug reactions. With respect to known risks for the TbMP, the only safety data available are from Study S245.3.126. As outlined in more detail in [section 3.1](#), the data from that study did not reveal any safety concerns. TEAEs in studies of the CMP include nausea, vomiting, constipation, abdominal distension, hyperglycemia, hypersensitivity reactions (reactions of the skin).

### **6.2.2 Anticipated Risks**

Other anticipated risks of the TbMP include those factors for which warnings or precautions have been included in the proposed label. These factors include the possibilities of, hyperuricemia, and irritation of oral mucosa and/or inactivation of enzymes due to crushing/chewing the capsules. Other symptomatology involving the GI tract other than described under known risk are abdominal pain and flatulence.

One anticipated risk that may be applicable to any pancreatic enzyme therapy is the possibility of FC associated with prolonged exposure to high doses. However, Solvay Pharmaceuticals has not been able to identify any instances of this condition in which the patient was taking CREON in the absence of another pancreatic enzyme supplement. Therefore, there has been no firm association between the use of CREON and the occurrence of FC. Nevertheless, Solvay Pharmaceuticals supports the guidelines for dosing outlined in the CF Consensus Conferences and intend to continue to include a warning on the label for the TbMP. In addition, data from post-marketing surveillance and clinical trials to monitor will continue to be scrutinized for any occurrence of this serious condition.

### **6.2.3 Potential Risks**

Because CREON and other pancreatic enzyme products are produced from native porcine pancreas, the possibility of contamination of the starting material with viruses relevant to swine and capable of infecting humans has to be considered. To determine the potential risk of viral contamination, Solvay Pharmaceuticals has performed a risk analysis and has instituted measures to reduce any risk at all steps of production beginning from careful selection of animal materials through to testing of the final product. A more detailed summary is provided in Appendix 2.

As also outlined in Appendix 2, Solvay Pharmaceuticals has identified four non-enveloped, potentially zoonotic viruses with Solvay Pharmaceuticals with relevance to human health and has developed and validated assays to test for these viruses in the drug substance. Nevertheless Solvay Pharmaceuticals understands that a future potential risk cannot be excluded. Solvay Pharmaceuticals will continue to be vigilant by monitoring



all new and evolving swine viruses and developing new methods to ensure effective viral testing. Solvay Pharmaceuticals controls reflects a commitment to a product with the highest possible quality and safety.

### **6.3 Conclusions**

There exists a substantial body of evidence for the medical need for pancreatic enzyme supplements, as well as abundant evidence for the efficacy and safety of CREON. Given the similar treatment effect now shown for the TbMP, this clearly establishes a benefit for approval of the TbMP. Approval of the TbMP for treatment of pediatric patients with CF would make available a proven therapy to improve nourishment and thereby maximize their potential lifespan. For patients of all ages with EPI due to CF, CP, PY, or any other underlying conditions, approval of the TbMP would make available a proven therapy to prevent malnutrition and potentially improve quality of life.

In addition to the abundant evidence for benefits on fat digestion, CREON treatment also provides symptomatic relief for patients with EPI. Furthermore, recent data also indicates improved protein digestion with the TbMP. Thus, it may be particularly beneficial that Solvay Pharmaceuticals formulates the TbMP to control the content of all three enzyme components – lipase, protease, and amylase. Labeling will reflect zero-overfill for each of these components and thereby ensure that patients and healthcare workers can be certain of the content of every capsule. Finally, the modifications to the TbMP are consistent with the ongoing commitment to ensure that CREON continues to be the safest possible option for treatment of EPI.

To date, there are no safety data to indicate a known risk with the TbMP. Based on experience with CREON MMS, it is anticipated that certain adverse drug reactions may occur, and these possibilities are included in the proposed label.

As with any products derived from animal tissues, the potential risk for infectious disease due to the transmission of an infective agent cannot be totally excluded. Therefore, Solvay Pharmaceuticals has instituted measures to minimize the potential for zoonotic agents in the source materials, to inactivate many such agents that may be present, to screen the finished product for those considered potentially resistant to inactivation, and to continuously update surveillance and manufacturing capabilities according to the most recent technology.

Solvay Pharmaceuticals is committed to develop, in cooperation with the FDA and medical community, an appropriate plan for risk identification and evaluation.

Based on these considerations, the benefits of approval of CREON TbMP far outweigh any of the risks. It is possible that a greater risk to patients' health might be posed by any measures that would restrict the availability of this proven therapy.

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## 8.0 SUPPLEMENTARY TABLES

**Table 8.1: Multiple-Dose Studies with CREON MMS (N=29)**

Indication	Disease	Study	N (1)	N (2)	N (3)	Blind	Design	Total Duration of Treatment	Test Drug (Duration of Treatment)	Control Drug (Duration of Treatment)	Remarks
EPI	CF	S245.3.126	32	32	-	DB	2-CO	2 weeks	CREON 24000 MMS (5 days)	Placebo (5 days)	TbMP
EPI	CF	S223.3.101	47	47 (18)	-	DB	2-PG	2-3 weeks	CREON 20000 MMS (1 week)	Placebo (1 week)	1-2 weeks run-in with MMS 20000
EPI	CF	S223.3.102	50	50 (18)	-	DB	2-PG	2-3 weeks	CREON 20000 MMS (6 days)	Placebo (6 days)	1-2 weeks run-in with MMS 20000
EPI	CF	K.245.5002	69	69	69	Open	2-CO	4 weeks	CREON 10000 MMS (2 weeks)	MS 12000 (2 weeks)	
EPI	CF	K.245.5004	34	33	34 (33)	DB	2-CO	7 weeks	CREON 10000 MMS (2 weeks)	MS 8000 (2 weeks)	3 weeks run-in with MS 8000
EPI	CF	S248.3.002	33	29	33 (29)	DB	2-CO	7 weeks	CREON 25000 MMS (2 weeks)	MS 25000 (2 weeks)	3 weeks run-in with MS 25000
EPI	CF	S245.3.105	59	57	59 (55)	Open	2-CO	10 weeks	CREON 10000 MMS (4 weeks)	MS 8000 (4 weeks)	2 weeks run-in with MS 8000
EPI	CF	KREO.629	11	11	-	SB	S	12 days	CREON 10000 MMS (6 days)	Placebo (6 days)	
EPI	CF	S245.3.118	40	40	-	Open	2-CO	30 days	CREON for Children (MMS) (15 days)	MMS 12000 (15 days)	
EPI	CF	S248.3.003	12	12	-	Open	S	8 weeks	CREON for Children (MMS) (8 weeks)	-	
EPI	CF	S245.3.117	3	3	-	Open	S	Not fixed	CREON 10000 MMS	-	The sachets administered contained 20000 lipase units of CREON MMS 10000. Max treatment duration before cut-off: > 4 years
EPI	CF	S245.2.002	5	5	-	Open	S	53 weeks	CREON 10000 MMS (53 weeks)	-	3 days run-in with placebo
EPI	CP	223.2.01	27	13	-	DB	2-PG	4 weeks	CREON 10000 MMS (2 weeks)	Placebo (2 weeks)	2 weeks run-in with placebo



**Table 8.1: Multiple-Dose Studies with CREON MMS (N=29)(continued)**

Indication	Disease	Study	N (1)	N (2)	N (3)	Blind	Design	Total Duration of Treatment	Test Drug (Duration of Treatment)	Control Drug (Duration of Treatment)	Remarks
EPI	CP	K.245.5005	40	17	39	DB	2-PG	4 weeks	CREON 10000 MMS (2 weeks)	Placebo (2 weeks)	1 week run-in with placebo and 1 week with CREON 10000 MS
EPI	CP	K.245.5003	37	23	28 (23)	DB	2-CO	7 weeks	CREON 10000 MMS (2 weeks)	CREON 10000 MS (3 weeks)	1 week run-in with placebo and 1 week with CREON 10000 MS
EPI	CP	S245.3.107	3	4	-	DB	2-CO	4 weeks	CREON 10000 MMS (1 week)	Placebo (1 week)	1 week run-in with placebo and 1 week with CREON 10000 MMS
EPI	CP, PY	S245.3.115	94	64	-	DB	3-PG	7 days	CREON 10000 MMS (1 week) (two-dose groups)	Placebo (1 week)	1 week run-in with placebo The sachets administered contained 20000 lipase units of CREON MMS 10000
EPI	CP, PY	K.245.5703	26	24	-	Open	2-PG	1-2 weeks	CREON 10000 MMS (1-2 weeks) (two dose groups)	-	5 days run-in with placebo, period with two parallel dose groups, period with three doses given sequentially (N's in brackets)
			(17)	(17)	-	Open	S	3 weeks	CREON 10000 MMS (3 weeks) (three doses sequentially, 1 week for each)	-	
EPI	CP, GY, PY	S245.3.103	63	63	-	Open	S	24-52 weeks	CREON 10000 MMS (24-52 weeks)	-	Extended from studies 3.104 and 5.703.

**Table 8.1: Multiple-Dose Studies with CREON MMS (N=29)(continued)**

Indication	Disease	Study	N (1)	N (2)	N (3)	Blind	Design	Total Duration of Treatment	Test Drug (Duration of Treatment)	Control Drug (Duration of Treatment)	Remarks
EPI	CP, GY, PY	S245.3.104	85	83	-	Open	S	4 weeks	CREON 10000 MMS (4 week)	-	5 days run-in with placebo
EPI	PY	S248.3.001	27	21	27 (21)	DB	2-CO	6 weeks	CREON 25000 MMS (2 weeks)	MS 8000 (2 weeks)	2 weeks run-in with CREON 8000 MS
EPI	GY	S245.3.102	11	3	9	DB	2-PG	4 weeks	CREON 20000 MMS (2 weeks)	Placebo (2 weeks)	1 week run-in with placebo and 1 week with CREON 10000 MS
EPI	AP	S248.4.001	56	27	-	DB	2-PG	26-30 days	CREON 25000 MMS (26-30 days)	Placebo (26-30 days)	
EPI	AP	S248.4.002	21	10	-	DB	2-PG	84 days	CREON 25000 MMS (84 days)	Placebo (84 days)	
EPI	DM	S245.3.112	6	3	-	DB	2-PG	7 days	CREON 10000 MMS (7 days)	Placebo (7 days)	
EPI	DM	S245.3.113	23	13	-	DB	2-PG	7 days	CREON 10000 MMS (7 days)	Placebo (7 days)	
Non-EPI	DM	S245.3.110	80	39	-	DB	2-PG	16 weeks	CREON 10000 MMS (16 weeks)	Placebo (16 weeks)	
Non-EPI	HIV	S245.3.116	10	6	-	DB	2-PG	4 weeks	CREON 10000 MMS (4 weeks)	Placebo (4 weeks)	
Non-EPI	HIV	S245.3.119	38	38	-	DB	2-CO	4 weeks	CREON 25000 MMS (2 weeks)	Placebo (2 weeks)	

Indication: EPI= exocrine pancreatic insufficiency.

Disease: CP=Chronic Pancreatitis; AP=Acute Pancreatitis; CF=Cystic Fibrosis; PY=Pancreatic Surgery; GY=Gastrectomy; DM=Diabetes Mellitus.

N: (1)=Number of patients randomized; (2)=Number of patients who took CREON MMS (First number includes run-in, second number not); (3)=Number of patients who took CREON MS (First number includes run-in, second number not).

Blind: DB=Double-blind; SB=Single-blind; O=Open-label.

Design: PG=Parallel groups; CO=Crossover (The preceding number is the number of treatment groups); S=Single treatment.

**Table 8.2: Single-Dose Studies with CREON MMS in CREON Safety Database (N=5)**

Indication	Disease	Study	N (1)	N (2)	N (3)	Blind	Design	Total Duration of Treatment	Test Drug (Duration of Treatment)	Control Drug (Duration of Treatment)	Remarks
EPI	CP	K.224.5011	5	5	-	DB	2-CO	Single dose	CREON 25000 MMS	Placebo	
EPI	CP	S245.2.003	14	14	-	DB	2-CO	Single dose	CREON 12000 MMS	CREON 10000 MMS	
EPI	CF	S245.3.111	21	20	-	Open	3-CO	Single dose	CREON 10000 MMS	Pancrease, Placebo	
EPI	CF	S245.4.004	12	12	-	DB	3-CO, 4 trtmts	Single dose	CREON 5000, 15000, 40000 MMS	Placebo	
EPI	CF	S248.2.001	11	11		Open	S	Single dose	CREON 25000 MMS	-	

Indication: EPI= Exocrine Pancreatic Insufficiency.

Disease: CP=Chronic Pancreatitis; CF=Cystic Fibrosis.

N: (1)=Number of patients randomized; (2)=Number of patients who took CREON MMS; (3)=Number of patients who took CREON MS.

Blind: DB=double-blind; SB=single-blind; O=open-label.

Design: PG=parallel groups; CO=cross-over (the preceding number is the number of treatment groups); S=single treatment.

**Table 8.3: Multiple-Dose Studies with CREON MS in CREON Safety Database (N=22)**

Indication	Disease	Study	N (1)	N (2)	N (3)	Blind	Design	Total Duration of Treatment	Test Drug (Duration of Treatment)	Control Drug (Duration of Treatment)	Remarks
EPI	CF	KREON 84/03	21	-	21	Open	2-CO	8 weeks	CREON 8000 MS (4 weeks)	Pancrex V Forte 5600 (4 weeks)	
EPI	CF	KREON 84/02	20	-	20	DB	2-CO	8 weeks	CREON 8000 MS (4 weeks)	Pancrex V Forte 5600 (4 weeks)	
EPI	CF	RR.1044-01	21	-	21	Open	2-CO	4 weeks	CREON 8000 MS (2 weeks)	Pancrease (2 weeks)	
EPI	CF	KREO.586	27	-	27	DB	2-CO	10 weeks	CREON 8000 MS (4 weeks)	Pancrease 5000 (4 weeks)	2-weeks run-in with CREON 8000 MS
EPI	CF	KREO.584	29	-	29	Open	S	104 weeks	CREON 8000 MS (104 weeks)	-	
EPI	CF	K.224.5001	89	-	89	DB	2-CO	8 weeks	CREON 25000 MS (4 weeks)	Panzytrat 20000 (4 weeks)	
EPI	CF	KREO.592	17	-	17	Open	2-CO	12 weeks	CREON 8000 MS (6 weeks)	CREON 8000 MS (6 weeks)	Capsules versus sachets
EPI	CF	223.8.01	33	-	33 (32)	Open	2-CO	5 weeks	CREON 25000 MS (2 weeks)	CREON 8000 MS (2 weeks)	1 week run-in with CREON 8000 MS
EPI	CF	K.224.5006	46	-	45	Open	S	26 weeks	CREON 25000 MS (13 weeks)	Pancrease 5000, CREON 8000 MS (13 weeks)	Pancrease 5000 or CREON 8000 MS during Phase 1 and CREON 25000 MS during Phase 2
EPI	CF	K.224.5010	18	-	14	Open	2-CO	6-10 weeks	CREON 25000 MS (2 weeks)	Cotazym Forte (2 weeks)	2-6 weeks run-in with other PERT
EPI	CF	KREO.636	64	-	63	Open	2-CO	2 weeks	CREON 8000 MS (1 week)	Pancrease (1 week)	
EPI	CP	RR.1044-03	58	-	57	DB	2-CO	8 weeks	CREON 8000 MS (4 weeks)	Placebo (4 weeks)	
EPI	CP	K.224.5003	11	-	11	DB	2-CO	5 weeks	CREON 25000 MS (2 weeks)	Pancrease 6200 (2 weeks)	1 week run-in with Pancrease
EPI	CP	KREO.628	31	-	30	DB	3-CO	12 weeks	CREON 10000 MS (8 weeks)	Placebo (4 weeks)	
EPI	CP	K.224.5008	6	-	6	Open	S	3 weeks	CREON 25000 MS (2 weeks)	-	1 week run-in with placebo

**Table 8.3: Multiple-Dose Studies with CREON MS in CREON Safety Database (N=22)(continued)**

Indication	Disease	Study	N (1)	N (2)	N (3)	Blind	Design	Total Duration of Treatment	Test Drug (Duration of Treatment)	Control Drug (Duration of Treatment)	Remarks
EPI	CP	K.224.5009	24	-	24	DB	2-CO	20 days	CREON 25000 MS (10 days)	Pancrease (10 days)	
EPI	CP	K.224.5016	65	-	64	DB	2-CO	5 weeks	CREON 25000 MS (2 weeks)	CREON 8000 MS (2 weeks)	1 week run-in with placebo
EPI	CP	CREO.635	20	-	19	DB	2-CO	4 weeks	CREON 8000 MS (2 weeks)	Placebo (2 weeks)	
EPI	PY	RK.223.00.02	16	-	16 (7)	DB	2-PG	8 wks	CREON 8000 MS (4 weeks)	Placebo (4 weeks)	4 weeks run-in with CREON 8000 MS
EPI	PY	K.224.5002	40	-	40 (39)	DB	2-CO	6 wks	CREON 25000 MS (2 weeks)	CREON 8000 MS (2 weeks)	2 weeks run-in with CREON 8000 MS
EPI	Chronic malnutrition in elderly	CREO.630	52	-	26	DB	2-PG	90 days	CREON 12000 MS (90 days)	Placebo (90 days)	
EPI	Chronic malnutrition in elderly	CREO.631	44	-	21	DB	2-PG	90 days	CREON 12000 MS (90 days)	Placebo (90 days)	

Indication: PEI= exocrine pancreatic insufficiency; Test/control drug: MS = CREON MICROSPHERES; MMS = CREON MINIMICROSPHERES; PERT=pancreatic enzyme replacement therapy.

Disease: CP=chronic pancreatitis; AP=acute pancreatitis; CF=cystic fibrosis; PY=pancreatic surgery; GY=gastrectomy; DM=diabetes mellitus.

N: (1)=number of patients randomized; (2)=number of patients who took CREON MMS (first number includes run-in, second number not); (3)=number of patients who took CREON MS (first number includes run-in, second number not).

Blind: DB=double-blind; SB=single-blind; O=open-label.

Design: PG=parallel groups; CO=cross-over (the preceding number is the number of treatment groups); S=single treatment.

**Table 8.4: Non-Integrated Studies (N=5)**

Study	N (1)	N (2)	N (3)	Blind	Design	Total Duration of Treatment	Test Drug (Duration of Treatment)	Remarks
S245.4.007	41	20	-	DB	2-PG	6 months	MMS 25000 (6 months)	No full study report available. Patients with gastrectomy, placebo control
S245.3.122	24	Unk(4)	Unk(4)	DB	3-PG	1 week	MMS 10000	CP and PY, ongoing, status per April 30, 2008
S245.3.123	-	10	10	O	S	1 year	MMS 10000	Extension of S2453122, ongoing, status per April 30, 2008
S245.3.124	23	Unk(4)	Unk(4)	DB	2-PG	6 months	MMS 12000/24000	CP and PY, ongoing, status per April 30,2008
LAUGIER	“&	“&	-	db	“-pg	6 months	MS 12000	Patients with CP, no full study report available

Blind: DB=double-blind; SB=single-blind; Open=open-label. Test/control drug: MS=CREON MICROSPPHERES; MMS=CREON MINIMICROSPPHERES.

Design: PG=parallel groups; CO=cross-over (The preceding number is the number of CO periods. The number of treatments (trmt) is additionally given if different from the number of CO periods); S=single treatment/sequential design.

N: (1)=number of patients randomized; (2)=number of patients who took CREON MMS; (3)=number of patients who took CREON MS; (4)=unknown because the study is still blinded.

**Table 8.5: Treatment Emergent Adverse Events by Age Category for CF patients  
(> 5 % and > 1 patient)**

Design	Studies with the TbMP		Studies with the CMP		
	Placebo controlled		Placebo controlled		All multiple dose studies
Preferred term	TbMP	Placebo	CMP	Placebo	CMP
<b>&lt; 4 years</b>					
<b>No. of Patients at Risk</b>	0	0	0	0	55 (100.0)
<b>Any TEAE</b>					39 (70.9)
Conjunctivitis					3 (5.5)
Abdominal pain					4 (7.3)
Constipation					4 (7.3)
Toothache					4 (7.3)
Vomiting					3 (5.5)
Pyrexia					4 (7.3)
Bronchitis					5 (9.1)
Nasopharyngitis					5 (9.1)
Rhinitis					3 (5.5)
Cough					9 (16.4)
Bronchial obstruction					3 (5.5)
<b>4 - 12 years</b>					
<b>No. of Patients at Risk</b>	0	0	9 (100.0)	6 (100.0)	143 (100.0)
<b>Any TEAE</b>			4 (44.4)	4 (66.7)	75 (52.4)
Abdominal pain			1 (11.1)	3 (50.0)	16 (11.2)
Vomiting			2 (22.2)	0 (0.0)	12 (8.4)
Headache			1 (11.1)	0 (0.0)	14 (9.8)
Cough			0 (0.0)	0 (0.0)	17 (11.9)
Pyrexia			0 (0.0)	0 (0.0)	10 (7.0)
<b>&gt; 12 – 18 years</b>					
<b>No. of Patients at Risk</b>	8 (100.0)	8 (100.0)	9 (100.0)	16 (100.0)	94 (100.0)
<b>Any TEAE</b>	3 (37.5)	3 (37.5)	7 (77.8)	11 (68.8)	54 (57.4)
Abdominal pain	0 (0.0)	1 (12.5)	2 (22.2)	5 (31.3)	8 (8.5)
Abdominal pain upper	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.3)	6 (6.4)
Vomiting	0 (0.0)	0 (0.0)	1 (11.1)	1 (6.3)	6 (6.4)
Diarrhea	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.3)	5 (5.3)
Pyrexia	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.3)	5 (5.3)
Lower respiratory infection	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (5.3)
Headache	0 (0.0)	3 (18.8)	0 (0.0)	1 (12.5)	18 (19.1)
Cough	1 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)	10 (10.6)
Pharyngolaryngeal pain	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	5 (5.3)

**Table 8.5: Treatment Emergent Adverse Events by Age Category for CF patients  
(> 5 % and > 1 patient) (continued)**

Design	Studies with the TbMP		Studies with the CMP		
	Placebo controlled		Placebo controlled		All multiple dose studies
Preferred term	TbMP	Placebo	CMP	Placebo	CMP
<b>&gt; 18 – 30 years</b>					
<b>No. of Patients at Risk</b>	21 (100.0)	20 (100.0)	16 (100.0)	13 (100.0)	52 (100.0)
<b>Any TEAE</b>	7 (33.3)	15 (75.0)	5 (31.3)	8 (61.5)	30 (57.7)
Abdominal pain	2 (9.5)	7 (35.0)	0 (0.0)	4 (30.8)	2 (3.8)
Abdominal pain upper	0 (0.0)	2 (10.0)	2 (12.5)	1 (7.7)	2 (3.8)
Diarrhea	0 (0.0)	0 (0.0)	2 (12.5)	1 (7.7)	3 (5.8)
Flatulence	2 (9.5)	7 (35.0)	0 (0.0)	4 (30.8)	2 (3.8)
Abnormal faeces	1 (4.8)	5 (25.0)	0 (0.0)	0 (0.0)	0 (0.0)
Frequent Bowel movements	2 (9.5)	7 (35.0)	0 (0.0)	5 (38.5)	0 (0.0)
Nausea	0 (0.0)	0 (0.0)	0 (0.0)	2 (15.4)	4 (7.7)
Fatigue	0 (0.0)	0 (0.0)	0 (0.0)	1 (7.7)	4 (7.7)
Pyrexia	0 (0.0)	1 (5.0)	1 (6.3)	0 (0.0)	4 (7.7)
Chills	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (5.8)
Bronchitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (5.8)
Neck pain	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (5.8)
Headache	2 (9.5)	5 (25.0)	1 (6.3)	0 (0.0)	9 (17.3)
Cough	0 (0.0)	0 (0.0)	1 (6.3)	0 (0.0)	7 (13.5)
Lung Disorder	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (7.7)
Productive Cough	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (7.7)
<b>50 – &lt; 60 years</b>					
<b>No. of Patients at Risk</b>	3 (100.0)	3 (100.0)	2 (100.0)	3 (100.0)	12 (100.0)
<b>Any TEAE</b>	2 (66.7)	1 (33.3)	2 (100.0)	0 (0.0)	8 (72.7)
Flatulence	1 (33.3)	1 (33.3)	0 (0.0)	0 (0.0)	2 (18.2)



**Table 8.6: Listing of Deaths**

No.	Study Number/Country	Treatment	Patient No.	Disease State	Age (Years)	Gender	Serious Adverse Event (Verbatim Term) /TE or Non-TE
<b>Open Trials and Compassionate Use</b>							
1	S2453117/Japan, integrated	CREON MMS	1-C1	Cystic Fibrosis	21	Male	Aggravation of cough, respiratory failure, TE
2	S2453103/Japan, integrated	CREON MMS	2102-L-01	Pancreatic surgery	66	Female	Hepatic metastasis of gall bladder carcinoma, non-TE
3	S2453104/Japan, integrated	CREON MMS	2032-O-04	Pancreatic surgery	52	Male	Liver failure secondary to recurrent metastatic pancreatic carcinoma, non-TE
4	Compassionate use/Japan, non-integrated	CREON MMS	2170-L-01	Pancreatic surgery	55	Male	Of recurrent metastatic pancreatic carcinoma, TE
5	Compassionate use/Japan, non-integrated	CREON MMS	1030-C-01	Cystic Fibrosis	9	Male	Pancytopenia, pneumonia, hepatic cirrhosis, aggravation of respiratory infection, TE
6	Compassionate use/Japan, non-integrated	CREON MMS	2200-C-01	Cystic Fibrosis	10	Female	Pneumonia, bronchiectasis, TE
7	Compassionate use/Japan, non-integrated	CREON MMS	2140-L-02	Chronic pancreatitis	70	Male	Cerebral hemorrhage, TE
<b>DB, Placebo-Controlled Trials</b>							
8	S2454007/Scandinavia, non-integrated	CREON MMS	402	Gastrectomy	71	Female	Recurrence of gastric cancer, TE
9	223.8.01/US, integrated	CREON MS	111	Cystic fibrosis	12	Male	Cardiorespiratory arrest, non-TE
10	Creo 630/France, integrated	CREON MS	7	Malnourished elderly	71	Male	Major alteration of general state, TE
11	Creo 630/France, integrated	CREON MS	10	Malnourished elderly	89	Female	Cardiac decompensation, TE
12	Creo 630/France, integrated	CREON MS	30	Malnourished elderly	86	Female	Aneurysmal rupture, TE
13	Laugier/Burundi, non-integrated	CREON MS	22	Chronic pancreatitis	unk	unk	HIV patient with cardiomyopathy, TE
14	Laugier/Burundi, non-integrated	CREON MS	21	Chronic pancreatitis	38	unk	Pancreatic cancer, TE
15	Creo 630/France, integrated	Placebo	5	Malnourished elderly	89	Female	Bronchial superinfection, TE
16	Creo 630/France, integrated	Placebo	11	Malnourished elderly	87	Female	Superinfection of lung with septicemia, non-TE
17	Creo 631/France, integrated	Placebo	39	Malnourished elderly	77	Male	Cardiovascular failure, TE
18	S2454007/Scandinavia, non-integrated	Placebo	208	Gastrectomy	85	Female	Metastatic cancer, pneumonia, TE