28 April 2016
EMA/340098/2016
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Enzepi

International non-proprietary name: pancreas powder

Procedure No. EMEA/H/C/002070/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

ADR	Adverse drug reaction
AE	Adverse event
BL	Bacterial lipase
BMI	Body mass index
BP	British Pharmacopoeia
CF	Cystic fibrosis
CFA	Coefficient of fat absorption
CFA-72h	Coefficient of fat absorption over 72 hours
CFQ	Cystic fibrosis questionnaire
CFQ-R	Cystic fibrosis questionnaire-revised
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CAN	Coefficient of nitrogen absorption
CNA-72h	Coefficient of nitrogen absorption over 72 hours
CP	Chronic pancreatitis
EC	Enteric coated
ECFS	European Cystic Fibrosis Society
EMA	European Medicines Agency
EPI	Exocrine pancreatic insufficiency
EU	European Union
FAS	Full analysis set
FDA	Food and Drug Administration
FE	Faecal elastase
GI	Gastrointestinal
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
HDL-C	High density lipoprotein cholesterol
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human use
ITT	Intention-to-treat

LDL-C	Low density lipoprotein cholesterol
LS	Least squares
MAA	Marketing Authorisation Application
MFAS	Modified full analysis set
NA	Not applicable
NDA	New Drug Application
p or P	P value
PO	Per os (oral administration)
PADER	Periodic Adverse Experience Report
PC	Pancreatic cancer
PDCO	Paediatric Committee
PEP	Pancreatic enzyme product
PERT	Pancreatic enzyme replacement therapy
Ph.Eur.	European Pharmacopoeia
PIP	Paediatric Investigation Plan
PIVKAII	Protein induced by vitamin K absence
PL	Package Leaflet
PP	Per protocol
PV	Phamacovigilance
RMP	Risk Management Plan
QoL	Quality of Life
SA	Scientific Advice
SAEs	Serious adverse events
SAWP	Scientific Advice Working Party
SD	Standard deviation
SE	Standard error
SmPC	Summary of Product Characteristics
SOCs	System Organ Classes
TEAEs	Treatment-emergent adverse events
US	United States
USP	United States Pharmacopeia

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Aptalis Pharma SAS submitted on 4 February 2015 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Enzepi, through the centralised procedure under Article 3(2)(b) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 26 June 2014. The eligibility to the centralised procedure under Article 3(2)(b) of Regulation (EC) No 726/2004 was based on demonstration of significant technical innovation.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/254/2011 on the granting of a product-specific waiver.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific Advice

The applicant received Scientific Advice from the CHMP on the following dates 19 November 2009, 22 July 2010, 23 June 2011, 23 August 2011 and 2 September 2011. The Scientific Advice pertained to quality, non-clinical and clinical aspects of the dossier.

Licensing status

The product was licensed in the following countries at the time of submission of the application: USA, Puerto Rico, Republic of Korea and Ukraine.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were

Rapporteur: Pierre Demolis Co-Rapporteur: Harald Enzmann

- The application was received by the EMA on 4 February 2015.
- The procedure started on 26 February 2015.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 15 May 2015. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 15 May 2015.
- PRAC assessment overview, adopted by PRAC on 11 June 2015.
- During the meeting on 25 June 2015, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 25 June 2015.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 22 December 2015.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 2 February 2016.
- PRAC RMP Advice and assessment overview, adopted on 14 February 2016..
- During the CHMP meeting on 25 February 2016, the CHMP agreed on a list of outstanding issues to be addressed by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 29 March 2016.
- Joint Rapporteur/Co-Rapporteur Assessment Report on the responses provided by the applicant, dated 15 April 2016.
- During the meeting on 28 April 2016, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Enzepi.

2. Scientific discussion

2.1. Introduction

Problem statement

Exocrine pancreatic insufficiency (EPI) is a condition in which the exocrine function of the pancreas is compromised and its ability to effectively deliver digestive enzymes to the duodenum is impaired. It is a serious health condition that leads to malabsorption of lipids, fat-soluble vitamins, proteins, and, to a lesser extent, carbohydrates from the digestive tract, and clinical manifestations such as steatorrhoea (excessive discharge of fat in the faeces). Chronic malnutrition due to EPI can lead to weight loss and anorexia. EPI can be caused by cystic fibrosis (CF), chronic pancreatitis (CP) from all causes, surgery (pancreaticoduodenectomy or Whipple procedure, with or without Wirsung duct injection, total pancreatectomy), obstruction (distal common bile duct obstruction, pancreatic and duodenal neoplasms, ductal stenosis), other pancreatic diseases that destroy exocrine function (hereditary, posttraumatic and allograft pancreatitis, hemochromatosis, Shwachman's syndrome, lipomatosis, hyperparathyroidism), and poor mixing (Billroth II gastrectomy, other types of gastric bypass surgery, and gastrinoma).

Exocrine pancreatic insufficiency due to cystic fibrosis

The primary cause of maldigestion and malabsorption in CF patients is deficiency of pancreatic enzymes. Clinical manifestations, such as steatorrhoea, increased stool frequency, intestinal bloating, pain, flatulence, and poor growth, can be alleviated by oral supplementation with pancreatic enzymes. Approximately 90% of subjects with CF have EPI, which is usually present from birth or develops during the first year of life.

Cystic fibrosis is an inherited, autosomal recessive genetic disorder resulting from mutations in the CF transmembrane conductance regulator (CFTR) gene. This affects the epithelial function of the gastrointestinal (GI) tract and the lung and leads to EPI and chronic pulmonary disease. The CFTR is present in the apical membranes of secretory epithelial cells lining the ducts in various organs, including the intestines, pancreas and lungs. It functions as a chloride channel regulated by cyclic adenosine monophosphate and cyclic guanosine monophosphate and also as a regulator of other ion channels such as those that control bicarbonate and sodium ion secretion across mucosal epithelial cells on surfaces. The prevalence of CF in the EU is 0.737 per 10,000 [Farrell 2008], and it most commonly affects Caucasians.

Loss of the CFTR chloride channel function in the apical membrane of the pancreatic ducts epithelia results in decreased chloride, bicarbonate, and sodium ion secretion across epithelial cells into the ducts, which in turn leads to retention of fluid volume and also to increased reabsorption of water across epithelial cells from the pancreatic ducts. These mucosal transport dysfunctions, desiccation of the intraluminal content, the lower than normal volume of secreted fluids, and the mechanical obstruction in the ducts, instigate a shortage of pancreatic digestive enzymes, thus, preventing adequate amounts of digestive enzymes from reaching the intestines to help break down and digest food. In addition, the impaired bicarbonate secretion can result in the proximal duodenum, in a fasting and postprandial intraluminal duodenal pH one to two pH units lower than in a healthy normal subject. In addition to the impaired mucosal transport, reduction of water content of secretions, and bicarbonate deficiency, motility differences, such as increased transit time through the digestive system also contribute to malabsorption.

It has been further suggested that the alteration of the acinar duct and duodenal pH can lead to enhanced autoactivation of inactive proenzymes (zymogens), which can damage acinar cells and mucosal cells, induce inflammation, and eventually result in destruction and fibrosis of pancreatic tissue, thus, contributing to EPI.

Exocrine pancreatic insufficiency due to chronic pancreatitis

Chronic pancreatitis is characterised by inflammation of the pancreas leading to typical irreversible morphological changes. Although the pathophysiology of CP is still not completely understood, the injury of the glandular anatomy leads to impairment of enzymes secretion. The majority of patients with CP suffer from EPI and present steatorrhoea. In the Western world, CP is most commonly caused by excessive alcohol consumption. However there are other aetiologies, for example it can also be hereditary, be the result of obstructed pancreatic ducts from stones and tumours or after trauma, or in up to one quarter of cases, be idiopathic. The prevalence of any-cause CP in Europe is difficult to ascertain with precision, in part because of the variable nature of clinical manifestations of the disease. There is tremendous variability in reported prevalence between countries and even within one country.

About the product

APT-1008 (previously known as EUR-1008, with a proposed European Trade name of Enzepi) is a pancreatic enzyme product (PEP) containing pancreas powder Ph. Eur. (European Pharmacopoeia), an extract derived from porcine pancreatic glands containing multiple enzyme classes, including lipases, proteases, and amylases. As with currently marketed PEPs and the enzymes that are physiologically secreted by the exocrine pancreas, APT-1008 catalyses the hydrolysis (in the duodenum and other portions of the proximal small intestine) of fats into monoglycerides, glycerol and free fatty acids, proteins into peptides and amino acids, and starch into dextrins and short chain sugars.

The pancreatic extracts used in PEPs are described in several Pharmacopoeias (pancreas powder Ph. Eur; Pancreatin [British Pharmacopoeia] and pancrelipase [United States (US) Pharmacopeia]).

PEPs have been available for many years; in the US they were originally supplied as dietary supplements in the 1920s. In the EU, PEPs have been licensed for use as medicinal products for several decades (eg, Pancrex V was approved in the UK in 1985) and have a well-established medicinal use, with recognised efficacy and an acceptable level of safety.

Type of Application and aspects on development

- Legal basis

The Marketing Authorisation Application (MAA) for Enzepi is made under the Optional Scope of the Centralised Procedure (Regulation (EC) No 726/2004, Article 3(2) b) – significant technical innovation.

The legal basis for the Marketing Authorization Application (MAA) is a full mixed application – known active substance under Article 8(3) of Directive 2001/83/EC as amended.

The Applicant received CHMP scientific advice regarding the structure of the clinical evaluation programme, and has conducted the programme in accordance with the majority of the recommendations received and in accordance with the CHMP guideline on the clinical development of medicinal products for the treatment of cystic fibrosis EMEA/CHMP/EWP/9147/2008-corr.

The proposed indication is as follows:

“Pancreatic enzyme replacement treatment in EPI due to CF or other conditions (eg chronic pancreatitis, post pancreatectomy or pancreatic cancer). Enzepi is indicated in adults, infants, children and adolescents.”

2.2. Quality aspects

2.2.1. Introduction

Enzepi is a pancreatic enzyme product (PEP) containing pancreas powder, extracted from porcine pancreatic glands containing multiple enzyme classes, including lipases, proteases, and amylases.

Enzepi finished product consists of hypromellose hard capsules filled with slightly brown gastro-resistant granules in the form of small tablets (also referred to as minitablets and/or microtablets) containing pancreas powder as an active substance.

Enzepi is supplied in several capsule strengths differing in size and colour, containing different amount of pancreas powder and accounting for different enzymatic activities.

2.2.2. Active Substance

General information

The active substance is pancreas powder extracted from pig or sow pancreas glands. As defined in Ph. Eur. monograph (0350) pancreas powder is a complex biological material containing various enzymes, including trypsin, chymotrypsin, kallikrein, amylase, lipase, colipase and some isoforms, having lipolytic, amylolytic and proteolytic activities.

Considering the complexity of the product, a complementary set of biochemical methods were adopted to characterize pancreas powder and to compare the results with published data of pancreatic enzymes. The molecular weights of the pancreatic enzymes determined in pancreas powder as produced by the active substance manufacturer Nordmark GmbH are in accordance with published data.

Manufacture, characterisation and process controls

Description of manufacturing process

The porcine pancreas glands are the starting material. The pancreas of the hog consists of water, fat, insoluble materials (tissue, fibres) and a mixture of soluble substances (peptones, proteins and enzymes etc.).

The manufacturing process to generate pancreas powder active substance is a traditional extraction process where enzymes contained in porcine pancreatic glands are extracted by autolysis and afterwards purified by precipitation before being dried, de-agglomerated, sieved and homogenized.

A new manufacturing step was implemented in order to improve viral safety. Pancreatin VR refers to pancreatin active substance that incorporates the additional step.

Process development and validation

The proposed pancreas powder manufacturing process was developed based on a historical manufacturing process being in place until 1983 at the Nordmark GmbH. Several optimisations have been implemented since then to manufacture a product of improved quality.

A formal prospective validation of the manufacturing process has been provided. All manufacturing steps (including the new additional step) were validated. The applied parameters were provided and complied with the ones applied in routine. The controls gave satisfactory results.

Process controls and intermediates

The process steps, process controls together with the respective acceptance criteria and scale of the manufacturing process have been adequately described. However, for the newly introduced manufacturing step it is recommended to revise IPCs and intermediate acceptance limits once more manufacturing experience has been obtained.

Control of Materials

Most of the materials of non-biological origin used in the manufacturing process of Pancreas powder are compendial and have to comply with the respective Ph. Eur. Monograph. Biological origin materials are controlled according to an in-house specification which is considered acceptable.

Characterisation

Characterisation section gathers characterisation data on the active substance without the additional manufacturing step and comparability studies on the active substance produced with and without the additional manufacturing step.

As regards comparability between pre-change material (Pancreatin) and the post-change material (Pancreatin VR), besides release data, additional characterisation data have been provided.

Summarising the results of the comparability studies, it was appropriately demonstrated that the detected differences are smaller than inter-batch variability and are therefore not considered to have an adverse impact on the finished product quality. Thus, Pancreatin and Pancreatin VR materials are considered comparable.

Specification

The provided active substance release specification includes appearance testing by visual inspection, testing of identification by proof of enzymatic activity and Test B of the EP Monograph, assay of lipolytic, amylolytic and total proteolytic activity, loss on drying, residuals of fat and solvent, RP-HPLC (used as a quantitative composition test), and microbial purity. In addition, a yearly control of mycotoxins and ochratoxin contents, residuals of heavy metals, dioxins, organochlorpesticides is proposed which is considered appropriate for this type of product.

Most of the analytical procedures mentioned in the specification are compliant to the methods indicated in the Ph. Eur. monograph for Pancreas Powder or official European or German legislation and thus, are considered validated. Determination of residual solvent is performed with an in-house method. The respective method validation is considered acceptable.

The provided justification of specification is based upon historical batch data. While the data set for pancreatin batches manufactured without the additional step is large, the data set for the proposed Pancreas powder process is currently very limited. The proposed enzymatic activity assay specification limits is considered acceptable as preliminary acceptance criteria that would need to be further reviewed when more commercial scale batches are available.

The information provided on the reference standards or materials in place at the active substance manufacturing site is considered acceptable with regard to the use of EP BRP standards as primary standard for enzyme activity determination and with regard to the solvent standard.

Regarding the pharmaceutical quality of the container material reference is made to EP Monograph 3.1.4. Sufficient details on the container used for storage of pancreas powder have been provided.

Stability

Stability data have been provided for batches without the additional manufacturing step in the proposed storage container for long-term stability (25 °C / 60% RH). Accelerated studies have been performed at 40 °C / 75% RH with the active substance stored both in the proposed storage container. Additional data for batches produced with the additional manufacturing step has been presented. The proposed stability protocol includes determination of enzyme activities, loss on drying, microbial purity as well as RP-HPLC as a quantitative composition test.

Based on the stability data provided for long-term stability and accelerated testing, the claimed shelf-life for the active substance when stored under climatic zone II conditions is considered acceptable.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

Enzepi finished product consists of hypromellose hard capsules filled with slightly brown gastro-resistant granules in the form of small tablets (also referred to as minitablets and/or microtablets) containing pancreas powder as an active substance. Enzepi is supplied in several capsule strengths differing in size and colour, containing different amounts of pancreas powder and accounting for different enzymatic activities.

Capsules are filled with proportional weights of identical minitablets to produce finished product of 10,000, 25,000, and 40,000 lipase units. The minitablets are 2.2 mm in diameter and 2.5 mm thick. The 5,000 lipase unit capsules are filled with smaller microtablets (1.8 mm in diameter and 2.0 mm thick) which are identical in qualitative composition but with a slight difference in the quantitative composition of the enteric coating.

Product development targeted at capsules with no overage. The products were developed based on prior knowledge with a strong focus on reducing the moisture content of the minitablets. Moisture sensitivity is the most critical material attribute of the active substance.

The rationale for the choice of the dissolution method, the procedure for gastro-resistance testing, and the procedures for testing on the enzyme activities with regard to differences to the respective Ph. Eur. procedures has been provided.

For the 5,000 units strength which is mainly targeted at paediatric patients the minitablets were found to be too large, and microtablets were developed. For these microtablets, qualitative and quantitative composition of the powder for tableting and the coating suspension remained the same. However, the ratio of core to coating was adapted.

The compatibility of minitablets and microtablets with food at pH 5 or below and microtablets as preferred for paediatric patients with infant formula (pH ca. 7) was studied. Whereas food at or below pH 5 showed no negative impact on gastro-resistance and dissolution of minitablets and microtablets, infant formula is not suitable for the administration of microtablets.

Enzepi should be taken during meals or snacks with a drink of water or juice. Capsules should be swallowed whole and not chewed or crushed. For patients who cannot swallow capsules, the capsules may be carefully opened and the content mixed (without crushing) with small amounts of acidic food such as a fruit puree which should be swallowed immediately without chewing. (It should not be mixed with water, milk, breast-milk, formula, flavoured milk or hot food).

The development of the manufacturing process is sufficiently described with respect to the choice of the active substance and the minitablets/microtablets based on the lipolytic activity for the different capsule strengths. The development objectives and investigations for all manufacturing steps were also presented.

The choice of the container closure system for the finished product as well as for bulk holding and shipping packaging has been sufficiently justified. Certificates of compliance with the applicable regulatory requirements are provided.

The capsules are packaged in high density polyethylene (HDPE) bottles closed with a white polypropylene child resistant push-down and turn cap and a peel-off sealing liner. Bottles contain also polyethylene sachets in contact with the product, containing molecular sieves desiccant.

Manufacture of the product and process controls

To manufacture Enzepi finished product to the required specification, pancreas powder must meet a certain set of criteria for lipolytic activity. Batches of Pancreatin VR active substance may be blended to achieve this desired enzyme activity. This blending, is the starting point of the finished product manufacturing process.

After optional blending of active substance batches, the manufacturing process of the finished products comprising sieving and mixing of the starting materials, tableting, coating of the minitablets/microtablets, capsule filling and packaging including in-process controls (IPCs) for all manufacturing steps has been sufficiently described.

The criticality of each manufacturing step has been discussed and critical operating parameters and critical process controls have been adequately set. A specification for the intermediates, i.e. pancreatin VR blend intermediate, coated minitablets and microtablets has been also included. Bulk density and particle size distribution testing are performed on the pancreatin blend to ensure that the material meets the criteria required for manufacturing the finished product.

Product specification

Except for microbial examination the tests of the finished product specification are either performed on capsule bulk product or intermediate product (minitablets or microtablets). This is accepted as thermal cycle studies demonstrated the stability of the finished product after exposure to conditions simulating potential temperature excursions during transportation of the bulk product to the packaging site in the intended bulk holding and shipping container closure system.

The proposed assays for lipolytic, amylolytic and proteolytic activity are adapted from the respective Ph. Eur. Monograph “Pancreas powder”. The differences have been described and equivalence of the proposed in-house methods with the respective Ph. Eur. methods was appropriately demonstrated. The analytical procedures have been sufficiently described.

Validation results for the test on lipolytic activity, amylolytic activity, proteolytic activity, loss on drying, phthalic acid, residual solvent acetone, dissolution, gastro-resistance and microbiological quality have been provided. The validations of the enzyme activity tests were performed using the Ph. Eur. BRP reference standard.

The provided batch analyses confirm consistency and uniformity of the products.

Potential impurities concerning residual solvents and degradation products of excipients have been sufficiently discussed.

The justification of specifications for identification test, tests on enzymatic activities, loss on drying, dissolution, gastro-resistance, alternative test on uniformity of dosage units, tests on phthalic acid and microbiological quality is appropriate. The proposed limits for amylolytic and proteolytic activities in the active substance blend intermediate specification, and in the finished product specification, were revised. However, considering the currently limited data set due to the newly introduced active substance manufacturing step, the Applicant is recommended to review the data from the first 30 commercial finished product batches and to revise the acceptance limits of finished product specification as appropriate.

Adventitious agents

The Applicant is recommended to provide the type and the results of the serological assay used for virus testing from US post-marketing study when available.

A discussion on critical key parameters has been provided.

The contribution of the solvent to viral clearance has been adequately discussed.

The validation studies acceptance criteria for critical key parameters presented are deemed acceptable and represent a worst-case scenario compared to industrial scale parameters.

Viral inactivation kinetics results have been provided and the results are acceptable.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

A new step into the active substance manufacturing process in order to improve viral safety was introduced. Comparability of the resulting Pancreatin VR active substance with Pancreatin active substance obtained from the initial manufacturing process was sufficiently demonstrated. While there are some qualitative and quantitative differences detectable between Pancreatin and Pancreatin VR these differences are smaller than inter-batch variability. Furthermore, the observed differences are not considered to have an adverse impact on the finished product quality.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

Information about the active substance and finished product was of acceptable quality. The manufacturing processes are well described and properly controlled both for active substance and finished product. Specification limits and analytical methods are suitable to control the quality of the active substance and the finished product. The stability program is considered satisfactory. The results generated during the stability studies support the proposed shelf life and storage conditions as defined in the SmPC.

2.2.6. Recommendations for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommended some additional points for further investigation.

2.3. Non-clinical aspects

2.3.1. Introduction

Given the knowledge and long history of the well-established use of PEPs in humans, new nonclinical testing of PEPs is considered unnecessary as further testing in animals is unlikely to usefully extend scientific knowledge. As such, the Applicant has conducted an up to date literature search. The Module 4 (Non-clinical) is based on bibliographical references and the Nonclinical Overview provides justification that generating additional nonclinical data is not necessary.

For all these studies reported in the published literature, no information regarding their Good Laboratory Practice (GLP) status is available. Based on the extensive clinical use of the active substance and the experience to date, the GLP status of the studies is not expected to affect the validity of the reported overall findings.

Among the literature, two studies were conducted in dogs and five were conducted in pigs. In these studies, PEPs showed efficacy and dose-response relationships; the effect of different formulations was also explored. Nonclinical studies with information relevant to secondary pharmacodynamics, safety pharmacology, and pharmacodynamic drug interactions with PEPs were not identified in the literature, nevertheless the extensive clinical experience with PEPs support the lack of preclinical studies.

The activity of PEPs in pigs or in dogs shows a reduced pancreatic steatorrhoea, a reduced plasma neurotensin level to a meal, an improvement in digestion of nutrients, an increase in daily faecal output, an increase weight gain and a greater absorption of vitamins A, E.

Relevant submitted literature submitted is summarized below.

2.3.2. Pharmacology

Primary pharmacodynamic studies

The pharmacological effects and efficacy of orally ingested PEPs have been established through their long-term use in humans to improve the nutritional status of patients with EPI. No pharmacology studies were performed with APT-1008.

Seven articles with information relevant to the pharmacology of PEPs were found in the literature search with many of PEP formulations used in clinical practice (see table below). Some of them were not gastro-resistant. Animal models of EPI were consistent with the disease in humans such as steatorrhoea and weight loss.

The doses of the PEPs used in the animal studies were considered consistent with the therapeutic doses of PEPs. In some cases the doses administered were twice the dose recommended for patients with EPI.

Table 2: primary pharmacodynamic studies with PEPs

Species / Type of Study Gender / No. per Group / Study reference	Doses / Treatment Duration / Method of Administration	Noteworthy Findings
Dog Pancreatic duct-ligated Treated N=9 Control N=1 (Pairent et al. 1969)	6 tablets or capsules per day for 9 weeks in two periods of 3 and 6 weeks with 3 weeks drug-free period in between. The 9 different products were weekly rotated. Oral gavage (Non–gastro-resistant formulation : Viokase tablet, Convertin tablet, Progestive tablet, Panteric granules, Festal tablet, Cotazym capsule, AL0834 (tablet), Kuzyme capsule, Kanulase tablet)	Beneficial effects in reducing steatorrhoea. Total lipid excretion in the animals with complete exocrine pancreatic insufficiency (EPI) ranged from 28% to 75%.
Dog Pancreatic duct-ligated Female : N=5 (Suzuki et al. 1999)	PL dose = 30,000, 135,000 or 300,000 International units [IU] Lipase/ 1.8, 8.1, or 17.94 g) and doses of BL (30,000, 135,000, 300,000 or 600,000 IU Lipase/ 12, 54, 120, or 240 mg). Single administration (PL: Viokase powder) Bacterial lipase (BL) in combination with different diets	Coefficients of fat (CFA) increased dose dependently with both PL and BL, but significantly more fat was absorbed with PL at each dose level. Correcting steatorrhea requires more porcine than bacterial lipase.
Pig Pancreatic duct-ligated Male :N=10 (Abello et al. 1989)	Eurobiol (non-gastro-resistant) = suspension of 10 g (average 67,800 IU of lipase, 2,800,000 IU of trypsin, 120,000 IU of chymotrypsin and 281,000 U of amylase) or placebo Intragastric injection Single administration	Decrease of plasma levels of digestive hormones, the neurotensin After 3 hours of administration, neurotensin concentrations tended to decrease more rapidly in EPI pigs receiving Eurobiol, compared to EPI pigs receiving the placebo.
Minipigs Pancreatic duct-ligated Male N=3 pancreatic duct-ligated N=3 control	Creon 10,000 (gastro-resistant microspheres): 0, 8, 16 and 24 capsules per meal, twice per day for 5 days Feed	Influence of pancreatic enzyme supplementation (PERT) on the digestibility and composition of ileal chyme and faeces following a high fat diet. Lipopolysaccharides (LPS)

(Tabeling et al. 1999)		concentrations were increased markedly in PDL pigs compared with control pigs but normalised following administration with Creon. Pre-caecal digestibility in PDL pigs was markedly increased, partly dose-dependently, following enzyme administration although it did not reach control values. Following enzyme substitution, the hindgut fermentation in PDL pigs was reduced in parallel with the increase in pre-caecal digestibility, however, hindgut production of fat stayed high. Daily faecal output was markedly increased in the PDL pigs, and treatment with Creon produced only a partial reversal of this effect.
Pigs pancreatic duct ligated Female and male castrated/ N=3-7 PDL and PERT group/ Shamoperation N=3/ PDL only N=5 (Saloniemi et al 1989)	Combizyme Forte granulate (non-gastro-resistant) 300,000 FIP Units lipase per day per animal/ For 20 days Feed	Increase in weight gain Weight gain of the ligated pigs without PERT was significantly lower than the weight gain of the shamoperated or PERT group. Weight gain of the PERT group was almost the same level to that of the shamoperated group.
Pigs pancreatic-duct ligated average age 12.2 ± 2.6 weeks old at start of treatment N=3-6 (Rengman et al. 2009)	Creon: 10,000 lipase Units per day (24 capsules). Approximately 15 000 lipase units/kg/day. 6 days treatment Feed	Effectiveness of pancreatic supplementation (Creon) in growth of young pigs with EPI The PDL pigs fed with the commercial feed or the fat-enriched feed, supplemented with pancreatin showed a weekly body weight increase (17.1% and 16.6%, respectively) similar to that of the control pigs (20.1%).
Pigs pancreatic-duct ligated Approximately 10-week old at start of treatment N=4 (Möβeler et al. 2012)	Creon 19.8g = 1,048,727 IU lipase/kg feed to PDL-pigs. Creon group, no vitamins Creon plus oral vitamin A and E group, Creon plus intramuscular (IM) injection of vitamin A and E group, Control group shamoperated/ 6 weeks treatment	administration of PERT to the EPI animals alongside very high oral doses of vitamin A and E supplementation in the diet (with an efficient emulsifier) enabled sufficient absorption of the fat soluble vitamins to maintain vitamin A and E in liver tissue within reference values

IM = intramuscular; PERT: Pancreas enzyme replacement therapy; PDL: pancreatic-duct ligated

Secondary pharmacodynamic studies

No secondary pharmacodynamics, safety pharmacology and pharmacodynamic drug interaction data in animals have been identified / submitted by the applicant, it is considered justified by the extensive clinical experience with PEPs.

Safety pharmacology programme

See chapter above

Pharmacodynamic drug interactions

See chapter above

2.3.3. Pharmacokinetics

No new pharmacokinetic studies in animals have been conducted with APT-1008. Pivotal literature references submitted are summarized below.

Abello et al. 1989: Total pancreatic insufficiency in pigs: a model to study intestinal enzymes and plasma levels of digestive hormones after pancreatic supplementation by a whole pancreas preparation.

Ten pigs (castrated, male, white, approximately 49 kg) were fed a standard diet (800 g of 17% protein, 7% fat, and 67% starch mixed with water twice a day). All animals were instrumented with cannulae in the duodenum, jejunum and ileum for sampling of the contents. EPI was induced by pancreatic duct ligation in five animals. Recovery after surgery was set to one week. EPI animals were substituted with 10 g Eurobiol (freeze-dried whole pig pancreas preparation; 67,800 IU lipase 12,800,000 trypsin; 120,000 chymotrypsin; 281,000 amylase) per meal during this period.

After a 24 hours fasting period pancreatic duct ligated animals were treated with 10 g whereas intact animals received placebo by an oral catheder 10 minutes after the start of feeding. Samples of gut contents were taken simultaneously from the duodenum, jejunum and ileum at several time points up to 24 hours afterwards.

Enzymatic activities in the homogenates of intestinal contents and plasma levels of the digestive hormones neurotensin, pancreatic polypeptide, secretin, gastrin, and cholecystokinin, were determined.

Results:

Study ID	Species	N	Dose (mg/kg)	Route	Anal.	Postprandial peak activites (% of unligated control of resp. bowl segment)	
						Duodenum	Jejenum
Abello et al. 1989	Pig	5 Pancreatic duct ligated 5 unligated	10 g Eurobiol (67,800 IU lipase 12,800,000 trypsin 120,000 chymotrypsin	Oral (gastric catheder)	Lipase	19	30

		control	281,000 amylase) placebo				

Gewert et al. 2004 The enzyme levels in blood are not affected by oral administration of a pancreatic enzyme preparation (Creon® 10,000) in pancreas-insufficient pigs.

Pancreatic duct-ligated pigs (n=8) and pancreatectomised pigs (n=5) were orally dosed with increasing doses of 0, 2, 4, or 8 g of Creon® 10 (lipase 10,000 United States Pharmacopeia [USP] units), mixed with 100 g of the morning feed, while duct-ligated pigs (n=4) received the same doses in a randomized order. Experiments were followed by one washout day before the next dose was given. Control pigs (n=9), duct-ligated (n=6) and sham-operated (n=3) did not receive Creon®. Blood samples were taken 0.5 hours before and at feeding/administration of Creon® (0 hours), and then up to 48 hours thereafter. The plasma pancreatic lipase activity and the (pro)colipase and cationic trypsin(ogen) levels were measured. Pancreatic amylase absorption was not determined, since it was already known that it is not absorbed in dogs after intraduodenal infusion [Levitt et al., 1981].

Results:

The results showed no absorption of pancreatic lipase, (pro)colipase, or cationic trypsin(ogen) into the blood after oral administration of up to 8 g of Creon® mixed together with the feed. The extrapancreatic lipase activity found in blood samples from control and Creon®-treated animals was thought to be due to the use of heparin as anticoagulant in the study which induced the release of endogenous lipoprotein lipase and hepatic lipase [Dörner and Schulze, 1996]. In conclusion, the evaluation of the absorption of orally administered PEPs in pancreatic insufficient pigs demonstrated that pancreatic enzymes administered exogenously were not absorbed into the bloodstream.

2.3.4. Toxicology

Pancreatic enzyme products have been commercially available for several decades and due to their extensive clinical use, they have a well-established human efficacy and safety profile. Therefore the Applicant has not performed any toxicology studies with APT-1008.

A literature search has identified a limited number of published studies relevant to the toxicological evaluation of pancreatic enzyme products in animals.

Single dose toxicity

Table 3: single dose studies with PEPs

Species/ Gender and No per Group Study reference	Doses (mg/kg) Method of Administration (Vehicle/Formulation)	Noteworthy Findings
Hamster Single dose study Female 6-week-old Treated group :N=15 Control group : N=5 [Saruc et al. 2012]	1000 : Equivalent to 15,000-40,000 USP lipase/kg (i.e. 4 times the maximum total daily dose recommended in humans) Control group: water + Pentobarbital (20 mg/kg) Oral gavage	- 3 hamsters died due to pulmonary aspiration procedure, not drug toxicity - No histological abnormalities in the lungs, pancreas, liver and kidney. Observed Maximum Non-Lethal Dose = 1,000 mg/kg

Hamster Single dose study Female 6-week-old Treated group: N=30 Water control group : N=10 Untreated control group N=10 [Saruc et al. 2012]	400 : Equivalent to 6,000-16,000 USP lipase Units/kg Control group: Water Oral gavage	- 6 hamsters died due to pulmonary aspiration procedure, not drug toxicity - The weights of the body and the pancreas, as well as the histological findings of the lungs, pancreas, liver and kidneys were similar in all groups. Observed Maximum Non-Lethal Dose = 400 mg/kg

In both studies no signs of toxicity were observed following histological examination of the lungs, pancreas, liver and kidneys at single doses up to 1,000 mg/kg/day tested, up to 40,000 USP lipase units/kg i.e. four times the maximum total daily dose recommended in humans.

Repeat dose toxicity

Table 4: repeat-dose studies with PEPs

Species/Strain Gender and No per Group Study Number	**Doses (mg/kg) Method of Administration (Vehicle/Formulation)**	**Noteworthy Findings**
Hamster 15 days repeat dose study Female/Male (6-week-old) N=5 per sex [Saruc et al. 2012]	400, 4 times per day Equivalent to 24,000-64,000 USP lipase units/kg/day No data on controls Oral gavage	- 2 male and 1 female hamster died on aspiration - Histological examination did not reveal any abnormalities in the pancreas, liver, kidneys and lungs. - No differences found in plasma concentrations of trypsin, amylase and lipase between groups. NOAEL not determinated
Hamster 65 days repeat dose study 18-days old N=10 per group [Saruc et al. 2012]	0, 400 kg/day (6,000-16,000 USP lipase units/kg/day) Drinking water	- Body weights in treated group significantly lower than in the control group. - In the pancreas, reduced size of islets and a lower number of insulin producing beta cells observed in the PPE-treated animals. Plasma insulin, lipase and amylase levels were significantly lower in the PPE-treated animals. Hypothesis: these effects were due to fat metabolism by exogenous pancreatic enzymes and/or reduction of the expression of insulin receptor protein in islet cells. NOAEL = 400 mg/kg/day

PPE: Porcine pancreatic enzymes

Genotoxicity

No genotoxicity studies have been performed in accordance with ICH S6 guideline.

Carcinogenicity

Two studies on the administration of pancreatic enzymes in animal models of pancreatic cancer are identified in the literature by the Applicant. Both evaluate the potential to support the proliferation of transformed cells and clonal expansion possibly leading to neoplasia.

Table 5: carcinogenicity studies with PEPs

Species/Strain Gender and No per Group Study Number	Doses (mg/kg) Method of Administration (Vehicle/Formulation)	Noteworthy Findings
Hamsters 43 weeks study 3-4 week-old 30/sex for control and 32/sex for 1000 mg/kg group [Nozawa et al. 2012]	0, 1000 (15,000-40,000 USP lipase units/kg/day) High fat diet Drinking water 1 week after treatment with PPE, all control and PPE-treated animals received a single SC dose of 40 mg/kg bw of BOP = a potent pancreatic carcinogen in hamsters [Pour et al. 1977] and acts as a tumour initiator	- hyperinsulinaemic as a result of a high fat diet - After administration of a single SC injection of a pancreatic tumour initiator in order to induce pancreatic cancer : the incidence of adenocarcinoma and their size were lower in animals exposed to PPE in drinking water at 1000 mg/kg/day than in the control group not treated with PPE. - Pancreatic islet sizes were smaller and the number of insulin-secretin beta cells lower in the PPE group. - Plasma insulin levels were lower in the PPE-treated group than in the control group - Plasma lipase levels were significantly higher in the PPE-treatment group which is unexplained given it is the converse of what was observed in the repeat-dose toxicity study and not in accord with the well-established knowledge that pancreatic enzymes are degraded in the lumen and therefore not absorbed systemically.
Nude mouse with malignant human PC cell line AsPC1 pancreatic xenograft 62 days study 13 males for control 14males for PPE group [Saruc et al. 2004]	0, 400 (6,000-16,000 USP lipase units/kg/day). Drinking water	- survival in days significantly greater and tumour size and volume smaller in PPE-treated animals compared to controls - Distribution of tumor weight at the time of death was higher for the treatment than control group, possibly due to significantly greater survival of mice in the treatment group. All animals in both groups developed poorly differentiated adenocarcinoma.

SC: subcutaneous; PPE: porcine pancreatic enzymes

Reproduction Toxicity

According to ICH guideline S6 (R1), preclinical safety evaluation of biotechnology derived pharmaceuticals, the need for reproductive/developmental toxicity studies is dependent upon the product, clinical indication and intended patient population. Although PEPs have a long history of use in humans there are no adequate data relating to the use of pancreas powder in pregnant women. As pancreatic enzymes degrade in the intestinal lumen and are not absorbed, no reproductive or developmental toxicity is expected. No studies on fertility, prenatal and postnatal development or juvenile studies in animals have been identified in the

literature / submitted in this application. No data on lactation are available. Only one published article is available relating to the embryo-fetal development stage.

Table 6: Embryo-foetal study with PEPs

Species/Strain Gender and No per Group Study Number	Doses (mg/kg) Method of Administration (Vehicle/Formulation)	Noteworthy Findings
Rabbits (NZW) [Nemec et al. 1986 (abstract)]	0, 260, 520, 1040 of PANCREASE® (gastro-resistant formulation) approximately 6,240 to 24,960 USP lipase units/animal During G6-G18 Oral gavage	No treatment related effects in maternal toxicity, teratogenicity or embryotoxicity were observed.

Toxicokinetic data

Local Tolerance

Two reports [Snead et al., 2006, and Rutz et al., 2002] of oral bleeding in dogs receiving pancreatic enzyme supplements in powder form were reported and are consistent with the known local tolerability issues that can occur if PEPs are not administered in accord with the prescribing information. Oral tolerability is addressed in the SmPC as it's indicated the capsules should be swallowed hole and not chewed or crushed.

Other toxicity studies

No novel excipients are present in the formulation of APT-1008. All of the excipients have established use in oral drug products. For HPMCP, the ADI estimated by the Applicant was 30 mg/kg bw/day. However, according to the guideline on the use of phthalates as excipients in human medicinal products (EMA/CHMP/SWP/362974/2012 corr 2) and given that HPMCP orally via gavage in rats, histopathology and organ weight evaluations revealed no effect on the reproductive organs following repeat-dosing of up to 6 g/kg body weight/day HPMCP for 6 months, the ADI can be estimated as being 60 mg/kg bw/day which is more than twice the ADI estimated by the Applicant. The impurity, phthalic acid as a potential degradation product of the gastro-resistant coating ingredient HPMCP had been identified. The toxicology assessment (Jones, 2005) did not reveal relevant safety concerns.

The impurity, phthalic acid as a potential degradation product of the gastro-resistant coating ingredient HPMCP has been identified, and a toxicology assessment in 2005 has been carried out to determine a PDE value for derived from enteric coatings for tablets pharmaceuticals which did not raise safety concerns.

2.3.5. Ecotoxicity/environmental risk assessment

The active substance is a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, pancreas powder is not expected to pose a risk to the environment.

2.3.6. Discussion on non-clinical aspects

APT-1008 is a pancreatic enzyme product (PEP) containing pancreas powder (Ph. Eur.), an extract derived from porcine pancreatic glands containing multiple enzyme classes, including lipases, proteases and amylases. APT-1008's proposed indication is in the treatment of exocrine pancreatic insufficiency (EPI).

The pharmacological effects and efficacy of orally ingested PEPs have been established through their long term use in the clinic. Therefore it was considered unnecessary to conduct animal studies on APT-1008; however, adequate literature references were submitted by the Applicant.

The activity of PEPs in pigs or in dogs shows a reduced pancreatic steatorrhoea, a reduced plasma neurotensin level to a meal, an improvement in digestion of nutrients, an increase in daily faecal output, an increase weight gain and a greater absorption of vitamins A, E.

The effects in animals reflect the observations in humans with pancreatic enzyme replacement therapy.

No secondary pharmacodynamics, safety pharmacology and pharmacodynamic drug interaction data in animals have been identified, it is considered that as justified by the extensive clinical experience with PEPs.

Pharmacokinetic studies in animals have not been conducted with APT-1008; however, adequate literature references were submitted by the Applicant.

PEPs do not require absorption to exert their effects as their full therapeutic activity is exerted from within the lumen of the GI tract. Furthermore, the active ingredients present in APT-1008 are proteins that undergo proteolytic digestion while passing along the tract before being absorbed as peptides and amino acids.

No specific studies to evaluate the distribution, metabolism and excretion studies of APT-1008 are justified since no systemic absorption of PEPs following oral administration in pancreatic-insufficient animals and in subjects with CF and EPI have been found.

Pancreatic enzymes are degraded in the lumen in humans and animals and consequently, intact enzymes are not absorbed systemically as was demonstrated in an animal model of EPI and in humans. Consequently, the oral administration of pancreatic enzymes is not anticipated to result in systemic toxicity.

Concerning the two studies submitted for repeat toxicology in only one species (rodent), the list of tissues histologically examined was limited in comparison to what would be expected in a repeated-dose toxicity study and the duration of the study was shorter than the 6 months generally considered appropriate for biopharmaceuticals in chronic indications according to the ICH S6 (R2) guideline. However, the limited repeat-dose toxicity data with porcine pancreatic enzymes in hamsters are considered adequate given the well-established safety profile of PEPs in humans and the clinical safety data available for APT-1008 in particular. Since only one dose level was used in the studies, evaluation of dose-response was not possible.

Furthermore, given that orally administered pancreatic enzymes are not absorbed, no systemic toxicity due to the enzymes is anticipated.

The 65 days repeat dose study shows in healthy hamsters the possible effect of PPE in the reduction insulin which is probably due to the way fat metabolism affected. In humans, a risk of abnormal blood glucose levels is identified and notified in undesirable effects section (4.8) in SmPC and a warning is also included in SmPC (section 4.4).

No evidence of tumour proliferation was observed in pancreatic cancer study models. A study (for which only the abstract is available) where PEPs were administered throughout the period of embryo-foetal development did not reveal any maternal, teratogenic or embryotoxic effects in rabbits. As there is no evidence of absorption of this medicinal product reproductive or developmental toxicity is not to be expected. Nevertheless the lack of data reflected in the SmPC for consideration of the prescriber.

Two cases of oral bleeding in dogs receiving pancreatic enzyme supplements in powder form were reported and are consistent with the known local tolerability issues that can occur if PEPs are not administered in accord with the prescribing information. Oral tolerability is addressed further in the Clinical section and advice is provided in the proposed SmPC that the capsules should be swallowed hole and not chewed or crushed.

Toxicity on excipients and the impurity phtalic acid did not lead to relevant safety concerns. Overall, the toxicology programme can be considered acceptable.

The active substance is a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, pancreas powder is not expected to pose a risk to the environment.

2.3.7. Conclusion on the non-clinical aspects

Considering the extensive clinical use of the active substance and the clinical experience the non clinical profile presented based on submitted literature is considered sufficiently characterized. Relevant findings are included in the SmPC.

2.4. Clinical aspects

2.4.1. Introduction

The clinical package submitted with this application includes a combination of full study reports for a range of studies conducted with APT-1008 (Phase I – III), US post-marketing data, as well as bibliographic references concerning the use of PEPs

The clinical development programme for APT-1008 comprises three Phase III clinical studies (PR-005, EUR-1008-M and EUR-1009-M), a Phase II/III study (PR-002), as well as two Phase IV studies (PR-011 and PR-018). Each of these studies provides information on the efficacy and safety of APT-1008.

Study PR-005 provides pivotal efficacy and safety data for the APT-1008 MAA submission, with studies EUR-1008-M, EUR-1009-M, PR-002, PR-011 and PR-018 providing supportive data.

In addition to the 6 clinical studies described above, the APT-1008 MAA includes a Phase I study (PR-001). PR-001 was a GI in vivo intubation study to evaluate the bioavailability of APT-1008 in gastric and duodenal aspirates.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Study ID Phase	No. centres/ location	Study design	Study and control drugs (dose strength) and total dose	Primary objective and subject population	Subject number Mean age (SD; Range)
PR-005 Phase III	34/ 7 countries in Europe	Randomised, double-blind, active-controlled, 2-treatment, crossover, multinational study	APT-1008 (25,000 Ph. Eur.), Kreon (25,000 Ph. Eur.) Up to 10,000 lipase units/kg/day, at a dose as close as possible to their existing stabilised PEP treatment	To evaluate the safety and efficacy of APT-1008 as compared to Kreon in the treatment of EPI associated with CF in subjects 12 years and older who were able to swallow capsules	Entered: 96 Evaluable: 83 19.2 years (7.90; 12-43) (for subjects entered)
EUR-1008-M Phase III	12/ US	Randomised, double-blind, placebo-controlled, 2-treatment, crossover study	APT-1008 (5,000, 10,000, 15,000, 20,000 USP), Placebo. Up to 10,000 lipase units/kg/day, titrated for each subject	To compare the CFA-72h following oral administration of APT-1008 or placebo in CF subjects with EPI aged ≥7 years	Entered: 34 Evaluable: 32 14.9 years (4.89; 7-23) (for subjects entered)
EUR-1009-M Phase III	10/ US	Open-label, uncontrolled multiple-dose, single-treatment study	APT-1008 (5,000 USP) Up to 10,000 lipase units/kg/day, titrated for each subject	To compare measures of malabsorption of fat after administration of APT-1008 versus previous treatment in CF subjects with EPI, age 1 to <7 years	Entered: 19 3.9 years (1.58; 1-6)
PR-002 Phase II/III	19/ US and Europe	Randomised, double-blind, dose response, crossover study	APT-1008 high dose (20,000 USP dose strength: 140,000 lipase units/day) APT-1008 low dose (5,000 USP dose strength: 35,000 lipase units/day), placebo (during the baseline period only)	To evaluate the difference in CFA-72h of subjects treated with high dose APT-1008 vs low dose APT-1008 in the treatment of signs and symptoms and management of malabsorption in subjects >18 years with EPI associated with CP	Entered: 82 Evaluable: 76 51.91 years (12.08; 22-82) (for subjects entered)
PR-011 Phase IV	6/ US	Open-label, multiple dose, crossover study	APT-1008 (3,000 USP) administered in apple juice (in a syringe nurser) or apple sauce (using a spoon)	To evaluate the acceptability of two methods of administration (with apple juice or apple sauce) by assessment of questionnaires and to evaluate the frequency, duration and severity of treatment-emergent AEs, in infants 1-12 months of age with EPI associated with CF	Entered: 15 Evaluable: 12 6.1 months (3.22; 1-12) (at first dose for subjects entered)
PR-018 Phase IV	6/ US	Open-label extension of PR-011	APT-1008 (3,000 USP) administered in apple juice or apple sauce	To evaluate the frequency, duration and severity of treatment-emergent AEs during long-term treatment with APT-1008 in infants 1-12 months of age with CF and EPI	Entered: 15 Evaluable: 15 7.6 months (3.27; 3-14)

2.4.2. Pharmacokinetics

The bioavailability of exogenous pancreatic enzymes is affected by a number of factors such as gastric pH, degradation by endogenous proteases, and gastric emptying times. The fasting gastric pH in CF subjects lies generally between 1.0 and 3.0 but can range from 0.5 to 5.0, with a median fasting gastric pH of 1.60. The lipase in PEPs is irreversibly inactivated at a pH below 4.0, so that, in unprotected enzyme preparations, over 90% of the administered lipase is inactivated by gastric acid. Preparations containing EC beads are designed to prevent this inactivation.

After passage through the stomach, EC beads release lipase, amylase, and protease into the proximal duodenum, where these enzymes facilitate the breakdown of fat, protein, and carbohydrates into smaller molecules that can be absorbed from the small intestine.

Samples in clinical studies were analysed for lipase, chymotrypsin, amylase, and cholecystokinin (CCK) activity in study PR-001, for faecal fat content in study EUR-1009-M, and for faecal fat and faecal nitrogen content in studies ATP-1008-M, PR-002, and PR-005. The assay methods were fully described and the relevant backup documentation is provided. Analyses performed used conventional methods.

Absorption

Study PR-001

Study PR-001 was a randomised, open-label, single-treatment, crossover study in 17 subjects with CP-associated EPI conducted at one centre in the US. The study was designed to determine the bioavailability of APT-1008 under fed conditions and to assess the effect of APT-1008 administration on blood cholecystokinin (CCK) levels.

The main objective of the study was to determine the bioavailability of lipase, chymotrypsin, and amylase from ATP-1008 in the duodenum under fed conditions after administration of a test meal (Ensure Plus) in patients with chronic pancreatitis (CP) with severe exocrine pancreatic insufficiency (EPI). The study also determined whether CCK blood levels were affected following the administration of ATP-1008.

The safety objectives were to determine the frequency, duration, and severity of treatment-emergent adverse events (AEs) and changes in clinical laboratory findings.

Methods

The study consisted of a screening period (within 30 days preceding hospitalisation) and a 5- to 6-day hospitalisation period during which two gastric and duodenal perfusion procedures were performed. Subjects were randomly assigned to receive Ensure Plus (Abbott Laboratories) alone and Ensure Plus with APT-1008 in a crossover sequence predetermined by the randomisation scheme, with a 24-hour washout between treatments.

Study Participants

The study population consisted of male and female subjects over the age of 18 years with a documented history of CP with severe EPI, significant steatorrhoea and a faecal elastase level below 100 µg/g. Evidence of CP had to be provided by an abnormal secretin test, diffuse calcification of the pancreas on plain film of the abdomen, an abnormal endoscopic retrograde cholangiopancreatogram or endoscopic ultrasound, an abnormal computed tomography scan (dilated main pancreatic duct, atrophy of the pancreas, or calcification of the pancreas), or a serum trypsinogen level > 20 ng/ml. Subjects who had CP with EPI had to have

evidence of steatorrhoea (fat content ⩾ 8 g/day on a 100 g of fat/day diet) as manifested by elevated quantitative faecal fat excretion or faecal elastase < 100 µg/g of stool.

Some of the primary reasons for exclusion from the study related to the bioavailability of APT-1008 were:

- Use of enzyme therapy, PPIs, H2-receptor antagonists, antacids, anticholinergics, antispasmodics, or octreotide within 7 days prior to study entry
- Acute pancreatitis or acute exacerbations of CP
- History of solid organ transplant or massive small bowel or stomach resection
- Use of an investigational new drug within 30 days prior to entry into the study

Treatment

The product was administered orally with 480 mL of Ensure Plus as a single fixed dose of 75,000 USP lipase units (the contents of 3 capsules of 5,000 USP lipase units plus the contents of 3 capsules of 20,000 USP lipase units) per procedure per patient.

Criteria for Evaluation

Primary efficacy endpoint:

Bioavailability of APT-1008 estimated based the amount of lipase released and recovered in the duodenum following administration of APT-1008 in fed conditions (lipase output)

Secondary efficacy endpoints included:

- Amount of amylase and chymotrypsin released and recovered in the duodenum following administration of APT-1008 in fed conditions (amylase output and chymotrypsin output)
- Levels of CCK in blood
- Gastric and duodenal pH

Results

Figure 1 Duodenal Samples : Lipase Dose Recovered (units) by treatment condition (eficacy population)

Patient No.	Dose Recovered (units) Ensure Plus and EUR-1008	Ensure Plus only	Bioavailability (%)
001	27480	20041	10.82
002	0	834	-1.21
003	99900	50853	71.31
004	20318	336	29.05
005	52292	684	75.03
006	25534	4551	30.51
007	0	35718	-51.93
009	33822	19152	21.33
012	23867	3105	30.19
014	222371	227393	-7.30
015	43045	0	62.58
016	289836	306057	-23.58
017	63876	26315	54.01
Total, n	13	13	13
Mean (SD)	69410.9 (88035.27)	53464.5 (97285.18)	23.19 (37.849)
Median (IQR[3])	33822 (59795.5)	19152 (42526.5)	29.05 (62.85)
CI 95%	16212 - 122610	-5324 - 113753	0.31 – 46.06
Wilcoxon Signed-Rank Test	p = 0.046		

[1] The patient number 010 (outlier) is removed from the analysis.
IQR = Inter Quartile Range.

The mean duodenal bioavailability in the Efficacy Population after administration of EUR-1008 was 23.19% (± 37.85) for lipase, 25.67% (± 25.90) for chymotrypsin and 15.66% (± 17.76) for amylase.

Potential sources for variable measurements are the heterogeneity of patients with CP-related EPI in their endogenous pancreatic enzyme release (both between patients and from day to day); gastric acidity; the difficulty of recovering complete and representative duodenal samples from patients during digestion; the rapidly changing dynamics of the physiological process of digestion once a liquid meal is ingested (including the digestion of all enzymes by proteases which are also present); and the difficulty of stabilizing aspirated samples that contain both enzymes and their substrates so that enzyme levels can be measured in an appropriate analytical laboratory.

Bioequivalence

Bioequivalence with an authorised PRP has not been formally studied. The Applicant has conducted a clinical study program comparing clinical baseline status on pancreatic enzyme replacement other than ATP-1008 to that after switching to ATP-1008 (see chapters on safety and efficacy of this report). Also, Study PR-005 is comparative to the marketed and widely used product Creon. Consequently it is considered acceptable that Bioequivalence to an authorised PRP is not formally studied.

Influence of food

APT-1008, like all pancreatic enzymes, is not absorbed, has to be mixed with food to exert its action and is degraded in the GI tract. Therefore, it has to be administered with every meal or snack.

Distribution

ATP-1008 undergoes proteolysis in the gastrointestinal tract and is either eliminated or absorbed as peptides and amino acids. The lack of dedicated studies is therefore accepted.

Elimination

See above

Dose proportionality and time dependencies

Dose proportionality has not been measured or estimated. This is acceptable as the product is dose titrated against the signs and symptoms of malabsorption.

Intra- and inter-individual variability

No formal studies of intra or inter-individual variability have been performed. Given the nature of the active substances and lack of absorption from GI tract such studies are probably not feasible. There is a wide inter-individual variation in response to enzymes, hence the range of recommended doses is large and should be individually titrated based on clinical symptoms, the degree of steatorrhea present, the fat content of the diet, or actual body weight.

Pharmacokinetics in target population

No formal pharmacokinetic studies have been conducted in the target population which is acceptable.

Special populations

No studies have been conducted in renal or hepatic impairment; the lack of these studies is considered acceptable in view of the mechanism of action of the product. Meaningful studies are not technically feasible as the active substance is not absorbed from the gut and are hydrolysed in situ to polypeptides and / or amino acids.

No gender or race differences in pharmacology would be anticipated; hence, the issue has not been studied. This is acceptable.

Pharmacokinetic interaction studies

Several published studies have investigated the use of antacids [Durie et al 1980; Mitchell et al 1982; Braggion et al 1987], proton pump inhibitors [Francisco et al 2002; Proesmans et al 2003; Bruno et al 1994], H_2 receptor antagonists [Boyle et al 1980; Carroccio et al 1992; Durie et al 1980; Mitchell et al 1982; Francisco et al 2002; Bruno et al 1994; Zentler-Munro et al 1985; Hubbard et al 1980] and prostaglandin E_1 analogues [Cleghorn et al 1988; Robinson et al 1990] to improve the efficacy of pancreatic enzyme supplementation. Overall, there were no reported increases in AEs associated with use of these drugs nor were there any reports of adverse interactions between the pancreatic enzyme supplements and the adjunct therapies.

2.4.3. Pharmacodynamics

Classical pharmacodynamics studies are not applicable to ingested pancreatic enzyme preparations, and therefore no such studies have been performed for APT-1008. The main effects on the body, increased fat and protein absorption, are discussed further below in the chapter on clinical efficacy.

Mechanism of action

Pancreas powder belongs to the family of pancreatic enzyme products and contains a defined amount of lipase, amylase and protease that have been extracted from porcine pancreas and purified using a process designed to inactivate viruses.

Gastro-resistant granules are thoroughly mixed with chyme when the capsule dissolves in the stomach, without inactivating the acid-sensitive enzymes. It is only in the duodenum, which has a different environment with a pH value greater than 5, that these digestive enzymes are released from the granules. Then, enzymes catalyze the hydrolysis of fats to monoglycerides, glycerol, and free fatty acids, protein into peptides and amino acids, and starch into dextrins and short chain sugars such as maltose and maltriose in the duodenum and proximal small intestine, thereby acting like digestive enzymes physiologically secreted by the pancreas.

Primary and Secondary pharmacology

No formal pharmacodynamics studies have been conducted with ingested pancreatic enzyme preparations. This is acceptable since ingested pancreatic enzyme preparations is a primary physiological product.

As described above pancreatic enzymes catalyze the hydrolysis of fats to monoglycerides, glycerol and free fatty acids, protein into peptides and amino acids, and starch into dextrin and short chain sugars in the duodenum and proximal small intestine. They are produced by the pancreas in all healthy animals and humans. Fat malabsorption (steatorrhoea) and protein maldigestion occur when the pancreas loses > 90% of its ability to produce digestive enzymes. This leads to malnutrition and weight loss in humans and animals.

2.4.4. Discussion on clinical pharmacology

The objective of trial PR-001 was to obtain a sufficient estimate of the GI bioavailability of ATP-1008 (i.e. the fraction of the administered dose recovered in the GI tract under fed conditions, expressed in lipase units). The design of the study is difficult to understand. Presumably the Ensure alone arm measures endogenous enzyme production in relation to a food stimulus. In the Ensure plus ATP-1008 arm there should be similar endogenous production of lipase, amylase and chymotrypsin, and in addition exogenous administration of those same enzymes but with no method of distinguishing between endogenous and exogenous enzyme. This is not a measure of bioavailability in the general use of that term as the enzymes are not absorbed from the gut. Arguably, the bioavailability is local but seems likely to be highly dependent on aspiration techniques.

Unsurprisingly, there was a very large inter-individual variability in enzyme recovery as indicated by the wide range and large standard deviation compared to the mean. In addition, for all three enzymes some individuals had a negative (less than zero) estimate of bioavailability – while this may not be biologically impossible it is highly unlikely (it is probably due to correction for the amount of 14C-PEG recovered).

Considering these limitations, the low number of subjects and the high variability of the result on lipase dose recovery in duodenum, it is difficult to draw any conclusion from this study.

Nevertheless it is well established that in humans, pancreatic lipase, protease and amylase enzymes degrade in the intestinal lumen; they are proteins, and therefore undergo proteolytic digestion while passing along the GI tract, before being absorbed as peptides and amino acids. Lipase activity is lost most rapidly; protease and amylase are more stable. Pancreatic enzyme supplements do not require absorption to exert their effects. On the contrary, their full therapeutic activity is exerted within the intestinal lumen.

Pharmacokinetic studies of their distribution, metabolism and excretion are therefore not considered to be relevant.

As ingested pancreatic enzyme preparations are primary physiological products no formal pharmacodynamics studies have been conducted. Some of the endpoints in the clinical studies such as reduction of fat and protein loss through malabsorption are, in a sense, pharmacodynamic endpoints and show clear evidence of benefit. The absence of formal pharmacodynamic studies is therefore considered acceptable.

No interaction studies have been performed. As outlined in the SmPC pancreatic enzyme medicinal products do not cause pharmacokinetic and pharmacodynamic interactions based on their pharmacology, as they are not absorbed from the gastrointestinal tract.

2.4.5. Conclusions on clinical pharmacology

A reduced clinical pharmacology program has been performed with Pancreas Powder. Given the nature of the active substances used to treat pancreatic exocrine insufficiency and their mode of action, this is acceptable

Some of the endpoints in the pivotal and supportive clinical studies such as reduction of fat and protein loss through malabsorption recompense pharmacodynamic endpoints and show clear evidence of benefit. The mechanism of action for pancreatic enzyme preparations is well established and understood and formal pharmacodynamic studies are not considered needed for this application.

2.5. Clinical efficacy

2.5.1. Dose response studies

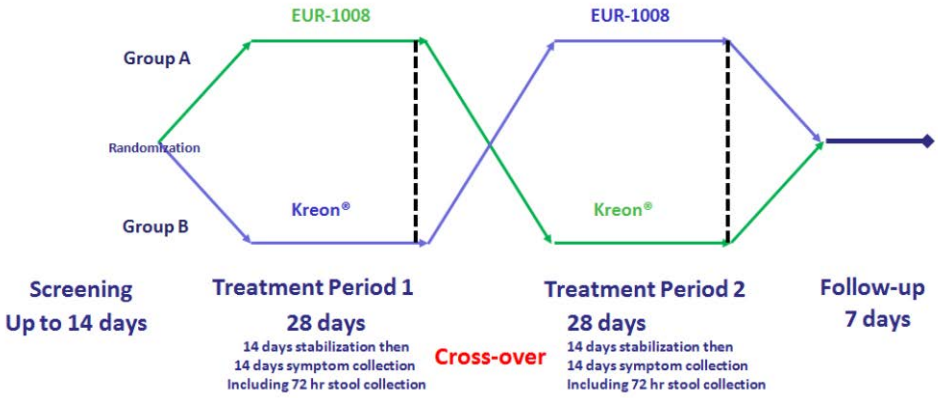
There is an important variation in individual responses to enzyme and the dosage of PEPs has to be individualized based on content of fat of the diet, on the degree of steatorrhoea and on clinical symptoms. At the time of enrolment patients were already under treatment and they began the APT-1008 treatment at a dose as close as possible as to their pre-existing PEP regimen. Thus, formal dose response studies have not been carried out which is acceptable.

2.5.2. Main study(ies)

STUDY PR-005 (study 1)

Study PR-005 was a randomised, double-blind, active-controlled, two-treatment, crossover study conducted at 34 centres in 8 countries in Europe comparing the efficacy and safety of APT-1008 versus Kreon administered orally with each meal and snack in subjects with CF and EPI.

Figure 1. PR-005 Study design



Study PR-005 consisted of a screening period (3 to 14 days), a randomisation visit, two 28-day (± 2 days) treatment periods, and a follow-up telephone contact 7 days after the completion of Treatment Period 2 (Figure above).

No washout periods were included in this study as any residual lipase from the prior treatment period was considered to have had a negligible influence on the subsequent CFA determination.

Sampling for CFA-72h occured during the last 3 days (72 hours) of Treatment Period 1 and Treatment Period 2 (during hospitalization or stay in a specialized center).

Methods

Study Participants

Eligible patients were male or female 12 years of age or older with a definite diagnosis of CF based on one clinical feature consistent with CF and either a genotype with two identifiable mutations known to cause CF or a sweat chloride concentration >60 mEq/L by quantitative pilocarpine iontophoresis.

Additional inclusion criteria were:

- Pancreatic insufficiency documented by a monoclonal faecal elastase (FE) ≤100 µg/g of stool at screening or within the previous 24 months.
- Currently receiving pancreatic enzyme replacement therapy.
- Adequate nutritional status based on a body mass index (BMI) >19 kg/m2 in adult patients or a BMI percentile ≥10th percentile for age in adolescent patients 12 to 17 years of age.
- Patients had to be clinically stable with no evidence of concomitant illness or acute upper or lower respiratory tract infection that required antibiotics during the 7-day interval prior to screening and preceding into the study.
- Likely adherence to a prescribed diet, and vitamin and nutritional supplement usage.
- Women of childbearing potential had to use a medically acceptable birth control method for the duration of the study (i.e., from screening) and for 30 days thereafter.

The main exclusion criteria were; known contraindication, hypersensitivity, or intolerance to pork or other porcine PEPs, current uncontrolled diabetes mellitus, history of solid organ transplantation, history of surgery

affecting the bowel function and weight gain, history or presence of fibrosing colonopathy, history of any other clinically significant co-morbidity.

Treatments

The Investigational Drug in this study was EUR-1008 25,000 European Pharmacopoeia (Ph.Eur.) lipase units/capsule; the Comparator Drug was Kreon 25,000 Ph.Eur. lipase units/capsule.

Dosage and administration

Eligible subjects were randomized in a 1:1 ratio to one of the following treatment-sequence groups:

Group A:

- EUR-1008 during Treatment Period 1 (28 ± 2 days);
- Kreon during Treatment Period 2 (28 ± 2 days).

Group B:

- Kreon during Treatment Period 1 (28 ± 2 days);
- EUR-1008 during Treatment Period 2 (28 ± 2 days).

During screening period, patients continued their current PEP regimen. The dose had to be stabilized before baseline evaluation. Stabilization was define has no dosage modification for at least 3 consecutive days.

In Treatment Period 1, patients began the assigned treatment at a dose as close as possible to their stabilized, existing PEP treatment, rounded up to the nearest number of capsules

In Period 2, subjects switched (crossed over) treatments and began the assigned treatment at the same starting dose utilized for Treatment Period 1.

On the second day of each treatment period, the dose could be titrated up or down, based on clinical symptoms. However, the dose could not exceed 10,000 lipase units/kg of body weight per day or 4000 lipase units/g of fat ingested per day.

After Day 14 of each study drug sequence treatment, the study drug dose could not be adjusted except for safety reasons.

Concomitant diet

During the study, all patients consume a diet that derived 45% of calories from fat, 20% of calories from protein, and 35% of calories from carbohydrate. The sponsor provided menus for the recommended diet and a nutritionist discussed all aspects of meal preparation with the patient (or parent/guardian). During home treatment periods, patient's daily food intake was recorded in a diary for review by the investigator. During the in-patient portions of the randomized treatment periods, all food were prepared under the supervision of a nutritionist experienced in the treatment of CF patients. The type and amount of food consumed were closely monitored during this time.

Objectives

The objective was to evaluate the safety and efficacy of APT-1008 as compared to Kreon in the treatment of EPI associated with CF in subjects 12 years and older who were able to swallow the capsules whole.

The secondary efficacy variables were the comparison of and changes from baseline to the end of each study period of: body weight , CNA over 72 hours , signs and symptoms of EPI (stool frequency and consistency, fat in stool, abdominal pain, bloating, and flatulence); impact on overall health , daily life, perceived well-being, and symptoms; laboratory assessments; fat-soluble vitamins (A, D, and E).

Outcomes/endpoints

The primary efficacy variable was the CFA over 72 hours (CFA-72h) calculated at the end of each treatment period. It was calculated, using fat intake data from the diet and fat excretion data from stools collected during the last 72 hours of each treatment period, according to the following algorithm:

$$\frac{\text{(fat intake over 72 h – fat excretion over 72 h)}}{\text{fat intake over 72 h}} \times 100$$

Fat intake was calculated by the dietician, in collaboration with the Investigator, using a validated tool such as tables of food nutrients or an electronic system.

Sampling for CFA-72h occurred during the last 3 days (72 hours) of Treatment Period 1 and Treatment Period 2 during hospitalization or stay in a specialized center. Determination of fat content in the stool was performed with nuclear magnetic resonance spectroscopy by a specialized central laboratory.

The secondary efficacy variables assessed in this study were the comparison of and changes from baseline to the end of each treatment period:

- Body weight;
- Coefficient of nitrogen absorption over 72 hours (CNA-72h). It was calculated at the end of each treatment period, based on dietary protein intake and protein excretion data from the stools collected during the last 72 hours of each treatment period.

- Control of signs and symptoms of EPI, as recorded in subject diaries :
    - o Stool frequency (number/day);
    - o Stool consistency (hard, formed/normal, soft, watery, overt diarrhoea);
    - o Fat or grease visible in stools (Yes/No);
    - o Abdominal pain (mild, moderate, severe);
    - o Bloating (mild, moderate, severe);
    - o Flatulence (mild, moderate, severe).
- Total cholesterol, calculated LDL-C and HDL-C, and fat-soluble vitamins A, D, and E, with sampling performed prior to randomization and at the end of each treatment period.
- Impact of the study drugs on overall health, daily life, perceived well-being, and CF symptoms as evaluated by the CFQ-R. The questionnaire encompasses general domains of quality of life (physical functioning, role functioning, vitality, health perceptions, emotional functioning, and social functioning) as well as domains specific to CF such as weight, body image, eating disturbances, treatment burden, and respiratory and digestive symptoms. Subjects completed the CFQ-R prior to randomization and at the end of each treatment period. The CFQ-R was administered by designated study personnel before completing any other procedural or clinical exam. This ensured that the interaction between the respondent and other study personnel did not influence the CFQ-R responses. Validated translations and age-appropriate versions of the CFQ-R were included in the Study Manual.

Sample size

Sixty-eight subjects provided 90% probability to demonstrate non-inferiority, with a 5 percentage point non-inferiority margin for the primary efficacy endpoint, CFA-72h. This was based upon use of a one-sided 97.5% confidence interval (CI) and assumed a SD for the differences of 12.5 percentage points and that the actual treatment means were identical. Assuming a premature dropout and/or non-evaluable subject rate of 20%, 86 subjects were to be randomised. Assuming a screening failure rate of ~20% (based on previous PEP studies), ~108 subjects were to be screened.

A blinded sample size re-estimation was performed after approximately half the subjects had both treatment periods. The purpose of this re-estimation was to examine the SD of the primary efficacy variable and to determine whether the study was sufficiently powered to meet its primary objective. In the event that the SD was larger than the 12.5 percentage points used for the original sample size calculation, the sample size could be increased to ensure the study is adequately powered. However, a maximum of 95 subjects were to be recruited into the study.

Randomisation

At Visit 2 (Randomisation), eligible subjects were randomised to a treatment sequence. The Investigator or designee contacted CTIVRS and entered the subject identification number. The CTIVRS system then assigned and recorded the randomised treatment sequence for the subject and assigned the appropriate study drug kit. Subjects were randomised to the two treatment sequences 1:1 ratio.

Blinding (masking)

Both EUR-1008 and Kreon were over-encapsulated to maintain blinding. The original capsule of each Investigational Drug and Comparator Drug was inserted into a larger (size 00), opaque capsule to give both drugs an identical appearance.

Statistical methods

The primary efficacy analysis was carried out on the Completers population (defined as all subjects from the intent-to-treat (ITT) population who completed both treatment periods and had complete CFA data). The analysis of the primary endpoint, CFA, and comparison of the two treatments, was based on the use of a mixed effects linear model, including subject nested within sequence as random effect and with treatment, period, and sequence as fixed effects. A two-sided 95% CI, the lower limit of which was equivalent to the lower limit of a one-sided 97.5%, for the difference between the treatments was derived from the mixed model.

Non-inferiority was concluded if the lower bound of this CI exceeded -5%.

If non-inferiority was concluded, equivalence of the two treatments was to be tested using the same mixed model as for the non-inferiority test with a 5% equivalence margin. If the 95% CI was completely between -5% and 5% and included 0, then equivalence was to be concluded. If the CI fell entirely above 0, then a conclusion of superiority would be drawn.

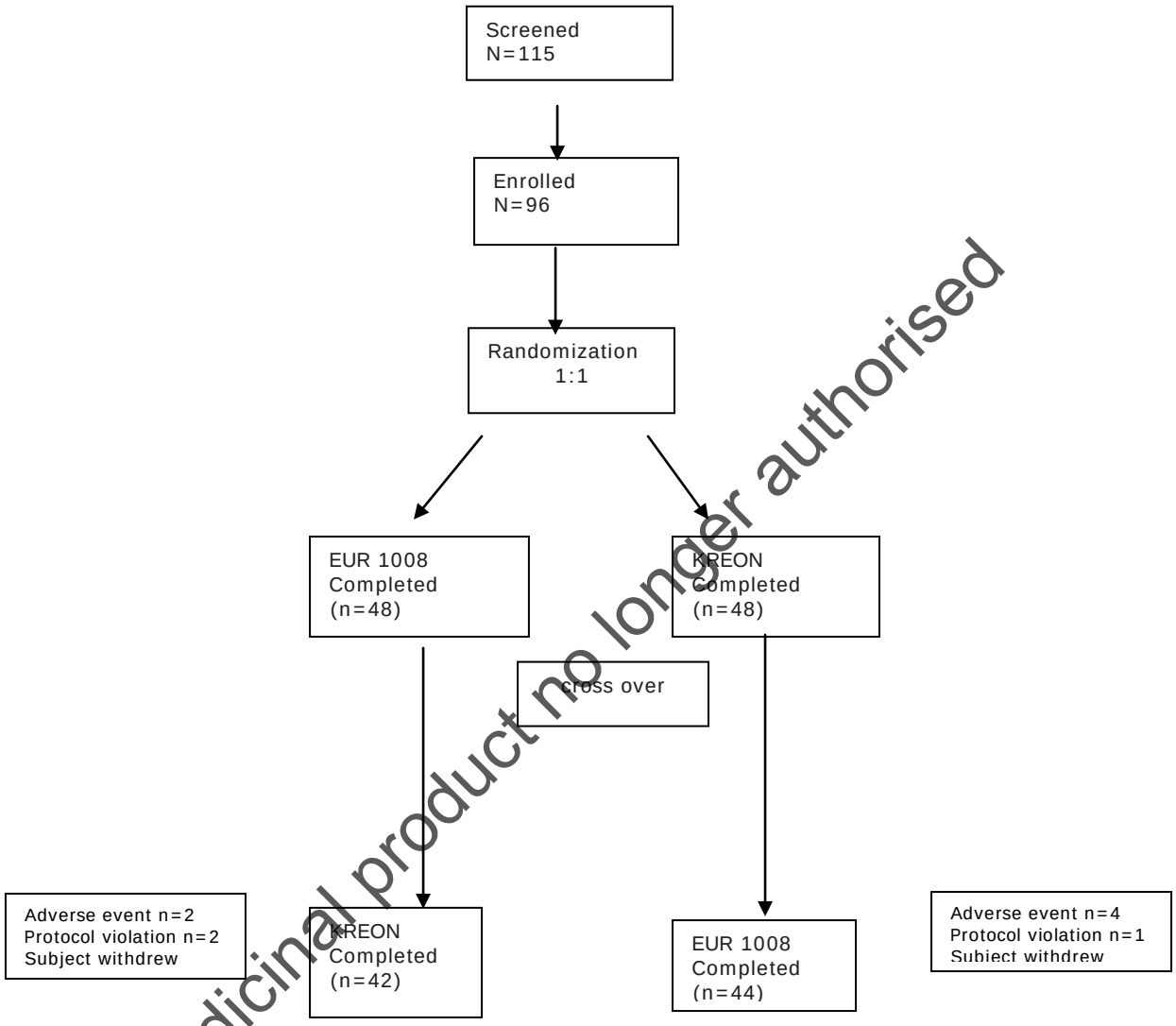
A minimum sample of 68 subjects provided 90% probability to demonstrate non-inferiority, with a 5% non-inferiority margin for CFA. This was based on the use of a one-sided 97.5% CI and assumed a standard deviation (SD) for the differences of 12.5% and that the actual treatment means were identical.

Mixed effects linear models were used to analyse body weight changes, CNA, average number of stools per day, and CFQ-R scores. A Poisson log-linear model with repeated counts was used to analyse total number of stools per day with number of stools as the dependent variable, the total number of days for which stool diary data were reported as the offset (log scale), fixed effects for treatment, period and sequence and subject within treatment sequence as a subject effect. Logistic regression models with repeated proportions were used to analyse stool consistency, visible fat/grease in stools, and symptoms of abdominal pain, flatulence, and bloating with fixed effects for treatment, period, and sequence and subject nested within sequence as a subject effect. Treatment differences were evaluated with 95% CIs and p-values. No hierarchy was defined for the secondary efficacy variables, and no multiplicity adjustments were made. Analyses of all efficacy endpoints were performed on the Completers population, ITT population (defined as all randomised subjects), and Per Protocol (PP) populations (defined as all subjects from the Completers population without significant protocol deviations).

As per Scientific Advice from the CHMP dated Jun-2011 [EMA/CHMP/SAWP/424704/2011], it was planned that if non-inferiority was concluded, equivalence of the two treatments was to be tested using the same mixed model as for the non-inferiority test, with a 5% equivalence margin. If the 95% CI was completely between –5% and 5% and included 0, then the two treatments were considered equivalent.

Results

Participant flow



Recruitment

Study Initiation Date: 03 September 2012

Study Completion Date: 03 January 2014

Report date: 04 June 2014.

Conduct of the study

The original study protocol dated 06 May 2010, had two amendments:

- Amendment 1, dated 13 February 2012 (prior to first subject enrolled)

In summary, the changes in Amendment 1 were made either to improve compliance with EMA Scientific Advice and therapy area guidelines, or to improve the accuracy, clarity and consistency of wording in the

protocol. The amendment was approved on 13 February 2012, significantly before the first subject was enrolled into the study. Thus, it is unlikely that changes introduced in Amendment 1 had any meaningful impact on the interpretation of the study.

- Amendment 2, dated 14 December 2012 (after first subject enrolled, prior to un-blinding)

Amendment 2 was approved on 14 December 2012, after study initiation but significantly before the database lock, unblinding and statistical analysis of the study (February 2014). Thus, it is unlikely that changes introduced in Amendment 2 had any meaningful impact on the interpretation of the study.

Baseline data

Demographic data

CF patients from age 12 to 43 years were enrolled. Subject mean age at screening was 19.2 years (standard deviation [SD] 7.90). Overall, the cohorts of adolescent (aged 12–17 years) and adult (≥18 years) patients were balanced, with 53.1% and 46.9%, respectively. More male (60.4%) than female (39.6%) patients participated in this study. All patients in this study were White/Caucasian, which was expected as CF predominantly affects this race.

Table Summary of Demographics – Completers Population

Demographic Characteristic Statistic/Category	EUR-1008/Kreon(N=41)	Kreon/EUR-1008 (N=42)	Total(N=83)
Age at screening (years)			
N	41	42	83
Mean	20.2	17.6	18.9
Standard deviation	8.25	6.71	7.58
Minimum	12	12	12
Median	19.0	14.0	16.0
Maximum	42	43	43
12–17 years	18 (43.9)	27 (64.3)	45 (54.2)
⩾ 18 years	23 (56.1)	15 (35.7)	38 (45.8)
Gender, n (%)			
Male	25 (61.0)	27 (64.3)	52 (62.7)
Female	16 (39.0)	15 (35.7)	31 (37.3)
Race, n (%)			
White/Caucasian	41 (100.0)	42 (100.0)	83 (100.0)

Medical history data

Patients had to have a confirmed diagnosis of EPI (faecal elastase level of ≤100 µg/g stool and currently receiving treatment with a commercially available PEP) and a confirmed diagnosis of CF (one clinical feature consistent with CF, and either a genotype with two identifiable mutations known to cause CF or a sweat chloride concentration >60 mEq/L by quantitative pilocarpine iontophoresis).

The patients participating in this study were diagnosed with CF an average of 14.06 years (SD 6.577) ago and with EPI a mean of 12.64 years (SD 9.130) ago. Cystic fibrosis diagnosis had been based on clinical features in all patients, on genotype data in 87.5%, and on sweat test results in 78.1% of patients. Most patients (77.1%) presented with monoclonal faecal elastase <15 µg/g.

Table Cystic Fibrosis (CF) Medical History and Baseline Characteristics – completers Population

Years since documented CF diagnosis	EUR-1008/Kreon (N=41)	Kreon/EUR-1008 (N=42)	Total (N=83)
N	41	42	83
Mean	13.86	14.18	14.02
Standard deviation	6.292	5.626	5.930
Minimum	4.1	4.3	4.1
Median	12.36	13.78	13.52
Maximum	30.6	27.9	30.6
Years since documented EPI diagnosis			
N	41	42	83
Mean	12.67	12.20	12.43
Standard deviation	10.348	7.582	9.002
Minimum	0.0	0.0	0.0
Median	12.04	13.47	12.61
Maximum	41.7	27.9	41.7
Diagnosis of CF based on, n (%)			
Clinical feature	41 (100.0)	42 (100.0)	83 (100.0)
Genotype with at least 2 CF causing mutations	34 (82.9)	39 (92.9)	73 (88.0)
Sweat test with Cl C° >60 mEq/L	33 (80.5)	35 (83.3)	68 (81.9)
Monoclonal faecal elastase (µg/g), n (%)			
"<15" µg/g1	29 (70.7)	32 (76.2)	61 (73.5)
N (%)2	12 (29.3)	10 (23.8)	22 (26.5)
Mean	22.6	21.8	22.2
Standard deviation	30.32	26.77	28.09
Minimum	0	1	0
Median	9.5	16.0	14.0
Maximum	84	94	94
Currently receiving PERT, n (%)			
Yes	41 (100.0)	42 (100.0)	83 (100.0)
No	0 (0.0)	0 (0.0) 0	(0.0)
Average daily dose of PERT (lipase units)			
N	36	38	74
Mean	221033.3	236381.6	228914.9
Standard deviation	87111.00	100541.94	93922.69

Minimum	60000	100000	60000
Median	223600.0	200000.0	200000.0
Maximum	425000	465000	465000
Average daily dose of PERT (lipase units/kg baseline body weight)			
N	36	38	74
Mean	4178.48	4560.91	4374.86
Standard deviation	1783.615	1660.999	
Minimum	1176.5	1123.6	1123.6
Median	3971.47	4692.98	4316.77
Maximum	7203.4	8303.6	8303.6

Prior pancreatic enzyme replacement therapy (PERT)

All patients were receiving pancreatic enzyme replacement therapy (PERT) before entering the study. The mean average daily dose of this PERT was 23,0112.8 lipase units or 4,479.32 lipase units/kg of baseline body weight. The mean body weight of patients in this study was 53.6 kg (SD 13.53), with a mean height of 161.8 cm (SD 12.39), resulting in an approximate mean BMI of 20.10 kg/m2.

The most frequently reported enzyme preparation was pancreatin, received most often in the form of Kreon or Creon®. Pancreatin was used by 92.7% of patients overall, 91.7% of those in the EUR-1008/Kreon treatment sequence, and by 93.8% in the Kreon/EUR-1008 treatment sequence. Few patients took pancrelipase (5.2% overall) or lipase (2.1% overall), with similar distributions across the two treatment sequences.

Numbers analysed

A total of 115 patients were screened at 34 investigative sites in 7 European countries. Of these patients, 96 patients were randomised at 32 investigative sites in 7 countries.

With the enrolment of 96 patients, the planned target of 86 randomized patients was met. The actual screening failure rate of 16.5% was lower than the projected rate of ~20%.

Most patients who were screened but not randomized (16 of 19 patients) did not meet the inclusion criteria or met the exclusion criteria for the study.

The 96 enrolled patients were randomized, in a 1:1 ratio, into one of the two treatment sequences (EUR-1008/Kreon and Kreon/EUR-1008), with 48 patients in each sequence. Eighty-six patients completed the study: 42 in the EUR-1008/Kreon sequence and 44 in the Kreon/EUR 1008 sequence.

Ten patients terminated the study early. The most frequent reasons for early termination were protocol violations (n=5) and AEs (n=3), with similar rates in both treatment sequences. All 10 patients withdrew prior to dosing in Treatment Period 2.

These early withdrawals took place at 6 study centers. At Centre 0601, 2 patients discontinued due to protocol violations and 1 due to AEs. At Centre 1103, 2 patients terminated early due to protocol violations; and at Centre 0301, 1 subject withdrew consent and 1 discontinued due to AEs. The remaining 3 centers (0105, 0407, and 1102) reported 1 early termination each, due to withdrawal of consent, an AE, and a protocol violation, respectively. None of the patients who withdrew consent had ongoing AEs at the time consent was withdrawn.

All efficacy variables were analysed in the Completers, intent to treat (ITT; all randomized patients) and Per protocol (PP; all patients from the Completers population without significant protocol deviations) populations.

The Completers population (defined as all patients from the ITT population who completed both treatment periods and had non-missing CFA-72h in both periods) was introduced following Scientific Advice, and was made the primary population for the analysis of efficacy variables.

Outcomes and estimation

Primary endpoint: coefficient of fat absorption over 72 hours (CFA-72h)

Global CFA- 72 h

The primary efficacy analysis was carried out on the Completers population (defined as all subjects from the intent-to-treat (ITT) population who completed both treatment periods and had complete CFA data).

Overall, 83 adolescents and adults with CF-associated EPI received EUR-1008 and Kreon and achieved LS mean CFA-72h values of 84.08% (standard error [SE] 1.109) and 85.33% (SE 1.109) with the two study drugs, respectively. This resulted in a difference in LS means of –1.25% (95% CI, –3.62% to 1.12%), with p=0.2972 for the between-drug difference.

Since the lower limit of the CI (–3.62%) exceeded the non-inferiority margin of –5%, and the 95% CI was completely between –5% and 5% and included 0 to show equivalency, EUR-1008 met the requirements for non-inferiority and equivalence to Kreon set forth in this study.

Table 1 Analysis of Coefficient of Fat absorption over 72 Hours, % Completers population

Variable Statistic	EUR-1008 (N=83)	Kreon (N=83)
Summary statistics		
N	83	83
Mean	84.11	85.34
Standard deviation	11.073	9.099
Minimum	47.4	53.5
Median	85.92	86.49
Maximum	99.5	97.3
Model-based statistics (EUR-1008 minus Kreon)		
LS mean (standard error)	84.08 (1.109)	85.33 (1.109)
Difference in LS means and 95% confidence limits (lower, upper)	-1.25 (-3.62, 1.12)	
P-value	0.2972	

Model-based statistics are from a mixed effects linear model using CFA-72h as the response variable, fixed effect factors for treatment, period and treatment sequence, and subject within treatment sequence as a random effect.

Analyses of CFA-72h for the PP and ITT Populations support these findings. In the PP Population, LS mean CFA-72h values of 83.90% (SE 1.231) and 84.72% (SE 1.231) were found for EUR-1008 and Kreon, respectively, with a difference in LS means of –0.82% (95% CI, –3.45% to 1.82%), with p=0.5378.

In the ITT Population (observed cases analysis), the LS mean CFA-72h value was 84.01% (SE 1.098) for EUR-1008 and 85.40% (SE 1.103) for Kreon, resulting in a difference in LS means of –1.39% (95% CI, –3.76% to 0.97%), with p=0.2437.

Table 2 Primary Efficacy Parameter: Coefficient of Fat Absorption (%) Over 72 Hours

Analysis Population	APT-008 LS Mean	Kreon LS Mean	Diff in LS Mean (95% CI)	P value
Completers	84.08	85.33	-1.25 (-3.62, 1.12)	0.2972
Per protocol	83.90	84.72	-0.82 (-3.45, 1.82)	0.5378
ITT (observed cases)	84.01	85.40	-1.39 (-3.76, 0.97)	0.2437

CFA-72h by treatment period

During Treatment Period 1, the mean CFA-72h with EUR-1008 (82.16%, SD 10.894) was numerically lower than with Kreon (85.61%, SD 8.671). During Treatment Period 2, the mean CFA-72h with EUR-1008 was numerically higher (86.01%, SD 11.041) than with Kreon (85.06%, SD 9.618).

Overall, the CFA-72h for EUR-1008 (84.11%, SD 11.073) was numerically lower than the overall result with Kreon (85.34%, SD 9.099).

CFA-72h by treatment sequence and treatment period

For each treatment period, the mean CFA-72h values for EUR-1008/Kreon (82.16% and 85.06%) were numerically lower than for Kreon/EUR-1008 (85.61% and 86.01%). However, these differences did not reach significance (p=0.2428).

For both treatment sequences, mean CFA-72h values were numerically lower for Treatment Period 1 than for Treatment Period 2. However, the difference was greater for the EUR-1008/Kreon (82.16% vs 85.06%) than for Kreon/EUR-1008 (85.61% vs 86.01%). The differences in CFA-72h between treatment periods was not significant (p=0.1696).

Normalised CFA-72h

Pancreatic enzyme products are dosed based on their lipase activity. Since lipase is unstable in the presence of moisture, many PEP products, such as Kreon, include an overfill of the active ingredient. EUR-1008, is produced without overfill.

Normalizing CFA-72h data addresses possible dosing differences between EUR-1008 and Kreon due to relative fill and to the permitted adjustment of doses during the two treatment periods.

The clinical lots of EUR-1008 (batch number Z9A232) and Kreon (batch number Z9A222) used in this study were sampled to measure the actual lipase activity (expressed as a fraction of 25,000), the first time shortly after enrolment started, in November 2012, and the second time after the end of treatment for the last subject, in December 2013. At the first sampling, the lipase activity of EUR-1008 was 23,800 lipase units per capsule, or 95.2% of the per-label activity. Lipase activity for Kreon during this sampling was 26,800 lipase units per capsule, or 107.2% of its per-label activity.

At the second sampling, the lipase activities per capsule for EUR-1008 and Kreon were 22,800 and 26,300 lipase units (91.2% and 105.2% of the per-label activity), respectively.

For this sensitivity analysis, the CFA-72h of each subject for each treatment was normalized in two ways, based on the average of the two lipase activity results from the sampling for each treatment.

Table 3 ***Analysis of the Normalized Coefficient of absorption over 72 Hours (%) Completers population***

Period Statistic	EUR-1008 (N=83)	Kreon (N=83)
Normalised CFA-72h per 25,000 lipase units[1]		
Summary statistics		
N	83	83
Mean	3.69	3.44
Standard deviation	1.643	1.543
Minimum	1.3	1.1
Median	3.26	3.10
Maximum	8.9	7.4
Model-based statistics (EUR-1008 minus Kreon)		
LS mean (standard error)	3.69 (0.176)	3.44 (0.176)
Difference in LS means and 95% confidence limits (lower, upper)	0.25 (0.07, 0.43)	
P-value	0.0079	
Normalised CFA-72h[2]		
Summary statistics		
N	83	83
Mean	90.24	80.35
Standard deviation	11.881	8.568
Minimum	50.8	50.4
Median	92.19	81.44
Maximum	106.7	91.6
Model-based statistics (EUR-1008 minus Kreon)		
LS mean (standard error)	90.22 (1.132)	80.35 (1.132)
Difference in LS means and 95% confidence limits (lower, upper)	9.87 (7.42, 12.31)	
P-value	<0.0001	

Model-based statistics are from a mixed effects linear model using CFA-72h as the response variable, fixed effect factors for treatment, period and treatment sequence and subject within treatment sequence as a random effect.
[1]The total dose during the 72-hour collection period was adjusted based on actual lipase activity. The calculated CFA-72h was divided by the adjusted dose to obtain CFA-72h per adjusted lipase unit and then multiplied by 25,000.
[2]The normalised CFA-72h is the calculated CFA-72h divided by average of the lipase activity results for each treatment.

Secondary efficacy variables
Body weight

In both the EUR-1008 and the Kreon treatment, subjects began the study with a mean baseline body weight of 54.1 kg, due to the crossover design of the study, and presented with a mean body weight of 54.6 kg at the End-of-Treatment check-up.

There was no difference in the overall change of body weight from baseline to the End-of- Treatment check-up between EUR-1008 and Kreon. Both drugs resulted in an overall LS mean gain in body weight of 0.5 kg.

Coefficient of Nitrogen Absorption

Coefficient of nitrogen absorption over 72 hours (CNA-72h) was calculated at the end of each treatment period, based on dietary protein intake and protein excretion data from the stools collected during the last 72 hours of each treatment period. Protein content in the stool was assessed by a specialized central laboratory by means of the Dumas combustion method. Dietary protein intake was calculated by the site dietician, in collaboration with the Investigator, using a locally defined tool such as tables of food nutrients or electronic system.

Overall, the LS mean CNA-72h values were similar for EUR-1008 (80.86%, SE 1.150) and Kreon (81.96%, SE 1.150), with a difference in LS means of –1.10 (95% CI, –3.34% to 1.15%) and p=0.3342. Analyses of CNA-72 for the PP and ITT Populations support this relationship.

Table 4 Coefficient of Nitrogen Absorption (%) Over 72 Hours

Analysis Population	APT-008 LS Mean	Kreon® LS Mean	Diff in LS Mean (95% CI)	P value
Completers	80.86	81.96	-1.10 (-3.24, 1.15)	0.3342
Per protocol	81.22	81.87	-0.65 (-3.02, 1.72)	0.5853
ITT (observed cases)	80.71	82.00	-1.29 (-3.53, 0.95)	0.2568

EPI Clinical Symptoms : stool frequency and consistency, and visible fat/grease in stool

Stool consistency, bowel movement and bowel movement with visible fat were recorded in a patient diary during the last 2 weeks of each treatment period.

For each patient, the average number of stools per day, the proportions of stools of specified consistency, the proportion of stools with visible fat/grease for each subject were used to calculate summary statistics.

Table 5 Analysis of Stool Related Symptoms over the last 2 Weeks of the Treatment Period – Completers Population

	APT-1008	Kreon®	Diff (95% CI)	P Value
Stool Frequency*	1.51	1.49	0.02 (-0.05, 0.09)	0.6362
Stool Consistency**				
Hard	0.060	0.071		0.3454
Formed/normal	0.665	0.678		0.9963
Soft	0.253	0.235		0.8596
Watery	0.015	0.011		0.5226
Diarrhea	0.007	0.004		0.4531
Hard & formed/normal	0.725	0.749		0.6983
Stools with Visible Fat/Grease	0.076	0.072		0.8264

*Average number of stools per day for each subject over the last two weeks of each treatment period.
**Proportion of stools with the given consistency/aspect for each subject over the last two weeks of each treatment period.

Stool frequency, stool consistency, and the presence of visible fat or grease in stools were similar for EUR-1008 and Kreon.

EPI Clinical Symptoms: Abdominal Pain, Flatulence, Bloating

Daily symptoms of abdominal pain, flatulence, and bloating were recorded and categorized for severity in the subject diary. For each subject, the proportion of days with each EPI symptom was calculated as the number of days for which the symptom of any severity was reported, divided by the total number of days for which the EPI symptoms CRF was completed during the last 2 weeks of the treatment period.

Table 6 EPI Clinical Symptoms - Proportion of Days with the Symptoms Present for each Subject over the Last Two Weeks of Each Treatment Period "Completers Population (N=83)"

	APT-1008 Mean Proportion	Kreon® Mean Proportion	P Value
Abdominal Pain	0.117	0.125	0.6911
Flatulence	0.383	0.360	0.4454
Bloating	0.186	0.130	0.0074*
**The majority of bloating episodes were reported to be of mild severity with both treatments. The difference in the proportion of subject-days with bloating between the two treatments was nominally statistically significant ; however, the clinical meaningfulness of this difference is unclear.*			

Reported subject-days with abdominal pain or flatulence with EUR-1008 were comparable to those seen with Kreon, with the majority being reported as mild with both treatments. A nominally significant difference in the proportion of subject-days with bloating was observed between EUR-1008 and Kreon (p=0.0074), with the majority being reported as mild with both treatments. However, the overall mean proportion of subject-days with bloating was low with EUR-1008 (0.186) and Kreon (0.130). The clinical meaningfulness of this difference is unclear.

Both EUR-1008 and Kreon had a similar impact on overall health, daily life, perceived well-being, and CF symptoms (as evaluated by the CFQ-R).

Laboratory parameters relevant to nutritional status such as levels of cholesterol and fat-soluble vitamins were similar with both EUR-1008 and Kreon.

Summary of main efficacy results

Table 1. Summary of efficacy for principal clinical trial PR-005

Title: A randomised, double-blind, active-controlled, two-treatment, crossover, multinational, comparison of two pancreatic enzyme products in the treatment of exocrine pancreatic insufficiency in patients with Cystic Fibrosis.	
Study identifier	PR-005
Design	As study title above

	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		28 days x 2 (crossover) 3 – 14 days not applicable
Hypothesis	Non-inferiority followed by analysis for equivalence		
Treatments groups	Adolescent and adult patients with CF and pancreatic exocrine insufficiency		ATP-1008 (candidate treatment) following clinical dose optimisation for 28 days.
	Adolescent and adult patients with CF and pancreatic exocrine insufficiency		Kreon (reference treatment) following clinical dose optimisation for 28 days.
Endpoints and definitions	Coefficient of fat absorption	CFA-72	Percentage of dietary fat absorbed measured over 72 hours
	Coefficient of nitrogen absorption	CNA	Percentage of dietary nitrogen (protein) absorbed measured over 72 hours
	Symptoms and signs of malabsorption	NA	Clinical history and examiniation

Results and Analysis

Analysis description	**Primary Analysis**	
Analysis population and time point description	Completers (those who completed both 28 day treatment periods).	
Descriptive statistics and estimate variability	Treatment group	83 patient constituted the completer population
	Number of subject	83
	CFA – 72h was 84.11% (s.d. 11.073) on ATP-1008 and 85.34% (9.099) on Kreon. The treatment difference & 95% CI was -1.25 (-3.62, 1.12) p = 0.297	
	CNA was 80.88% (s.d. 10.67) on ATP-1008 and 81.97% (10.32) on Kreon. The treatment difference & 95% CI was -1.10 (-3.34, 1.15) p = 0.33	
	There were no important differences between treatments with respect to the clinical signs and symptoms of malabsorption.	

Analysis description	APT-1008 was compared to Kreon for CFA with a non-inferiority with a margin of 5% (i.e. APT-1008 no worse the 5%). If non-inferiority was concluded, equivalence of the two treatments would be tested using the same mixed model as for the non-inferiority test, with a 5% equivalence margin. If the 95% CI was completely between −5% and 5% and included 0, the two treatments would be considered equivalent. Equivalence was demonstrated.

Analysis performed across trials (pooled analyses and meta-analysis)

This submission contains efficacy data from one pivotal Phase III study (PR-005), two supportive Phase III studies (EUR-1008-M and EUR-1009-M), one supportive Phase II/III study (PR-002) and two supportive Phase IV studies (PR-011 and PR-018) of APT-1008 in subjects with EPI.

According to the Applicant, pooled analysis of efficacy data from studies included in this Marketing Authorisation Application has not been carried out on the basis that the pivotal study (study PR-005) was appropriately designed and powered to assess the efficacy of APT-1008 without pooling with efficacy data from the other studies. Furthermore, the study designs and subject populations of the supportive studies were too varied, with different study designs (including different comparators), populations and endpoints, to allow for robust pooling of efficacy outcomes.

Clinical studies in special populations

No studies have been conducted in renal or hepatic impairment. The lack of these studies is considered acceptable in view of the mechanism of action of the product. Meaningful studies are not technically feasible as the active substance is not absorbed from the gut and are hydrolysed in situ to polypeptides and / or amino acids.

Supportive studies

STUDY EUR-1008-M (Study 2)

EUR-1008-M was the pivotal study for the original US NDA submission in 2007 and was designed in accordance with FDA guidance on EPI drug products and recommendations provided to the Applicant by the FDA.

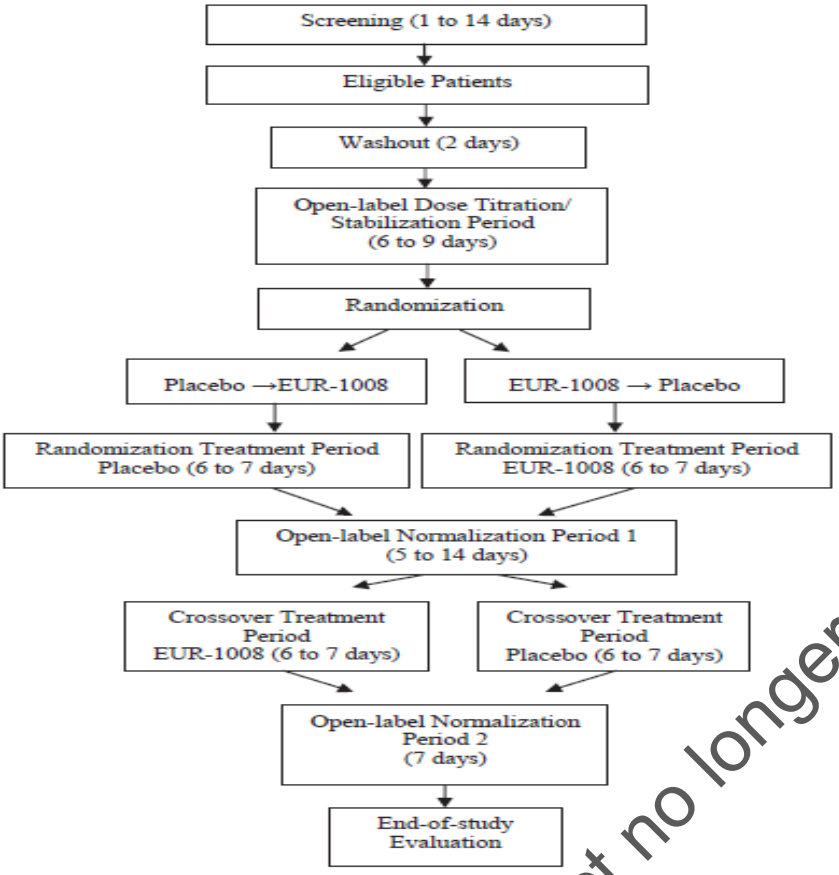
Design

It was a randomised, double-blind, placebo-controlled, two-treatment, crossover, multicenter study to assess the efficacy and safety of APT-1008 in subjects aged ⩾7 years with CF and EPI. The primary efficacy endpoint was CFA-72h measured during treatment with APT-1008 versus placebo.

The study consisted of a screening period (1 to 14 days), a two-day washout period from current PERT, an open-label dose-titration/-stabilisation period (6 to 9 days), a randomisation treatment period (6 to 7 days), an open-label normalisation period (5 to 14 days), a crossover treatment period (6 to 7 days), followed by a second open-label normalisation period (7 days).

All subjects received APT-1008 during the three open-label periods.

Figure 2. EUR-1008M study design



Population

Thirty four subjects (over 7 years) were enrolled and received at least one dose of open-label treatment with APT-1008; 33 subjects were randomised to the double-blind treatment sequence, and 32 subjects, who completed both double-blind treatment periods, were included in the efficacy analysis population. Thirty-one subjects completed all parts of the trial.

Most of the subjects (32 of 34, 94.1%) were white. The overall mean age of subjects was 4.9 years (range 7 to 23 years). Subjects had a mean height of 155.73 cm, a mean weight of 51.15 kg, and a mean BMI of 20.47 kg/m2. The mean duration of CF was 14.0 years (range 3 to 23 years). Half of the subjects were males.

Results

The CFA (LS means) for subjects treated with APT-1008 (88.28%) was statistically significantly higher than for subjects treated with placebo (62.76%) ($p < 0.001$). The LS mean difference between APT-1008 and placebo was 25.52% (95% CI: 19.32% to 31.73%).

CNA (LS means) for subjects treated with APT-1008 (87.17%) was also statistically significantly higher than for subjects treated with placebo (65.67%) ($p < 0.001$).

Mean levels of cholesterol, HDL-C, and vitamins A and E in blood showed statistically significant increases after APT-1008 treatment versus placebo, while mean PIVKA II levels showed a statistically significant decrease.

There was an overall improvement in the clinical symptoms of EPI during treatment with APT-1008 compared with placebo.

Table 2. Overview of selected efficacy variables data are LS means (SD)

	Eur-1008 n= 32	**Placebo n = 31**
Primary efficacy variable		
CFA – 72h (%)	88.31 (7.92)	62.72 (3.43)
	Treatment difference & 95% CI -25.52 (-31.73, -19.32) p <0.001	
Secondary efficacy variables		
CNA – 72h (%)	87.25 (6.39)	65.71 (16.21)
	Treatment difference & 95% CI -21.50 (-26.85, -16.14) p < 0.001	
Weight change from screening (kg)	+ 0.41	NA
Stool frequency/day	1.76 (0.16)	2.66 (0.25)
Proportion of formed/normal stools (%)	53.86 (6.59)	33.25 (6.08)
Cholesterol change from screening (mg/dL)	4.0 (20.99)	-16.1 (17.51)
HDL cholesterol change from screening (mg/dL)	3.1 (8.06)	-4.8 (7.69)
LDL change from screening (mg/dL)	0.5 (15.84)	-11.7 (12.48)
Vitamin A change from screening (ug/L)	41.6 (89.40)	-21.3 (98.63)
Vitamin E change from screening (mg/L)	8.25 (3.115)	6.69 (2.648)
PIVKA II change from screening (ng/mL)	-6.67 (13.76)	1.40 (15.902)

Study EUR-1009-M

Design

Study EUR-1009-M was an open-label, multiple-dose, single-treatment study conducted at 10 centers in the US. The study was designed to compare measures of fat malabsorption before (while receiving therapy with other commercial pancreatic enzymes) and after oral administration of APT-1008 in subjects aged 1 to < 7 years with CF and EPI.

The primary efficacy endpoint was the percentage of "responders," defined as those subjects without steatorrhoea (defined as < 30% faecal fat content) and without signs and symptoms of malabsorption after 1 and 2 weeks of treatment with APT-1008, to be assessed versus a baseline response (under current PEPs).

Population

Nineteen subjects (1 to 6 years old) were enrolled and completed the study Overall, more males (63.2% 12/19) than females (36.8% 7/19) participated in the study, and all subjects were White. The mean age (SD) for subjects was 3.9 (1.58) years, with a minimum age of 1 year and a maximum age of 6 years.

Of the subjects, 47.4% (9/19) were less than 3 years of age with 7 (36.8%) subjects in the 4 to 5 year age category. Subjects had a mean height of 99.42 cm, a mean weight of 16.60 kg, and a mean BMI of 16.67 kg/m2. The mean duration of CF/EPI was 3.3 years.

Results

The number of responders (subjects with less than 30% faecal fat content and without signs and symptoms of malabsorption) at baseline (under treatment with currently available PEPs) was 10/19 (52.6%), 13/19 (68.4%) after 1 week of treatment (stabilisation) and 11/19 (57.9%) after the second week of open-label treatment with APT-1008. The mean faecal fat content was 24.8% at baseline, 27.0% after stabilisation and 27.3% after the second week of open-label treatment.

The proportion of responders was not statistically significantly different after one week and two weeks of treatment with study drug when compared with previous PEP therapy.

Table 3. Responder count and mean (s.d.) weight by study visit

Responders number (%)	
• Baseline	10/19 (52.6%)
• Visit 3	13/19 (68.4%)
• End of treatment	11/19 (57.9%)
Weight (kg)	
• Baseline	16.60 (3.84)
• Visit 3	16.75 (3.95)
• End of treatment	16.63 (3.97)

Study PR-002

Design

Study PR-002 was a randomised, double-blind, dose-response control, crossover study conducted at 19 centres in the US and Europe comparing the efficacy and safety of two fixed-doses of APT-1008 administered orally with each meal and snack. This study was conducted in subjects with CP.

The primary efficacy objective was to evaluate the difference in CFA of subjects treated with high dose APT-1008 versus low dose APT-1008 in CP subjects with EPI. The secondary endpoints assessed included: CNA, stool frequency and consistency, visible oil/grease and blood in stool, bloating, pain and flatulence, lipids, vitamins A and E, PIVKA II, body weight and BMI.

Population

Eighty two subjects (adults) were enrolled into the placebo baseline period; 76 subjects were randomised to one of two double-blind treatment sequence groups (39 to the high-low dose sequence and 37 to the low-high dose sequence). A total of 73 (96.05%) subjects (37 [94.87%] in the high-low group and 36 [97.30%] in the low-high group) completed the entire study period.

The median total dose in the high-low treatment group was 1,670,000 USP lipase units in the first crossover period and 365,000 USP lipase units in the second crossover period. The median total dose in the low-high treatment group was 420,000 USP lipase units in the first crossover period and 1,520,000 USP lipase units in the second crossover period.

Most of the subjects in the FAS population (71 of 82, 86.59%) were Caucasian, and 53 (64.63%) were male. The overall mean age for subjects was 51.91 years (range 22 to 82 years). Subjects had a mean height of 171.53 cm, a mean weight of 68.75 kg, and a mean BMI of 23.36 kg/m2. The mean duration of CP was 3.33 years (range 0.11 to 18.11), and the mean duration of EPI diagnosis was 1.14 years (range 0.04 to 14.48).

Results

The difference in LS means of CFA between APT-1008 high dose and low dose treatment was 1.023 % (95% CI, -0.656 to 2.701), and the difference between the two doses was not statistically significant (p = 0.228).

The CFA means were significantly higher following treatment with both APT-1008 dose levels than at the end of the placebo baseline period. Mean ± SD absolute values of CFA (%) at baseline were: placebo 81.68 ± 22.13, APT-1008 low dose 88.87 ± 12.44; and APT-1008 high dose 89.86 ± 8.77. The mean changes from the placebo baseline period were 7.19 ± 14.49 (95% CI, 3.78 to 10.59) (p < 0.001) with APT-1008 low dose and 8.18 ± 17.35 (95% CI, 4.10 to 12.26) (p<0.001) with APT-1008 high dose.

Study PR-011

Design

Study PR-011 was an open-label, Phase IV, multiple-dose, single-treatment study conducted at six centres in the US. The study was designed to assess the acceptability of two modes of administration of APT-1008 3,000 (USP lipase units) capsules in infants aged 1 to 12 months with CF and EPI.

The primary objectives were to evaluate the acceptability of two methods of administration (with apple juice or with apple sauce) by assessment of questionnaires completed by the subject's parent or caregiver, and to evaluate the frequency, duration and severity of treatment-emergent AEs.

Secondary efficacy objectives included the evaluation of efficacy at the end of the study by assessment of signs and symptoms of EPI.

Population

The study population comprised nine male (60.0%) and six female (40.0%) infants ranging in age at screening from one to 11 months (median age of six months). The majority of subjects were Caucasian (11 subjects [73.3%]); one subject (6.7%) was Black, and three subjects (20.0%) were reported as “Other”.

Median weight, height, and BMI were 7.1 kg (range of 4.5 to 9.2 kg), 65.0 cm (range of 55.0 to 75.0 cm), and 16.7 kg/m2 (range of 14.6 to 19.3 kg/m2), respectively. The height-to-weight ratio for all 15 subjects was > 10% on the normal growth curve.

Of the 15 randomised subjects, 12 completed both assigned treatment arms (apple sauce and apple juice) and were considered evaluable.

Results

Caregivers were satisfied overall with apple sauce as a dosing method of APT-1008 3,000 (using a spoon) when compared with apple juice (using the syringe nurser), which they indicated was not as easy to use, required more time to administer, and was less accepted by their infants.

Evaluation of the efficacy of APT-1008 by assessment of the signs and symptoms of EPI was based on recordings in daily diaries. Caregivers reported stool frequencies during treatment with APT-1008 3,000 (means of 2.76 stools/day and 2.44 stools/day for apple juice and apple sauce, respectively). Results were similar to frequencies reported during treatment with Zenpep 5,000 (mean of 2.73 stools/day) received during screening period.

Mean stool consistency scores during treatment with APT-1008 3,000 were similar when compared with mean scores during treatment with Zenpep 5,000.

Study PR-018

Design

Study PR-018 was an open-label, multiple-dose, extension of study PR-011 conducted at six centres in the US. The study was designed to assess the long-term safety of APT-1008 3,000 (lipase units) capsules in infants with CF and EPI.

The primary objective was to evaluate the frequency, duration and severity of treatment-emergent AEs during long-term treatment with APT-1008.

The secondary efficacy objective was to evaluate the effects of long-term treatment with APT-1008 by evaluating subjects' ability to thrive as evaluated through descriptive statistics for weight, length, and percentiles for weight-for-age and weight-for-length.

Population

The study population comprised 9 male (60.0%) and 6 female (40.0%) infants ranging in age at the Enrolment Visit from 3 to 14 months (median age of 9 months). Twelve subjects completed the study.

Results

Overall, enrolled subjects demonstrated an improvement from baseline to study completion in terms of growth indices including weight-for-age, length-for-age, and weight-for-length percentiles.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The cross over, versus active control, design and the primary endpoint (coefficient of fat absorption) of the pivotal study (PR-005) are in line with the CHMP guideline on the clinical development of medicinal products for the treatment of cystic fibrosis EMEA/CHMP/EWP/9147/2008-corr. for "me-too" pancreatic enzyme preparation. The active comparator Kreon consists of orally administered capsules containing enteric-coated spheres consisting of porcine-derived pancreatic enzymes containing pancreas powder as the active ingredient. Kreon is a coated pancreas enzyme preparation widely used in Europe and considered an acceptable comparator.

In addition to the pivotal study, the Applicant submitted 5 supportive studies to ascertain the efficacy profiles of APT-1008 across a wide age range to support the intended target population. The main efficacy and safety data was generated in the pivotal study (PR-005) vs. active-comparator and in one placebo-controlled study (EUR-1008-M) involving a total of130 patients.

The supportive studies included 2 controlled studies: a double-blind, cross over placebo-controlled study in adults and children over 6 years old with enzyme pancreatic insufficiency due to cystic fibrosis (EUR-1008-M) and a randomized, double-blind, dose-response control, crossover study in adults with enzyme pancreatic insufficiency due to chronic pancreatitis (PR-002).

Three supportive open-label studies in paediatric patients with enzyme pancreatic insufficiency due to cystic fibrosis (EUR-1009-M, PR-011, PR-018) have been submitted: 1 open-label Phase III in young children aged 1 to <7 years, 1 phase IV study in infant (aged 1 to 12 months) to assess the acceptability of two modes of administration and 1 extension of the previous phase IV study.

Overall, in the clinical program, APT 1008 had been studied in:

- Infants over a month, children, adolescents and adults with enzyme pancreatic insufficiency due to cystic fibrosis,
- Adults with enzyme pancreatic insufficiency due to chronic pancreatitis.
- The design of the clinical studies had been discussed with the scientific advice CHMP, and for the most part the Applicant has conducted the trials in accordance with the advice received during that procedure.

Paediatric patients with chronic pancreatitis and enzyme pancreatic insufficiency which are a part of the indication have not been studied in the clinical programme which is acceptable taking into account the rarity of chronic pancreatitis in children and the mechanism of action of pancreatic enzyme replacement therapy that is independent of the underlying condition.

With the exception of Study PR-018 (in infants with Cystic fibrosis) the duration of exposure to APT-1008 in the supportive studies was no greater than four weeks but the limited amount of long term data generated can be accepted based on extrapolation from other products and from the published literature.

Efficacy data and additional analyses

Significant variation in individual responses to pancreas enzyme preparations and their dosage are well known and the doses are individualized based on content of fat of the diet, the degree of steatorrhoea and clinical symptoms. No formal dose response studies have been carried out which is acceptable in this context.

The proposed dosages are based on the current European consensus recommendation [Sinaasappel et al. 2002]) which states that:

- For children <1 year old, the recommended dose is 2,000 to 5,000 lipase units/120 ml of formula or per breast-feeding or 400 to 800 lipase units/g of dietary fat.

- For children aged 1 to 4 years, the recommended starting dose is 1,000 lipase units/kg/meal, and for children >4 years old and adults patients, the recommended starting dose is 500 lipase units/kg/meal.

- A dose titration as appropriate for individual patients is recommended within the standard limits of maximum 2500 lipase units/kg/feeding with a maximum of 10,000 lipase units/kg/day.

In both phase IV, infants were treated with capsules which contained 3,000 lipase units; the capsules were opened and the content (micro-tablets) sprinkled over apple sauce or added to apple juice. This particular strength was developed for use in infants and children with low body weight to provide an age- and weight-appropriate dosage strength. It allows dosing in increments of 3,000 lipase units and avoids the need to split the content of higher-strength capsules to achieve proper dosing, thus potentially reducing the risk of dosing errors.

Although a wide range of ages has been studied the youngest individuals included were infants of one to twelve months (Study PR-011). In view of the lowest capsule strengths to be marketed (5000 UI) the applicant initially proposed to share the content of one unit with the aiming at delivering the proposed dose for infants under one year. The CHMP raised concern that technically an accurate dosing will be impossible due to the fact that each 5000 Unit capsule contains variable numbers of microtablets (approximately ranging from 15 to 32 microtablets / capsule) depending on nominal lipolytic activity of the microtablet batch. This variability would be confusing for the person preparing the dose.

As part of the answers to the questions raised by the CHMP, the Applicant removed from the SmPc the proposal to open the capsule and divide its content as well as the initially claimed indication in neonates, a population who had not been included in clinical trials. The starting dose for the youngest infant (below 1 year) is 5,000 UI per 120 ml of milk with a maximum recommended total dose is 2,500 lipase units*/kg of body weight per meal (or 10,000 lipase units*/kg of body weight per day) which is in line with the Cystic Fibrosis Foundation Evidence-Based Guidelines (Borowitz 2009) that states that PEP should be started at a dose of 2,000 to 4,000 up to 5,000 UI for each feeding. This was considered acceptable by the CHMP. Furthermore, the applicant indicated that the feasibility of a lower dosage for the youngest infant population is under study.

Patients with cystic fibrosis

In the pivotal study PR-005 ATP-1008 demonstrated both non inferiority and equivalence to Kreon on fat absorption as the LS mean CFA-72h was 84.08% with APT-1008 vs 85.33% with Kreon. Similar results were seen for APT-1008 and Kreon for signs and symptoms of enzyme pancreatic insufficiency chosen as secondary endpoints in this study except for proportion of subject-days with bloating.

The supportive study EUR-1008 showed a significant difference in fat absorption as LS mean CFA-72h was 88% with APT 1008 vs 63% with placebo.

The supportive study EUR-1009 showed no difference in proportion of responder after 2 weeks of treatment with APT-1008 vs previous treatment in children aged 1 to 6 years. One notable exception in this study is the use of “responder” (defined as < 30% fat faecal content) as primary endpoint in the study instead of CFA 72.

This choice is considered acceptable in view of the risks and inconvenience associated with a 72-hour stool collection in a hospital environment in very young children with CF.

Study PR-011 and its one year extension Study PR-018 evaluated efficacy and safety in a population of CF infants 1 to 12 months old at the time of their initial recruitment and evaluated two methods of administration (opened capsules in semisolid or liquid) and long term efficacy and safety.

The Supportive studies provide information additional to that in the principal efficacy studies and appear to have been generally well conducted. Supportive studies in infants and children suggest similar benefits as seen in the pivotal trials.

Patients with chronic pancreatitis

The study conducted in the chronic pancreatitis population (PR-002) had a cross over design comparing two different doses of APT-1008 on steathorrea assessed by CFA-72 h in adults with enzyme pancreatic insufficiency and chronic pancreatitis.

In this sole study, no statistically significant difference between the two doses (primary endpoint) was observed. A modest but significant difference was only reached for a secondary endpoint of this study: the differences in CFA-72h at the end APT-1008 period vs baseline (placebo). According to the Applicant this is due to the fact that mean CFA for the placebo baseline period was unexpectedly high. In an additional analyses patients were stratified by CFA-72h values at baseline. In this analyse patients with severe steatorrhea (CFA-72h <65%) treatment with high-dose APT-1008 was associated with greater increases in CFA-72h (36.8%) compared to low-dose APT-1008 (27.1%).

This dose response study only reach significance on a secondary endpoint. Nevertheless, cystic fibrosis can be considered as an appropriate model of exocrine pancreatic insufficiency as such and cystic fibrosis patients are often more severely affected from exocrine pancreatic insufficiency than chronic pancreatitis patients.

Therefore data generated in the CF population with EPI can be extrapolated to the other causes of EPI such as chronic pancreatitis, post pancreatectomy or pancreatic cancer.

2.5.4. Conclusions on the clinical efficacy

Pancreatic enzyme preparations have a well-established use, with recognized efficacy.

Submitted data show that APT-1008 is non-inferior and equivalent to an existing and widely used PEP (Kreon) in fat absorption in a short term study in adult and adolescent patients with enzyme pancreatic insufficiency due to Cystic Fibrosis. APT-1008 showed a statistically significant improvement in fat absorption over placebo in adults, adolescents and children over 7 years old with enzyme pancreatic insufficiency due to CF. Similar efficacy results were also seen on younger patients aged 1 month to 6 years old.

APT-1008 has demonstrated efficacy over placebo in adult patients with enzyme pancreatic insufficiency due to chronic pancreatitis but only on a secondary endpoint but as cystic fibrosis can be considered as an appropriate model of exocrine pancreatic insufficiency data generated in the CF population with EPI can be extrapolated to the other causes of EPI

2.6. Clinical safety

Patient exposure

In the six clinical safety and efficacy studies and the single clinical pharmacology study conducted by the Applicant 270 patients recruited and 251 were treated with ATP-1008 were included in the safety populations; 153 (61%) were male and 98 (39%) were female. The underlying cause of their exocrine pancreatic insufficiency was CF for 255 and primary pancreatic disease for 15.

Duration of treatment ranged from a single dose in Study PR-001 to 379 days in Study PR-018

Table 4. Patient numbers treated with APT-1008 by study type

	Patients exposed	**Patients exposed to the proposed dose range**	**Patients with long term safety data**
Placebo-controlled	34	The dose is based on weight, diet, and residual enzyme production so the question is not directly applicable.	0
Active -controlled	92		0
Dose ranging and open studies	125		15 infants
Post marketing	Estimated 36,326 patient-years to the end of April 2014		

Table 5. Duration of exposure (Studies PR-005, EUR-1008-M1, EUR-1009-M, PR-0022, PR-0113, PR-018 and PR-001)

Duration	**No. of patients (%)**
≤ 2 days	16 (6.4%)
3 - 10 days	4 (1.6%)
11- 18 days	25 (100%)
19 - 42 days	190 (75.7%)
43 - 58 days	1 (0.4%)
59 days - 12 months	4 (1.6%)
> 12 months	11 (4.4%)
Total	251 (100%)

Table 7 Cumulative patient exposure to APT-1008 in the development program

Study ID	Population (age category)	Dosage	Planned Duration	Subjects exposed to APT-1008
PR-005	≥ 12 years of age.	Maximum dose of 10,000 Ph. Eur lipase units/kg/day.	28 ± 2 days.	92
EUR-1008-M	Aged 7 years or older.	Dose not to exceed 10,000 USP lipase units/kg/day.	6-7 days double-blind, 18-30 days open-label	34[1]
EUR-1009-M	1 to <7 years of age.	Three doses per day at approximately 2,000 USP lipase units/kg/meal	14 days.	19
PR-002	Over 18 years of age.	140,000 or 35,000 USP Lipase Units per full calendar day	9-11 days for each of low and high dose APT-1008.	36
PR-011	Between 1 and 12 months of age.	2,000 to 4,000 USP lipase units per 120 mL of formula or per breast-feeding	Up to 30 days.	15
PR-018	Between 3 and 14 months of age.	For children up to 12 months: 2,000 to 4,000 USP lipase units per 120 mL of formula or per breast-feeding. For children over 12 months: 1,000 - 2,500 USP lipase units/kg/meal	12 months	15[2]
PR-001	Over 18 years of age.	75,000 USP lipase units per procedure per subject.	One administration	15
TOTAL				251

USP = United States Pharmacopeia

[1] In study EUR-1008-M the N for the double-blind period was 33, ie, one patient received APT-1008 during the open-label stabilisation period but discontinued prior to the first double-blind period.

[2] The 15 subjects exposed in the extension study PR-018 are the same subjects as in study PR-011. They were counted once only in the total.

PEI is a rare condition and the size of the patient database for CF related disease is adequate.

Adverse events

The table below provides an overview of frequency of AEs in the clinical programme (Studies PR 005, ATP-1008 M, EUR 1009 M, PR 002, PR 011 and PR 018).

There were no deaths in the studies and very few patients had SAEs or TEAEs of severe intensity or had to discontinue the study due to an AE. There were more TEAEs reported in the paediatric studies (PR 011 and PR 018) but in the other studies the percentage of TEAEs and of study drug-related TEAEs was generally low. The incidence of TEAEs was comparable between APT 1008 and Kreon in study PR 005 and (in the double-blind treatment period) between APT 1008 and placebo in study EUR-1008 M.

Table: Overview of treatment emergent adverse events in studies PR-005, ATP-1008-M, EUR-1009-M, PR-002, PR-011, PR-018 – Safety population

	Active controlled Phase III Study in CF		**Phase III Studies in CF**				**Supportive Phase II/III Study in CP**			**Supportive Phase IV Studies in CF**	
	PR-005		**EUR-1008-M**			**EUR-1009-M**	**PR-002**			**PR-011**	**PR-018**
TEAE Category	**APT-1008 (N=92)**	**Kreon (N=90)**	**APT-1008 (Entire Study) (N=34)**	**APT-1008 (Double-Blind) (N=33)**	**Placebo (N=32)**	**APT-1008 (N=19)**	**Placebo Baseline (N=82)**	**APT-1008 Low Dose (N=74)**	**APT-1008 High Dose (N=75)**	**APT-1008 (Entire Study) (N=15)**	**APT-1008 (N=15)**
Number of Events:											
TEAEs	36	36	117	43	43	51	100	82	95	145	234
Treatment-related TEAEs	17	15	50	NR	36	17	58	25	19	63	15
Severe TEAEs	5	4	15	NR	5	2	NR	NR	NR	9	2
Serious TEAE	0	2	2	0	0	1	2	2	5	0	3
Number of patients with at least one:											
TEAE	18 (19.6%)	23 (25.6%)	27 (79.4%)	19 (57.6%)	16 (50.0%)	13 (68.4%)	35 (42.7%)	29 (39.2%)	31 (41.3%)	15 (100.0%)	15 (100.0%)
Drug-related TEAE	5 (5.4%)	8 (8.9%)	16 (47.1%)	10 (30.3%)	12 (37.5%)	5 (26.3%)	17 (20.7%)	10 (13.5%)	7 (9.3%)	10 (66.7%)[1]	5 (33.3%)
Severe TEAE	2 (2.2%)	2 (2.2%)	4 (11.8%)	NR	3 (9.4%)	2 (10.5%)	NR	NR	NR	2 (13.3%)	2 (13.3%)
Serious TEAE	0	2 (2.2%)	2 (5.9%)	0	0	1 (5.3%)	2 (2.4%)	2 (2.7%)	2 (2.7%)	0	3 (20.0%)
TEAE leading to study discontinuation	2 (2.2%)	1 (1.1%)	0	0	0	0	2 (2.4%)	0	1 (1.3%)	0	1 (6.7%)

Table 6. Incidence of TEAEs occurring in ⩾ 3% of patients - All Studies, APT 1008 treatments only, pooled and by individual study – Safety population

	Double-Blind, Controlled Studies			Open-Label, Uncontrolled Studies			Pooled	
System Organ Class **Preferred Term**	**PR-005** **(N=92)** **n (%)**	**EUR-1008-M[1]** **(N=34)** **n (%)**	**PR-002[2]** **(N=76)** **n (%)**	**EUR-1009-M** **(N=19)** **n (%)**	**PR-011[3]** **(N=15)** **n (%)**	**PR-018** **(N=15)** **n (%)**	**All Studies[4]** **(N=236)** **n (%)**	**Short-Term Studies** **(N=236)** **n (%)**
Patients with at least one TEAE	18 (19.6)	27 (79.4)	42 (55.3)	13 (68.4)	15 (100.0)	15 (100.0)	115 (48.7)	115 (48.7)
Gastrointestinal disorders								
Abdominal distension	2 (2.2)	5 (14.7)	2 (2.6)	1 (5.3)	5 (33.3)	2 (13.3)	17 (7.2)	15 (6.4)
Abdominal pain	3 (3.3)	9 (26.5)	16 (21.1)	5 (26.3)	5 (33.3)	0	38 (16.1)	38 (16.1)
Constipation	0	1 (2.9)	6 (7.9)	0	2 (13.3)	3 (20.0)	12 (5.1)	9 (3.8)
Diarrhoea	3 (3.3)	0	3 (3.9)	1 (5.3)	3 (20.0)	5 (33.3)	13 (5.5)	10 (4.2)
Flatulence	3 (3.3)	6 (17.6)	12 (15.8)	2 (10.5)	5 (33.3)	2 (13.3)	29 (12.3)	28 (11.9)
Nausea	1 (1.1)	2 (5.9)	4 (5.3)	0	0	0	7 (3.0)	7 (3.0)
Steatorrhoea	1 (1.1)	2 (5.9)	0	3 (15.8)	5 (33.3)	4 (26.7)	13 (5.5)	11 (4.7)
Vomiting	1 (1.1)	2 (5.9)	3 (3.9)	2 (10.5)	0	5 (33.3)	13 (5.5)	8 (3.4)
General disorders								
Pyrexia	1 (1.1)	2 (5.9)	3 (3.9)	3 (15.8)	5 (33.3)	10 (66.7)	21 (8.9)	14 (5.9)
Infections and infestations								
URTI	0	0	0	2 (10.5)	1 (6.7)	6 (40.0)	9 (3.8)	3 (1.3)
Nervous system disorders								
Headache	0	8 (23.5)	4 (5.3)	1 (5.3)	0	0	13 (5.5)	13 (5.5)
Respiratory disorders								
Cough	0	4 (11.8)	0	1 (5.3)	8 (53.3)	11 (73.3)	17 (7.2)	13 (5.5)
Nasal congestion	0	2 (5.9)	0	2 (10.5)	2 (13.3)	7 (46.7)	12 (5.1)	6 (2.5)
Productive cough	1 (1.1)	1 (2.9)	1 (1.3)	0	0	4 (26.7)	7 (3.0)	3 (1.3)
Rhinorrhoea	0	1 (2.9)	0	3 (15.8)	2 (13.3)	12 (80.0)	16 (6.8)	6 (2.5)
Wheezing	0	0	0	0	0	8 (53.3)	8 (3.4)	0

Table 7. TEAEs reported as GI disorders in study PR 005 by relationship to study drug Safety population

	APT-1008 (N=92)		**Kreon (N=90)**	
System Organ Class Preferred Term	**No Reasonable Possibility n (%)**	**Reasonable Possibility n (%)**	**No Reasonable Possibility n (%)**	**Reasonable Possibility n (%)**
Any TEAE	13 (14.1)	5 (5.4)	15 (16.7)	8 (8.9)
Gastrointestinal Disorders	5 (5.4)	3 (3.3)	4 (4.4)	6 (6.7)
Abdominal pain	0 (0.0)	3 (3.3)	0 (0.0)	3 (3.3)
Diarrhoea	2 (2.2)	1 (1.1)	2 (2.2)	1 (1.1)
Flatulence	1 (1.1)	2 (2.2)	0 (0.0)	1 (1.1)
Abdominal distension	2 (2.2)	0 (0.0)	0 (0.0)	1 (1.1)
Vomiting	0 (0.0)	1 (1.1)	1 (1.1)	0 (0.0)
Abdominal pain, upper	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.1)
Abnormal faeces	0 (0.0)	1 (1.1)	0 (0.0)	0 (0.0)
Nausea	1 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)
Steatorrhoea	0 (0.0)	1 (1.1)	0 (0.0)	0 (0.0)
Toothache	0 (0.0)	0 (0.0)	1 (1.1)	0 (0.0)

In the pivotal Phase III study, PR-005, two subjects reported 4 TEAEs that led to discontinuation of study drug during treatment with APT-1008:

- One subject reported moderate abdominal pain and mild vomiting
- the other subject reported severe abdominal pain and moderate diarrhoea.

All of these TEAEs were non-serious and the Investigator considered the events to be possibly related to treatment with study drug.

One other subject in the study reported 1 TEAE that led to discontinuation of study drug during treatment with Kreon. This was the subject who had the SAE of liver function deterioration due to portal vein thrombosis.

In supportive Phase II/III study PR-002, three subjects discontinued the study due to TEAEs:

- two due to events that started during treatment with placebo and
- one due to events that started during treatment with high dose APT-1008.

The TEAEs that led to study drug discontinuation during treatment with placebo comprised abdominal pain, upper abdominal pain, diarrhoea, dizziness, nausea and vomiting in one subject and abdominal pain and hepatic enzymes increased in another subject. The TEAE that led to study drug discontinuation during treatment with high dose APT-1008 was pancreatic pseudocyst of severe intensity, which was also a SAE; the Investigator considered this event to be unrelated to study drug.

Serious adverse event / deaths / other significant events

No deaths were reported in studies PR-005, EUR-1008-M, PR-002, EUR-1009-M, PR-011, PR-018 or PR-001 SAEs were reported for 17 of the 255 patients treated in the seven clinical studies; all SAEs were considered by the Investigators not to be related to study drug. For two patients the SAE lead to discontinuation from the study. One subject, treated with Kreon in Study PR-005, discontinued due to portal vein thrombosis and another subject, treated with high dose APT-1008 in Study PR-002 discontinued due to pancreatic pseudocyst.

In the pivotal study PR-005, two treatment-emergent SAEs (hypospadias surgery and liver function deterioration due to portal vein thrombosis) were reported and both occurred while the patients were receiving Kreon. The Investigator considered the events to be unrelated to the study drug.

In the supportive trial EUR-1008-M, there were two SAEs reported by two patients (5.9%) while receiving APT-1008 during the open-label dose titration/stabilisation period. The Investigators considered neither of these SAEs (haemoptysis and lung disorder).

Table 8 Patients experiencing treatment-emergent serious adverse events by study - Safety population

Study	Subject	Sex	Age	Treatment at onset	SAE	Onset Date	End Date	Intensity	Related to study drug	Action taken with study drug	Outcome
PR-005	0404-003	M	12 yrs	Kreon	Urethral repair	28 Aug 2013	30 Aug 2013	Mild	No	None	Resolved
PR-005	0407-004	M	19 yrs	Kreon	Portal vein thrombosis	27 Nov 2012	24 Dec 2012	Severe	No	Discontinued	Resolved
EUR-1008-M	101805	M	20 yrs	APT-1008	Lung disorder	19 Oct 2006	7 Nov 2006	Moderate	No	None	Resolved
EUR-1008-M	116801	M	22 yrs	APT-1008	Haemoptysis	12 Jan 2006	22 Jan 2006	Severe	No	None	Resolved
EUR-1009-M	102902	F	27 mths	APT-1008	Upper respiratory tract infection	23 Aug 2006	26 Aug 2006	Moderate	No	None	Resolved
PR-002	30201	M	55 yrs	Placebo	Wrist fracture	2 Jul 2008	4 Aug 2008	Moderate	No	None	Resolved
PR-002	10708	M	44 yrs	Placebo	Nephrolithiasis	16 Sep 2008	19 Sep 2008	Severe	No	Interrupted	Resolved
PR-002	10708	M	44 yrs	APT-1008 [2]	Pancreatic pseudocyst	6 Oct 2008	Unknown	Severe	No	Discontinued	Unknown
PR-002	10708	M	44 yrs	APT-1008 [2]	Obstruction gastric	6 Oct 2008	24 Oct 2008	Severe	No	None	Resolved
PR-002	10708	M	44 yrs	APT-1008 [2]	Bile duct obstruction	6 Oct 2008	24 Oct 2008	Severe	No	None	Resolved
PR-002	11102	M	50 yrs	APT-1008 [1]	Gastrointestinal haemorrhage	23 Feb 2009	26 Feb 2009	Severe	No	None	Resolved
PR-002	30102	M	64 yrs	APT-1008 [1]	Pyrexia	30 Jun 2008	2 Jul 2008	Severe	No	None	Resolved
PR-002	11204	M	66 yrs	APT-1008 [2]	Renal injury	29 Jan 2009	30 Jan 2009	Moderate	No	None	Resolved
PR-002	11204	M	66 yrs	APT-1008 [2]	Cognitive disorder	29 Jan 2009	2 Feb 2009	Moderate	No	None	Resolved
PR-018	0201	F	9 mths	APT-1008	Viral infection	01 May 2011	08 May 2011	Moderate	No	None	Resolved
PR-018	0402	M	10 mths	APT-1008	Bronchopneumonia	25 Jan 2011	04 Feb 2011	Moderate	No	None	Resolved
PR-018	0701	M	5 mths	APT-1008	Anaphylactic shock	03 Apr 2011	03 Apr 2011	Severe	No	None	Resolved

SAE = serious adverse event; M = male; F = female
[1] low dose
[2] high dose
Note that no SAEs were reported for subjects in studies PR-011 and PR-001

Laboratory findings

In APT-1008 clinical studies, there have been no adverse trends seen in any of the serum chemistry, haematology or urinalysis parameters, or vital signs, physical examination or quality of life assessments measured. There have been no cases (with APT-1008) of clinically significant elevations in serum uric acid levels, or cases with normal uricosuria at baseline and clinically significant abnormalities at the end of treatment, despite both effects being seen (although with low frequency) with the use of other pancreatic enzymes, particularly at high doses.

In study PR-005, the most common parameters that changed from normal values at baseline to abnormally high values after treatment were urate (five subjects on APT-1008; four subjects on Kreon), phosphate (4 subjects on APT-1008; five subjects on Kreon) and potassium (four subjects on APT-1008; four subjects on Kreon). The most common parameter that changed from normal values at baseline to abnormally low values after treatment was creatinine (eight subjects on APT-1008; four subjects on Kreon). None of these changes were considered to be clinically significant and none were associated with any AEs.

One patient in study EUR-1008-M had an aspartate transaminase (AST) level of 93.00 IU/L and an alanine transaminase (ALT) level of 177.0 IU/L that were considered clinically significant, and was reported as having an AE of hepatitis during treatment with APT-1008, which was considered by the Investigator to be not related to study drug. All other laboratory results were considered not clinically significant.

In study PR-009, treatment-emergent clinical laboratory abnormalities in uric acid (serum) occurred in three subjects. Two subjects shifted from normal at baseline to high at end of study, while one subject shifted from normal at baseline to low at end of study. None of these shifts were reported as AEs during the study or were considered clinically significant. No events of hyperuricaemia or hyperuricosuria were reported. Of particular note, uric acid (urine) levels were normal at both baseline and end of study for all subjects

In study PR-002, one subject had normal urinary glucose at baseline and a clinically significant abnormality at the end of treatment with high dose APT-1008. Another subject had a non-clinically significant urinary uric acid value at baseline and a clinically significant value at the end of treatment with placebo.

Safety in special populations

As discussed above in the efficacy section of this report no studies have been carried out in 'special populations'. The APT-1008 clinical program included studies in infants, young children, adolescents and adults. There were no clinically significant differences in the AEs observed between the different age groups included in these studies.

Immunological events

Hypersensitivity type reactions with enzyme replacement in general and with ATP-1008 post authorisation have been reported, this is not unexpected in view of the animal source of the administered protein and an identified risk of the products RMP. The possibility is indicated in Sections 4.4 and 4.8 of the proposed SmPC.

Safety related to drug-drug interactions and other interactions

In the literature, there have been no reports of adverse interactions between PEPs and adjunct therapies.

Discontinuation due to adverse events

There were no TEAEs leading to discontinuation of study drug during study PR-011 but in the safety extension study PR-018, one subject experienced a TEAE of poor weight gain of moderate intensity and had treatment permanently discontinued and was withdrawn from the study; the Investigator considered this event to be possibly related to study drug. There were no TEAEs leading to interruption or discontinuation of study drug during the EUR-1008-M, EUR-1009-M, or PR-001 studies.

Overall, patient retention in the clinical studies was good. This is to be expected as with one exception the studies were short, only one involved a placebo controlled arm, and generally patients received a rapid benefit from treatment in terms of less symptoms of malabsorption.

Post marketing experience

APT-1008 has been marketed in the US as Zenpep since November 16, 2009 and in Puerto Rico since 2011. APT-1008 is not marketed in any other country aside from the US and Puerto Rico. As of 30 April 2014 the total estimated exposure to APT-1008 during marketed use was approximately 27,000 patient treatment years.

Table 8. Estimated age of Zenpep treatment population – post authorisation sales

Custom Age Group	Estimated Patient Count	Percentage (%)
0 – 64 years	79,888	55.2
≥ 65 years	64,688	44.7
Unknown	149	0.1
Total	144,725	100

Cumulatively 902 AEs were reported, comprising 834 non-serious and 68 serious AEs.

The list of AEs that have been observed with the investigational drug and for which a causal relationship with the drug is suspected or confirmed is:

- Gastrointestinal disorders: abdominal distension, abdominal pain, constipation, diarrhoea, flatulence, irritation of oral mucosa, nausea, steatorrhoea.
- Immune system disorders: allergic reaction, anaphylaxis
- Investigations: blood glucose abnormal
- Nervous system disorders: headache
- Skin and subcutaneous tissue disorders: pruritus, rash, urticaria
- Respiratory, thoracic and mediastinal disorders: asthma

A total of 12 cases with fatal outcome have been reported during post-marketing experience but none suggest a causal association with Zenpep.

There are two ongoing joint-sponsor post-marketing safety studies in the US:

- Study PR-015 – A 10-year prospective, observational safety study of the incidence of and risk factors for fibrosing colonopathy in US subjects treated with a PERT. A harmonised protocol across a number of sponsors who market pancrelipase.
- Study PR-016 – An 18-month point prevalence study to evaluate the prevalence of antibodies to selected porcine viruses in subjects with CF who are receiving porcine-derived PERT: A harmonised protocol across a number of sponsors who market pancrelipase.

2.6.1. Discussion on clinical safety

Clinical safety was assessed through six clinical studies that were performed in the target population: patients with exocrine pancreatic insufficiency due to cystic fibrosis and patients with exocrine pancreatic insufficiency due to chronic pancreatitis. A total of 251 patients were exposed to APT-1008 during the clinical programme (including 15 patients from a phase 1 bioavailability study).

The study population included adult and paediatric patients:

- 15 patients aged 1 to 12 months
- 19 patients aged 1 to 6 years
- 8 patients aged 7 to 11 years
- 68 patients aged 12 to 17 years
- 126 patients aged >18 years (50 with cystic fibrosis and 76 with chronic pancreatitis)

PEI is a rare condition and the size of the patient database for CF related disease is adequate. Cystic fibrosis was selected as a model condition of EPI in accordance with Committee for Medicinal Products for Human Use (CHMP) 2010 guidance on the clinical development of medicinal products for the treatment ofCF [EMEA/CHMP/EWP/9147/2008-corr] and CF is recognised as a suitable model for an EPI indication as CF patients are usually more severely affected with EPI than patients with CP.

Across all studies, 48.7% of APT-1008-treated subjects had a TEAE. The most common treatment-related TEAEs across all studies were abdominal pain (24 subjects [10.2%]) and flatulence (15 subjects [6.4%]).

The safety and tolerability of APT-1008 was comparable to Kreon, with numerically fewer subjects experiencing TEAEs with APT-1008 (18 subjects, 19.6%) than with Kreon (23 subjects, 25.6%) in the pivotal study. Five (5.4%) patients treated with APT-1008 and in eight (8.9%) patients treated with Kreon had TEAEs judged to be treatment-related.

Adverse reactions were consistent with the underlying disease; the most common TEAEs reported were in the System Organ Classes 'GI disorders'. No patient who participated in the clinical development programme died. No clinically significant differences in the AEs were observed between the different age groups (infants, children, adolescents and adults).

APT-1008 was approved for use in the US under the invented name Zenpep in 2009 for the treatment of EPI due to CF or other conditions. No new major safety issues have been revealed; the majority of AEs reported were non-serious adverse events and supported what is known about the safety of Zenpep and its overall benefit risk profile.

In the clinical trials conducted, only 11 (4.4%) of the total population was over sixty-five years old, this is to be expected as considering that beside Study PR-002 the majority of EPI subjects treated with APT-1008 in the clinical studies had underlying CF where life expectancy is currently slightly over forty years. In the post marketing experience 44.7% of the exposed population is estimated to be at least 65 years old. Analysis of adverse drug reactions (ADRs) reported in the elderly population compared with the non-elderly population (patients <65 years and of unknown age) did not revealed significant differences in the safety profiles are observed between the gender groups.

A number of class effects have been considered in SmPC and RMP of Zenpep:

It is known that glycaemic control can be affected by administration of PEP in patients at risk. Some cases of abnormal high blood glucose levels were reported in the clinical study program but only 3 were clinically relevant. It is acknowledged, that fluctuations in blood glucose could be associated with the underlying disease and not with the administration of APT-1008. The warning statement in the SmPC that glycaemic control may be affected is considered reasonable as a precautionary measure. This potential risk is also outlined in the RMP.

An important potential risk relating to overdose of APT-1008 is the risk of hyperuricaemia and hyperuricosuria that has been recognised to occur with high doses of older formulations of PEPs. Patients with gout, renal impairment and with hyperuricaemia are at increased risk. This is caused by some components of PEPs such as purines, being absorbed into the bloodstream and at high doses leading to unintended side effects including hyperuricaemia and hyperuricosuria. No cases were observed during the APT-1008 clinical development programme and only a single case of elevated uric acid levels has been reported post-authorisation with Zenpep in addition to three cases of gout in elderly patients. The APT-1008 SmPC contains appropriate warnings measures concerning the risk of hyperuricaemia/ hyperuricosuria especially at high doses in sections 4.4 and 4.9.

No cases of fibrosing colonopathy were observed during the APT-1008 clinical development programme or during post-authorisation with Zenpep. Nonetheless fibrosing colonopathy remains a class effect of PEPs and is defined as an important potential risk in the RMP of APT-1008. Sections 4.4 and 4.9 of the SmPC warn about the risk associated with high doses of PEPs and possible associated symptoms. Similarly fibrosing colonopathy as a class effect of PERT is included in section 4.8.

As a medicinal product of porcine origin there is a theoretical risk of transmission of porcine viruses and viral diseases to patients treated with APT-1008, despite no case of viral transmission to humans from PEPs reported throughout the long history of PERT use. Overall the risks for patients taking pancreas powder based drugs are minimal to non-existent. Nevertheless, transmission of viral diseases to humans is considered an important potential risk of APT-1008 and is included in the RMP.

Patients known to be hypersensitive to pancreas powder or to any of the excipients, to other porcine PEPs or to pork were excluded from clinical trials because of the risk of hypersensitivity or anaphylactic type reactions. No severe allergic reactions were observed during the clinical development programme but one serious adverse event of anaphylactic shock to peanuts judged by the investigator and sponsor not to be related to APT-1008 was observed. In addition 20 non-serious allergic reactions including cough, dyspnoea, asthma, stridor, wheezing, pruritus, rash and rash generalised were reported in clinical trials. Anaphylactic reaction is considered an important identified risk of APT-1008 and appropriate warning statements are included in the SmPC.

From the safety database all the adverse reactions reported in clinical trials and post-marketing have been included in the Summary of Product Characteristics

2.6.2. Conclusions on the clinical safety

Overall, APT-1008 was well tolerated. Adverse effects seen with APT-1008 therapy appear to be not serious and are mostly related to the underlying disease condition. The safety profile reported in the studies and in post marketing experience is in line with the safety profile of PEPs as reported in the literature.

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8. Risk Management Plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 0.3 is acceptable.

The CHMP endorsed the Risk Management Plan version 0.3 with the following content:

Safety concerns

Summary of safety concerns	
Important identified risks	Anaphylactic reactions
Important potential risks	Long-term high doses as a potential risk factor for the occurrence of fibrosing colonopathy
	Transmission of viral diseases to patients
	Hyperuricaemia and hyperuricosuria

Summary of safety concerns	
Missing information	Use in pregnancy
	Use during lactation
	Effect on fertility

Pharmacovigilance plan

Study/activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
Study PR-015: A long-term prospective observational safety Study of the incidence of and risk factors for fibrosing colonopathy in US patients with cystic fibrosis treated with pancreatic enzyme replacement therapy: A harmonized protocol across sponsors (Category 3 study)	The primary objective of this study is to quantify over a 10-year period the incidence of fibrosing colonopathy in US patients with CF treated with PERT. The secondary objective is to quantify the association between potential risk factors and the development of fibrosing colonopathy in patients with CF	Risk of fibrosing colonopathy with different PEPs commercially available in the US. Risk factors for developing fibrosing colonopathy will also be addressed.	Study initiated: July 2012	Final report: Q4 2022

Risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Anaphylactic reactions (important identified risk)	• Contraindication in section 4.3 for patients with hypersensitivity to pancreas powder or to any of the excipients • Warning in section 4.4 that anaphylactic reactions have been reported with other PEPs with guidance in case of occurrence • Listed as an adverse reaction in section 4.8 with APT-1008 and as a class effect of PEPs with a frequency of not known • Prescription only medicine	None
Long-term high doses as a potential risk factor for the occurrence of fibrosing colonopathy (important potential risk)	• Guidance in section 4.2 to keep under the maximum recommended dose and that increases in dosage should be under medical supervision with careful monitoring	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	• Warning in section 4.4 that fibrosing colonopathy has been reported in CF patients taking high dose PEPs with guidance on monitoring • Listed as a class effect of PEPs in section 4.8 with a frequency of not known • Warning that chronic high doses of PEPs have caused fibrosing colonopathy in section 4.9 • Prescription only medicine	
Transmission of viral diseases to patients (important potential risk)	• Manufacturing process and routing testing eliminate or reduce the presence of viruses	None
Hyperuricaemia and hyperuricosuria (important potential risk)	• Warning in section 4.4 to exercise caution when prescribing to patients with a history of gout, renal impairment, or hyperuricaemia as PEPs contain purines that may increase blood uric acid levels • Listed as a class effect in section 4.8 with a frequency of not known • Warning in section 4.9 that chronic high doses of PEPs may cause hyperuricosuria and hyperuricaemia and should be used with caution in patients with a history of gout, renal impairment or hyperuricaemia • Prescription only medicine	None
Use in pregnancy (missing information)	• Guidance in section 4.6 with a risk benefit statement • Prescription only medicine	None
Use during lactation (missing information)	• Guidance in section 4.6 concerning use during lactation • Prescription only medicine	None
Effect on fertility (missing information)	• Information in section 4.6 concerning effect on fertility • Prescription only medicine	None

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

3. Benefit-Risk Balance

Benefits

Beneficial effects

Exocrine pancreatic insufficiency is a condition in which the exocrine function of the pancreas is compromised and its ability to effectively deliver digestive enzymes to the duodenum is impaired; it leads to malabsorption of lipids, fat-soluble vitamins, proteins, and, to a lesser extent, carbohydrates from the digestive tract. Enzepi is a pancreatic enzyme product presented in a form of capsule containing enteric coated mini-tablets.

In the pivotal study PR-005 Enzepi demonstrated both non inferiority and equivalence to Kreon on fat absorption in adolescents and adults. Subjects achieved a mean CFA-72h of 84.08 with Enzepi and of 85.33 with comparator. The difference in means was -1.25 (95% CI: -3.62 to 1.12), with p=0.2972. Similar results were seen for Enzepi and Kreon for signs and symptoms of enzyme pancreatic insufficiency chosen as secondary endpoints in this study except for proportion of subject-days with bloating.

The supportive study EUR-1008 showed a significant difference in fat absorption. The mean CFA-72h was 88% with Enzepi treatment compared to 63% with placebo treatment. The mean difference in CFA-72h was 26 percentage points greater with Enzepi treatment with a 95% Confidence Interval of (19, 32) and p<0.001.

The supportive study EUR-1009 showed no difference in proportion of responder (defined as < 30% fat faecal content) after 2 weeks of treatment with APT-1008 vs previous treatment in children aged 1 to 6 years.

In summary Enzepi showed a statistically significant improvement in fat absorption over placebo in adults, adolescents and children over 7 years old with enzyme pancreatic insufficiency due to CF. Similar efficacy results were also seen on younger patients aged 1 month to 6 years old.

In the sole study in adult patients with enzyme pancreatic insufficiency due to chronic pancreatitis a modest but significant difference was only reached for a secondary endpoint of this study: the differences in CFA-72h at the end APT-1008 period vs baseline (placebo). Nevertheless, cystic fibrosis can be considered as an appropriate model of exocrine pancreatic insufficiency as such and cystic fibrosis patients are often more severely affected from exocrine pancreatic insufficiency than chronic pancreatitis patients.

Uncertainty in the knowledge about the beneficial effects.

With the exception of Study PR-018 (in infants with Cystic fibrosis) the duration of exposure to APT-1008 in the supportive studies was no greater than four weeks but the limited amount of long term efficacy data generated can be accepted based on extrapolation from other products and from the published literature.

Risks

Unfavourable effects

In the different studies of the programme, the most frequently treatment-emergent adverse events reported were gastro intestinal disorders such as abdominal pain, diarrhoea and flatulence.

Also adverse events reported in the post marketing use in the US market (from 08/2009 to 04/2014) were mostly gastro-intestinal. The most relevant class effects of the pancreatic enzyme products include fibrosing colonopathy, hyperuricemia/ hyperuricosuria and severe allergic reactions (anaphylactic reactions) and appropriate warning statements are included in the SmPC.

There were no reports of fibrosing colonopathy which is a rare event probably related to high daily doses taken over long time spans and no cases hyperuricaemia, or hyperuricosuriae were reported.

Uncertainty in the knowledge about the unfavourable effects

In the study programme, patients treated only few weeks (maximum 28 days in pivotal study) thus most of safety data from this application are only short term but the limited amount of long term efficacy data generated can be accepted based on extrapolation from other products and from the published literature.

Effects Table

Table 9. Effects Table

Effect	Short Description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
Prevention of malnutrition	Fat and nitrogen absorption	CFA CNA	84.1% (11.1) 80.1% (10.7)	85.3% (9.1) 82.0% (10.3)	Carefully measured under lab conditions	Study PR-005
Prevention of vitamin deficiency	Fat soluble vitamin levels	Vitamin A,E,K levels	No evident difference to Kreon		Studies too short to detect a difference	Study PR-005
Relief of malabsorption symptoms	Individual symptom frequency and global index	Proportion of days with symptoms	No evident difference to Kreon		Too many variables to interpret easily	Study PR-005
Unfavourable Effects						
Hypersensitivity reactions	Events with clinical description	Frequency	None	None	Class effect Clinical trial database too small to detect	NA
Fibrosing colonopathy	Intestinal stricture	Frequency	None	None	Class effect Clinical trial database too small to detect	NA
Hyperuricaemia and uricosuria	Blood and urine urate levles	As left	None	None	Class effect Clinical trial database too small to detect	NA
Aggravation of glucose intolerance	Blood glucose levels	As left	Unknown frequency	Unknown frequency	Class effect Clinical trial database too small to detect	NA
Malabsorption symptoms	Clinical symptoms	Frequency proportion of days with event	Frequent	Frequent	Likely due to lack of efficacy and not a true adverse event	NA

Benefit-risk balance

Importance of favourable and unfavourable effects

Exocrine pancreatic insufficiency is a condition in which the exocrine function of the pancreas is compromised and its ability to effectively deliver digestive enzymes to the duodenum is impaired; it leads to malabsorption of lipids, fat-soluble vitamins, proteins, and, to a lesser extent, carbohydrates from the digestive tract. Clinical manifestations of EPI in general are steatorrhoea (excessive amount of fat in stool), increased stool frequency, alterations in stool consistency (loose, mushy, or watery), abdominal bloating, abdominal pain, flatulence, weight loss, malnutrition, and secondary complications such as poor growth and development.

APT-1008 is a pancreatic enzyme product containing pancreas powder intended as pancreatic enzyme replacement therapy to treat a number of conditions associated with exocrine pancreatic insufficiency such as cystic fibrosis, chronic pancreatitis, pancreatectomy or pancreatic cancer.

The efficacy of pancreatic enzyme products in exocrine pancreatic insufficiency especially due to cystic fibrosis is well established. Enzepi is a new formulation which has demonstrated equivalence versus another well-known marketed PEP.

Side effects do not differ from what usually occurs with other marketed products. Overall the safety profile of ATP-1008 appears favourable and no particular safety issues with this new product have been identified.

Benefit-risk balance

Discussion on the benefit-risk balance

APT-1008 is intended as pancreatic enzyme replacement therapy (to control consequences of in exocrine pancreatic insufficiency such as maldigestion and malabsorption of fats, proteins and carbohydrates and resulting in nutritional deficiencies).

The use of pancreatic enzyme products to treat exocrine pancreatic insufficiency due to cystic fibrosis or chronic pancreatitis has been well established and documented in the literature over a period of more than 20 years.

The Applicant has demonstrated in the pivotal study the non-inferiority / equivalence of APT-1008 with Kreon (another enteric coated pancreatic enzyme products) in adolescents and adults with exocrine pancreatic insufficiency due to cystic fibrosis. Results from other studies are supportive of the effectiveness of APT-1008 in paediatric patients with exocrine pancreatic insufficiency due to cystic fibrosis, aged one to six years. Similar efficacy results were also seen on younger patients aged 1 month to 6 years old.

Data in patients with exocrine pancreatic insufficiency due to chronic pancreatitis are based on a dose response study that only reach significance on a secondary endpoint. Nevertheless, cystic fibrosis can be considered as an appropriate model of exocrine pancreatic insufficiency as such and cystic fibrosis patients are often more severely affected from exocrine pancreatic insufficiency than chronic pancreatitis patients. Furthermore APT-1008 was well tolerated in clinical trials and post marketing. Overall the safety of ATP-1008 appears not to be dissimilar from other marketed PEPs which have a well-established safety profile.

Therefore, acceptable safety and efficacy exocrine pancreatic insufficiency due to other conditions is also be considered demonstrated.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Enzepi indicated in infants, children, adolescents and adults in pancreatic enzyme replacement treatment in exocrine pancreatic insufficiency due to cystic fibrosis or other conditions (e.g. chronic pancreatitis, post pancreatectomy or pancreatic cancer) is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list)) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.