



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

25 June 2015
EMA/CHMP/76739/2015
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Respreeza

International non-proprietary name: human alpha1-proteinase inhibitor

Procedure No. EMEA/H/C/002739/0000

Note

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



Administrative information

Name of the medicinal product:	Respreeza
Applicant:	CSL Behring GmbH Emil-von-Behring-Strasse 76 35041 Marburg GERMANY
Active substance:	Human Alpha1-Proteinase Inhibitor
International Nonproprietary Name/Common Name:	Human Alpha1-Proteinase Inhibitor
Pharmaco-therapeutic group (ATC Code):	Alfa1 antitrypsin (B02AB02)
Therapeutic indication:	Respreeza is indicated for maintenance treatment, to slow the progression of emphysema in adults with documented severe alpha ₁ -proteinase inhibitor deficiency (e.g. genotypes PiZZ, PiZ(null), Pi(null,null), PiSZ). Patients are to be under optimal pharmacologic and non-pharmacologic treatment and show evidence of progressive lung disease (e.g. lower forced expiratory volume per second (FEV ₁) predicted, impaired walking capacity or increased number of exacerbations) as evaluated by a healthcare professional experienced in the treatment of alpha ₁ -proteinase inhibitor deficiency.
Pharmaceutical form(s):	Powder and solvent for solution for infusion
Strength:	1000 mg
Route of administration:	Intravenous use
Packaging:	vial (glass)

Package size:	The pack contains 1 powder vial + 1 solvent vial + 1 transfer device
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List of abbreviations

AAT	Alpha ₁ -antitrypsin
AATD	Alpha1-Antitrypsin deficiency
ADME	Absorption, distribution, metabolism, excretion
A1PI	Human alpha1-proteinase inhibitor
A1-PI	Alpha1-proteinase inhibitor (also known as alpha1-antitrypsin)
Adjusted P15	Lung volume-adjusted 15th percentile of the lung density
ANCOVA	Analysis of covariance
ANEC	Anti-neutrophil elastase capacity
AUC	Area under the concentration-time curve
BAL	Bronchoalveolar lavage
BET	Bacterial endotoxin test
BMI	Body mass index
b.w.	Body weight
CE1226	Substance number for CSL Behring's A ₁ -PI (Human)
CI	Confidence interval
C _{max}	Maximum concentration
COPD	Chronic obstructive pulmonary disease
CSR	Clinical study report
CT	Computed tomography
DL _{CO}	Diffusion capacity of the lung for carbon monoxide
DSMB	Data safety monitoring board
DTT	Dithiothreitol
EAIR	Exposure adjusted incidence rate
ELF	Epithelial lining fluid
FEV ₁	Forced expiratory volume in 1 second
FRC	Functional residual capacity
GalN	D-galactosamine
GLP	Good laboratory practice
HPLC	High performance liquid chromatography
IAIR	Infusion adjusted incidence rate
IMP	Investigational medicinal product
ISS	Integrated summary of safety
ISWT	Incremental shuttle walking test
ITT	Intention-to-treat
i.a.	Intraarterial
i.d.	Intradermal
Table 1. i.v.	Intravenous(ly)
IgG	Immunoglobulin G
LoQ	List of Questions
LoI	List of outstanding issues
kDa	KiloDalton
MAA	Marketing authorisation application
MedDRA	Medical Dictionary for Regulatory Activities

N/A	Not applicable
NE	Neutrophil elastase
NHLBI	National Heart, Lung, and Blood Institute of the US National Institutes of Health
nM	NanoMolar = nanomoles per liter
NOAEL	No observed adverse effect level
Table 2. n.s.	Not significant
OMCL	Official medicines control laboratory
Ph. Eur.	European Pharmacopoeia
PK	Pharmacokinetic
P15	15th percentile of the frequency histogram of the lung voxels
PMC	Post-marketing commitment
PT	Preferred term
p.v.	Perivenous
QoL	Quality of life
R&D	Research and development
s.c.	Subcutaneous
Table 3. SEC	Size exclusion chromatography
SDS	Sodium Dodecyl Sulfate
SDS PAGE	SDS – polyacrylamide gel electrophoresis
SGRQ	St. George’s Respiratory Questionnaire
SOC	System Organ Class
TCRAE	Temporally or causally related TEAE
TEAE	Treatment-emergent adverse event
TLC	Total lung capacity
UF/DF	Ultrafiltration/Diafiltration
USP	United States Pharmacopoeia
WFI	Water for injection
vs.	Versus
µM	MicroMolar = micromoles per liter

1. Background information on the procedure

1.1. Submission of the dossier

The applicant CSL Behring GmbH submitted on 2 December 2013 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Respreeza, 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 19 July 2012. The eligibility to the centralised procedure under Article 3(2)(b) of Regulation (EC) No 726/2004 was based on demonstration of interest of patients at Community level.

The applicant applied for the following indication: maintenance treatment to slow the underlying destruction of lung tissue leading to emphysema in adults with alpha₁-proteinase inhibitor deficiency (also called alpha₁-antitrypsin deficiency) with clinically evident lung disease.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application. The applicant indicated that Human Alpha1-Proteinase Inhibitor was considered to be a known active substance.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and bibliographic literature supporting certain test or studies.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/260/2012 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 did not seek scientific advice at the CHMP.

Licensing status

Respreeza has been given a Marketing Authorisation in the USA on 8th July 2003, in New Zealand on 24 March 2011, in Puerto Rico on 27 June 2011, in Brazil on 25 June 2012. A new application was filed in Switzerland.

1.2. Manufacturers

Manufacturer of the active substance

CSL Behring LLC
Route 50 North 1201 N. Kinzie
Bradley, IL 60915
USA

Manufacturer responsible for batch release

CSL Behring GmbH
Emil-von-Behring-Strasse 76
D-35041 Marburg
Germany

1.3. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP:

Rapporteur: Kristina Dunder

Co-Rapporteur: Jan Mueller-Berghaus

- The application was received by the EMA on 2 December 2013.
- The procedure started on 26 December 2013.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 17 March 2014 . The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 13 March 2014.
- During the meeting on 10 April 2014 the Pharmacovigilance Risk Assessment Committee (PRAC) adopted the PRAC Advice on the submitted Risk Management Plan
- During the meeting on 25 April 2014, 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 April 2014.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 17 September 2014.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 24 October 2014.
- During the meeting on 6 November 2014 the Pharmacovigilance Risk Assessment Committee (PRAC) adopted the PRAC Advice on the submitted Risk Management Plan.
- During the CHMP meeting on 20 November 2014, the CHMP agreed on a list of outstanding issues to be addressed in writing and/or in an oral explanation by the applicant.
- During a meeting of a SAG on 14 January 2015, experts were convened to address questions raised by the CHMP.
- The applicant submitted the responses to the CHMP list of outstanding issues on 23 February 2015.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the list of outstanding issues to all CHMP members on 03 March 2015.

- During the meeting on 12 March 2015 the Pharmacovigilance Risk Assessment Committee (PRAC) adopted the PRAC Advice on the submitted Risk Management Plan.
- During the CHMP meeting on 26 March 2015, the CHMP agreed on a second list of outstanding issues to be addressed in writing and/or in an oral explanation by the applicant.
- The applicant submitted the responses to the CHMP's second list of outstanding issues on 31 March 2015.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the second list of outstanding issues to all CHMP members on 10 April 2015.
- During the CHMP meeting on 23 April 2015, the CHMP agreed on a third list of outstanding issues to be addressed in writing and in an oral explanation by the applicant.
- The applicant submitted the responses to the CHMP's third list of outstanding issues on 20 May 2015.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the third list of outstanding issues to all CHMP members on 4 June 2015.
- During the CHMP meeting on 24 June 2015, outstanding issues were addressed by the applicant during an oral explanation before the CHMP.
- During the meeting on 22 to 25 June 2015, 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 Respreeza.

2. Scientific discussion

2.1. Introduction

Problem statement

Alpha1-proteinase inhibitor (A1-PI) deficiency, also known as alpha1-antitrypsin deficiency, is inherited as an autosomal recessive disorder caused by mutations in the SERPINA1 gene encoding A1-PI with more than 150 different genetic variants recognized. The most common deficiency alleles in North Europe are PI Z and PI S, and the majority of individuals with severe A1-PI deficiency are PI type ZZ.

The prevalence in Western Europe and in the USA is estimated at approximately 1 in 2,500-5, 000 (0.04-0.02%) in newborns, and is highly dependent on the Scandinavian descent within the population.

The diagnosis can be established by detection of low serum levels of A1-PI and isoelectric focusing (Fregonese, Stolk 2008). This serious and life-threatening, chronic pulmonary disease often becomes clinically apparent by the third to fourth decade of life, and usually progresses to severe respiratory insufficiency and premature death.

The clinical manifestations may widely vary between patients, and are pulmonary emphysema, liver cirrhosis and, rarely, as the skin disease panniculitis, and is characterized by low serum levels of A1-PI, the main protease inhibitor (PI) in human serum.

Type ZZ and SZ A1-PI deficiency are risk factors for the development of respiratory symptoms (dyspnoea, coughing), early onset emphysema, and airflow obstruction early in adult life. Environmental factors such as

cigarette smoking, and dust exposure are additional risk factors and have been linked to an accelerated progression of this condition.

The pathogenesis of emphysema is understood to evolve as described in the “protease-antiprotease imbalance” model (Gadek 1990). A1-PI is considered to be the primary antiprotease in the lower respiratory tract, where it inhibits neutrophil elastase (NE) produced by activated neutrophils (Gadek 1981). Normal healthy individuals produce sufficient A1-PI to control NE activity and are thus able to prevent inappropriate proteolysis of lung tissue by NE and the subsequent development of emphysema. Conditions that increase neutrophil accumulation and activation in the lung, such as respiratory infection and smoking, in turn increase pulmonary levels of NE. Individuals who are severely deficient in endogenous A1-PI are unable to maintain an appropriate antiprotease defence and are thereby subject to more rapid proteolysis of the alveolar walls, leading to chronic lung disease (emphysema). Although more than 150 allelic variants of the Pi genotype have been identified, more than 95% of all patients with severe emphysema caused by A1-PI deficiency have the PiZZ genotype (DeMeo 2004).

Table 1 - Risk of emphysema and serum A1-PI concentrations associated with common Pi genotypes

Genotype	Risk of emphysema	Serum A1-PI concentrations (µM)
ZZ	Very high	2 to 7
SZ	Intermediate	9 to 23
SS	Unknown	15 to 33
MZ	Low, but > normal	17 to 33
MM (normal)	Normal (low)	20 to 53

A1-PI = Alpha1-proteinase inhibitor.

Source: Adapted from ATS/ERS Statement 2003, Sandford 1999, Crystal 1990.

Source: Clinical Overview, Table 1

The most direct therapeutic approach for A1-PI deficiency in patients with emphysema is to replace the missing protease inhibitor, thus re-establishing anti-NE protection of the lower respiratory tract.

Individuals with low endogenous serum A1-PI concentrations, below 11 µM, generally manifest a significantly increased risk for development of emphysema above the general population background risk (Eriksson 1964, Eriksson 1965, Gadek 1983, WHO 1996).

A1-PI is a glycoprotein produced by hepatocytes and mononuclear phagocytes. A1-PI acts as the primary inhibitor of neutrophil elastase (NE) in the lower respiratory tract. Neutrophil elastase is a protease capable of destroying alveolar walls in the lower respiratory tract (Wewers 1987). It is produced and secreted by activated neutrophils, and is primarily found in the alveolar and bronchial lumina. If NE is present in the lung and not regulated by its naturally occurring inhibitor A1-PI, as is the case in A1 PI deficiency, NE can cause excessive inflammation and proteolysis of alveolar tissue, leading to progressive emphysema.

Replacement of the missing protease inhibitor is thought to be the most direct approach to therapy by re-establishing the protease/anti-protease balance in the lower respiratory tract. This is thought to prevent unopposed destruction of lung tissue and thus slow down emphysema progression.

Purified human alpha1-proteinase inhibitor (A1-PI) concentrate has been used for almost 2 decades for A1-PI augmentation therapy in individuals who have a reduced level or absence of functional A1-PI and a clinically evident lung disease. A target of achieving A1-PI serum concentrations above the 11 µM threshold has been the concept of biochemical efficacy in clinical studies of A1-PI augmentation therapies and thought to provide therapeutically relevant anti-NE protection in the lung (Crystal 1990).

Knowledge of comparative outcomes in different disease subtypes remains limited due to the rarity of diagnosis and variability in other risk factors such as smoking.

No clinical guideline or core SmPC exist for alpha 1-proteinase inhibitor products. No prospective studies have addressed optimal treatment levels of A1-PI in plasma for different genetic variants. There are also no prospective studies that have determined whether additional incremental clinical benefits may be achieved at a population level with treatment to A1-PI concentrations above 11 µM (50 mg/dL) when measured by immunonephelometry (or 80 mg/dl when measured by radial immunodiffusion), although the epidemiologic evidence suggests this possibility based on the decreasing risk of emphysema and the increasing A1-PI concentrations in patients with ZZ, SZ, MZ, and MM genotypes. With the lack of such evidence, the 11 µM threshold is still often seen as the concentration to be achieved with augmentation therapy.

About the product

Human alpha1-proteinase inhibitor CSL Behring GmbH (powder and solvent for solution for infusion, 1000 mg), contains human alpha1-proteinase inhibitor, A1-PI (H), (company code "CE1226") as the active drug substance. A1-PI (H) has been developed for maintenance treatment to slow the underlying destruction of lung tissue leading to emphysema in adults with alpha1-proteinase inhibitor (A1-PI) deficiency with clinically evident lung disease. The recommended dose is 60 mg/kg body weight administered intravenously once a week.

Type of application and other comments on the submitted dossier

Legal basis: This application for Human alpha1-proteinase inhibitor CSL Behting GmbH 50mg/ ml, powder and solvent for solution for infusion, is an application for a known active substance and is submitted in accordance with article 8(3) of Directive 2001/83/EC.

2.2. Quality aspects

2.2.1. Introduction

Respreeza contains as active substance human Alpha1-proteinase Inhibitor (A1-PI), a 52 kDa globular, single polypeptide glycoprotein with significant structural similarity to other members of the serine proteinase inhibitor family.

The active substance is isolated from pooled human plasma by means of a modified Cohn fractionation process and subsequently purified. The active substance manufacturing process includes two dedicated viral reduction steps. The active substance is defined in the dossier as sterile bulk which is further manufactured to the drug product by filling and lyophilisation.

The finished medicinal product is supplied as a powder and solvent for solution for infusion. It is presented in a single strength of 1000 mg of active A1-PI per vial of powder. The solvent is Water for Injection (WFI). The reconstituted product is a clear, colourless to slightly yellow solution with a concentration of 50 mg/ml. Also a single-use transfer device is supplied in the presentation.

2.2.2. Active Substance

General information

The general information about the nomenclature, structure and biochemical characteristics of the active substance is considered adequate.

Briefly, human alpha1-proteinase inhibitor (A1PI) is a 394 amino acid protein which circulates in plasma and belongs to the Serpin protein family. Sufficient information on secondary and tertiary structure has been provided. The average molecular weight of A1PI cited in the literature varies considerably from 49 to 59 kDa, depending on the methodology used. Most values center around 50 – 52 kDa.

In addition to three N- linked glycosylations at positions 46, 83, and 247, the A1PI molecule may contain other potential modifications. Amino acid side chain modifications may include methionine oxidation and asparagines deamidation. Oxidation of two methionines in particular, residues 351 and 358 located in the reactive center loop, are known to have functional implications for the molecule. Proteolytic cleavage of the five N-terminal residues and the C-terminal lysine have also been reported.

Manufacture, characterisation and process controls

Manufacturer

See above section 1.2.

Description of manufacturing process and in-process controls

The active substance manufacturing process has been sufficiently described, flow charts have been provided and the batch scale has been defined.

In summary, the active substance is manufactured from pooled human plasma through to the sterile bulk in a continuous process. There are two main manufacturing stages: (1) modified Cohn fractionation to obtain Fraction IV₁ Precipitate from the plasma pool and (2) subsequent purification of the active substance from Fraction IV₁ Precipitate. Two dedicated virus inactivation/elimination steps are included in the later manufacturing stage.

Plasma pooling and fractionation

Fraction IV₁ Precipitate, from which the active substance is purified, is isolated from pooled human plasma using a modified Cohn ethanol fractionation process. In the first step, separation of the cryoprecipitate from the plasma pool is accomplished by temperature control and centrifugation. Subsequently, two alternative optional steps for the removal of the Prothrombin Complex by physical adsorption to a resin are possible. In the following steps, the fractionation process employs the technique of precipitation of specific plasma proteins at defined pH, temperature and alcohol concentrations followed by filtration for separation of the precipitates to obtain Fraction IV₁ Precipitate.

Purification process, starting from Fraction IV₁

The purification process starts with the extraction of A1-PI from fraction IV₁ precipitate, DTT and aerosil treatment followed by ion exchange chromatography (IEC) and hydrophobic interaction chromatography (HIC). After ultra/diafiltration the solution is stabilised followed by pasteurisation. The pasteurised solution is ultra/diafiltered, and then nanofiltered for virus removal. The nanofiltration eluate is adjusted/diluted and sterile

filtered into a sterile bulk vessel yielding the active substance. In response to the Day 120 LoQ additional details about the manufacturing process were provided and the description updated accordingly.

Control of materials

For the human plasma used as starting material for the manufacture of Human Alpha1-Proteinase Inhibitor reference was given to the centrally certified CSL Behring Plasma Master File (EMA/H/PMF/000001/04). Relevant information on and evaluation of the collection, testing, storage and transportation of individual plasma donations and plasma pool testing are included in the PMF which is yearly updated.

Compendial and non-compendial ingredients used in the production process of the active substance were listed. The ingredients sodium chloride, mannitol, and sodium phosphate (monobasic monohydrate) were identified as excipients in the final formulation. Also auxiliary materials and filter materials were listed. Specifications for non-compendial and auxiliary materials were provided including also specification details for the HIC material, IEC material, nanofilters and sterile filters.

Control of critical steps and intermediates

Although the general approach for defining critical steps, critical quality attributes and critical process parameters was found reasonable, further justification of process parameters and quality attributes chosen was asked for at Day 120. In the response the description of the manufacturing process was updated to include all key process parameters (KPP) and general process parameters (GPP). Also further justification about limits/ranges for the quality attributes and process parameters proposed was provided and limits of two parameters were narrowed. The response was considered acceptable.

Process validation

Comprehensive validation data covering the fractionation and the different steps in the purification part of the manufacturing process were provided, demonstrating that the process is capable of producing consistently a product of the intended quality within the defined process parameters and quality attributes.

The validation of the fractionation down to Fraction IV₁ was one part of the validation of the revised process for another product produced by the manufacturer. These validation data were submitted as part of the MAA for Respreeza. All acceptance criteria were met. For the pooling and cryoprecipitation steps the results complied with established historical/procedural conditions. The two alternative process steps, involving an optional removal of the Prothrombin Complex, were both covered by the process validation and the use of the optional steps in the very early part of the plasma fractionation process is found acceptable.

In addition, process validation of the packaging of chromatography columns (IEC; HIC) has been performed. Hold time for the intermediates and filtrates were established based on appropriate validation data. Critical and key process parameters were adequately defined in the validation and were satisfactorily covered by the validation

A worst-case approach was used for the validation of pasteurization and nanofiltration.

In conclusion, the commercial active substance manufacturing process has been adequately validated.

Manufacturing process development

During development and since licensing of the product in the USA several changes were made to the manufacturing process.

The Applicant showed in the development part that the changes introduced to the manufacturing process of A1-PI had no detrimental effects on the quality attributes of A1-PI drug product and that over time comparable A1-PI drug product was manufactured.

The major process changes for the material used in the clinical and nonclinical studies have been sufficiently described. Material manufactured at the commercial plant and with all changes introduced except one, has been included in the latest clinical extension study which was still on-going at the time of opinion. An overview on batches by lot numbers used in clinical and non-clinical studies and the respective purification process applied has been provided.

In conclusion, the changes introduced during the development of the current proposed process were adequately addressed and in general satisfactorily justified. Comprehensive comparability studies including relevant test attributes have been performed and the results demonstrate acceptable comparability to the process previously used. Material manufactured throughout the different process changes has been included in clinical trials.

Characterisation

The structure of A1-PI was characterised in detail with respect to isoforms, post translational modifications, aggregates and C-terminal and N-terminal truncations as well as secondary structure/tertiary structure. Process related impurities were identified which were present in low mM concentrations or below the detection limit of the method of analysis. According to the provided reference these concentrations were far below any toxic effect. It is considered acceptable not to test every batch for these impurities because they are removed during manufacture, e.g. diafiltration steps.

Specification

The sterile bulk has been defined as the active substance. Although a sterile bulk is normally not defined as the active substance, the structure of this dossier was accepted. Considering that no other steps than filling of the sterile bulk into vials and lyophilisation is used for the further manufacture to obtain the drug product, this control strategy is found acceptable.

The active substance specification includes one additional control parameter. For the control of other quality attributes, reference is made to the drug product specification. In response to the Day 120 LoQ the specification limit for the additional control parameter was slightly tightened and an action limit was established based on a statistical evaluation of historical data. In addition, the specification was updated accordingly.

Analytical procedures

A brief summary of the analytical procedures used to test the sterile bulk were provided. Two alternative test methods for bacterial endotoxins (Limulus Amebocyte Lysate (LAL) Gel-clot assay and kinetic turbidimetric method) are used and have been acceptably validated. These analytical procedures are performed according to European Pharmacopoeia (Ph. Eur.) and United States Pharmacopoeia (USP) methodology.

Batch analysis

Results from three batches were provided demonstrating results meeting the active substance specification.

Reference standard

For the potency assay an A1-PI in-house standard preparation is used. The same material is used for drug product control testing.

In the beginning, CSL Behring used an in-house preparation which was calibrated based on its inhibition of a titrated trypsin preparation. When the 1st International Standard for A1-PI (plasma derived, NIBSC code: 05/162) became available CSL Behring calibrated the in-house lot L426403 against this standard for use in potency testing of in-process samples and finished product. To keep equivalence between the two methodologies and consistency in A1PI product a correction factor was used. Further information about the assignment of the correction factor was requested in the Day 120 LoQ. It was responded that a mean difference of 8.9% had been observed upon testing of twenty finished product lots using both the old (Y400106) and the new (L426403) in-house standards. Subsequently, a correction factor of 8.9% was established to assign potency of the new standard and to maintain the same patient dose as what was administered during the pivotal clinical trial.

Also in future, any new Alpha1-Proteinase Inhibitor Potency Standard, used for final product potency determination will be calibrated against the current WHO Standard with the 8.9% correction factor applied. This approach, using a correction factor when assigning the potency of a new reference standard calibrated against the International WHO standard, can be agreed to. The policy for the establishment of a new reference standard and the calibration in case of a change of the international standard, as well as the criteria for acceptance of obtained values, has been acceptably described.

Stability

The manufacturing process for A1PI is a continuous process thus stability studies for the active substance were not part of the CSL Behring stability program. The hold time for the active substance sterile bulk has been acceptably justified. At least 3 batches underwent the respective hold (or cumulative holds) and the hold time was set based on the shortest hold times applied. No formal hold time studies were performed which is considered acceptable.

2.2.3. Finished Medicinal Product

Drug product (powder)

Description of the product and pharmaceutical development

The drug product is a sterile, white, lyophilized preparation of highly purified A1-PI to be reconstituted and administered by the intravenous route. The drug product is supplied as powder and solvent for solution for infusion. The presentation consists of one vial with the lyophilized drug product (1000 mg) and one vial with the solvent (Water for injections, 20 ml). The concentration of the reconstituted product is 50 mg/ml. Also a CE-marked single-use transfer device is supplied in the presentation.

Table 2 on Composition of A1-PI Drug Product

Ingredient	Reference	Amount per vial	Concentration	Function
Alpha1-Proteinase Inhibitor (Human)	Ph. Eur.	1000 mg		Active substance
Sodium Phosphate Monobasic Monohydrate	Ph. Eur.			Buffer Provides isotonicity
Sodium Chloride	Ph. Eur.			Provides isotonicity

Ingredient	Reference	Amount per vial	Concentration	Function
Mannitol	Ph. Eur.			Bulking agent
HCl and or NaOH	Ph. Eur.	Sufficient for pH adjustment		pH adjustment

Pharmaceutical Development

The data presented on pharmaceutical development is considered satisfactory. The development strategy of the final formulation was based on the Applicant's own experience with products already manufactured by the Company as well as information obtained from a competitor's A1PI(H) product.

The same formulation was used in A1-PI manufacturing for all preclinical toxicity studies and all clinical trials. The aseptic filling operation did not undergo any major process changes from production of the early clinical lots of A1-PI. The lyophilisation has been qualified for the current process in two lyophilisers. The lyophilisation cycle parameters, as described in the dossier, have remained the same throughout all qualification activities.

Manufacture of the product and process controls

Manufacturer

See above section 1.2.

Description of manufacturing process, in-process controls and validation

The manufacturing process covers aseptic filling of the drug product, lyophilisation, stoppering and sealing of the vial. After vial inspection unlabelled vials are shipped to CSL Behring Marburg for secondary packaging and labelling. Based on the control test at CSL Behring, Marburg and the OMCL batch release the batch is released by the Qualified Person to the EU/EEA market.

On request, the description of the drug product manufacturing process has been revised and is now considered acceptable. The batch formula was provided. Process parameters and quality attributes and the corresponding process controls have been clearly described and are deemed suitable for controlling and monitoring the manufacturing process.

Acceptance criteria and data for media fills were given and comply with the requirements in the EU Guidelines to Good Manufacturing Practice Medicinal Products for Human and Veterinary Use, Vol 1, Annex 1.

Criticality of process parameters/quality attributes was assessed and it was concluded that there were no critical process parameters or critical quality attributes for the formulation and lyophilisation steps.

Process validation

The drug product manufacturing process is considered properly validated. Process simulations of aseptic filling were performed at a minimum of every three months on each active filling line and every six months on each active lyophiliser. Process simulations were performed utilizing the same equipment and personnel qualified for routine production. The lyophilisation process was evaluated in depth showing batch homogeneity within a lyophiliser from tray to tray and within a tray.

Media fills were routinely performed for the aseptic filling step and the lyophilisation. The provided data demonstrates acceptable maintenance of sterility during the aseptic filling procedure and lyophilisation.

The transport validation provided for the drug product from the site in Kankakee to the Marburg site verified that the temperature is maintained at the temperature range of 2 to 25°C.

Control of excipients

The excipients used in the formulation comply with Ph Eur requirements. They are common excipients used in marketed parenteral pharmaceutical products. No excipients of human or animal origin are used in the manufacture of the drug product. The specification for each of the excipient was provided.

Product specification

The drug product specifications were considered, in principle, in compliance with the Ph. Eur. monograph for Human alpha-1-proteinase inhibitor. For chosen alternative test methods acceptable correlations to the methods referred to in the monograph were demonstrated.

During the evaluation procedure further justification of the specifications limits has been provided. Release and end-of-shelf life specifications for molecular size distribution and protein profile/purity have been introduced based on data from clinical trial batches and stability studies. Lower shelf life limits proposed for molecular size distribution and protein profile/purity were found acceptable considering the demonstrated good consistency between batches both at release and between batches included in the different stability studies. In conclusion, the revised specification limits were found acceptably justified.

Analytical methods

Acceptable descriptions of all analytical methods were provided in the dossier, also for the methods with reference to Ph. Eur. Although the compendial test methods were very briefly described this was found acceptable for these methods covered by the Ph. Eur.

Validation data have been submitted for all methods, also for compendial test methods. The results complied with the acceptance criteria and the methods were found suitable for the intended use. At D120 additional data was requested for a few test methods to demonstrate that they can be considered comparable to the PhEur methods and the response was considered satisfactorily.

The Applicant applied for approval of an alternative method to the Ph. Eur. pyrogen test for batch release. After submission of additional information the use of the alternative method was considered approvable.

For the A1-PI potency assay an in-house method is used which is similar to the method given in the Ph. Eur. monograph. The in-house potency assay was found acceptably validated and the results demonstrated an acceptable comparability to the method given in the monograph. As requested the applicant resolved questions on the statistical evaluation of results obtained with the in-house potency assay and subsequently, the assay was considered approvable for bath release.

Batch analysis

The batch analysis data presented for the 3 commercial final container batches (pasteurized in glass bottles) complied well with the limits in the proposed drug product specification and demonstrated a satisfactory batch to batch consistency.

Reference materials

See above.

Container Closure System

Information provided on the container closure system is found sufficient. Alpha1-Proteinase Inhibitor (Human) is aseptically filled into 50 ml Type I glass vials, stoppered with a 20 mm bromobutyl rubber closure and sealed with a 20 mm aluminum body flipcap seal with a polypropylene flip-off cap. The vial and closure were in compliance with PhEur. monographs. Relevant specifications were provided, which also included drawings.

Stability of the product

The submitted real time/real temperature stability data support the shelf life claim in the SmPC.

Real time /real temperature stability data as well as data from accelerated studies were provided to support the shelf life claim. Therefore, the claimed shelf-life is found acceptably justified. Furthermore, stability after reconstitution was claimed. In the response to the day 120 LoQ, results acceptably justifying the proposed in-use time and temperature have been provided.

Adventitious agents

Non-Viral Adventitious Agents

Prions

No material of animal origin is used in the manufacture of human alpha1-proteinase inhibitor and therefore the TSE risk is only related to the use of human plasma as starting material.

In the summary report and in the adventitious agent safety assessment report, the Applicant has thoroughly described all measures taken to minimize the risk of transmitting vCJD with this medicinal product.

The risk to transmit prions, by the application of human alpha1-proteinase inhibitor is significantly reduced due to careful selection of donors (i.e. exclusive use of plasma sourced according to the centrally certified CSL Behring Plasma Master File (PMF; EMA/H/PMF/000001/04). In addition, only a very low prion load in human plasma – if any – can be assumed based on studies with laboratory animals. Furthermore, the removal of prions (if present in the plasma pool) by selected steps of the manufacturing process of plasma derivatives was shown in investigational studies. Results from spiking experiments investigating the capacity of the manufacturing process to reduce prions have been provided. This investigation has been performed with another medical product, A1-PI (Human) Inhalation Solution. In the response to day 120 LOQ the applicant explained that the manufacturing steps investigated for prion removal were identical for A1-PI (Respreeza) and A1-PI (Human) Inhalation Solution. The provided studies are therefore applicable also for A1-PI (Respreeza).

Furthermore, data has also been provided that demonstrates that the routine cleaning procedures implemented in the manufacturing process to sanitise equipment and material utilising alkaline solutions effectively remove / inactivate prions and therefore a potential cross-contamination by prions to subsequently produced batches can be excluded.

Taken into consideration the low prion load in plasma, the epidemiological situation of vCJD in the donor population, the amount of plasma used to produce one dose of final product, and the prion reduction capacity of the overall manufacturing process, the risk that Human alpha1-proteinase inhibitor will transmit TSEs seems remote.

Viral Adventitious Agents

Measures taken to reduce the risk of viral contamination of Respreeza include three principal complimentary approaches ((1) donor selection and testing of single donations and minipools for viral markers; (2) testing of plasma pools for viral markers; (3) inclusion of virus inactivation and/or removal steps in the active substance manufacturing process).

A1-PI (H) is produced from human plasma collected in the USA. The overall viral safety strategy includes selection of qualified donors, a deferral policy and a look-back procedure. Single donations are screened by an adequate testing program for viral markers (anti-HIV-1/2, HBsAg, anti-HCV) and by NAT for HAV, HBV, HCV, HIV-1 and high titers of B19V at a minipool level. The plasma pool is also tested for anti-HIV-1/2 and HBsAg and by NAT for HAV, HBV, HCV, HIV-1 and high titers of B19V (limit: less than 10^4 IU B19V DNA per ml). The donor selection and donation/plasma testing strategy for viral markers is considered adequate.

Adequate virus validation studies have been performed to evaluate selected manufacturing steps, pasteurisation and virus filtration, for their capacity to inactivate or remove various viruses. Experiments were performed on a validated scaled down version of the manufacturing process both at standard conditions and worst case conditions to demonstrate robustness of virus reduction. Detailed validation reports (one for each virus tested) have been provided.

For the calculation of the overall reduction factor, the highest reduction factor of the individual step was used by the Applicant when in all experiments no residual virus infectivity could be detected (complete virus inactivation). If at least one experiment for an individual step resulted in residual virus infectivity, the mean virus reduction factor of all these experiments was calculated. It is, however, considered appropriate to take the mean values from the replicate runs.

An estimate of virus particles in the finished product was submitted by the Applicant in the initial MAA as outlined in chapter 9 of Guideline on plasma-derived medicinal products (EMA/CHMP/BWP/706271/2010). In this risk assessment, the Applicant assumed that only one of 1000 B19V genomes would represent an infectious virus particle. This assumption was made based on cell culture data. However, guideline EMEA/CHMP/BWP/706271/2010 (Chapter 9.2) outlines that in-vitro data were not acceptable and that a conservative approach using virus genomes should be taken. Therefore a revised risk assessment was performed by the assessor.

Based on the revised risk assessment it was concluded at D120 that the applicant should validate additional manufacturing steps for reduction of parvovirus B19 in order to maintain the proposed safety claim in the SmPC. Otherwise a precautionary warning statement for parvovirus B19 should be introduced in the SmPC section 4.4. With the response to the D120 LoQ, the Applicant provided additional virus validation data on parvovirus B19 removal by fractionation steps in the upstream manufacturing process demonstrating additional reduction of parvovirus B19. The additional data contributes to demonstrate sufficient safety margin for B19 to support the Applicant's statement in section 4.4 of the SmPC that the measures taken are considered effective for parvovirus B19.

Furthermore, data has also been provided demonstrating that any virus potentially retained in the production system would be adequately removed and/or inactivated prior to re-use of the system, e.g., by sanitisation of equipment and material.

Taken together, safety with regard to enveloped and non-enveloped viruses has been demonstrated in compliance with the relevant CHMP guidelines.

Drug product (solvent)

In the presentation of the finished medicinal product one vial containing 20 ml Water for Injections (WFI) is supplied to be used for the reconstitution of the powder.

Pharmaceutical Development

The pharmaceutical development of the WFI solvent has been sufficiently described and addressed.

Manufacture

The manufacturer of the WFI is listed in section 1.2 of this report.

Water for Injections in bulk is produced by a distillation process. Starting material for the final product Water for Injections is Potable Water which is processed to Purified Water by reverse osmosis. After distillation of Purified Water, the Water for Injections in bulk is filled automatically into depyrogenised containers. Immediately after filling the containers are automatically stoppered, sealed and sterilised prior to release testing.

Two different steam sterilisers can be used for the sterilisation process of the filled final WFI containers. The sterilisation is performed according to an automated sterilisation program, which is used for both steam sterilisers. The qualification documents confirmed the effective sterilisation process of the filled WFI final containers.

The information provided in the dossier for manufacturing of Water for injections is considered sufficient to conclude that the WFI is manufactured under GMP compliant conditions in a fully validated process.

Control of drug product

The product specification and the choice of routine tests were mostly based on the Ph. Eur. monograph "Water for Injections" or equivalent to the monograph. However, some additional tests (Carbon dioxide, TOC and pH) were performed according to USP in long term stability studies. This is acceptable.

All relevant information addressing the control of WFI solvent has been provided.

Container closure

The container closure components consist of a 25 ml glass vial (Ph. Eur. type I) and a gray infusion stoppers made of chlorobutyl rubber. The stopper is free of latex. They are sealed with crimp caps consisting of a colored plastic disc made of polypropylene and an aluminum cap.

The container closure system for WFI solvent is sufficiently described.

Stability

Formal stability studies have been carried out in accordance with ICH guidelines. The performed analytical methods and the respective specifications were according to Ph. Eur.

Stability data in support of the shelf-life claim and storage conditions for Water for Injections were submitted covering long-term storage and accelerated storage. All stability lots reported meet the specification of all parameters under all conditions applied. The presented stability data from all stability studies are considered sufficient to justify the claimed shelf life.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

The applicant submitted a full dossier for the product Respreeza (human Alpha1-proteinase Inhibitor (A1-PI)). The dossier is in general of good quality and no major issues were identified in the submitted documentation on quality during the evaluation procedure.

In summary, the manufacture of the A1-PI active substance and drug product lead in a validated manufacturing process to A1-PI drug product of consistent batch-to-batch quality complying with the monograph "human α -1-proteinase inhibitor (2387)". The quality of the active substance and drug product is controlled by adequate test methods and specifications. Safety with regard to transmissible agents, such as human TSE and enveloped and non-enveloped viruses has been demonstrated in compliance with the relevant CHMP guidelines.

From a quality point of view the product is recommended for approval.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.2.6. Recommendation for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

All toxicology and local tolerance studies conducted with Human alpha1-proteinase inhibitor CSL Behring GmbH (studies No CPG 006/982668/AC, CPG 005/982664/AC, DS 94-053, DS 94-059, CHV 656-193, DS 94-114, CPG 009/982936, CPG 007/982329/SE, CPG 008/982330/SE), as well as the safety pharmacology study (CPG010/983098), were performed in accordance with good laboratory practice (GLP). The neoantigenicity study (SR 98-014), was not performed under GLP but rather under "GLP-like" conditions. Two pharmacology *in vitro* studies (BD#158-95-07, SR-71r) were not conducted according to GLP. The CHMP is of the view that the absence of GLP compliance does not affect the conclusions that can be drawn from these two studies.

2.3.2. Pharmacology

Primary pharmacodynamic studies

The pharmacodynamic effect of A1-PI(H) was demonstrated *in vitro* by inhibition of its target enzyme, elastase. No *in vivo* pharmacology studies have been performed.

The Applicant has performed a literature review, citing studies conducted in mice, rats, rabbits and dogs with human A1-PI. In summary, these studies provide support for the notion that human A1-PI is pharmacologically active in mice, rats and rabbits. With regard to dogs, a few studies have been conducted where human A1-PI has been administered via inhalation. Lung lavage fluid obtained from dogs after inhalation of human A1-PI aerosols demonstrated an increase in inhibitory activity against porcine pancreatic elastase, in proportion to the presence of human A1-PI.

The short-term pharmacodynamic activity of aerosolized Prolastin for treatment of pulmonary *Pseudomonas aeruginosa* infection associated with acquired A1-PI deficiency has been demonstrated in a rat model (Cantin and Woods, 1999). A similar short-term study could have been conducted with A1-PI(H) in the pallid mouse model, not only to show proof of principle but also to obtain valuable information on pharmacokinetic parameters.

The lack of *in vivo* pharmacology studies is considered acceptable by the CHMP since human plasma-derived A1-PI has a well-established physiologic effect in humans.

Secondary pharmacodynamic studies

No secondary pharmacodynamic studies have been performed because no other pharmacodynamic effects are expected. This is regarded as acceptable by the CHMP.

Safety pharmacology programme

A safety pharmacology study has been performed in anaesthetized dogs. The results showed that intravenous administration of A1-PI(H) at 60 or 240 mg/kg bw (corresponding to estimated human equivalent doses of 33.3 mg/kg and 133.3 mg/kg, respectively) had no effect on ECG, arterial blood pressure, heart rate, contractile status of the myocardium, or respiratory parameters in any of the animals. A slight increase in femoral blood flow and concurrent decrease in femoral resistance were observed in the three dogs that received A1-PI(H) at 240 mg/kg bw. There were no consistent changes in blood biochemistry, haematology or blood gas parameters that could be related to treatment with A1-PI(H) at either dose level. The NOAEL in this study was 60 mg/kg, based on the slight effects on femoral blood flow and resistance after administration of 240 mg/kg bw. The NOAEL is approximately 0.6x the intended clinical dose, after conversion of the dose in dogs to human equivalent dose.

In vitro electrophysiology studies to assess the potential for delayed ventricular repolarization (e.g. hERG assay) have not been conducted with A1-PI(H). No justification for the absence of such studies has been given. However, it is considered unlikely that A1-PI(H) would block the potassium channel of hERG, since the relatively small pore size would exclude access to proteins the size of A1-PI(H).

No safety pharmacology study has been conducted to evaluate effects on the central nervous system. In view of the nature of the product this is considered acceptable by the CHMP.

Pharmacodynamic drug interactions

No pharmacodynamic drug interaction studies have been performed. This is regarded as acceptable by the CHMP.

2.3.3. Pharmacokinetics

Pharmacokinetic studies (absorption, distribution, metabolism and excretion) in animals have not been performed with A1-PI(H) due to interference of elimination kinetics with immune reactions directed against the human heterologous protein and as PK data obtained with human proteins in animals are not representative for the situation in man. The lack of PK studies is regarded as acceptable by the CHMP. The pharmacokinetics of A1-PI(H) is known from clinical studies with the competitor product. The half-life of about 5 days has also been confirmed for A1-PI(H). Furthermore, A1-PI(H) is a naturally occurring human plasma protein which will undergo the physiological catabolic processes of endogenous proteins which are well defined.

2.3.4. Toxicology

Single dose toxicity

Single dose toxicity study no. CPG 006/982668/AC: Alpha₁-Proteinase Inhibitor (human) acute intravenous toxicity to the mouse

Three groups of ten mice (5 males/5 females) received a single intravenous injection of API at the ascending dose of levels of 60, 240 and 600 mg/kg body weight. A further group has been similarly treated with API placebo. After 14 days of observation all animals were sacrificed as scheduled at study termination day 15. Clinical signs were confined to transient piloerection in all dose groups and temporarily increased respiration within the high dose group. There were no other treatment related effects observed. The NOAEL is 240 mg/kg body weight, the acute lethal intravenous dose to mice was shown to be greater than 600 mg/kg body weight.

Single dose toxicity study no. CPG 005/982664/AC: Alpha₁-Proteinase Inhibitor (human) acute intravenous toxicity to the rat

4 groups of 10 rats (5 male/5 female) were treated intravenously by a single dose of API placebo, 60, 240 and 600 mgAPI/kg body weight. The results of this study demonstrated that transitory clinical signs (piloerection) were confined to the high dose group. There were no other evidence of systemic response to treatment. The acute lethal intravenous dose to rats was demonstrated to be greater than 600mg/kg body weight.

Repeat dose toxicity

As proteins of human origin are immunogenic to animals, long-term administration of CE1226 to animals would not generate useful data. Repeat dose toxicity testing was therefore restricted to five daily doses in rats and rabbits.

Repeat dose toxicity study no. DS 94-053: 5-day intravenous toxicity study of Alpha₁-Antitrypsin in rats

60 HSD: Sprague Dawley rats (30males/30females) were used to assess the intravenous toxicity of 60 and 240 mg API/kg when administered once daily for 5 consecutive days. 10 animals per sex were used for the control group (API placebo) and the both treatment groups. The dosing volume was 1.37 ml/kg for the 60 mg/kg/day group and 5.50 ml/kg/day for the control and the 240 mg/kg/day group. The results of this study demonstrated that i.v. administration of API at 240 mg/kg/day to male and female rats was associated with decreases in some blood chemistry parameters (e.g. triglycerides, total protein, albumin, albumin/globulin ratio). The changes in blood chemistry parameters were within the historical control range. In addition, increases in the absolute and relative splenic weights (females: 17 and 15% higher; males: 12 and 11% higher) were observed in the high dose group; however, these changes were not associated with pathological modifications. There were no treatment-related clinical signs recorded during the study. No modifications have been found in animals receiving 60 mg/kg/day.

Repeat dose toxicity study no. DS 94-059: 5-day intravenous toxicity study of Alpha₁-Antitrypsin in rabbits

Repeated dose toxicity has been investigated in 24 New Zealand White rabbits (12 males, 12 females) when administered intravenous 60 and 240 mg API/kg body weight compared to placebo once daily for 5 consecutive days. The dosing volume was 1.4 ml/kg/day for the 60 mg/kg/day group and 5.5 ml/kg/day for the control and 240 mg/kg/day group. There was no mortality nor any clinical signs related to treatment with API. There were no treatment related modifications in body weight, food consumption, or haematology and blood chemistry parameters. In both treatment groups increases of the mean lung/bronchus weights of both sexes have been found, which are regarded to be possibly correlated with the increased incidence and grade of microscopic findings in the lungs. Dose-related increases in the incidence and severity of focal inflammatory changes in both

the lung and myocardium have been found in both treatment groups. In addition, mild to moderate increase in absolute and relative group mean spleen weight have been found in the high dose group.

Repeat dose toxicity study no. CHV 656-193: 5-day intravenous toxicity study of Alpha₁-Antitrypsin in rabbits

Due to the findings of the previous study this study was designed to determine the toxicity of API using a different source of rabbits and a test article lot with improved impurity profile. 4 female rabbits were dosed with API at a dose level of 240.1 mg/kg for 5 consecutive days compared to a control group receiving API placebo. Mean absolute and relative spleen weights were significantly increased; in addition, absolute and relative uterus and ovary weights were significantly decreased when compared to the control group. Although not statistically significant, the thymus weights were slightly lower in the treatment group. All other organ data were generally comparable between control and treatment group. No other treatment-related effects have been observed.

Repeat dose toxicity study no. DS 94-114: 5 day intravenous toxicity study of Alpha₁-Antitrypsin in rabbits

24 NZW (SPF) rabbits (12males/12 females) were used to assess the intravenous toxicity of API when administered once daily for five consecutive days. 4 animals per sex were used in each group. Rabbits in the control group received API vehicle, while the treatment groups were assigned to dosage levels of 60 and 240 mg/kg/day. The dosing volume was 2.2 ml/kg for the low dose group, 8.7 ml/kg for the high dose group, and 2.2 or 8.7 ml/kg respectively for the control group. No treatment related clinical signs, effects on body weight, food consumption and gross or microscopic observations have been found. The rabbits of the control group of study no. DS 94-114 accidentally showed extreme high uterus weights in comparison to the control groups of the other studies whereas the uterus weights of the treated animals were in the normal range.

Repeat dose toxicity study no. CPG 009/982936: Alpha₁-Protease Inhibitor (API) Toxicity study by intravenous (bolus) administration to rabbits for 5 days

This study has been conducted to assess the systemic toxicity of API to the rabbit after daily intravenous bolus injection for 5 days. Groups of 5 male and 5 female NZW rabbits were intravenously administered 60 or 240 mg/kg/day, using 1.4 or 5.5 ml/kg respectively. A further group of 10 rabbits (5 per sex) received the vehicle only at same volume of 5.5 ml/kg as the high dose group. The results showed no unscheduled deaths or treatment correlated clinical signs. No treatment-related effects on haematology, biochemistry have been noted. Females and males receiving 240 mg/kg showed increased spleen weights in comparison with controls.

Genotoxicity

No studies on the genotoxic potential of A1-PI(H) have been conducted as this is a physiological human plasma protein and is not expected to have mutagenic effects. This is regarded as acceptable by the CHMP and is reflected in section 5.3 of the SmPC.

Carcinogenicity

No carcinogenicity studies have been performed, since A1-PI(H) is a naturally occurring human plasma protein and no carcinogenic effects in humans are expected. In addition, life-long administration of A1-PI(H) to animals is not possible due to the antigenicity of A1-PI(H) for other species. This is regarded as acceptable by the CHMP and is reflected in section 5.3 of the SmPC.

Reproduction Toxicity

No animal reproduction studies have been conducted with A1-PI(H) and its safety for use in human pregnancy has not been established in controlled clinical trials. The CHMP agreed that since human alpha₁-proteinase

inhibitor is an endogenous human protein, it is considered unlikely that A1-PI(H) will cause harm to the foetus when given at recommended doses this is reflected in section 4.6 of the SmPC.

The excretion of human α_1 -proteinase inhibitor in milk has not been studied in animals. This is reflected in section 4.6 of the SmPC.

No animal fertility studies have been conducted with A1-PI(H) and its effect on human fertility has not been established in controlled clinical trials. The CHMP agreed that since human α_1 -proteinase inhibitor is an endogenous human protein, no adverse effects on fertility are expected when given at recommended doses. This is reflected in section 4.6 of the SmPC.

Toxicokinetic data

No studies were performed. This is regarded as acceptable by the CHMP.

Local Tolerance

Local tolerance of A1-PI(H) was tested New Zealand White Rabbit model as a part of the repeat dose study and did not produce any treatment related local reactions.

Other toxicity studies

Neoantigenicity study no. SR 98-014: A study on the neoantigenicity of pasteurized Alpha₁-Proteinase Inhibitor (human) in rabbits

One lot of A1-PI(H) pasteurized using 3 different conditions was tested for the presence of neoantigens in a rabbit model system. The present study was conducted with A1-PI(H) pasteurized under standard operating conditions, as well as 2 more extreme pasteurisation conditions. The results of this study reveal no evidence for the existence of neoantigens in the A1-PI(H) samples as a result of pasteurization with the 3 conditions used.

2.3.5. Ecotoxicity/environmental risk assessment

In accordance with the Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMA/CHMP/SWP/4447/00), vitamins, electrolytes, amino acids, peptides, proteins, carbohydrates and lipids are exempted from a detailed environmental risk assessment because they are unlikely to result in a significant risk to the environment. A1-PI(H), being a plasma protein, falls within this category of substances and thus no further assessment of the environmental risk of A1-PI(H) is needed.

2.3.6. Discussion on non-clinical aspects

The most relevant animal model is a genetic mouse model, the so-called pallid mouse, which has an inherited A1-PI deficiency and develops emphysema spontaneously (Martorana et al., 1993; De Santi et al., 1995). Furthermore other animal models with pulmonary damage or emphysema that comprise direct instillation of elastase or repeated endotoxin administration to animals with reduced A1-PI levels do not adequately reflect the pathophysiology of emphysema due to A1-PI deficiency.

Since efficacy testing of A1-PI(H) in adequate animal models is hampered by the development of antibodies against A1-PI(H) in animals, no *in-vivo* studies on the pharmacodynamic properties of A₁-PI(H) were conducted. However, *in-vitro* pharmacodynamic studies using a neutrophil elastase inhibition assay demonstrate equal specific activity of CE1226 as compared to the registered plasma-derived human A₁-PI(H) that has already proved efficacy in clinical use. Inhibition of elastase activity is thought to be the major beneficial mechanism of

A₁-PI(H) augmentation therapy in emphysema patients, thus, *in-vitro* demonstration of elastase inhibitory activity is considered a good parameter for pharmacodynamic efficacy.

The toxicological program comprises single and repeated dose toxicity tests in several species, and includes local tolerance testing and addresses the potential formation of neoantigen due to pasteurization.

The performed nonclinical experiments revealed no evidence of toxicological findings at the intended clinical dose, a good local tolerability and the absence of the formation of neo-epitopes. However, from a non-clinical point of view no safety margin can be identified for A1-PI(H).

The toxicity studies with intravenous administration of A1-PI(H) up to 5 day duration revealed that potential target organs for toxicity could be lung, heart, spleen and uterus.

Repeat dose toxicity studies longer than 5 days, reproductive toxicity studies and carcinogenicity studies, have not been performed. Such studies are not considered meaningful due to the production of antibodies against the heterologous human protein in animals. Since A1-PI(H) is a protein and a physiological constituent of human blood, it is not expected to present carcinogenic, genotoxic, or teratogenic effects.

2.3.7. Conclusion on the non-clinical aspects

The safety of Respreeza has been assessed in several preclinical studies. Non-clinical data reveal no special risk for humans based on safety pharmacology and short term toxicity studies. This is reflected in section 5.3 of the SmPC. Since A1-PI(H) is a protein and a physiological constituent of human blood, it is not expected to present carcinogenic, genotoxic, or teratogenic effects. No animal reproduction studies have been conducted with A1-PI(H). This is reflected in section 4.6 in the SmPC.

2.4. Clinical aspects

2.4.1. Introduction

GCP

A GCP inspection performed by the Irish Medicines Board on the 13th to 16th December 2011 identified critical and major deficiencies at the Professor McElvaney, Ireland, centre (studies CE1226_4001 and CE1226_3001). The satisfactory responses to its findings have been provided.

The final FDA inspection Report regarding compliance with GCP for human alpha1-proteinase inhibitor CSL Behring GmbH (Respreeza, aka Zadalfa and Zemaira in US) has been completed and findings breaching GCP were found. The GCP-related FDA inspection findings were related to treatment allocation, dosing irregularities, improper dosing documentation, frequency of double-dose infusions, drug accountability, maintenance of the blinding of the IMP, lack of documentation relating to inclusion/exclusion criteria and the training of staff. Considering clarifications provided by the applicant in writing and in an oral explanation, it is the view of the CHMP that it is not expected that the GCP findings would influence the results of the studies that the overall B/R of Respreeza could be affected.

- Tabular overview of clinical studies

At the primary cut-off date of 1 April 2013, the clinical development program of CE1226 included 6 studies (see Table below). Study CE1226_3001 is ongoing and an interim analysis report was submitted for this study.

Table 6 - Overview of clinical studies

Study No.	Objectives	Design, study population	Dosage regimen (i.v. infusion), number of subjects treated
Single-dose studies			
RPR118635-101 ("Study 101")	Pharmacokinetics, dose-ranging	Open-label, non-randomized study in subjects with A1-PI deficiency	CE1226: single dose of 15, 30, 60, or 120 mg/kg b.w. (N = 19)
CE1226/2-1002 ("Study 1002")	Comparative bioavailability	Double-blind, randomized (1:1), 2-way cross-over study of CE1226 versus Prolastin in subjects with A1-PI deficiency	CE1226 and Prolastin: single dose of 60 mg/kg b.w. (N = 18)
Multiple-dose studies			
RPR118635-201 ("Study 201")	Biochemical efficacy, safety	Open-label, non-randomized study in subjects with A1-PI deficiency	CE1226: 60 mg/kg b.w. once weekly for 26 weeks (N = 9)
CE1226/2-2002 ("Study 2002")	Biochemical efficacy, safety	Randomized (2:1), active-controlled, blinded (first 10 weeks), multicenter, non-inferiority study of CE1226 versus Prolastin in subjects with A1-PI deficiency	CE1226: 60 mg/kg b.w. once weekly for 24 weeks (N = 29) Prolastin: 60 mg/kg once weekly for 10 weeks, then subjects switched to CE1226 60 mg/kg once weekly for a further 14 weeks (N = 14)
CE1226_4001	Clinical efficacy (decline in CT-measured lung density), safety	Randomized (1:1), placebo-controlled, double-blind, multicenter study in subjects with A1-PI deficiency	CE1226: 60 mg/kg b.w. once weekly for 24 months (N = 93) Placebo: once weekly for 24 months (N = 87)
CE1226_3001	Clinical efficacy (decline in CT-measured lung density), safety	Ongoing, open-label, uncontrolled, multicenter study in subjects with A1-PI deficiency	CE1226: 60 mg/kg b.w. once weekly for 24 months (N = 140 for safety of which 106 contribute to efficacy assessments)
ONGOING			

A1-PI = Alpha1-proteinase inhibitor; b.w. = Body weight; CT = Computed tomography; i.v. = Intravenous; N = Number of subjects treated.

All 4 of the earlier studies (studies 101, 1002, 201, and 2002) investigated the biochemical effect of CE1226 i.v. administration in subjects with A1-PI deficiency.

The single-dose studies were used primarily to characterize the pharmacokinetics of single doses of CE1226 and, in the case of study 1002, its bioavailability compared with Prolastin, another A1-PI product.

The multiple-dose studies were designed to show the long-term maintenance of a trough serum antigenic A1-PI concentration above a threshold level of 11 µM during therapy with CE1226 (the basis for demonstrating biochemical efficacy) and to show the non-inferiority of CE1226 compared with Prolastin when used for therapy of A1-PI deficiency.

The 2 more recent clinical studies (study 4001 and its extension study 3001) investigated the clinical efficacy and safety of CE1226 in support of the current application and proposed indication. Serum concentrations of antigenic and functional A1-PI were also measured during these studies, and these variables were considered as secondary endpoints in support of the assessments of clinical efficacy.

2.4.2. Pharmacokinetics

The applicant has performed a number studies investigating the long-term maintenance of a trough serum antigenic A1-PI concentration above a threshold level of 11 μM during therapy with CE1226. There are no CHMP guidelines on the clinical investigation of human plasma-derived α_1 -proteinase inhibitor to apply.

No conventional pharmacokinetic studies (absorption, distribution, metabolism, excretion, interaction etc.) studies were performed with CE1226. This is in principle acceptable as the application concerns a plasma derived drug product where the aim of the treatment is to raise the plasma level of A₁-PI in patients with A₁-PI deficiency above the 11 μM threshold.

Bioanalysis

Antigenic and serum functional A1-PI concentrations have been measured throughout the clinical programme. In general significantly lower values were obtained via the functional assay.

Study 4001 (pivotal)

Study 4001 was a randomized, double-blind, placebo-controlled, multinational, multicenter study that investigated the clinical efficacy of CE1226 in terms of slowing the progression of emphysema in subjects with A1-PI deficiency. Secondary endpoints included trough serum antigenic A1-PI concentrations. A total of 180 subjects were randomized 1:1 to receive weekly 60 mg/kg body weight (b.w.) i.v. infusions of either CE1226 or placebo for a period of 24 months. Of the 180 subjects enrolled, 93 were randomized to CE1226 and 87 subjects to placebo. Eighty-four subjects in the CE1226 group and 69 subjects in the placebo group completed the study.

The serum antigenic A1-PI concentrations over time were as follows:

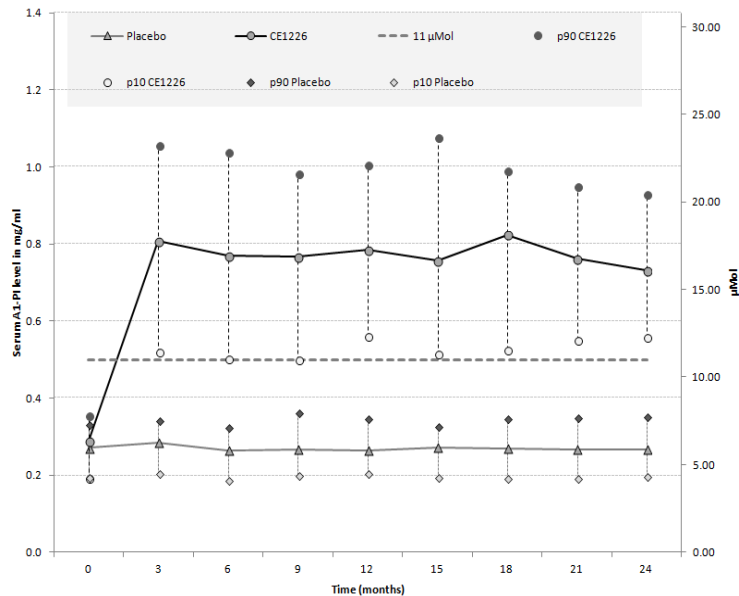


Figure 8 - Mean serum antigenic A1-PI concentrations (with 10th and 90th percentiles) in subjects treated with CE1226 or placebo in study 4001 (Baseline to Month 24)

Table 7 - Antigenic A1-PI concentration at each time point in subjects treated with CE1226 in study 4001 (Screening to Day 720)

	Screen (N=90)		Day 1 (N=90)		Day 90 (N=87)		Day 180 (N=86)		Day 270 (N=83)	
	mg/mL	µM	mg/mL	µM	mg/mL	µM	mg/mL	µM	mg/mL	µM
100% Max	1.82	40.04	2.01	44.15	4.23	93.13	3.23	71.13	5.32	117.04
99%	1.41	31.03	0.83	18.19	2.52	55.36	1.99	43.82	2.74	60.21
95%	0.69	15.25	0.60	13.16	1.25	27.50	1.14	25.16	1.09	24.00
90%	0.38	8.38	0.35	7.75	1.06	23.22	1.04	22.81	0.98	21.56
75% Q3	0.30	6.53	0.28	6.26	0.84	18.51	0.84	18.52	0.80	17.49
50% Median	0.25	5.49	0.24	5.27	0.72	15.88	0.71	15.53	0.68	15.05
25% Q1	0.22	4.85	0.21	4.72	0.60	13.19	0.62	13.69	0.59	13.04
10%	0.19	4.27	0.19	4.20	0.52	11.40	0.50	11.02	0.50	10.96
5%	0.19	4.19	0.19	4.12	0.48	10.49	0.48	10.54	0.44	9.74
1%	0.18	3.98	0.17	3.79	0.46	10.05	0.39	8.61	0.35	7.75
0% Min	0.17	3.81	0.14	3.17	0.46	10.03	0.36	7.92	0.35	7.70
Mean	0.31	6.89	0.29	6.34	0.81	17.75	0.77	16.95	0.77	16.88
SD	0.23	5.16	0.21	4.65	0.47	10.24	0.34	7.59	0.56	12.26
% > 11 µM		7.78		6.67		90.80		89.53		87.95

	Day 360 (N=84)		Day 450 (N=84)		Day 540 (N=83)		Day 630 (N=83)		Day 720 (N=83)	
	mg/mL	µM	mg/mL	µM	mg/mL	µM	mg/mL	µM	mg/mL	µM
100% Max	1.86	40.85	2.08	45.69	4.18	91.89	2.59	57.05	1.20	26.47
99%	1.75	38.53	1.82	40.09	3.19	70.25	2.12	46.58	1.19	26.18
95%	1.15	25.41	1.15	25.29	1.55	34.19	1.04	22.81	1.03	22.71
90%	1.00	22.11	1.07	23.65	0.99	21.76	0.95	20.86	0.93	20.39
75% Q3	0.86	18.96	0.81	17.81	0.84	18.47	0.82	18.05	0.81	17.89
50% Median	0.76	16.71	0.71	15.54	0.71	15.55	0.72	15.80	0.71	15.60
25% Q1	0.62	13.73	0.60	13.18	0.62	13.74	0.63	13.89	0.63	13.76
10%	0.56	12.32	0.51	11.31	0.53	11.56	0.55	12.10	0.56	12.25
5%	0.53	11.72	0.49	10.80	0.49	10.69	0.49	10.75	0.51	11.16
1%	0.43	9.51	0.41	9.13	0.39	8.52	0.40	8.70	0.35	7.75
0% Min	0.35	7.70	0.35	7.72	0.35	7.77	0.37	8.05	0.34	7.57
Mean	0.78	17.26	0.76	16.66	0.82	18.13	0.76	16.75	0.73	16.07
SD	0.24	5.26	0.27	5.97	0.51	11.28	0.29	6.41	0.17	3.76
% > 11 µM		96.43		94.05		92.77		93.98		95.18

In total, 33 out of 90 subjects treated with CE1226 had 1 or more values below 11 µM at some point during the study. In 23 of these subjects, this was a single occurrence. In a further 6 subjects, this happened twice, in 3 subjects 3 times, and in 1 subject 5 times. Overall, these cases represent approximately 6% of all doses of CE1226 administered in the study. Most of these values were narrowly below the limit of 11 µM. The lowest single value measured during the study in subjects treated with CE1226 was 7.6 µM.

Based on a population PK analysis, the residual variability (which approximates the population intra-subject variability) of Ctrough was 21.4%.

Study 3001 (extension to Study 4001)

In study 3001, non-US subjects who completed study 4001 are receiving CE1226 at a dose of 60 mg/kg/week for 2 years. Data are available from 76 subjects who had previously been treated in study 4001 with CE1226 (Early Start subjects) and 64 subjects who had previously been treated with placebo (Delayed Start subjects). Full 48-month data were available from 40 Early Start subjects and 39 Delayed Start subjects.

Across all time points, a similar proportion of subjects treated with CE1226 as in Study 4001 had A1-PI concentrations above 11 µM.

Study 2002

The primary objectives of this multicenter, randomized, controlled, multiple-dose study in subjects with A1-PI deficiency and emphysema were to demonstrate: (1) that the steady-state trough serum antigenic A1-PI

concentrations achieved by weekly i.v. infusion of CE1226 were not inferior to those achieved by weekly i.v. infusion of Prolastin, and (2) that CE1226 maintained weekly trough serum antigenic A1-PI concentrations above the threshold of 11 μ M. Of the 44 subjects (28 men, 16 women) enrolled, 30 were randomized to the CE1226-CE1226 group, and 14 subjects were randomized to the Prol-CE1226 group.

A1-PI levels over time were above the therapeutic threshold of 11 μ M with the exception of 2 measurements in one subject. Subject 246 had levels of 9.8 μ M and 10.4 μ M at Weeks 13 and 23, respectively.

Study 201

This open-label, multicenter, non-randomized, multiple-dose study investigated the safety, tolerability, and biochemical efficacy of CE1226 when administered by weekly i.v. infusion for 6 months at a dose of 60 mg/kg (functional activity) to subjects with A1-PI deficiency and emphysema. The primary efficacy endpoint was maintenance of weekly trough serum antigenic and functional A1-PI concentrations above a threshold level of 11 μ M from Week 7 to Week 26.

Approximately 50 subjects were to enter study 201 to ensure completion of 40 evaluable subjects. Because of discussions with the Food and Drug Administration (FDA) regarding the planned statistical analysis as well as changes in the manufacturing process of CE1226, the study was discontinued prematurely and replaced by study 2002. At the time recruitment was stopped, 9 subjects (7 men, 2 women) had been enrolled at a single study center. All 9 subjects completed the 6-month treatment period according to the protocol as well as 2 to 5 months of additional compassionate-use therapy.

A total of one single data point was below 11 μ M, and that value was 10.5 μ M (trough level of Patient No. 10 at Week 11).

Study 1002

This was a double-blind, single-center, randomized, single-dose, 2x2 crossover study, whose primary objective was to compare the bioavailability of CE1226 and Prolastin when administered to subjects with A1-PI deficiency. CE1226 and Prolastin were administered as an i.v. dose of 60 mg/kg.

Study 101

This open-label, multicenter, non-randomized, single-dose study investigated the safety, tolerability, and pharmacokinetics of CE1226, administered as single i.v. infusion doses ranging from 15 to 120 mg/kg to subjects with A1-PI deficiency.

Nineteen subjects (11 men, 8 women) were enrolled in the study and 15 patients were evaluable.

The 60 mg/kg administration achieved A1PI trough serum concentrations above the 11 μ M protective threshold.

The results were as follows:

Table 8 PK results in study 101

	Dose group			
	30 mg/kg	60 mg/kg	120 mg/kg	Total
No. of patients evaluable	3	6	6	15
Pre-infusion value (μM)				
median	5.1	5.1	4.7	4.9
range	4.5-5.6	4.1-7.1	4.2-5.4	4.1-7.1
C_{max} (μM)				
median	18.6	34.1	56.3	38.4
range	16.1-24.7	23.4-43.2	51.6-67.4	16.1-67.4
t_{max} (minutes)				
median	1	11	30	15
range	0-30	2-66	0-62	0-66
Terminal half-life (days)				
mean	5.4	4.7	5.4	5.1
median	5.2	4.9	5.3	5.2
range	4.6-6.4	2.4-6.8	4.5-6.7	2.4-6.8
AUC ($\mu\text{M}\cdot\text{days}$)				
median	98	115	243	137
range	63-109	89-163	197-324	63-324

Absorption

The bioavailability is 100 % as the product is administered intravenously.

Distribution

Not studied this was regarded acceptable by the CHMP.

Elimination

Not studied this was regarded acceptable by the CHMP.

Dose proportionality and time dependencies

- Dose proportionality**

Study 101

This open-label, multicenter, non-randomized, single-dose study investigated the safety, tolerability, and pharmacokinetics of CE1226, administered as single i.v. infusion doses ranging from 15 to 120 mg/kg to subjects with A_1 -PI deficiency.

Nineteen subjects (11 men, 8 women) were enrolled in the study. At screening, serum antigenic A_1 -PI concentrations were between 4.4 and 9.4 μM (mean 5.7 μM).

Each subject received a single i.v. infusion of either 15 mg/kg (N = 2), 30 mg/kg (N = 5), 60 mg/kg (N = 6), or 120 mg/kg (N = 6) of CE1226. All 19 subjects completed the 21-day observation period according to protocol.

Fifteen subjects in the 3 highest dose groups (3 subjects in the 30 mg/kg group, and 6 subjects each in the 60 and 120 mg/kg groups) had blood samples drawn at pre-infusion, at the end of infusion, 30 minutes after the

end of infusion, and 1, 3, 6, 12, and 24 hours after the end of infusion and on Days 4, 7, 10, 14, 17, and 21 for pharmacokinetic measurements.

The 60 mg/kg administration achieved A1PI trough serum concentrations above the 11 µM protective threshold.

Results, based on an antigenic assay, are shown below:

Table 9

	Dose group			
	30 mg/kg	60 mg/kg	120 mg/kg	Total
No. of patients evaluable	3	6	6	15
Pre-infusion value (µM)				
median	5.1	5.1	4.7	4.9
range	4.5-5.6	4.1-7.1	4.2-5.4	4.1-7.1
C_{max} (µM)				
median	18.6	34.1	56.3	38.4
range	16.1-24.7	23.4-43.2	51.6-67.4	16.1-67.4
t_{max} (minutes)				
median	1	11	30	15
range	0-30	2-66	0-62	0-66
Terminal half-life (days)				
mean	5.4	4.7	5.4	5.1
median	5.2	4.9	5.3	5.2
range	4.6-6.4	2.4-6.8	4.5-6.7	2.4-6.8
AUC (µM*days)				
median	98	115	243	137
range	63-109	89-163	197-324	63-324

- Time dependency**

No A1-PI antibodies were detected in any subject in any of the clinical studies.

Studies 4001 and 3001

See Figure 1, mean concentration versus days (day 90-1440).

Studies 201 and 2002

In the long-term (6-month), multiple-dose studies 201 and 2002, the slope for mean trough serum A₁-PI concentrations at steady-state was evaluated to assess whether there was a decline over time.

In study 201, there was no evidence of a downward trend over time.

Although in study 2002 there was a downward trend in mean trough serum antigenic A₁-PI concentrations in subjects treated with CE1226 from Week 7 to Week 24, the mean concentration at steady-state remained above the threshold of 11 µM, as did the mean trough concentrations in each subject. The negative slope in steady-state antigenic A₁-PI concentrations appeared to be transient, with a plateau of approximately 16 µM being reached after approximately 20 weeks of treatment.

Intra- and inter-individual variability

Based on a population PK analysis, the residual variability (which approximates the population intra-subject variability) of C_{trough} was 21.4%.

Special populations

- **Impaired renal function**

Not studied.

- **Impaired hepatic function**

Not studied.

- **Gender**

The effect of gender was not evaluated as a covariate in the dose-exposure model

- **Race**

The effect of race/ethnicity was not evaluated as a covariate in the dose-exposure model due to limited data, 100 % of the evaluated subjects were white.

- **Weight**

Body weight was found to influence the A1-PI slope vs. dose rate in the dose-exposure analysis (coefficient -0.836). Higher body weight resulted in higher predicted A1-PI concentrations as a result of the proportional weight (mg/kg) based dosing. The mean bodyweight in the evaluated patient population was 77.4 (SD 15.2) kg (range 47-170.8 kg).

- **Elderly**

In the dose-exposure analysis, no statistically significant effect of age on A1-PI baseline or A1-PI slope vs. dose rate was found. The mean age of the evaluated patient population was 53.1 (SD 7.3) years (range 31-67 years).

- **Children**

No studies have been conducted to investigate the pharmacokinetics of CE1226 in pediatric subjects.

Pharmacokinetic interaction studies

CHMP considered acceptable that no interaction studies, *in vitro* or *in vivo*, has been performed given that the active substance is an endogenous compound of a pharmacological class not expected to affect PK related processes.

Pharmacokinetics using human biomaterials

Plasma Protein Binding Study Reports

CE1226 is a plasma protein presented in its native form, therefore it is considered highly unlikely that it would be subject to alterations in biological activity due to plasma protein binding. . This was regarded as acceptable by the CHMP.

Reports of Hepatic Metabolism and Drug Interaction Studies

The metabolism of CE1226 is understood through the historical study of naturally occurring A1-PI. Normal A1-PI and neutrophil elastase are eliminated in the lung in a mutually suicidal interaction uninfluenced by hepatic status. Thus product specific hepatic metabolism studies have not been considered necessary. Similarly, as the

therapeutic goal of A1-PI substitution therapy is to replace a deficiency in the circulating level of a naturally occurring protein with that same protein of human plasma origin, there is no expectation of a pharmacological effect on other drugs.

Reports of Studies Using Other Human Biomaterials

For the same reasons as given above for studies using other human biomaterials have not been deemed necessary. This was regarded as acceptable by the CHMP.

2.4.3. Pharmacodynamics

Human alpha1-proteinase inhibitor (A1-PI), is a 52 kDa single polypeptide glycoprotein produced by hepatocytes and mononuclear phagocytes. A1-PI acts as the primary inhibitor of neutrophil elastase (NE) in the lower respiratory tract. Neutrophil elastase is a protease capable of destroying alveolar walls in the lower respiratory tract. It is produced and secreted by activated neutrophils, and is primarily found in the alveolar and bronchial lumina (epithelial lining fluid [ELF]). If NE is present in the lung and not regulated by its naturally occurring inhibitor A1-PI, as is the case in A1-PI deficiency, NE can cause excessive inflammation and proteolysis of alveolar tissue, leading to progressive emphysema.

Epithelial lining fluid (ELF) was obtained by bronchoalveolar lavage (BAL) in a subset of subjects in studies 101 and 2002. While study 101 was a single-dose study and BAL was performed 6 days after dosing, the BAL in study 2002 was performed 11 weeks after the start of weekly dosing (7 days after the 10th dose), at a time when serum A1-PI concentrations had achieved steady-state.

ELF levels were effectively raised.

Table 10 - ELF results (nM) on Day 7 in single-dose study 101 and at Week 11, 7 days after the last blinded dose, in multiple-dose study 2002

Parameter	Median (range)		
	Study 101	Study 2002	
	CE1226 60 mg/kg (N = 3)	CE1226 60 mg/kg (N = 10)	Prolastin 60 mg/kg (N = 5)
Antigenic A₁-PI concentrations			
Baseline	370 (214 - 557)	256 (59 - 356)	292 (86 - 945)
Change ^a from baseline	336 (322 - 2046)	810 (156 - 3424)	907 (481 - 1664)
ANEC			
Baseline	17 (13 - 504)	787 (2 - 6808)	104 (0 - 1918)
Change ^a from baseline	951 (8 - 1500)	73 (-4533 - 2718)	793 (-884 - 1985)
Free NE			
Baseline	150 (11 - 1685)	Not detectable	Not detectable
Change ^a from baseline	82 (-1540 - 5052)	Not detectable	Not detectable
A₁-PI:NE complexes			
Baseline	2 (2 - 2)	13 (0 - 39)	12 (0 - 37)
Change ^a from baseline	13 (1 - 62)	49 (9 - 399)	161 (66 - 660)

A₁-PI = Alpha1-proteinase inhibitor; ANEC = Anti-neutrophil elastase capacity; N = Number of evaluable subjects; NE = Neutrophil elastase.

^a Difference between post-baseline and baseline value.

Source: section 5.3.3.2.1, RPR118635-101 CSR, Table 6.4.1, Table 6.4.2, Table 6.4.3, Table 6.4.4 and Table 6.4.5; section 5.3.3.2.4, CE1226/2-2002 CSR, Table 6.1.4.2, Table 6.1.4.12 and Table 6.1.4.17

Purified human human alpha1-proteinase inhibitor (A1-PI) concentrate has been used for almost 2 decades for A1-PI augmentation therapy in individuals who have a reduced level or absence of functional A1-PI and a clinical evident lung disease. A target of achieving A1-PI serum concentrations above the 11 µM threshold has been the concept of biochemical efficacy in clinical studies of A1-PI augmentation therapies. The “protective level” of 11 µM threshold (50 mg/dL) when measured by immunonephelometry (or 80 mg/dl when measured by radial immunodiffusion) has evolved from the observation that patients with heterozygote phenotypes whose levels of A1-PI exceed this level are usually free from emphysema (Crystal, 1998).

The 11 µM threshold has been used as a target in a number of A1-PI augmentation studies also for products who have gained approval. Although, there is now at least one ongoing study which explores higher doses of purified human alpha1-proteinase inhibitor, 120 mg/kg b.w. intravenously every week (SPARTA study). This study is aiming at reaching higher levels of serum A1-PI, i.e. 20 µM, which would be at the lower end of the normal range for a healthy subject (20-53 µM). Although the 11 µM threshold has been used in a number of A1-PI augmentation studies it cannot truly be considered an optimised established therapy since the A1-PI plasma trough levels values in the normal range has not been explored.

PK/PD

A post-hoc exposure-response analysis of data in study 4001 indicated a linear relationship between exposure and the rate of decline in CT scan lung density. FEV1 was identified as a covariate, patients with lower FEV1 at baseline were found to have greater lung density decline rates. The results from the exposure-response analysis indicates that doses above 60 mg/kg and a target level higher than 11 µM may add further benefit in terms of a slower rate of decline in lung density.

Mechanism of action

Human alpha₁-proteinase inhibitor is understood to be the primary anti-protease in the lower respiratory tract, where it inhibits neutrophil elastase (NE). Normal healthy individuals produce sufficient alpha₁-proteinase inhibitor to control the NE produced by activated neutrophils and are thus able to prevent inappropriate proteolysis of lung tissue by NE. Conditions that increase neutrophil accumulation and activation in the lung, such as respiratory infection and smoking, will in turn increase levels of NE. However, individuals deficient in endogenous alpha₁-proteinase inhibitor are unable to maintain appropriate antiprotease defence and experience more rapid proteolysis of the alveolar walls starting prior to the development of clinically evident chronic obstructive lung disease in the third or fourth decade.

Primary and Secondary pharmacology

No studies have been submitted this was regarded as acceptable by the CHMP.

2.4.4. Discussion on clinical pharmacology

Pharmacokinetics

There are no CHMP guidelines on the clinical investigation of human plasma-derived alpha1-proteinase inhibitor to apply.

No conventional absorption, distribution, metabolism, or excretion studies were performed with CE1226. This is in principle be acceptable as the application concerns a plasma derived drug product where the aim of the treatment is to raise the plasma level of A1-PI in patients with A1-PI deficiency above the 11 µM threshold.

Individuals with endogenous serum concentrations of A1-PI below 11 µM generally manifest a significantly increased risk for development of emphysema compared with the background risk in the general population (World Health Organization 1996, Gadek 1983, Eriksson 1965, Eriksson 1964). Therefore, the maintenance of serum antigenic A1-PI concentrations above 11 µM has, for almost 2 decades, been thought to provide therapeutically relevant anti-NE protection in the lung (Crystal 1990).

Previous studies with other products containing plasma derived alpha1-proteinase inhibitor have demonstrated that weekly i.v. infusions at a dose of 60 mg/kg body weight increased A1-PI concentrations above the 11 µM threshold in a majority of patients (Brantley et al. 2013).

The focus of this assessment has been to bring clarity regarding the proportion of patients which are expected to be above the 11 µM threshold over time following weekly 60 mg/kg i.v. infusions also for this product.

The possible influence of covariates, e.g. body weight or baseline levels of A1-PI, in relation to the wanted outcome, i.e. to be above the 11 µM threshold over time, was also focused on.

Antigenic and serum functional A1-PI concentrations have been measured throughout the clinical programme. Study 4001 may be seen as the pivotal PK study given it included the largest sample size, the most heterogeneous population and included CE1226 from process C.

Based on the presented data, it is expected that 99 % of the patients will reach an average trough serum antigenic A1-PI concentration above the threshold level of 11 µM. No clear correlation between specific patient characteristics and poor response (A1-PI concentrations below 11 µM) was found.

Across the studies, PK data has not been stratified according to genotype. On the other hand, considering that the majority of patients had the ZZ genotype, conclusions are likely hard to draw regarding other genotypes and no request for an additional analysis is made. As subjects with the ZZ genotype has the lowest baseline levels of A1-PI, the study population represented "worst case scenario" in terms of increasing A1-PI concentration above the threshold level.

Based on a limited number of patients in study 101, dose proportionality is indicated (although AUC in the 30 mg/kg dose group is unexpectedly high).

Pharmacodynamics

Bronchoalveolar lavage (BAL) was performed in 3 subjects each at baseline and at Day 7 in the 30, 60, and 120 mg/kg dosing groups of the single dose Study 101. A subset of 15 subjects (10 on CE1226 and 5 on Prolastin) participated in the BAL investigations in Study 2002, each before first infusion and 7 days after last blinded infusion at Week 11. In Study 2002 subjects were treated with weekly infusions of 60 mg/kg of A1-PI. An increase of antigenic A1-PI levels and A1-PI:NE complexes could be found in the epithelial lining fluid. This supports the hypothesis that after intravenous administration, A1-PI arrives in its active form in the lower lung where it has the ability to complex with free NE by building complexes.

As the disease only occurs in adult age, the paediatric population is excluded from the indication and from clinical investigations with the product as reflected in section 4.2 of the SmPC after having received a product-specific waiver covering all subsets of the paediatric population from birth to less than 18 years of age has been granted (waiver decision number P/260/2012).

Tobacco smoke increases the activity of neutrophil elastase in the lungs and thus directly compromises the effect of alpha 1-proteinase inhibitor. This should be referenced in the product information.

Although the 11 µM threshold has been used in a number of A1-PI augmentation studies it cannot truly be considered an optimised established therapy since the A1-PI plasma trough levels values in the normal range has not been explored.

2.4.5. Conclusions on clinical pharmacology

Augmentation therapy increases the plasma A₁-PI concentrations above 11 µM as intended in subjects with emphysema with a moderate airflow reduction. The achieved level of A₁-PI concentrations in the study CE1226_4001 were 16 µM (11-23 µM, 90 % prediction interval) when measured at the end of the dosing period and the average serum A₁-PI concentration throughout a dosing interval was estimated to be in the order of 19 to 20 µM which is in the lower range of normal. The CHMP agreed to an approval of A1-PI(H) from a pharmacokinetic point of view.

2.5. Clinical efficacy

2.5.1. Dose response studies

Single doses of CE1226 (15, 30, 60, or 120 mg/kg) were administered in study 101 for a dose-ranging assessment of serum concentrations of A1-PI. Based upon these data, as well as the no observed adverse effect level seen in nonclinical studies, the 60 mg/kg weekly dose of CE1226 was chosen for investigating biochemical efficacy in the multiple-dose studies because it was expected to maintain serum antigenic A1-PI concentrations well above the widely-published "protective" threshold of 11 µM (Crystal 1990). In addition, this was the approved dose for Prolastin, which was used as the active comparator in study 2002. No study has prospectively addressed whether additional incremental benefit on lung density or function may be achieved with A1-PI levels above the 11 µM level.

To conclude, the 60 mg/kg weekly dose was chosen based on the expectancy to maintain serum antigenic A1-PI concentrations above the threshold of 11 µM.

2.5.2. Main studies

Two phase III studies, CE1226_4001 and CE1226_3001 (ongoing), were performed to evaluate the efficacy and safety of A1 PI augmentation therapy over 2-4 years in subjects with A1 PI deficiency.

CE1226_4001

Title: A randomized, placebo-controlled, double-blind, multicenter Phase III/IV study to compare the efficacy and safety of 60 mg/kg body weight of Zemaira® weekly i.v. administration with placebo weekly i.v. administration in chronic augmentation and maintenance therapy in subjects with emphysema due to alpha1-proteinase inhibitor deficiency.

This was a randomized, double-blind, placebo-controlled, multicenter Phase 3/4 study to compare safety and efficacy of a weekly intravenous (i.v.) dose of 60 mg/kg body weight (b.w.) CE1226 with placebo. The study population comprised A1-PI deficient subjects with emphysema and reduced lung function, with forced expiratory volume in 1 second (FEV1) ≥ 35% and ≤ 70% predicted. Subjects were randomized in a ratio of 1:1 to CE1226 or placebo.

The study consisted of a screening period of 1 week to 1 month, and a treatment period of 24 months.

During the treatment period, each subject received weekly infusions of the investigational medicinal product (IMP). The first dose of the IMP and the doses given during the following quarterly visits at the study center were

administered by the investigator or designate. All other weekly doses could be given by the nurses of a home care service or by the family doctor. Where possible, all doses were given at the study center. The subjects returned to the study center every 3 months for a physical examination including AE collection, blood draw, and study specific procedures. Each subject kept a diary to document all AEs and exacerbations observed, and/or any concomitant medication taken during the time between hospital visits.

CT scans for the primary efficacy analysis were conducted in all subjects prior to start of IMP administration, and after 3, 12, 21, and 24 months. Assessment of quality of life (QoL) using the SGRQ were performed in all subjects prior to start of IMP administration, after 12 and after 24 months.

CE1226_3001

Title: An open-label, non-controlled, multicenter, multinational study to evaluate the efficacy and safety of Zemaira® administration in chronic augmentation and maintenance therapy in subjects with emphysema due to alpha1-proteinase inhibitor deficiency who completed clinical study CE1226_4001.

This is an **ongoing, open-label, non-controlled**, multicenter, multinational study. A1-PI deficient individuals with emphysema, who had completed the 2-year treatment and observation period in the

CE1226_4001 study, except those participating in the USA, were invited to participate in study CE1226_3001.

All subjects are planned to be treated with treated with weekly intravenous (i.v.) administrations of CE1226 at a dose of 60 mg/kg b.w. for up to 2 years.

Considering the longitudinal results of the 2 studies sequentially, subjects can be considered as early or delayed starters on CE1226 treatment. Those subjects who had already been allocated to receive

CE1226 treatment during study CE1226_4001 represent the Early Start group and had received up to 4 years of continuous therapy at the end of study CE1226_3001. Subjects who received placebo in study CE1226_4001 and only began to receive CE1226 treatment upon entry into study CE1226_3001 represent the Delayed Start group and had a maximal exposure of 2 years at the end of study CE1226_3001.

The subjects returned to the study center every 3 months for a medical review and study-specific procedures. Each subject kept a diary to document all AEs and exacerbations (ie, onset and duration) observed, and any concomitant medication taken during the time between hospital visits. The investigator or delegate documented the use of the investigational medicinal product (IMP) and any AEs he/she might have observed in the subject diary. These diaries were collected and checked by the investigator/designate during each visit.

CT scans for the primary efficacy analysis were performed at Month 36 and at the end of study CE1226_3001 (Month 48).

The planned interim analyses compared the efficacy witnessed within and between the Early Start and Delayed Start groups in the periods of Baseline to Month 24, Baseline to Month 48, and Month 24 to Month 48.

Specifically this interim analysis was conducted to:

- Confirm, through the pattern of response between the Early Start and Delayed Start groups, that CE1226 treatment is a disease modifying intervention in emphysema due to A1-PI deficiency (cut-off date: 06 February 2013).
- Examine the 3 hypotheses for exploratory purposes to support the notion of disease modifying effects by comparing lung density decline measured by CT in the Early Start and Delayed Start groups within study CE1226_3001 and across studies CE1226_4001 and CE1226_3001 (cut-off date: 06 February 2013).
- Explore the safety and tolerability profiles between the Early Start and Delayed Start groups within study CE1226_3001 and across studies CE1226_4001 and CE1226_3001 (cut-off date: 01 April 2013).

Methods

Study Participants

Study CE1226_4001:

Inclusion criteria

- 18 to 65 years of age and willing to sign informed consent.
- Males, and non-pregnant, non-lactating females, whose screening pregnancy test was negative, and who were using contraceptives deemed reliable by the investigator or who were not of child-bearing potential.
- Diagnosis of A1-PI deficiency (serum A1-PI levels $< 11 \mu\text{M}$, or $< 50 \text{ mg/dL}$ [as determined by nephelometry]). This included newly diagnosed subjects, previously untreated subjects, currently treated subjects, and subjects currently not on treatment therapy but on treatment in the past.
- Subjects with emphysema and $\text{FEV1} \geq 35\%$ and $\leq 70\%$ (predicted).
- No signs of chronic or acute hepatitis A, hepatitis B, hepatitis C or human immunodeficiency virus (HIV) infection (negative serologies for HIV and viral hepatitis). In case of positive serologies for viral hepatitis, vaccination status or negative immunoglobulin M were to be available.

Exclusion criteria

Any one of the following criteria excluded potential subjects from the study:

- Any relevant chronic diseases or history of relevant diseases (eg, severe renal insufficiency) except respiratory or liver disease secondary to A1-PI deficiency. Subjects with well-controlled, chronic diseases were to be included after consultation with the treating physician and the sponsor.
- Current evidence of alcohol abuse or history of abuse of illegal and/or legally prescribed drugs such as barbiturates, benzodiazepines, amphetamines, cocaine, opioids, and cannabinoids.
- History of allergy, anaphylactic reaction, or severe systemic response to human plasma derived products, or known mannitol hypersensitivity, or history of prior adverse reaction (AR) to mannitol.
- History of transfusion reactions.
- Selective immunoglobulin A (IgA) deficiency.
- Acute illness within 1 week prior to the first administration of the IMP. Start of treatment after recovery was possible.
- Current tobacco smoker (smoking had to be ceased at least 6 months prior study inclusion). Subjects with a positive cotinine test due to nicotine replacement therapy (eg, patches, chewing gum) or snuff were eligible.
- Conditions or behaviors that interfered with attending scheduled study visits in the opinion of the investigator.
- History of non-compliance.
- Administration of any other experimental new drug or participation in an investigation of a marketed product within 1 month prior to the screening visit date.
- Inability to perform necessary study procedures.
- Lung transplantation, lung volume reduction surgery or lobectomy, or being on a waiting list for any such surgeries.

The study was performed as a multicenter study at 28 study centers internationally. i.e., Region Australia, Region North America, Region Nordic (Denmark, Finland, Sweden) and Region Europe (Czech Republic, Estonia, Germany, Ireland, Poland, Romania, and Russia).

Study CE1226_3001:

Inclusion criteria

- Subjects who had completed the 2-year treatment and observation period in study CE1226_4001 and were willing to sign informed consent.
- Males and non-pregnant, non-lactating females whose screening pregnancy test was negative and who were using contraceptive methods deemed reliable by the investigator or who were not of childbearing potential.

Exclusion criteria

- Individuals residing in the USA.
- Current evidence of alcohol abuse or abuse of drugs such as barbiturates, benzodiazepines, amphetamines, cocaine, opioids, and cannabinoids.
- History of allergy, anaphylactic reaction, or severe systemic response to human plasma derived products, or known mannitol hypersensitivity, or history of prior adverse reaction to mannitol.
- Current tobacco smoker. Smoking had to be discontinued at least 6 months prior to study participation.
- Conditions or behaviors that interfered with attending scheduled study visits in opinion of the investigator.
- History of non-compliance.
- Administration of any other experimental new drug or participation in an investigation of a marketed product.
- Inability to perform necessary study procedures.

The study was performed as a multicenter study at 22 study centers internationally (Region Australia, Region Nordic and Region Europe).

Treatments

Study CE1226_4001

CE1226_4001:

- **Early Start group:** subjects who were randomized to CE1226 in study CE1226_4001 and continued to receive CE1226 in study CE1226_3001.
- **Delayed Start group:** subjects who were randomized to placebo in study CE1226_4001 and were reallocated to receive CE1226 during study CE1226_3001.

Patients were randomly assigned in a 1:1 ratio to receive CE1226 (60 mg) or placebo by i.v. infusion (over approximately 15 minutes) every week during the 24 month double blind treatment period.

The infusion rate was 0.08 mL/kg/min.

In exception cases (eg. holidays) a single weekly dose of 120 mg/kg b.w. was allowed to cover a 2-week time period.

Placebo contained with exception of the active ingredient all other components of the test product.

Study CE1226_3001

All eligible subjects for this study kept their subject numbers from study CE1226_4001 and entered study CE1226_3001, in which they were all treated with CE1226. For analysis purposes, subjects were assigned to groups based on their previous treatment in study

CE1226 was administered i.v. at weekly intervals at a dose of 60 mg/kg b.w. up to 24 months and at a rate of 0.08 mL/kg/min to all subjects, as determined by the response and comfort of the subject.

In exceptional cases (eg, holidays) a single weekly dose of 120 mg/kg b.w. was allowed to cover a 2-week time period.

Placebo contained with exception of the active ingredient all other components of the test product.

Objectives

Study CE1226_4001

Primary objective

To investigate the effect of CE1226 on the progression of emphysema, assessed by the decline of lung density, measured by CT.

Key Secondary objective

The key secondary objectives were to assess the effect of treatment with A1-PI on the following clinical assessments:

- Change in exercise capacity assessed by the ISWT
- Change in symptoms assessed by the SGRQ
- The rate of pulmonary exacerbations

Additional secondary objectives included assessments of the effect of CE1226 on pulmonary function test (PFT) parameters. Incidence and nature of adverse events (AEs), viral serology, and serum A1-PI antibodies, laboratory parameter levels, and vital signs were further safety variables.

Study CE1226_3001 (interim analysis)

Primary objective

The primary objective of this interim analysis was to investigate the long-term effect of a disease modifying benefit of CE1226 on the progression of emphysema, assessed by volume adjusted lung density, measured by yearly CT scans.

Secondary objective

The following secondary objectives were evaluated during this interim analysis:

- Absolute and relative (%) change in lung density, as measured by CT scans across time points between study CE1226_4001 (Baseline to Month 24) and study CE1226_3001 (Month 24 to Month 48) within the Early Start and Delayed Start groups.
- Safety of CE1226, as assessed throughout study CE1226_3001 by standard adverse event(AE) reporting.

Outcomes/endpoints

Study CE1226_4001

Primary Endpoint:

- The primary efficacy variable was the lung volume-adjusted lung density (Adjusted P15) estimated by the 15th percentile of the frequency histogram of the lung pixels.

Key secondary Endpoints:

- The distance (m) a subject walked in the ISWT comprised a maximum of 12 levels of 1 minute duration, each with increasing walking speeds. The exercise capacity test was assessed at Day 1 and at each quarterly visit at the study center.
- Change in symptoms assessed by the SGRQ
- The rate of pulmonary exacerbations.

Other secondary endpoints

- Adjusted P15 change from baseline to Month 24: The change between Adjusted P15 obtained by CT scans at baseline and at Month 24.
- Pulmonary function (spirometry): FEV1, FEV1 % predicted by the Crapo criteria (Seersholm et al. 1997), FEV1/FVC ratio, and DLCO were measured at baseline and at all visits.

- Characteristics of pulmonary exacerbations: Time to the first pulmonary exacerbation event was assessed. In addition, the duration and severity of pulmonary exacerbations was assessed by exacerbation days, requirement for antibiotics (i.v., oral), and requirement for hospitalization. Information on pulmonary exacerbations was documented in the subject diary and the CRF.

Exploratory and correlation variables

- PFT parameters: TLC, FRC, RV, VC, FVC, and PEF assessed at Day 1 and each quarterly visit and measured by % change from baseline to Month 24.
- BMI: assessed at Day 1 and each quarterly visit and measured as change from baseline to Month 24.
- Pulmonary exacerbation characteristics: Duration of primary diagnostic criteria (dyspnea, increased sputum volume, and development of sputum purulence) and supporting diagnostic criteria relative to total treatment duration as well as the scores of the American Thoracic Society Dyspnea Scale are provided in listings.
- Data on subjects who prematurely stopped the ISWT at Day 1 and at each quarterly visit and the reason for stopping are provided in a listing.
- SGRQ activity score, impacts score, and total score: assessed at Day 1, and Months 12 and 24.
- Mortality: incidence and time to the occurrence of death.
- CRP: assessed at Day 1 and at each quarterly visit.
- Antigenic A1-PI levels and functional A1-PI trough levels: assessed at screening, Day 1, and at each quarterly visit.

Study CE1226_3001 (Interim analysis)

Primary efficacy endpoint:

- Primary efficacy variable is the 15th percentile of the lung density measured by the frequency histogram of the lung pixels in yearly CT scans.

Key secondary Endpoints:

- The key secondary efficacy variables were the absolute and % change of lung density as measured by Adjusted P15 from CT scans acquired between Baseline and Month 48, also taking into account measures from study CE1226_4001.
- The absolute and % change from Baseline to Month 48 were derived using the values of

Adjusted P15 of the last assessment of CT scans from study CE1226_3001 and the first assessment of CT scans from study CE1226_4001.

Sample size

Study CE1226_4001

It was initially planned to enrol 100 subjects in study 4001, randomized 1:1 to 2 treatment groups (CE1226 and placebo). This sample size estimation was based on the results of Dirksen et al. 1999 evaluating the difference in yearly decline of lung density between placebo and active treatment in a total of 56 subjects with A1-PI deficiency. The average estimates obtained in the Dirksen study from CT scans of the whole lung and of a single slice 5 cm below the carina were used for the sample size estimation. With this assumption and considering the loss to follow-up, it was estimated that 50 subjects per treatment group would enable the study to achieve 80% power at a 1-sided level of significance of 0.025 to detect an effect size of 1 g/L/year on the decline in lung density, with a standard deviation (SD) of approximately 2.5 g/L/year.

Due to the small sample size of the Dirksen study, an unblinded interim analysis was planned to re-estimate the sample size of study. The interim analysis was planned to be conducted when 50 subjects had completed the 2-year treatment period in the study. It was also planned that if 100 subjects had been randomized but the interim analysis was not yet able to be performed because an insufficient number of subjects had reached the 2-year treatment period at the time enrolment reaches 100, then, in order to avoid halting enrolment and

thereby introducing a discontinuity in recruitment, enrolment would continue up to 180 randomized subjects or until the interim analysis results were available, whichever occurred first. The decision of enrolment of 180 subjects was based on the previous sample size assumption and was estimated that it would increase the study power to 92% at a 1-sided level of significance of 0.025. If the interim analysis results were available prior to the completion of 180 subjects, a decision on the final sample size would be made.

Based on this, in 2009 CSL Behring submitted a protocol amendment to continue enrolment up to a maximum of 180 randomized subjects or until 50 subjects had completed the study so the planned interim analysis could be conducted.

In 2010, a blinded re-estimation of the study sample size was done using data accrued on 69 subjects with at least 1 post-baseline CT scan who had either completed the study already or discontinued prematurely. In addition, this analysis was also performed for all subjects with at least 2 post-baseline density measurements. The slope of the regression line for the decline in lung density based on this blinded sample size re-estimation indicated that the SD used in the original sample size estimation can be employed and no re-estimation was needed. It also indicated that 180 subjects would provide at least 88% power to detect the previous assumed effect size of 1 g/L (SD = 2.5 g/L) difference in the yearly decline in lung density at a 1-sided significance level of 0.025, or would be sufficient to maintain at least 80% power to detect 1.07 g/L (SD = 2.17 g/L) difference in the yearly decline if the estimate was based on the results generated from CT scans of the whole lung published by Dirksen et al. 1999. Since enrolment was almost complete by the time the interim analysis could be performed, the decision not to carry out the interim analysis planned in the original protocol was made.

Study CE1226_3001

All subject completing study 4001 and meeting the inclusion criteria were eligible for inclusion in study 3001. No sample size calculations were performed.

Randomisation

Study CE1226_4001

In study 4001 all subjects screened for the study were entered chronologically on the "subject screening log" at the initial visit to the study center. If a subject was not enrolled into the study, the reason was documented on the subject screening log. Subjects were randomized at a ratio of 1:1. The randomization was stratified by center. A randomization list containing the assignment of subject numbers to treatment groups (CE1226 or placebo) was reproducibly generated by a computerized pseudo-random number generator. A copy of the randomization list was transferred to the drug supply and logistics group of the Clinical Operations Department at CSL Behring. Standard operating procedures were followed to ensure confidentiality of the randomization list.

Study CE1226_3001

Study 3001 is an open-label non-randomized study with one single treatment.

Blinding (masking)

Study CE1226_4001

Study 4001 was a double-blind study. CE1226 and placebo were packaged identically. Individual packages were identified only by the subject number. The treatment groups randomized to the subject numbers were only known to the randomization code administrator, and to the drug supply and logistics group of the Clinical Operations Department at CSL Behring. A potential compromise to the blinding of the IMP was identified early in the study due to a visual difference between the reconstituted CE1226 and placebo preparations. This issue was addressed by ensuring that the IMP was physically masked after reconstitution. However, it appears that this measure was not implemented in a timely fashion at center 11. Thus, for the analyses of AEs, a robustness analysis was carried out to account for the potential unblinding issue at center 11.

Study CE1226_3001

Study 3001 was an open-label study without blinding.

Statistical methods

Study CE1226_4001

The following analysis populations were defined for the analyses in study 4001:

Randomized population: All randomized subjects.

Intention-to-treat (ITT) population: All subjects with A1-PI deficiency that were included in the study and randomized. In the ITT analysis, subjects were assigned to the treatment to which they were randomized.

Per-protocol (PP) population: A subset of the ITT population, in which subjects with a major protocol deviation were excluded. Pre-specified definitions of major protocol deviations are summarized in the study report. Only data affected by the protocol deviations were excluded. The final decision regarding which subjects and which data were excluded from the PP analysis was made before the data were unblinded, during the Blind Data Review Meeting. In the PP analysis, subjects were assigned to the treatment groups to which they were randomized.

Safety population: All subjects who were included in the study and who received at least 1 dose of IMP. The Safety population was used for the safety analysis. In the safety analysis, subjects were analyzed according to the treatment they actually received, defined as the treatment received most of the time during the study.

The ITT population was the primary population for the analysis of the primary efficacy variable.

The **primary efficacy endpoint** in study 4001 is the annual rate of change of lung density, measured as 15th percentile from the frequency histogram of the lung pixels (p_{15}) using CT scans. Data were collected at 2 states of inspiration, total lung capacity (TLC) and functional residual capacity (FRC) which were used separately or in combination according to different analytical approaches.

The two different methods proposed to standardize percentile densities for variations in lung volume measured from CTs are the physiologic adjustment method and the statistical adjustment method by Dirksen et al (2009). Since the physiologic adjustment has the advantage of being intuitively meaningful, and each measured density value can be adjusted for simultaneously measured lung volume independent of measurements from other scans, the primary efficacy variable, of the study, adjusted P15, is based on the physiologic adjustment.

adjusted P15 = observed p_{15} · (measured lung volume / predicted TLC). Predicted TLC will be derived as

$7.99 \cdot [\text{height in m}] - 7.08$ for males, and

$6.60 \cdot [\text{height in m}] - 5.79$ for females.

This will be taken at full inspiration (TLC) and full expiration (FRC).

For the primary statistical analysis, no values were imputed. All available data were included in the analysis. All randomized subjects with at least 1 valid CT scan (at any time point) were included. Missing values were assumed to be missing at random (MAR). Descriptive statistics are provided for measured values of Adjusted P15 (g/L), change from baseline, and % change from baseline at TLC and FRC inspiration states, and mean of TLC and FRC, by quarterly visit and at last visit. Descriptive statistics are presented overall and stratified by the baseline

The primary efficacy variable, Adjusted P15 values, were analyzed at TLC and FRC inspiration states, meaning the TLC and FRC values were included in the primary model simultaneously (i.e., TLC and FRC states combined). A linear random regression model was applied using SAS PROC MIXED, with country, inspiration state, time

elapsed since Day 1 (year), treatment, and treatment-by-time interaction (i.e., a regression of Adjusted P15 on time within treatment) as fixed effects and subject and subject-by-time interaction as random coefficients. Thus, the primary efficacy model contained the subjects' individual intercept and individual slope.

The principal interest was in the magnitude of the treatment-by-time interaction (difference of the regressions on time within treatment) and its level of significance, because this indicated whether the 2 treatments differed in their effect on the rate of decline of Adjusted P15. The difference between the regression coefficients from each of the treatments (CE1226 minus placebo), 95% CI for the difference and the 1-sided p-value are presented. A 1-sided p-value less than 0.025 and a positive estimate of the treatment difference of CE1226 minus placebo, i.e., the lower bound of the 95% CI being greater than zero, were taken to indicate superiority of CE1226 compared to placebo.

In addition, the primary efficacy endpoint was analyzed by applying the primary efficacy analysis model (without the fixed effect for inspiration state) to the CT scans at TLC and FRC states separately.

Statistical adjustment was performed by including the logarithm of measured TLV as a covariate in the statistical model.

Based on the European Medicines Agency's recommendation ("Guideline on missing data in confirmatory clinical trials" dated 02 July 2010), a set of analyses where the missing data were handled in different ways were used as sensitivity analyses to verify the results from the primary analysis. The following sensitivity analyses were conducted to support the primary analysis using the subject populations:

- Complete-case analysis (baseline and Month 24): All subjects with valid CT scans at baseline and Month 24 were included in this analysis. Missing CT scans at Months 3, 12, or 21 were not imputed. The missing values were assumed to be missing completely at random (MCAR). This analysis was considered to have more bias in favor of CE1226, as completers are expected to have a better treatment outcome.
- Pattern-mixture model with placebo-based pattern imputation: The ITT population was used for this imputation including randomized subjects without any valid CT scans. All missing data were replaced by multiple imputation based on the subjects randomized to placebo. The missing values were assumed to be missing not at random (MNAR). Since the imputations were sampled from the subjects randomized to placebo, this analysis was considered to be conservative in favor of placebo.
- Worst-case approach: The ITT population was used for this imputation including randomized subjects without any valid CT scans. All subjects with a valid CT scan at baseline and a scan at any given time point were used for worst-case estimation for the given time point. The missing scans will be imputed in the following steps: 1) At each time point scheduled for obtaining CT scans after baseline (i.e., 3, 12, 21, and 24 months), a mixed model will be applied similar to the primary model including all subjects with data up to this time point. The individual slopes obtained from the model at time i will be ranked. The 10% subjects with the worst slopes will be selected, provided their slopes fall into a range of ± 3 SD around the mean slope (note that the mean slope is by definition 0 in this model). The restriction that the individual slopes must fall into a range of ± 3 SD will prevent from selecting extreme outliers which are not representative of the data. 2) The individual data at time i of the selected 10% subjects with the worst slopes will be used to estimate a linear regression of Adjusted P15 at time t on the baseline value of Adjusted P15. The regression model will include sex, age, and the baseline value of Adjusted P15. The regression will be estimated for each inspiration state (TLC and FRC) separately. The missing value of a subject at this time point will be imputed by the subject's baseline value multiplied by the regression coefficient associated with the baseline value of Adjusted P15 obtained from the regression model as described above (at each inspiration state). This method will be repeated at all scheduled time points

after baseline and missing values at each time point will be imputed accordingly. 3) For subjects without any CT scans or without CT scan at baseline, the data points for each inspiration state (TLC and FRC) at time t will be imputed based on averaged values of Adjusted P15 at time t obtained from the 10% subjects with the worst slopes (falling inside a range of ± 3 SD) by this time point. The Adjusted P15 at baseline will be imputed based on averaged values of Adjusted P15 at baseline from the 10% subjects with the worst slopes who were ever selected at any time t .

The effect of the region will be investigated using the primary model with country replaced by region. The difference between the regression coefficients from each of the treatments (Zemaira® minus Placebo), 95% CI for the difference and the one-sided p-value will be presented.

Study CE1226_3001

The results of the interim analysis is included in this application, the purpose and methods for this analysis was defined in a protocol amendment

The following analysis populations were defined for the interim analyses in study 3001:

ITT population: All subjects included in study CE1226_3001 after having provided signed informed consent.

ITT* population: A reduced ITT population limited to those subjects with at least 2 valid CT scans during study CE1226_3001.

Safety population: All subjects included in study CE1226_3001 and who received at least 1 dose of IMP during the study.

The ITT and ITT* populations were used for the analysis of efficacy variables. For endpoint analyses, observed cases, where subjects with a Baseline and an endpoint assessment available, was included. The Safety population was used for all safety analyses.

In study CE1226_3001, all subjects received CE1226. However, based on the randomization assignment during study CE1226_4001, 2 treatment groups were defined as follows:

- Early Start group: subjects who were randomized to CE1226 in study CE1226_4001 and continued to receive CE1226 in study CE1226_3001.
- Delayed Start group: subjects who were randomized to placebo in study CE1226_4001 and were reallocated to receive CE1226 in study CE1226_3001.

In the original protocol the study objective was to collect long-term data on safety and efficacy using the weekly dosage of 60 mg/kg b.w. The analysis plan was to use descriptive analysis of the efficacy variables stratified according to the assigned treatment in study CE1226_4001 and adverse events were to be summarized on a preferred term basis with reference to intensity and presumed relationship to study drug. In substantial amendment no. 1 the analysis plan was changed to state:

The statistical analysis will follow the same lines as planned for the Phase III/IV Zemaira® CE1226_4001 study. Efficacy and safety variables will be compared with respect to the randomized treatment group in the Phase III/IV Zemaira® CE1226_4001 study. Similar statistical models and methods will be applied. Baseline will be the final assessment of the Phase III/IV Zemaira® CE1226_4001

In version 4 of the protocol the interim analysis was defined. It defined 3 hypotheses to be tested:

1. Confirm the efficacy of CE1226 in the first 2 years for those subjects continuing into study CE1226_3001 (Baseline to Month 24).

2. Explore the difference in achieved efficacy between the Early Start and Delayed Start groups across all 4 years (Baseline to Month 48).
3. Compare the rate of disease progression between the Early Start and Delayed Start groups in the last 2 years (Month 24 to Month 48).

The ITT population was used to examine Hypothesis 1. The ITT* population was used to examine Hypotheses 1, 2, and 3.

Substantial amendment no 1. was implemented early, but during patient enrolment period, substantial amendment no 2 as resulted in protocol version 4, was implemented in 2013 in order to implement the interim analysis.

The primary endpoint was the 15th percentile of the lung density measured by yearly CT scans. The hypotheses tested were not for confirmatory purposes, all analyses were exploratory. No values were imputed. The primary efficacy endpoint was the annual rate of change in volume-adjusted lung density, Adjusted P15, obtained from a linear random regression (mixed effects) model and was expressed as a slope of time and treatment interaction from the model.

The change in the annual rate of lung density decline as measured by Adjusted P15 was calculated based on a mixed effects model at TLC and FRC inspiration states separately, as well as at a combined inspiration state. For the values corresponding to the TLC and FRC combined inspiration state, a fixed effect of inspiration state corrected for the different levels at each inspiration state. The principal interest was in the magnitude of the treatment-by-time interaction used to estimate the annual rate of change in lung density decline and its level of significance using the data obtained at TLC inspiration state.

The lung density as measured by Adjusted P15 obtained at TLC state was expected to be less affected by unexplained variation (noise) than those taken at FRC (Stoel and Stolk, 2004). The difference between the regression coefficients from each of the treatment groups indicated whether the 2 treatment groups differed in their effect on the annual rate of change in lung density decline as measured by Adjusted P15 from the CT scans. The detailed model specification is provided in the SAP (Appendix 16.1.9). Exploratory examination of Hypothesis 1 was made by applying the same primary efficacy endpoint analysis as used in study CE1226_4001, however restricted to the smaller subset of subjects who were included in study CE1226_3001.

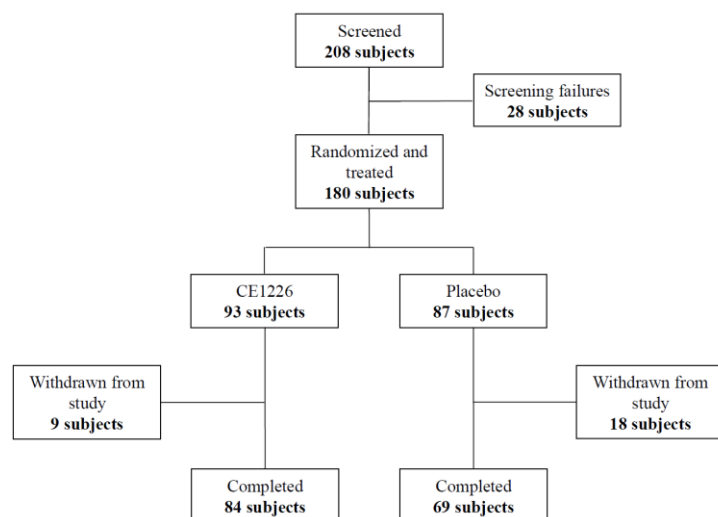
Since the data from study CE1226_3001 were no longer obtained from a randomized sample and comparisons were exploratory, missing data were not considered to be relevant given the exploratory nature of this interim analysis.

Results

Participant flow

Study CE1226_4001:

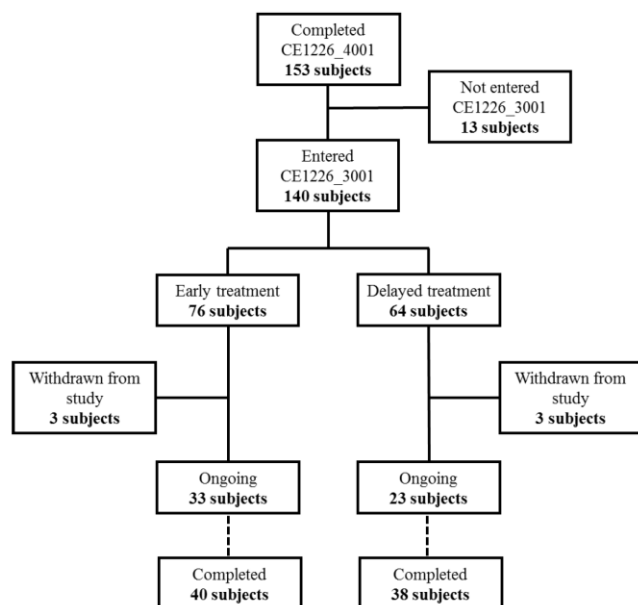
Figure 2– Overview of subject disposition



Source: CSR CE1226_4001,

Study CE1226_3001 (Interim analysis):

Figure 3– Overview of subject disposition



Source: CSR CE1226_3001

Table 11- Summary of subjects withdrawn from the study and reasons for withdrawal - studies CE1226_4001 (Randomized population) and CE1226_3001 (interim) (ITT population)

	Number (%) of subjects CE1226_4001		CE1226_3001 (interim)	
	CE1226 (N=93)	Placebo (N=87)	Early Start (N=76)	Delayed Start (N=64)
Any reason	9 (9.7)	18 (20.7)	3 (3.9)	3 (4.7)
Death	1 (1.1)	3 (3.4)	1 (1.3)	0 (0.0)
Adverse event	1 (1.1)	4 (4.6)	0 (0.0)	0 (0.0)
Withdrawn consent	5 (5.4)	7 (8.0)	1 (1.3)	1 (1.6)
Protocol violation	0 (0.0)	1 (1.1)	0 (0.0)	0 (0.0)
Missing reason	1 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)
Other	1 (1.1)	3 (3.4)	1 (1.3)	2 (3.1)
Investigator and subject decision to withdraw due to suspicion of pulmonary cancer	0 (0.0)	1 (1.1)	0 (0.0)	0 (0.0)
Lung transplantation	1 (1.1)	1 (1.1)	1 (1.3)	1 (1.6)
Not interested in spending time as a participant in the study	0 (0.0)	1 (1.1)	0 (0.0)	0 (0.0)
Subject left for prolonged vacation to Argentina	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)

ITT = Intention-to-treat;

N = Number of subjects in the population.

Study CE1226_4001

Most of the subjects who withdrew consent had previously experienced TEAEs (Listing 16.2.7), which may have contributed to their decision to withdraw from the study.

A post-hoc analysis of the proportion of subjects who withdrew from the study over time comparing the CE1226 and placebo groups revealed a statistically significantly ($p = 0.04$) lower probability for withdrawal of subjects in the CE1226 group

Protocol deviations (CE1226_4001):

The number of subjects with major protocol deviations was comparable between the CE1226 (10 [10.8%] subjects) and placebo (11 [12.6%] subjects) groups. All subjects with major protocol deviations were excluded from the PP population.

Other deviations

Deviations related to the conduct of the study were noted at 1 center (Professor McElvaney, Ireland, center 11; 11 subjects in each treatment group, where a number of exacerbations were confirmed clinically and recorded as AEs without recording the symptoms related to the Anthonisen criteria in the CRF. The AEs corresponding to the clinically confirmed exacerbations were flagged. For center 11, all exacerbations that fulfilled the Anthonisen criteria were included as exacerbations. In addition, the clinically confirmed exacerbations identified by the corresponding AE number were also included as exacerbations, irrespective of any symptoms entered in the CRF for exacerbations. Sensitivity analyses were carried out after censoring data from center 11 to assess whether this issue had any effect on the overall analyses of the exacerbation data. These analyses were performed for the exercise capacity test, and for the rate of exacerbations, and showed trends that were similar to the analyses including data from center 11.

Furthermore, a potential compromise to the blinding of the IMP was identified early in the study due to a visual difference between the reconstituted CE1226 and placebo preparations.

This issue was addressed by ensuring that the IMP was physically masked after reconstitution. However, it appears that this measure was not implemented in a timely fashion at center 11. Thus, for the analyses of AEs, a robustness analysis was carried out to account for the potential unblinding issue at center 11. PTs that were deemed “at least possibly related” when they occurred as AEs in subjects at centers other than center 11 were all upgraded to “possibly related” at center 11 if they occurred at center 11, regardless of their original causality assessment. This robustness analysis revealed no relevant effect on the TEAE or SAE profiles for CE1226 or placebo treatments.

Recruitment

Study CE1226_4001 First subject in: 1 March 2006
Last subject out: 26 September 2012

Study CE1226_3001 First subject in: 2 April 2008
Database cut-off date: 1 April 2013
Database cut-off date for lung density analyses: 06 February 2013

Conduct of the study

Study CE1226_4001

Protocol amendments

There were 6 substantial amendments to the original study protocol (version 1, dated 25 July 2005). The main substantial changes are summarized below. Apart from Amendment 1, all amendments were implemented after the first subject had been enrolled into the study (01 March 2006). In addition, there were numbers of non-substantial amendments.

The main substantial changes:

Protocol version 3.0, 26 September 2005, *Amendment 1*

The text was updated to provide, in very rare cases, for additional CT scans that could have been necessary because of incorrect scans due to technical or human error. A respective reference to literature regarding the exercise capacity test was also made.

Protocol version 4.0, 29 August 2006, *Amendment 2*

- The inclusion criteria have been changed; i.e. the upper age limit has been changed from 60 to 65 years.
- A coordinating investigator was nominated.
- Missing actions (handing over and reviewing of subject diaries) during the Visits 1 and 2 were added.
- No IMP was to be given during Visit 10, because no follow-up period was planned.
- The description of the statistical analysis was revised after it was found that, due to an oversight, changes to the proposed analysis made in response to discussions with the FDA had not been implemented in the protocol.
- Revisions were made to describe the nomination of a central laboratory and the involvement of a distribution center for issuing the IMP.
- The responsible person for SAE reporting was changed.
- Incorrect terms and wording in the study protocol were changed.

Protocol version 5.0, 28 September 2006, *Country specific Amendment Czech Republic*

- The patients were offered the possibility to select the most appropriate and convenient way for the regular study medication applications (to either in the study center, or by nurses of a home care service, or by the family doctor)

Protocol version 6.0, 23 July 2008, *Amendment 3*

- Inclusion criteria were revised to clarify that vaccinated subjects with positive hepatitis A and/or B serology and no signs of chronic or acute hepatitis A and/or B could be enrolled in the study.
- Exclusion criteria were revised to allow for inclusion of subjects with a positive cotinine test due to nicotine replacement therapy (eg, patches, chewing gum) or snuff.
- The number of planned study centers was increased due to the low recruitment rate.
- Provision was made for genotyping at a central laboratory in countries where genotyping could not be performed due to technical reasons.
- Appendix 5 (CT Scan) was amended as follows:
 - Clarification of the procedure for acquiring whole lung density evaluations,
 - Clarification of the procedure for replacement of a CT scanner at an institution during conduct of the study,
 - Provision for availability of additional phantom scans during the center qualification procedure,
 - Clarification of the use of a short acting bronchodilator to facilitate holding of breath in the CT procedure, as needed. (*Change from:* A short acting bronchodilator (beta-mimetic spray) with a standardized dose needs to be applied within the 4 hours preceding the CT scanning, for standardization purposes and to facilitate breath hold.
Change to: If optimal therapy for the treatment of the subject's emphysematous condition is interrupted for any reason, a short acting bronchodilator (beta sympathomimetic amine spray) with a standardized dose should be used by the subject within the 4 hours preceding the CT scanning to facilitate the required breath holds in the procedure.)
- The description of the statistical analysis of CT evaluations was updated. In the previous version of the study protocol, the analysis was defined for the 15th percentile of the lung density (P15) without reference to the lung volume. The text was modified to account for this dependency.

- The abbreviation list was updated.
- The text on documentation and use of study findings was revised.
- Changes in department name and staff were implemented.
- The name of the sponsor was changed from ZLB Behring to CSL Behring.
- Protocol version 7.0, 12 January 2009, *Amendment 4*
- Sample size adaption: up to 180 subjects were to be enrolled until the (originally intended) interim analysis, whichever occurred first.
- Changes in study personnel were documented.
- Contact information (fax and email) was updated for SAE reporting.

- The text was revised to include the need for pregnancy occurring during the study to be reported.
- Additional units (or < 80 mg/dL) were added for the serum A1-PI levels specified in the inclusion criteria to < 11 µM or < 80 mg/dL)
- Diagnosis of A1-PI deficiency criteria, A1-PI level was changed from < 11 µM to < 11 µM or < 80 mg/dL.
- Accovion GmbH was removed from the protocol.
- Administrative changes were documented.

Protocol version v.2.0, 12 October 2010, *Amendment 5*

Changes were made to the proposed statistical analysis (see below), and the SAE reporting process was clarified.

Protocol version V1.0, 27 June 2012, *Amendment 6*

- The document was placed into the latest version of CSL Behring's protocol document template (STPRE011 version 9).
- The analysis of the primary endpoint was clarified.
- The key secondary objectives were listed separately from the remaining secondary objectives and were ranked in the following hierarchical order: change in exercise capacity assessed by ISWT, change in symptoms score assessed by SGRQ, and risk of pulmonary exacerbation assessed by the annual rate of exacerbations. The rationale for this change was to identify those key secondary efficacy parameters that would help to explain the clinical relevance of the primary objective, ie, lung density change measured by CT scan. The text pertaining to secondary endpoints and efficacy variables, as well as exploratory endpoints and efficacy variables, was adjusted accordingly throughout the study protocol.
- Text describing determination of the sample size and the study population was modified to reflect the historical data more accurately and describe each subject population in this study more extensively.
- The primary efficacy analysis was updated because a physiological adjustment (lung volume-adjusted) lung density was applied in this study for the primary analysis.
- The secondary efficacy analysis was updated and elaborated according to the order of the adjusted key and additional secondary objectives mentioned above.
- The safety analysis was updated to include details of the analysis method and an updated definition of ARs to "AEs starting within 72 hours of the end of IMP administration plus all AEs at least possibly related to the administration of IMP"; this update to the definition was made in order to comply with FDA requirements.
- The interim analysis was removed from the study protocol per communication with the FDA dated 10 May 2011.

Changes in the planned analyses

Originally (amended protocol 4 dated 12 January 2009) it was planned to carry out an unblinded re-estimation of the sample size once 50 subjects had completed the 2-year treatment period. Instead, in 2010 a blinded reestimation of the study sample size was done using data accrued on 69 subjects with at least 1 post-baseline CT scan who had either completed the study already or withdrew prematurely. Due to the outcome of this blinded re-estimation of the study sample size the planned unblinded interim analysis was not conducted.

In the amended protocol 6 dated 27 June 2012, it was stated that the number of exacerbations (and related symptoms) would be analyzed using a Poisson regression model, and that the procedure GENMOD would be used for the Poisson regression. This was a typographic error in the protocol. The number of exacerbations (and related symptoms) were analyzed using a negative binomial model, as stated in the synopsis of, and elsewhere in, the protocol.

During blinded review of the data, it was decided to implement the following changes to the analysis:

- Present analysis of other pulmonary function assessments, BMI, SGRQ total, activity, and impacts scores, and CRP only for ITT population. The ITT population was the population of primary interest.
- Present correlation analyses only for the PP population. It was assumed that the variation in the PP population would be smaller than in the ITT population. Relationships between variables would be more pronounced in the PP population.
- Omit the analysis of exacerbation related symptoms. Only very few symptoms were entered on the CRF when the definition of an exacerbation was not fulfilled. The data did not support the analyses outlined in the study protocol.
- Omit the stratification based on i-BODE score as the dyspnea scale was only collected for subjects with exacerbations that fulfilled the Anthonisen criteria.
- Omit the analysis of proportion of subjects who stopped the exercise capacity test. The question in the CRF "Was the test stopped prematurely?" was not answered consistently because "premature stop of the test" was not clearly defined.
- Calculate "expected compliance" in addition to "overall compliance." It was considered of interest to relate compliance, not only to the actual treatment duration, but also to the planned treatment duration.
- Include the number of screening failures in summary tables and listings. This is a requirement from regulatory authorities.

In addition, an error was corrected in the description of the "worst-case approach" sensitivity analysis of the primary efficacy variable. The 99% CI originally suggested is a measure for the accuracy of the estimated mean and is not suitable for identifying outliers. Outliers among estimates for the individual slopes were instead defined by all values outside a range of ± 3 SD around the mean (the mean being 0 by definition in this model).

The summary tables for demographic and other baseline characteristics were only presented overall, and not stratified by the baseline parameters described in the SAP.

The mean annual rate of change in Adjusted P15 and its 95% CI were presented based on subjects with particular patterns of valid CT scans only for the primary analysis, but not for the sensitivity analyses.

Study CE1226_3001 Protocol amendments

There were 2 substantial amendments to the original study protocol (dated 30 November 2007). The main changes are summarized below.

The first of 2 global substantial amendments in study CE1226_3001 was implemented on 23 July 2008 to harmonize the statistical analysis methods to match those foreseen for study CE1226_4001 and introduce a more detailed efficacy analysis under the assumptions that the full results for study CE1226_3001 would follow 2 years after closure of study CE1226_4001 and, more importantly, that no interim analysis was anticipated in study CE1226_3001.

The second amendment dates from May 2013 and reflects changes to the SAP for study CE1226_3001 following the corroboration of study CE1226_4001 data with the 4-part methodology published by Dirksen et al 2009. Specifically, both study CE1226_4001 and the EXACTLE study achieved statistical significance with similar methodology assessing the change from Baseline using statistically adjusted lung density obtained at the TLC inspiration state. Confirming this pattern of efficacy over a 4-year period as well as examining the disease modifying effects of CE1226 through the 3 hypotheses postulated, 2 years prior to study completion was the rationale for introducing this interim analysis into study CE1226_3001.

Changes in the planned analyses

The statistical analyses included in this interim were performed as specified in the protocol

Amendment 2 and the SAP, both dated on 15 May 2013.

This interim analysis is in addition to the planned analyses after completion of the study.

Specifically, the following analytical changes were introduced for the interim analysis:

- Tables for demography and Baseline characteristics added for subjects with CT scans until Month 36 and until Month 48.
- Add analysis of rate of change in Adjusted P15 for subjects who have at least 2 valid scans from Month 24 to 48.
- Use only subjects who have Baseline, Month 24, and Month 48 CT scans for analyses of absolute and % change in Adjusted P15.
- Use Baseline CT scan as covariate for analyses of change in Adjusted P15 from Baseline at Month 24 and change from Baseline at Month 48 analyses. Use Month 24 CT scan as covariate for change from Month 24 at Month 48 analysis.
- Use 1-sided p-value for analyses of rate of change in Adjusted P15 according to impact of exploratory covariates.
- Use arithmetic means instead of least-squares means to estimate mean change in Adjusted P15 from Baseline at Month 24 and mean Change from Month 24 at Month 48. Use paired t-test to compare the mean difference of changes between the 2 periods instead of the mixed model approach proposed in the SAP.

Baseline data

Study CE1226_4001 and CE1226_3001 (interim)

Table 12– Baseline demographic characteristics and disease characteristics – studies CE1226_4001 and CE1226_3001 (interim) (ITT population)

Study	CE1226_4001		CE1226_3001 (interim)	
Treatment Group Treatment	CE1226 (N=93)	Placebo (N=87)	Early Start Group (N=76)	Delay Start Group (N=64)
Age, years; mean (SD)	53.8 (6.91)	52.4 (7.81)	56.4 (6.87)	53.3 (7.82)
Sex; n (%)				
Male	48 (51.6)	50 (57.5)	41 (53.9)	38 (59.4)
Female	45 (48.4)	37 (42.5)	35 (46.1)	26 (40.6)
Race; n (%)				
White	93 (100.0)	87 (100.0)	76 (100.0)	64 (100.0)
Ethnicity; n (%)				
Hispanic or Latino	4 (4.3)	1 (1.1)	2 (2.6)	0
Not Hispanic or Latino	89 (95.7)	86 (98.9)	74 (97.4)	64 (100.0)
Body mass index, kg/m ² ; mean (SD)	25.5 (4.79)	26.6 (4.07) ^a	25.2 (4.11)	26.0 (3.61)
Region; n (%)				
Australia	9 (9.7)	11 (12.6)	8 (10.5)	9 (14.1)
North America ^b	24 (25.8)	22 (25.3)	14 (18.4)	11 (17.2)
Nordic	30 (32.3)	30 (34.5)	29 (38.2)	26 (40.6)
Europe	30 (32.3)	24 (27.6)	25 (32.9)	18 (28.1)
FEV ₁ ; L	1.58 (0.51)	1.60 (0.47)	1.49 (0.48)	1.57 (0.47)
FEV ₁ % predicted; %	47.4 (12.1)	47.2 (11.1)	45.7 (12.7)	46.4 (11.9)
FEV ₁ /FVC ratio	0.45 (0.11)	0.43 (0.10)	0.43 (0.11)	0.42 (0.09)
DL _{CO} ; mL/mmHg/min	13.6 (5.31)	15.0 (5.62)	-	-
Adjusted P15 lung density at TLC and FRC state combined; g/L	46.6 (15.6)	49.8 (15.1)	43.0 (14.8)	44.8 (14.1)
Adjusted P15 lung density at TLC state; g/L	45.5 (15.8)	48.9 (15.5)	42.2 (15.1)	43.6 (14.5)
Adjusted P15 lung density at FRC state; g/L	47.6 (15.7)	50.7 (15.0)	43.9 (14.7)	46.0 (14.0)
Exercise capacity: distance walked; m	424.5 (183.0)	435.1 (199.7)	-	-
SGRQ total score	44.3 (17.1)	42.4 (18.0)	-	-
SGRQ activity score	62.1 (18.6)	60.1 (21.4)	-	-
SGRQ impacts score	33.6 (18.4)	31.4 (17.6)	-	-
SGRQ symptoms score	46.5 (22.7)	44.1 (24.8)	-	-
Duration of disease ^c ; years	5.63 (6.14)	6.14 (6.56)	5.81 (6.30)	6.25 (6.91)
Antigenic A ₁ -PI concentrations; µM	6.34 (4.65)	5.95 (2.46)	15.87 (3.74)	5.86 (2.47)
Functional A ₁ -PI concentrations; µM	2.80 (3.62)	2.31 (1.42)	9.72 (2.74)	2.41 (1.42)
A ₁ -PI genotype; n (%)				
ZZ	83 (89.2)	83 (95.4)	67 (88.2)	61 (95.3)
SZ	2 (2.2)	0	2 (2.6)	0
Z/Null	2 (2.2)	1 (1.1)	1 (1.3)	0
Other	6 (6.5)	3 (3.4)	6 (7.9)	3 (4.7)

n = number of subjects; N = number of subjects in the population; SD = standard deviation.

^a N = 86; 1 subject had a missing value

A₁-PI = alpha1-proteinase inhibitor; DLCO = diffusion capacity of carbon monoxide; FEV₁ = forced expiratory volume in 1 second; FRC = functional residual capacity; FVC = forced vital capacity; N = number of subjects in the population; PEF = peak expiratory flow; RV = residual volume; SD = standard deviation; SGRQ = St. George's Respiratory Questionnaire; TLC = total lung capacity; VC = vital capacity.

For some individual characteristics, the number of subjects with data may be less than the total ITT population.

Table 13 - Disease characteristics at baseline (frequencies and descriptive statistics) (ITT population)

	Zemaira (N=93)	Placebo (N=87)	Total (N=180)
Antigenic AI-PI levels [mg/mL] at Day 1			
n	90	86	176
Mean (SD)	0.2881 (0.21130)	0.2705 (0.11202)	0.2795 (0.16994)
SE	0.02227	0.01208	0.01281
Q25	0.2140	0.2150	0.2145
Median	0.2395	0.2450	0.2425
Q75	0.2860	0.3020	0.2920
Min, Max	0.144, 2.007	0.161, 1.037	0.144, 2.007

Source: CSR CE1226_4001,

Study CE1226_4001

Medical history

The proportion of subjects who had a medical history that was not ongoing at baseline was 72.0% in the CE1226 group and 63.2% in the placebo group. Among these subjects, the SOC with the highest incidence of medical history was surgical and medical procedures, with an incidence of 41.9% in the CE1226 group and of 42.5% in the placebo group. The next most common (at least 10% of subjects in either group) SOCs affected, were infections and infestations (19.4% with CE1226 and 9.2% with placebo), gastrointestinal disorders (11.8% with CE1226 and 10.3% with placebo), and respiratory, thoracic and mediastinal disorders (8.6% with CE1226 and 11.5% with placebo).

Within the SOC of infections and infestations, medical history PTs present in more than 1 subject in either treatment group were: pneumonia (7 subjects in the CE1226 and 1 subject in placebo group), hepatitis A (5 subjects in the CE1226 and 1 subject in placebo group), hepatitis B (1 subject in the CE1226 and 2 subjects in placebo group), and bronchitis (no subjects in the CE1226 and 2 subjects in placebo group). The incidences in the remaining SOCs were generally comparable between the 2 treatment groups.

Concurrent illnesses

The proportion of subjects with concurrent illnesses was 93.5% in the CE1226 group and 95.4% in the placebo group. The majority of subjects in each group had concurrent illnesses that were mild or moderate in severity. The proportion of subjects with severe concurrent illnesses was 21.5% in the CE1226 group and 27.6% in the placebo group. As expected for the study population, the highest incidence of concurrent illnesses was in the SOC of respiratory, thoracic and mediastinal disorders; the proportion of subjects in this SOC was 63.4% in the CE1226 group and 72.4% in the placebo group.

Table 14- Concurrent illnesses and severity of the condition at baseline (frequencies) (ITT population)

System Organ Class Preferred Term	Zemaira (N=93) n (%)	Placebo (N=87) n (%)	Total (N=180) n (%)
Any Present Medical Condition	87 (93.5)	83 (95.4)	170 (94.4)
MILD	20 (21.5)	20 (23.0)	40 (22.2)
MODERATE	47 (50.5)	39 (44.8)	86 (47.8)
SEVERE	20 (21.5)	24 (27.6)	44 (24.4)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	59 (63.4)	63 (72.4)	122 (67.8)
MILD	6 (6.5)	9 (10.3)	15 (8.3)
MODERATE	38 (40.9)	38 (43.7)	76 (42.2)
SEVERE	15 (16.1)	16 (18.4)	31 (17.2)
CHRONIC OBSTRUCTIVE PULMONARY DISEASE	39 (41.9)	28 (32.2)	67 (37.2)
MILD	2 (2.2)	2 (2.3)	4 (2.2)
MODERATE	28 (30.1)	17 (19.5)	45 (25.0)
SEVERE	9 (9.7)	9 (10.3)	18 (10.0)
EMPHYSEMA	22 (23.7)	27 (31.0)	49 (27.2)
MILD	2 (2.2)	2 (2.3)	4 (2.2)
MODERATE	15 (16.1)	19 (21.8)	34 (18.9)
SEVERE	5 (5.4)	6 (6.9)	11 (6.1)

Medical histories were coded using MedDRA version 15.0. If a subject recorded multiple system organ classes and/or preferred terms, the subject was counted only once in the subject count in the "Any Present Medical Condition" and in the System Organ Class row.
Subject ID 11103 and 11104 are IDs for the same individual. This individual discontinued after 2 months and was randomized again 9 months later. Therefore these two subject IDs are treated as different individuals.

Source: CSR CE1226_4001

The next most common incidences ($\geq 20\%$ of subjects in either group) were in the SOC of nervous system disorders (31.2% with CE1226 and 28.7% with placebo), musculoskeletal and connective tissue disorders (30.1% with CE1226 and 24.1% with placebo), gastrointestinal disorders (28.0% with CE1226 and 25.3% with placebo), vascular disorders (24.7% with CE1226 and 27.6% with placebo), congenital, familial and genetic disorders (21.5% with CE1226 and 16.1% with placebo), and psychiatric disorders (14.0% with CE1226 and 21.8% with placebo). The proportion of subjects with concurrent illnesses in the remaining SOC was less than 20% in both groups.

Prior and/or concomitant medications

The proportion of subjects with prior medications was 34.4% in the CE1226 group and 33.3% in the placebo group. The most frequent prior medications, used by at least 5% of subjects in either group, were hepatitis vaccines (5.4% subjects with CE1226 and 8.0% subjects with placebo), selective beta-2-adrenoreceptor agonists (7.5% subjects with CE1226 and 3.4% subjects with placebo), glucocorticoids (5.4% subjects with CE1226 and 3.4% subjects with placebo), and propionic acid derivatives (2.2% subjects with CE1226 and 5.7% subjects with placebo). The proportions of subjects for all remaining classes of prior medications were less than 5% in both groups.

The proportion of subjects on concomitant medications was 98.9% in the CE1226 group and 97.7% in the placebo group. The most frequent concomitant medications (by the Anatomical Therapeutic Chemical [ATC] Classification System), used by at least 20% of subjects in either group, were influenza vaccines (54.8% with CE1226 and 55.2% with placebo), anilides (54.8% with CE1226 and 49.4% with placebo), glucocorticoids (47.3% with CE1226 and 39.1% with placebo), macrolides (39.8% with CE1226 and 39.1% with placebo), selective beta-2-adrenoreceptor agonists (35.5% with CE1226 and 36.8% with placebo), propionic acid derivatives (31.2% with CE1226 and 39.1% with placebo), combinations of penicillins (including beta-lactamase) (34.4% with CE1226 and 34.5% with placebo), fluoroquinolones (33.3% with both CE1226 and placebo), penicillins with extended spectrum (34.4% with CE1226 and 29.9% with placebo), natural opium alkaloids (25.8% with CE1226 and 27.6% with placebo), and adrenergics and other drugs for obstructive airway (23.7% with CE1226 and 27.6% with placebo).

with placebo). The proportions of subjects for all remaining concomitant medications were less than 20% in both groups.

Numbers analysed

Study CE1226_4001:

Population	Number (%) of subjects	
	CE1226	Placebo
Randomized	93 (100.0)	87 (100.0)
Intention-to-treat	93 (100.0)	87 (100.0)
Per-protocol	83 (89.2)	76 (87.4)
Safety	93 (100.0)	87 (100.0)

Source: CSR CE1226_4001, Table 4

Study CE1226_3001:

Study Population	Number of subjects	
	Early Start	Delayed Start
Subjects enrolled	76	64
Intention-to-treat	76	64
Intention-to-treat* ^a	53	53
Safety ^b	76	64

Intention-to-treat* population corresponds to all subjects who have at least 2 valid scans in study CE1226_3001 (Month 24 to Month 48) (interim).

^a Cut-off date of 06 February 2013.

^b Cut-off date of 01 April 2013.

Source: CSR CE1226_3001, Interim analysis, Table 4

Outcomes and estimation

Study CE1226_4001

Primary efficacy endpoint

- Lung volume-adjusted lung density (Adjusted P15) estimated by the 15th percentile of the frequency histogram of the lung pixels.

Table 15– Study CE1226_4001: Physiologically Adjusted P15 (g/L) measured values at 0, 12 and 24 Months at TLC, FRC, and mean of TLC and FRC states (ITT population)

Months at T26, T46, and mean of T26 and T46 values (ITT population)						
	0 Monhts		12 Months		24Months	
	Mean (standard deviation)					
Parameter	CE1226	Placebo	CE1226	Placebo	CE1226	Placebo
Adjusted P15 at mean of <u>TLC and FRC</u> , g/L	46.6 (15.6) (N=90)	49.8 (15.1) (N=83)	45.6 (16.6) (N=84)	47.2 (13.7) (N=72)	44.4 (15.5) (N=82)	45.5 (13.9) (N=69)
Adjusted	45.5 (15.8)	48.9 (15.5)	44.7 (16.8)	46.1 (13.7)	43.6 (16.0)	43.9 (13.8)

P15 at TLC , g/L	(N=90)	(N=83)	(N=84)	(N=72)	(N=82)	(N=68)
Adjusted P15 at FRC , g/L	47.6 (15.7) (N=90)	50.7 (15.0) (N=83)	46.6 (16.6) (N=84)	48.4 (14.1) (N=72)	45.3 (15.3) (N=82)	46.8 (13.8) (N=69)

Source: CSR 1226_4001

Table 16– Physiologically Adjusted P15 (g/L) measured values and change and % change from baseline at TLC, FRC, and mean of TLC and FRC states (ITT population)

Inspiration state	Treatment	Adjusted P15 (g/L) Mean (SD)			
		Baseline	Month 24	Change from baseline	% change from baseline
Mean of TLC + FRC	CE1226 (N=90)	46.6 (15.6)	44.4 (15.5)	-2.67 (4.30)	-6.06 (9.67)
	Placebo (N=83)	49.8 (15.1)	45.5 (13.9)	-3.93 (4.02)	-8.28 (8.89)
TLC	CE1226 (N=90)	45.5 (15.8)	43.6 (16.0)	-2.60 (4.44)	-6.22 (9.66)
	Placebo (N=83)	48.9 (15.5)	43.9 (13.8)	-4.20 (4.50)	-8.97 (10.3)
FRC	CE1226 (N=90)	47.6 (15.7)	45.3 (15.3)	-2.74 (4.75)	-5.81 (11.3)
	Placebo (N=83)	50.7 (15.0)	46.8 (13.8)	-3.73 (4.46)	-7.59 (9.64)

FRC = functional residual capacity; N = number of subjects; P15 = 15th percentile of the lung density; TLC = total lung capacity; SD = standard deviation.

Baseline was the computed tomography scan at Day 1 or close to Day 1.

Source: [Table 14.2-1.1](#); [Table 14.2-1.1.1](#)

Source: CSR CE1226_4001, Table 9

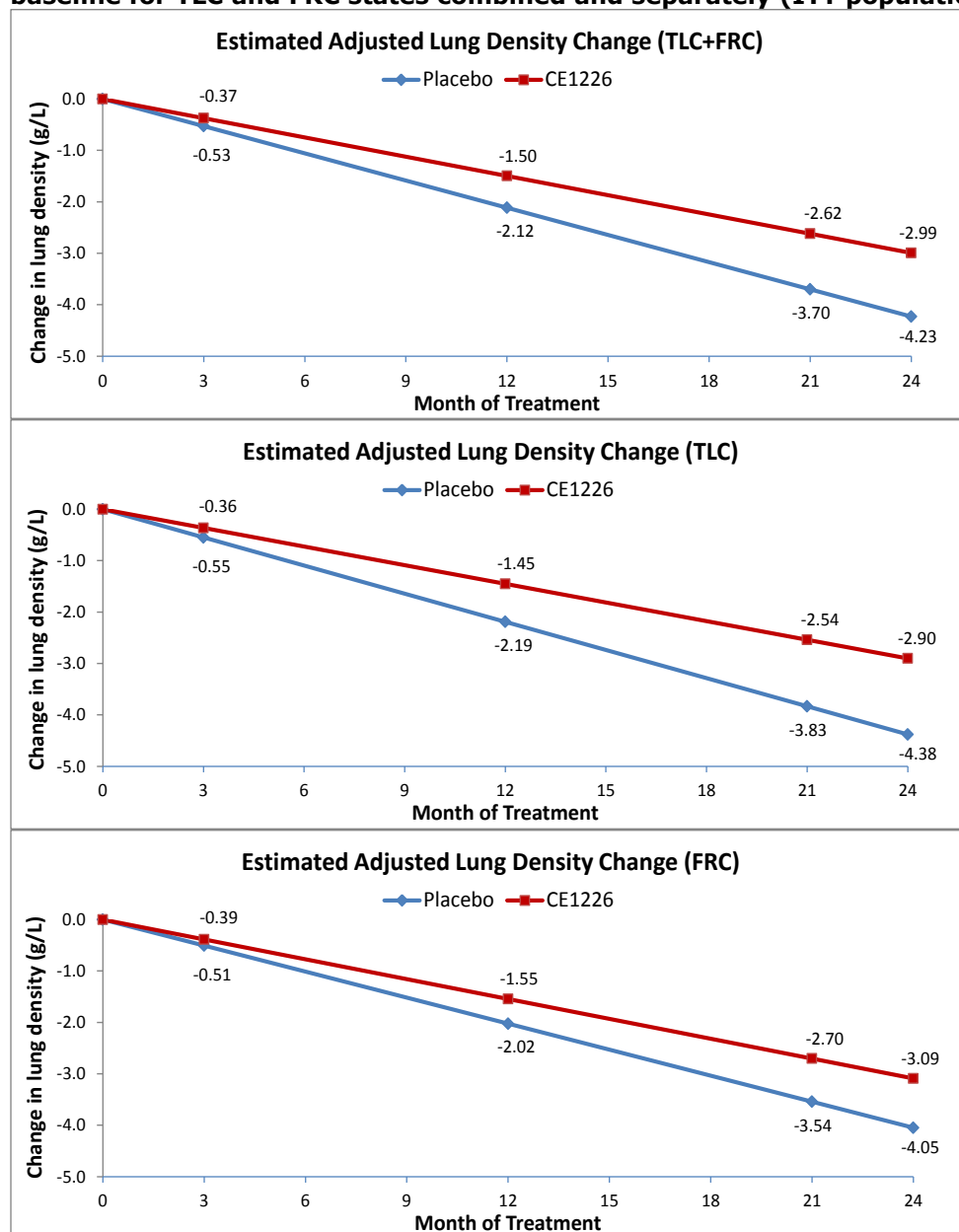
Table 17– Treatment comparison for annual rate of change in physiologically Adjusted P15 (g/L) at TLC and FRC states combined and separately based on a random regression model (ITT population)

Inspiration state	N		Point estimate (SE)		Difference CE1226 - placebo		
	CE1226	Placebo	CE1226	Placebo	Difference	95% CI	1-sided p-value
TLC and FRC combined	92	85	-1.50 (0.22)	-2.12 (0.24)	0.62	-0.02; 1.26	0.029
TLC only	92	85	-1.45 (0.23)	-2.19 (0.25)	0.74	0.06; 1.42	0.017
FRC only	92	85	-1.55 (0.24)	-2.02 (0.26)	0.48	-0.22; 1.18	0.090

Adjusted P15 = Lung volume-adjusted 15th percentile of the lung density; CI = confidence interval; FRC = functional residual capacity; TLC = total lung capacity; N = number of subjects who had at least 1 computed tomography scan available; SE = standard error;

Source: Summary of clinical efficacy

Figure 4 – Estimated rate of decline in physiologically Adjusted P15 (g/L) shown as change from baseline for TLC and FRC states combined and separately (ITT population)



Adjusted P15 = Lung volume-adjusted 15th percentile of the lung density; FRC = Functional residual capacity; ITT = Intention-to-treat; TLC = Total lung capacity.

Source: Summary of clinical efficacy

Post Hoc analysis:

The primary efficacy analysis was repeated using statistically Adjusted P15 values. In the ITT population, the treatment difference for the annual rate of change in statistically Adjusted P15 at the TLC and FRC states combined was 0.64 g/L in favour of CE1226 and marginally not statistically significant (1-sided p-value of 0.029). The difference in the annual rate of decline in Adjusted P15 of 0.65 g/L in favour of CE1226 at the TLC state was statistically significant (p-value of 0.021). The 0.61 g/L difference in favour of CE1226 at FRC state did not achieve significance (p-value of 0.068).

Extrapolation of data and clinical relevance of results according to the Applicant

The importance of the reduced decline in lung density for subjects treated with CE1226 is potentially very high. The terminal event for a patient with severe A₁-PI deficiency and progressive emphysema is usually death or lung transplantation. Within study CE1226_4001, the average lung density based on the last available measurement at TLC state for the 5 subjects who died, underwent lung transplantation, or had severe respiratory dysfunction, irrespective of treatment group, was just below 20 g/L (n = 5; section 5.3.5.1.1, CE1226_4001 CSR, Listing 16.2.6.1, subjects 5104, 5201, 9107, 1116, and 5105). Using this level of lung density as a threshold level, and the observed reduction in alveolar tissue destruction in subjects treated with CE1226, the time towards respiratory failure can theoretically be extrapolated. Such a hypothetical calculation is shown below in the Table, where the available data for CE1226 are projected over time.

While acknowledging the limitation of basing this calculation on lung density data from only 5 subjects, this example indicates that for subjects treated with CE1226 the time to reach putative terminal respiratory function is potentially extended by 5.8 years, representing an approximately 50% increase. CSL Behring therefore believes that the results of study CE1226_4001 indicate an important benefit of CE1226 treatment for patients with A₁-PI deficiency and symptomatic loss of lung function.

Table 18- Extrapolation of CE1226 effect on the time to reach putative terminal respiratory function (data from study CE1226_4001)

	CE1226 (N=93)	Placebo (N=87)
Baseline lung density at TLC state (g/L)		47.1
Annual change in lung density at TLC state (g/L/year)	-1.5	-2.2
Lung density at terminal respiratory function (g/L)		20
Change in lung density to terminal respiratory function (g/L)		27.1
Time to terminal respiratory function (y)	18.1	12.3

N = Number of subjects; TLC = Total lung capacity.

Formula used for calculation of time to terminal respiratory function/death:

Change in lung density to terminal respiratory function / annual change in lung density.

Source: Summary of clinical efficacy

Secondary key efficacy endpoints

- Change in exercise capacity assessed by the incremental shuttle walking test (ISWT).

In the ITT population, the mean distance walked in the exercise capacity test at Day 1 was slightly lower with CE1226 (424.5 m [SD: 183.0]) compared with placebo (435.1 m [SD: 199.7]). The mean change from Day 1 to Month 24 in the distance walked was lower with CE1226 (10.8 m [SD: 139.8]) compared with placebo (16.1 m [SD: 101.6]). In the PP population, the mean change from Day 1 to Month 24 in the distance walked was higher with CE1226 (17.7 m [SD: 141.7]) compared with placebo (14.0 m [SD: 103.6]).

Analysis of the treatment difference for the change from Day 1 to Month 24 for observed values using an ANCOVA revealed a change in the distance walked that was 13.1 m in favour of placebo, as compared with CE1226 (Table 16). However, this difference was not statistically significant. A similar trend was observed for the PP population.

- Change in symptoms assessed by the St. George's Respiratory Questionnaire (SGRQ).

Higher scores in the SGRQ indicate more limitations in terms of overall health, daily life, and perceived well-being in subjects with obstructive airways disease.

In the ITT population, the mean SGRQ symptoms score with CE1226 (46.5 [SD: 22.7]) and placebo (44.1 [SD: 24.8]) was comparable at Day 1. The mean change from Day 1 to Month 24 in the SGRQ symptoms score was -1.39 (SD: 16.7) with CE1226 and 2.01 (SD: 20.1) with placebo. Similar trends were also seen in the PP population.

Analysis of the treatment difference for the change from Day 1 to Month 24 in SGRQ symptoms score for observed values using an ANCOVA revealed a change of 1.11 in favour of CE1226, as compared with placebo. However, this difference was not statistically significant. A similar trend was observed for the PP population.

- The rate of pulmonary exacerbations.

Table 19- Number of exacerbations (frequencies) (ITT population)

Subgroup: Overall		
	Zemaira (N=93)	Placebo (N=87)
Number of Exacerbations	n (%)	n (%)
0 exacerbations	25 (26.9)	28 (32.2)
>= 1 exacerbations	68 (73.1)	59 (67.8)
1-3 exacerbations	38 (40.9)	35 (40.2)
4-6 exacerbations	14 (15.1)	16 (18.4)
> 6 exacerbations	16 (17.2)	8 (9.2)

[1] Other comprises countries with less than 7 subjects (Czech Republic, Estonia, Finland, Poland, Romania, and Russia). Subject ID 11103 and 11104 are IDs for the same individual. This individual discontinued after 2 months and was randomized again 9 months later. Therefore these two subject IDs are treated as different individuals.

Source: CSR, Table 14.2-2.3.1

The annual exposure-adjusted incidence rate of exacerbations in the ITT population was 1.70 (95% CI: 1.51 to 1.89) exacerbations/subject year with CE1226 and 1.42 (95% CI: 1.23 to 1.61) exacerbations/subject year with placebo. The annual exposure adjusted incidence rate of exacerbations in the PP population was 1.80 (95% CI: 1.59 to 2.01) exacerbations/subject year with CE1226 and 1.35 (95% CI: 1.16 to 1.55) exacerbations/subject year with placebo. Analysis of the treatment difference for the rate of exacerbations per subject year using a negative binomial regression model revealed an estimated exacerbation ratio of 1.26 in favour of placebo, as compared with CE1226. However, this difference was not statistically significant. A similar trend was observed for the PP population.

Other secondary efficacy endpoints

- Adjusted P15 change from baseline to Month 24: The change between Adjusted P15 obtained by CT scans at baseline and at Month 24.

The analysis of the treatment difference for the change from baseline to Month 24 in Adjusted P15 was planned in the protocol as a secondary efficacy analysis. Analysis of the treatment difference for the change from baseline to Month 24 in physiologically Adjusted P15 for observed values using a mixed effects model revealed changes ranging from 0.89 to 1.32 g/L and in favor of CE1226, i.e. TLC+FRC: 1.04 g/L (p=0.058, one sided p-value), TLC: 1.32 g/L (p=0.028, one sided p-value) and FRC: 0.89 g/L (p=0.115, one sided p-value).

Similar differences were observed for the PP population, but they did not achieve statistical significance.

- Pulmonary function - Key spirometry variables

Analysis of the treatment difference for the overall rate of change in FEV₁ in the ITT population using a random regression model revealed a change of 0.003 L in favour of placebo, as compared with CE1226. This difference was not statistically significant. A similar trend was also seen in the PP population.

Table 20– Treatment comparison for % change from baseline (Day 1) to Month 24 in key spirometry variables for observed values (ANCOVA) (ITT population)

Analysis	Least squares means (SE)		CE1226 minus placebo	95% CI	2-sided p-value
	CE1226 (N=89)	Placebo (N=84)			
FEV ₁	-4.29 (1.26)	-2.06 (1.30)	-2.24	-5.73; 1.26	0.208
FEV ₁ % predicted	-4.16 (1.27)	-1.90 (1.31)	-2.26	-5.79; 1.26	0.207
DL _{CO}	-3.16 (1.96)	-1.85 (2.03)	-1.31	-6.80; 4.19	0.639
FEV ₁ /FVC ratio	-2.68 (1.36)	1.56 (1.40)	-4.24	-8.04; -0.45	0.029

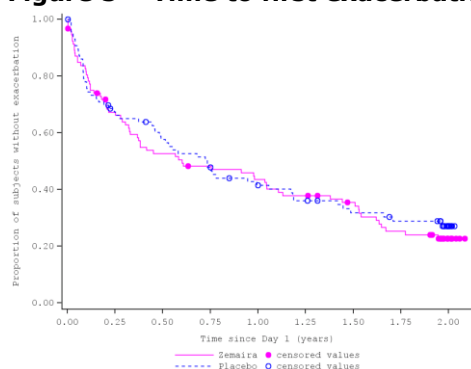
CI = confidence interval; DL_{CO} = diffusion capacity of carbon monoxide; FEV₁ = forced expiratory volume in 1 second; FVC = forced vital capacity; N = number of subjects; SE = standard error.

Source: CSR, Table 19

- Characteristics of pulmonary exacerbations

Time to first exacerbation

Figure 5 – Time to first exacerbation (Kaplan-Meier plot) (ITT population)



Source: CSR

Duration and severity of exacerbations

Table 21– Duration of exacerbations, duration of hospitalizations due to exacerbations, and duration of antibiotic treatment due to exacerbations (ITT population)

Analysis	Mean (SD)	
	CE1226 (N=68)	Placebo (N=59)
Duration of exacerbations, years	0.26 (0.26)	0.18 (0.19)
Duration of exacerbations relative to total study duration, %	13.83 (15:03)	10.76 (11.61)
Duration of hospitalizations due to exacerbations, years	0.04 (0.03)	0.02 (0.02)
Duration of hospitalizations due to exacerbations relative to total study duration, %	6.22 (8.79)	2.16 (1.67)
Duration of antibiotic treatment for exacerbations, years	0.03 (0.01)	0.02 (0.01)

Duration of antibiotic treatment for exacerbations relative to total study duration, %	6.32 (6.75)	5.55 (6.80)
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Source: CSR, Table 20 and ERRATUM TO FINAL CLINICAL STUDY REPORT CE1226_4001, Date: 18 November 2013.

Duration of exacerbations

The mean duration of exacerbations and the mean relative duration of exacerbations (relative to subject's total treatment duration) were slightly higher with CE1226 (0.26 years and 13.8%, respectively) compared with placebo (0.18 years and 10.8%, respectively) (see Table above). Similar trends were also seen in the PP population. Analysis of the treatment difference for the relative duration of exacerbations using a Wilcoxon rank sum test revealed a Hodges-Lehmann estimate for the median difference of 0.56 in favour of placebo, as compared with CE1226. This difference was not statistically significant. A similar trend was also seen in the PP population (1.37 in favour of placebo), although in this case the treatment difference was statistically significant.

Hospitalizations due to exacerbations

The proportion of subjects with no hospitalization due to exacerbations was comparable between CE1226 (86.0%) and placebo (89.7%). The number of subjects with 1 hospitalization was 10 (10.8%) subjects with CE1226 and 5 (5.7%) subjects with placebo; there were no relevant differences in the proportion of subjects with 2, 3, or > 3 hospitalizations between the 2 groups.

Table 22- Number of hospitalizations due to exacerbations (frequencies) (ITT population)

Subgroup: Overall		
	Zemaira (N=93)	Placebo (N=87)
Number of Hospitalizations due to Exacerbations	n (%)	n (%)
0 hospitalization	80 (86.0)	78 (89.7)
1 hospitalization	10 (10.8)	5 (5.7)
2 hospitalizations	1 (1.1)	1 (1.1)
3 hospitalizations	1 (1.1)	3 (3.4)
>3 hospitalizations	1 (1.1)	0

Subject ID 11103 and 11104 are IDs for the same individual. This individual discontinued after 2 months and was randomized again 9 months later. Therefore these two subject IDs are treated as different individuals.

Source: CSR CE1226_4001

The proportions of subjects requiring hospitalization due to exacerbations were comparable between the 2 groups in every quarterly visit interval. Similar trends were also generally seen in the PP population.

The exposure-adjusted incidence rate of hospitalizations due to exacerbations in the ITT population was 0.11 hospitalizations/subject year with both CE1226 and placebo. Similar results were also seen in the PP population. The mean duration of hospitalizations and the mean relative duration of hospitalizations due to exacerbations (relative to subject's total treatment duration) were 0.04 years and 6.22%, respectively, with CE1226 and 0.02 years and 2.16%, respectively, with placebo (see table above). Similar trends, but with smaller treatment differences, were seen in the PP population. Analysis of the overall treatment difference using different statistical models for the relative duration of hospitalization, for the number of hospitalizations due to exacerbations, and for the number of subjects requiring hospitalization due to exacerbations showed no statistically significant differences between the 2 treatment groups in the ITT or PP populations.

Antibiotic treatment for exacerbations

The mean duration of antibiotic treatment and the mean relative duration of antibiotic treatment for exacerbations (relative to subject's total treatment duration) were comparable for CE1226 (0.03 years and

6.32%, respectively) and placebo (0.02 years and 5.55%, respectively) (see Table above). Similar trends were also seen in the PP population.

The proportion of subjects requiring antibiotic treatment for exacerbations were generally higher with CE1226 compared with placebo in the quarterly visit intervals; proportion during these intervals ranged between 21.5% and 32.3% with CE1226, and between 17.2% and 24.1% with placebo (See Table below). A similar trend was also seen in the PP population.

Table 23- Number and percentage of subjects requiring antibiotic treatment for exacerbation symptoms by quarterly visit interval (frequencies) (ITT Population)

Subgroup: Overall		
Visit Interval	Zemaira (N=93) n (%)	Placebo (N=87) n (%)
Day 1 to <Month 3	22 (23.7)	19 (21.8)
Month 3 to <Month 6	29 (31.2)	20 (23.0)
Month 6 to <Month 9	24 (25.8)	15 (17.2)
Month 9 to <Month 12	21 (22.6)	17 (19.5)
Month 12 to <Month 15	30 (32.3)	21 (24.1)
Month 15 to <Month 18	21 (22.6)	15 (17.2)
Month 18 to <Month 21	26 (28.0)	15 (17.2)
Month 21 to Month 24	20 (21.5)	15 (17.2)

Subject ID 11103 and 11104 are IDs for the same individual. This individual discontinued after 2 months and was randomized again 9 months later. Therefore these two subject IDs are treated as different individuals.

Source: CSR CE1226_4001

Analysis of the overall treatment difference using different statistical models for the relative duration of antibiotic treatment for exacerbations and for the number of subjects requiring antibiotic treatment for exacerbations showed no statistically significant differences between the 2 treatment groups in the ITT or PP populations.

Exploratory efficacy variables

- Antigenic A1-PI levels and functional A1-PI trough levels

Table 24- Antigenic A1-PI levels (mg/mL), functional A1-PI trough levels (mg/mL) measured values and changes from baseline by visit (descriptive statistics)

Month Statistics	Zemaira (N=93)		Placebo (N=87)	
	Measured Values	Change from Day 1	Measured Values	Change from Day 1
Antigenic A1-PI levels (mg/mL)				
Day 1				
n	90		86	
Mean (SD)	0.288 (0.2113)		0.271 (0.1120)	
SE	0.0223		0.0121	
Q25	0.214		0.215	
Median	0.240		0.245	
Q75	0.286		0.302	
Min, Max	0.14, 2.01		0.16, 1.04	

Month 24				
n	83	83	68	68
Mean (SD)	0.730 (0.1707)	0.459 (0.1610)	0.266 (0.1091)	-0.003 (0.0572)
SE	0.0187	0.0177	0.0132	0.0069
Q25	0.625	0.357	0.207	-0.030
Median	0.709	0.451	0.237	-0.008
Q75	0.816	0.547	0.275	0.017
Min, Max	0.34, 1.20	0.07, 0.99	0.18, 0.95	-0.12, 0.24

Subject ID 11103 and 11104 are IDs for the same individual. This individual discontinued after 2 months and was randomized again 9 months later. Therefore these two subject IDs are treated as different individuals.

Functional A1-PI levels (mg/mL)

Day 1				
n	91		86	
Mean (SD)	0.146 (0.1886)		0.120 (0.0737)	
SE	0.0198		0.0079	
Q25	0.091		0.091	
Median	0.103		0.108	
Q75	0.124		0.128	
Min, Max	0.06, 1.67		0.03, 0.68	
Month 24				
n	83	83	67	67
Mean (SD)	0.512 (0.1424)	0.381 (0.1258)	0.125 (0.0722)	0.006 (0.0468)
SE	0.0156	0.0138	0.0088	0.0057
Q25	0.425	0.310	0.096	-0.010
Median	0.482	0.370	0.116	0.002
Q75	0.567	0.449	0.134	0.014
Min, Max	0.16, 1.00	0.07, 0.89	0.02, 0.60	-0.08, 0.25

Subject ID 11103 and 11104 are IDs for the same individual. This individual discontinued after 2 months and was randomized again 9 months later. Therefore these two subject IDs are treated as different individuals.

Source: CSR, Table 14.2-7.1 The values in mg/ml can be calculated to μM values by multiplication: 22* values mg/ml.

At Month 24, the mean plasma antigenic A1-PI level was 0.73 mg/mL (SD: 0.17), median 0.71, range 0.34-1.20 mg/mL with CE1226 and 0.27 mg/mL (SD: 0.11), median 0.24, range 0.18-0.95 g/ml, with placebo. The mean change from Day 1 to Month 24 was 0.46 mg/mL (SD: 0.16) with CE1226 and -0.00 mg/mL (SD: 0.06) with placebo. For the functional A1-PI trough levels at Month 24, the mean level was 0.51 mg/mL (SD: 0.14) with CE1226 and 0.13 mg/mL (SD: 0.07) with placebo. The mean change from Day 1 to Month 24 was 0.38 mg/mL (SD: 0.13) with CE1226 and 0.006 mg/mL (SD: 0.05) with placebo.

- Correlation analysis of antigenic A1-PI levels and functional A1-PI trough levels with Adjusted P15, key secondary efficacy variables, and key spirometry variables

There were no relevant correlations overall or per treatment group between measured values or changes from baseline in functional and antigenic A1-PI levels versus measured values or changes from baseline and Adjusted P15 values, exercise capacity test – distance walked, key spirometry variables, and annual exacerbation rate in the PP population.

Study CE1226_3001 (Interim analysis)

Primary efficacy endpoint

Table 25 – Study CE1226_3001: Physiologically Adjusted P15 (g/L) measured values at 24, 36 and 48 Months at TLC, FRC, and mean of TLC and FRC states (ITT* population)

	24 Monhts		36 Months		48 Months	
	Mean (standard deviation)					
Parameter	Early Start	Delayed Start	Early Start	Delayed Start	Early Start	Delayed Start
Adjusted P15 at mean of <u>TLC and FRC</u> , g/L	40.2 (14.0) (N=53)	44.9 (14.0) (N=53)	38.8 (14.2) (N=53)	43.9 (14.5) (N=51)	37.2 (15.9) (N=32)	41.9 (16.3) (N=33)
Adjusted P15 at <u>TLC</u> , g/L	39.2 (14.4) (N=53)	42.8 (13.4) (N=52)	38.1 (15.0) (N=53)	42.6 (14.2) (N=51)	36.0 (16.4) (N=32)	40.1 (15.4) (N=33)
Adjusted	41.2 (13.8)	46.4 (14.2)	39.6 (13.6)	45.1 (15.1)	38.5 (15.7)	43.8 (17.3)

P15 at **FRC**, (N=53) (N=53) (N=53) (N=50) (N=32) (N=33)
g/L

Source: CSR 1226_3001,

Table 26– Study CE1226_3001: Summary of data at Month 24 for subjects who completed Month 36 or Month 48 (ITT population)

	24 Months		36 Months		48 Months	
	Mean (standard deviation)					
Parameter	Early Start (N=76)	Delayed Start (N=64)	Early Start (N=53)	Delayed Start (N=52)	Early Start (N=32)	Delayed Start (N=33)
Adjusted P15 at mean of <u>TLC and FRC</u> , g/L	43.0 (14.8)	44.8 (14.1)	40.2 (14.0)	44.9 (14.1)	39.5 (14.7)	44.7 (14.2)
Adjusted P15 at <u>TLC</u> , g/L	42.2 (15.1)	43.6 (14.5)	39.2 (14.4)	43.4 (14.1)	38.0 (15.1)	42.7 (14.5)
Adjusted P15 at <u>FRC</u> , g/L	43.9 (14.7)	46.0 (14.0)	41.2 (13.8)	46.4 (14.3)	41.0 (14.6)	46.6 (14.0)
FEV1, L	1.49 (0.48)	1.57 (0.47)	1.43 (0.43)	1.58 (0.50)	1.37 (0.47)	1.59 (0.51)
FEV1 % predicted, %	45.7 (12.7)	46.4 (11.9)	44.3 (11.6)	47.0 (12.5)	43.1 (11.5)	46.2 (11.7)
FEV1/FVC ratio	0.43 (0.11)	0.42 (0.09)	0.43 (0.10)	0.42 (0.09)	0.43 (0.10)	0.41 (0.08)
Duration of disease, years	5.82 (6.30)	6.25 (6.91)	6.45 (6.99)	6.33 (6.88)	6.23 (6.47)	5.63 (6.32)
Antigenic A1-PI levels, mg/mL	0.72 (0.17) (N=75)	0.27 (0.11) (N=64)	0.75 (0.36) (N=66)	0.81 (0.36) (N=56)	0.73 (0.22) (N=40)	0.77 (0.36) (N=39)
Functional A1-PI levels, mg/mL	0.51 (0.14) (N=75)	0.13 (0.07) (N=63)	0.56 (0.24) (N=66)	0.59 (0.27) (N=56)	0.58 (0.18) (N=39)	0.57 (0.29) (N=39)

A1-PI = alpha1-proteinase inhibitor; FEV1 = forced expiratory volume in one second; FRC = functional residual capacity; FVC = forced vital capacity; ITT = intention-to-treat; N = number of subjects in the population; P15 = 15th percentile of the lung density; TLC = total lung capacity.

a Duration of the disease at Baseline (start of study CE1226_4001).

For some individual characteristics, the number of subjects with data may be less than the total ITT population.

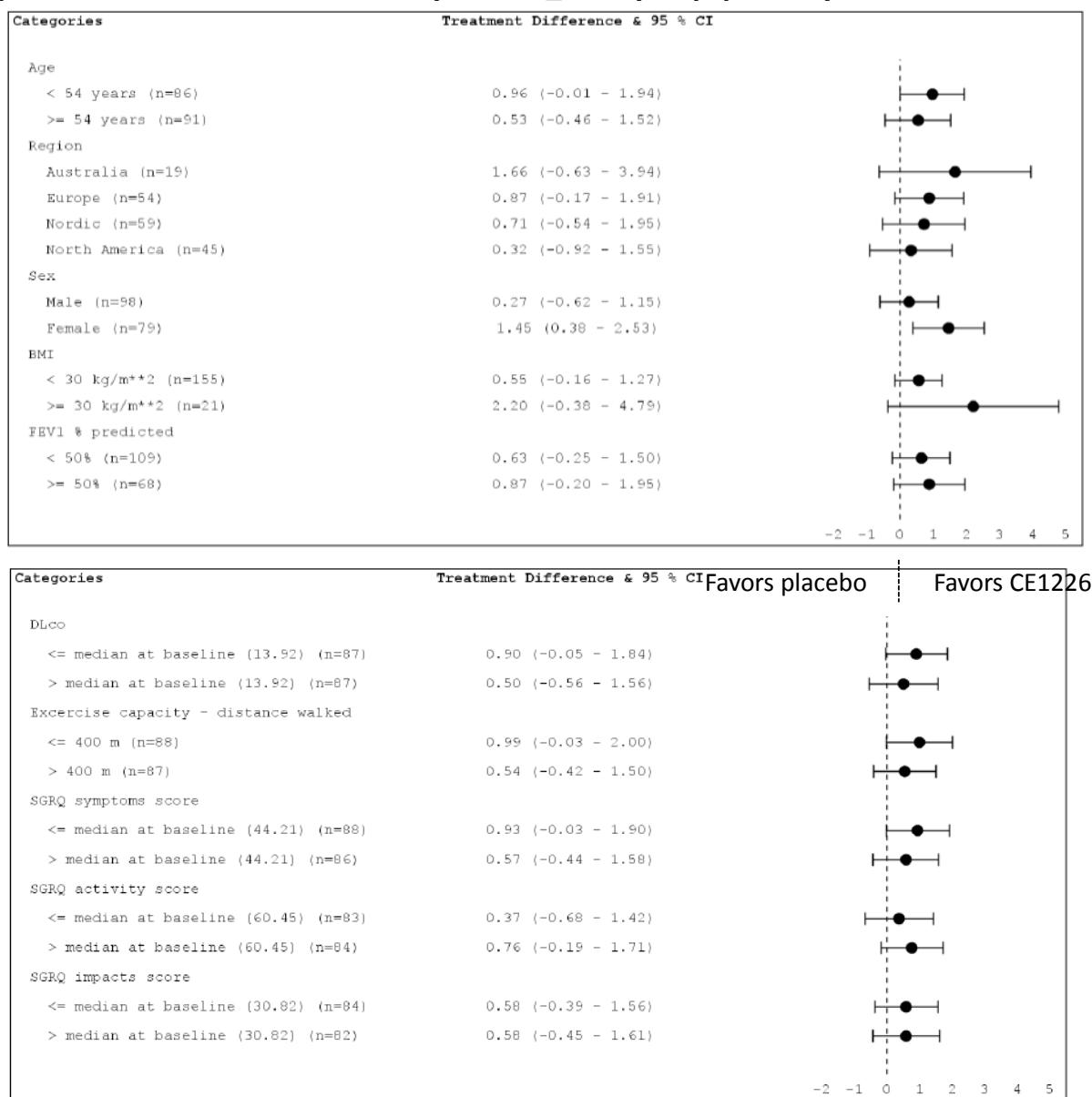
Source: CSR CE1226_3001

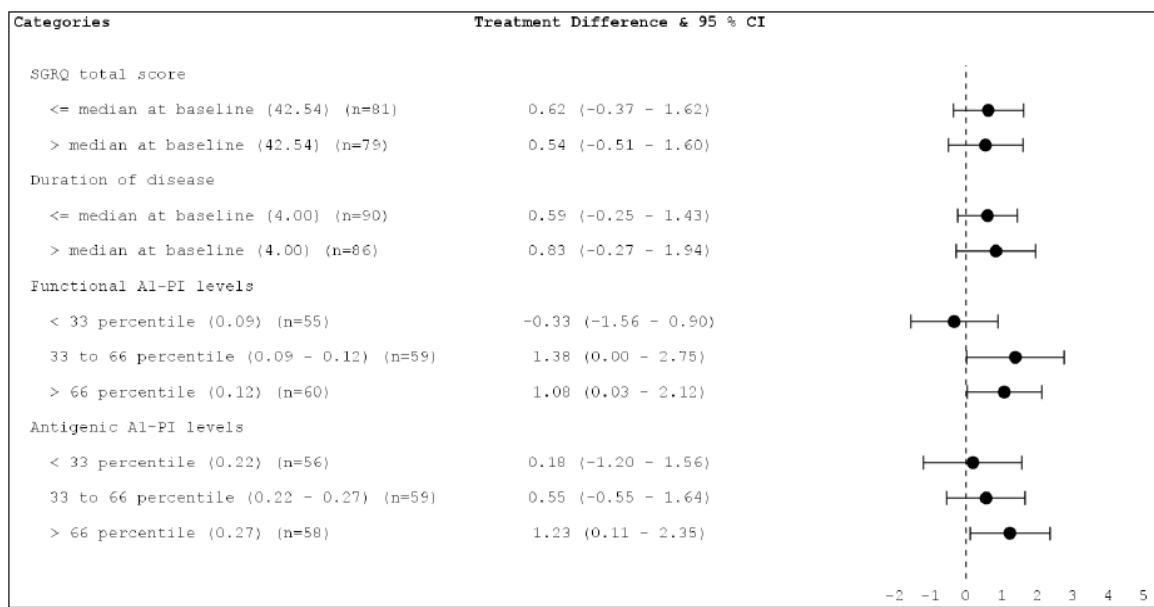
A1-PI levels have incorporated from Table 17, 20, 22-23, 25 in the Summary of Clinical Pharmacology.

Ancillary analyses

The effect of various baseline parameters on the annual rate of change in Adjusted P15 was investigated in studies CE1226_4001 and CE1226_3001 (interim) by performing the primary efficacy analysis within various sub-populations of interest. Sub-population analyses are presented below in the Figure.

Figure 6- Treatment differences in rate of decline in Adjusted P15 (g/L) by various baseline parameters at the TLC state in study CE1226_4001 (ITT population)





Favors placebo | Favors CE1226

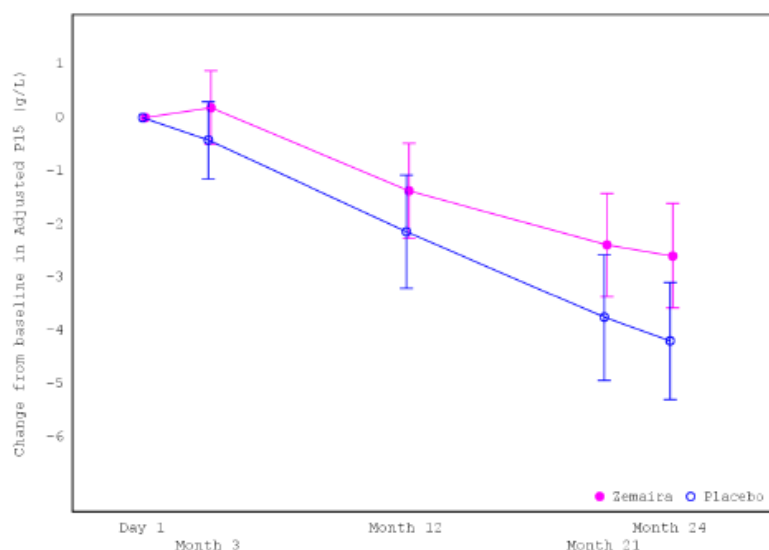
A₁-PI = Alpha₁-proteinase inhibitor; Adjusted P15 = Lung volume-adjusted 15th percentile of the lung density; BMI = Body mass index; CI = Confidence interval; DL_{CO} = Diffusion capacity of carbon monoxide; FEV₁ = Forced expiratory volume in 1 second; FRC = Functional residual capacity; ITT = Intention-to-treat; n = Number of subjects; SGRQ = St George's Respiratory Questionnaire; TLC = Total lung capacity.

Source; Summary Clinical Efficacy,

Clinical relevance of the efficacy results in study CE1226 4001

Lung loss measured via whole lung CT densitometry, i.e. the 15th percentile point, is a physiological endpoint used in clinical A1-PI augmentation therapy studies. CT densitometry has previously been accepted by the CHMP as an acceptable method to detect progression of emphysema in patients with A1-PI deficiency. It is agreed that "TLC" inspirations state is the most suitable endpoint to use in studies since it has the best possibility to detect small differences in lung density. Thus, lung density measured at the "TLC" inspiration state is a relevant parameter to use as it measures the physiological change in the organ which is affected of the disease.

Figure 7 Mean change from baseline in Adjusted P15 (g/L) (+/- 95% CI) over time (TLC state) (ITT population)



Source: CSR CE1226_4001

The observed magnitude of advantage of CE1226 over placebo, is ranging between 0.5 to 0.7 g/L/year in lung density decline across the inspiration state analyses.

Table 27– Study CE1226_4001: Treatment comparison for annual rate of change in physiologically Adjusted P15 (g/L) at TLC and FRC states combined and separately based on a random regression model (ITT population)

	Point estimate (SE)			95% CI	1-sided p-value
	CE1226 (N=92)	Placebo (N=85)	CE1226 minus placebo		
TLC+FRC combined	-1.50 (0.22)	-2.12 (0.24)	0.62	-0.02;1.26	0.029
TLC	-1.45 (0.23)	-2.19 (0.25)	0.74	0.06;1.42	0.017
FRC	-1.55 (0.24)	-2.02 (0.26)	0.48	-0.22; 1.18	0.090

CI = confidence interval; FRC = functional residual capacity; TLC = total lung capacity; N = number of subjects who had at least 1 computed tomography scan available; SE = standard error;

Source: CSR CE1226_4001, Tables 10, 11

The nearly significant efficacy results for the pre-defined primary analysis of “TLC/FRC combined” supported by the result of the analysis of “TLC only” having a nominal p-value less than 0.05 support the evidence of effect, i.e. of a reduction of the rate of lung density decline. The data was also reanalysed using the mixed effects model repeated measures model used by Stolk (2007) and this method gave p=0.001 for the treatment difference when analysing “TLC/FRC combine”. Hence, supporting the primary analysis.

Summary of main efficacy results

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 28 - Summary of efficacy for trial Study CE1226_4001

Title: A randomized, placebo-controlled, double-blind, multicenter Phase III/IV study to compare the efficacy and safety of 60 mg/kg body weight of Zemaira® weekly i.v. administration with placebo weekly i.v. administration in chronic augmentation and maintenance therapy in subjects with emphysema due to alpha1-proteinase inhibitor deficiency			
Study identifier	CE1226_4001		
Design	This was a randomized, double-blind, placebo-controlled study.		
	Duration of main phase:	24 months	
	Duration of Run-in phase:	Not applicable	
	Duration of Extension phase:	See Ongoing study CE1226_3001	
Hypothesis	A 1-sided p-value less than 0.025 and a positive estimate of the treatment difference of CE1226 minus placebo, i.e., the lower bound of the 95% CI being greater than zero, were taken to indicate superiority of CE1226 compared to placebo.		
Treatments groups	Placebo		Placebo, 24 month, 87 (ITT)
	CE1226		CE1226, 60 mg/kg bw i.v. once weekly, 24 months, 93 (ITT)
Endpoints and definitions	Primary endpoint:	Lung density (g/L) as measured by Adjusted P15 from CT scans obtained at total lung capacity (TLC) and functional residual capacity (FRC), and TLC and FRC combined, inspiration states	Physiologically Adjusted P15 (g/L) measured at <u>TLC and FRC combined</u> (measured value, annual rate of decline) Physiologically Adjusted P15 (g/L) measured at <u>TLC</u> (measured value, annual rate of decline) Physiologically Adjusted P15 (g/L) measured at <u>FRC</u> (measured value, annual rate of decline)
	Secondary endpoint		-Change in exercise capacity (by <u>ISWT</u>) (m) -Change in symptoms (by <u>SGRQ</u>) -Rate of pulmonary exacerbations -FEV1 (L)
	Other Secondary endpoints		-Durations of exacerbations (yrs) -Durations of hospitalization due to exacerbations (yrs) Duration of antibiotic treatment of exacerbations (yrs)
Database lock	1 April 2013		

<u>Results and Analysis</u>				
Analysis description	Primary Analysis			
Analysis population and time point description	Intent to treat: 180; Per protocol: 159 0, 3, 12, 21 and 24 months			
Descriptive statistics and estimate variability	Treatment group	Placebo	CE1226	
	Number of subject	87 (Month 0)	93 (Months 0)	
	<u>Primary endpoint:</u> Physiologically Adjusted P15 (g/L) measured at <u>TLC and FRC combined</u> (measured value, annual rate of decline)	Point estimate Mean (SD) (g/L) <u>TLC+FRC</u> 0 Months: 49.8 (15.1) 12 Months: 47.2 (13.7) 24 Months: 45.5 (13.9) <u>TLC</u> 0 Months: 48.9 (15.5) 12 Months: 46.1 (13.7) 24 Months: 43.9 (13.8) <u>FRC</u> 0 Months: 50.7 (15.0) 12 Months: 48.4 (14.1) 24 Months: 46.8 (13.8)	Point estimate (mean (SD)) (g/L) <u>TLC+FRC</u> 0 Months: 46.6 (15.6) 12 Months: 45.6 (16.6) 24 Months: 44.4 (15.5) <u>TLC</u> 0 Months: 45.5 (15.8) 12 Months: 44.7 (16.8) 24 Months: 43.6 (16.0) <u>FRC</u> 0 Months: 47.6 (15.7) 12 Months: 46.6 (16.6) 24 Months: 45.3 (15.3)	
	Physiologically Adjusted P15 (g/L) measured at <u>TLC</u> (measured value, annual rate of decline)	Annual rate of decline (g/L) <u>TLC+FRC</u> -2.12 (0.24) <u>TLC</u> -2.19 (0.25) <u>FRC</u> -2.02 (0.26)	Annual rate of decline (g/L) <u>TLC+FRC</u> -1.50 (0.22) <u>TLC</u> -1.45 (0.23) <u>FRC</u> -1.55 (0.24)	
	Physiologically Adjusted P15 (g/L) measured at <u>FRC</u> (measured value, annual rate of decline)			
	Difference CE1226-placebo in annual rate of lung density change (95% CI, 1-sided p-value)	<u>TLC+FRC</u> 0.62 (-0.02; 1.26, 0.029) <u>TLC</u> 0.74 (0.06; 1.42, 0.017) <u>FRC</u> 0.48 (-0.22; 1.18, 0.090)		

<u>Results and Analysis</u>				
Analysis description	Primary Analysis			
	<u>Secondary endpoint:</u> ISWT (mean change from Day 1 to Months 24, m)	16.1 (141.7)	10.8 (139.8)	
	<variability statistic>	n.s.		
	SGRQ (mean change from Day 1 to Months 24, points):	2.01 (20.1)	-1.39 (16.7)	
	<variability statistic>	n.s.		
	Annual exposure-adjusted incidence rate of exacerbations/subject year:	1.42 95% CI (1.23;1.61)	1.70 95% CI (1.51;1.89)	
	<variability statistic>	n.s.		
Notes	FEV1: No clinically relevant changes between the two armed are observed. Exacerbations: The mean duration of hospitalizations (0.04 vs 0.02 years) and the mean relative duration of hospitalizations (6.22% vs 2.16%) due to exacerbations were slightly higher for the CE1226 treated group compared to placebo group.			

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

Not applicable, this was accepted by the CHMP.

Clinical studies in special populations

Not applicable, this was accepted by the CHMP.

Supportive study

Not applicable, this was accepted by the CHMP.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The efficacy of human alpha1-proteinase inhibitor (A1-PI, company code CE1226), also known as alpha1-antitrypsin, is supported by one completed phase 3 study (CE1226_4001) and one ongoing study (CE1226_3001, interim analysis) for the final claimed indication "*Respreeza is indicated for maintenance treatment, to slow the progression of emphysema in adults with documented severe alpha₁-proteinase inhibitor deficiency (ie, serum alpha₁-proteinase inhibitor levels <11 µM or phenotypes PiZZ, PiZ(null), Pi(null,null), PiSZ).*

Patients are to be under optimal pharmacologic and non-pharmacologic treatment and show evidence of progressive lung disease (eg, lower forced expiratory volume per second (FEV1) predicted, impaired walking capacity or increased number of exacerbations) as evaluated by a healthcare professional experienced in the treatment of alpha₁-proteinase inhibitor deficiency."

Study CE1226_4001 was a randomized, placebo-controlled, double-blind, multicenter Phase III/IV study to compare the efficacy and safety of 60 mg/kg body weight of CE1226 weekly i.v. administration with placebo weekly i.v. administration. The study duration was 24 months. The use of placebo as the comparator arm is supported. Completion of the study took more than six years, lasting from March 2006 to September 2012.

Starting in April 2008 an open-label extension study (CE1226_3001) was set up. Study CE1226_3001 is still ongoing, and is an open-label, non-controlled, multicenter, multinational study. Subjects who had completed the 2-year treatment and observation period in the CE1226_4001 study, except those participating in the USA, were invited to participate in study CE1226_3001 now solely with active treatment. All subjects are planned to be treated with weekly intravenous administrations of CE1226 at a dose of 60 mg/kg b.w. for up to 24 months. Those subjects who had already been allocated to receive CE1226 treatment during study CE1226_4001 represent the "Early Start" group and will have received up to 48 months of continuous therapy at the end of study CE1226_3001. Subjects who received placebo in study CE1226_4001 and only began to receive CE1226 treatment upon entry into study CE1226_3001 represent the "Delayed Start" group and will have a maximal exposure of 24 months at the end of study CE1226_3001. This study is awaited to be finished in September 2015 and is included in the RMP.

The Applicant has performed a second interim analysis of study CE1226_3001 with a cut-off date of 31 December 2013. The data now includes 97 subjects who have completed the study in contrast to 65 subjects who were included in the first interim analysis.

The study populations consist of male and female A1-PI deficient subjects (serum A1-PI levels < 11 µM, or < 50 mg/dL as determined by nephelometry), non-smokers, with emphysema and reduced lung function, with forced expiratory volume in 1 second (FEV1) ≥ 35% and ≤ 70% predicted. A recommendation to restrict A1-PI therapy to subjects with moderate airflow obstruction is supported by data of Seersholm (Seersholm et al. 1997), who stratified subjects by initial FEV1% predicted showing a significant effect of treatment only in the group of patients with an initial FEV1% predicted of 31-65%. The same is reflected in the statement of the American Thoracic Society/European Respiratory Society (2003) which states that benefits of augmentation therapy in individuals with severe (e.g. FEV1 ≤35% predicted) or mild (e.g. FEV1 ≥50-60% predicted) airflow obstruction are less clear. Subpopulation analysis with regards to the FEV1 was not concluded at the end in section 4.2 of the SmPC, but rather to show evidence of progressive lung disease (e.g. lower forced expiratory volume per second (FEV₁) predicted, impaired walking capacity or increased number of exacerbations) as evaluated by a healthcare professional experienced in the treatment of alpha₁-proteinase inhibitor deficiency.

The time points for evaluation of the primary endpoint and key secondary endpoints were 3, 12, 21, and 24 months in study CE1226_4001 and 12 and 24 months in study CE1226_3001. The primary objective in both studies was to investigate the effect of CE1226 on the progression of emphysema, assessed by the decline of lung density, measured by CT.

The primary efficacy variable was the lung volume-adjusted lung density (Adjusted P15) estimated by the 15th percentile of the frequency histogram of the lung pixels. Lung loss measured via whole lung CT densitometry, i.e. the 15th percentile point, is a physiological endpoint used in clinical A1-PI augmentation therapy studies. CT densitometry has previously been accepted by the CHMP as an acceptable method to detect progression of emphysema in patients with A1-PI deficiency. It is agreed that "TLC" inspirations state is the most suitable endpoint to use in studies since it has the best possibility to detect small differences in lung density. Thus, lung density measured at the "TLC" inspiration state is a relevant parameter to use as it measures the physiological change in the organ which is affected of the disease.

The used primary endpoint in the clinical study CE1226_4001 the "Lung volume-adjusted lung density (Adjusted P15) estimated by the 15th percentile of the frequency histogram of the lung pixels" is a complex endpoint since it not only includes CT scans at different inspiration states, TLC and FRC, but also combines the different inspiration states (TLC+FRC, TLC, FRC) and uses two methods to standardise density values for total lung volume (physiological and statistical). In the primary efficacy analysis the physiological adjustment (Adjusted P15 = observed P15 x (observed mTLV/predicted TLC)) was used for the analysis for "TLC and FRC combined", "TLC" and "FRC" inspirations states. The inclusion of only the "TLC" inspiration state" seems the most suitable endpoint for future studies.

A large number of secondary endpoints were included in the study and during the study the objectives have been clarified and the ranking of them have been altered during the study. However, no formal statistical hierarchical ranking has been performed. Among the secondary endpoints FEV1, exacerbations, and antigenic and functional A1-PI plasma levels are considered most relevant when considering the disease.

A GCP inspection performed by the Irish Medicines Board on the 13th to 16th December 2011 identified critical and major deficiencies at the Professor McElvaney, Ireland, centre (studies CE1226_4001 and CE1226_3001). Satisfactory responses to its findings have been provided.

Respreeza is approved by the FDA since 2003. The pivotal studies (4001 and 3001) for the current EU application was also submitted to the FDA as an efficacy supplement along with an application for an extended indication. In this context, the FDA performed a GCP inspection of 4 study sites. The inspection report (July 2014)

identified some GCP departures which was communicated to the company September 2014 and the FDA concluded that the studies were not adequate to consider for supporting the requested new application. The Applicant has acknowledged that during the course of the CE1226_4001 study, there were GCP departures. Many of the issues identified by the FDA inspectors were identified by CSLB/contract research organizations (CROs) during routine study monitoring, review of monitoring reports, and/or during CSLB quality assurance audits. In addition, an independent clinical quality assurance has been performed. Following identification of issues, related corrective measures/actions were implemented, including process updates, training, and site communications. For those topics that could have potentially impacted the integrity of the clinical data, the Applicant has demonstrated that the corrective actions applied during the course of the studies did positively impact the overall GCP compliance. The main concerns were inability to verify that subjects received the correct active or placebo investigational medicinal product and issues referring to dosing irregularities as well as issues related to blinding of the IMP.

The Applicant's has submitted their responses to the inspection findings in the response to the Day 180 outstanding issues and has provided additional clarifications in subsequent responses. During an oral explanation at the CHMP, the applicant clearly justified, from a GCP perspective that the pivotal studies for the MAA, inspected by the FDA in July 2014 and previously for one site by the Irish medicines Board 2011 are adequate to support an approval. The CHMP concluded that the GCP findings would not influence the results of the studies in a way that the B/R of the product could be affected.

Efficacy data and additional analyses

In the ITT population the majority of the patients were Caucasian with approximately equal numbers of females and males. The age ranged from 31 to 67 years in study CE1226_4001 and from 33 to 69 in study CE1226_3001. As far as available, the Applicant provided information regarding smoking history from most of the study subjects. No relevant differences were found between the two treatment groups with regard to smoking history.

The dosing regime in both studies was 60 mg /kg b.w once weekly. Approximately 80% of the subjects in the study received a 120 mg/kg dose, although, the total exposure of the 120 mg/kg dose was low and roughly corresponds to 4 weeks exposure for the concerned 75 subjects. Thus, there is limited safety data for the 120 mg/kg dose.

The predefined primary statistical analysis, i.e. assessing the annual rate of change in lung density, using physiologically Adjusted P15 at "TLC and FRC states combined" in a mixed effects model, resulted in a difference in the annual rate of decline in Adjusted P15 of 0.62 g/L in favour of CE1226 ($p = 0.029$, one sided p-value). In study CE1226_4001, the annual rate of change in lung density, using physiologically Adjusted P15 using only the total lung capacity "TLC" state in a mixed effects model, rendered a difference of 0.74 g/L ($p=0.017$, one sided p-value) in favour of CE1226 in study CE1226_4001. The documented difference in decline of the lung density between CE1226 and placebo treatment indicate that CE1226 has an effect on this parameter. The observed value is slightly lower but is of the same magnitude as the observed value of 0.86 g/L/year in the EXACTLE study (Dirksen et al, 1999).

The nearly significant efficacy results for the pre-defined primary analysis of "TLC/FRC combined" supported by the result of the analysis of "TLC only" having a nominal p-value less than 0.05 support the evidence of effect, i.e. of a reduction of the rate of lung density decline. The data was also reanalysed using the mixed effects model repeated measures model used by Stolk (2007) and this method gave $p=0.001$ for the treatment difference when analysing "TLC/FRC combine". Hence, supporting the primary analysis. The Applicant has performed both *a priori* and *post hoc* sensitivity analyses to evaluate whether baseline differences in lung density between the treatment groups have driven the direction of primary efficacy variable outcomes, consistently favouring

CE1226 over placebo, or have a profound impact on the magnitude of effect. To explore this question, sensitivity analyses of the primary endpoint were completed with baseline lung density as a covariate. Overall the results were similar to the primary analysis and their impact on the results was negligible. Thus, a decline in lung loss, measured via whole lung CT densitometry using TLC state, is observed for the CE1226 treated arm compared to the placebo arm.

Regarding the secondary endpoints in study CE1226_4001, very slight trends in favour of CE1226 for FEV1, DLco, ISWT and total SGRQ are seen although a negative trend for rates and proportion of severe exacerbations is observed. The results may not be unexpected since the study CE1226_4001 was not large enough or long enough to detect differences in secondary endpoints. The subjects were further permitted to use concomitant respiratory medications without any restriction and there were some differences between the two arms. Furthermore, it seems that the subjects in the CE1226 arm had a more severe disease when compared to the placebo arm, i.e. lung density at TLC state values were 45.5 vs 48.9 g/L for the CE1226 and placebo groups, respectively, which could possibly affect the results. Overall, it has to be concluded that there is no support from secondary endpoints.

The Applicant has performed a second interim analysis of study CE1226_3001 with a cut-off date of 31 December 2013. The data now includes 97 subjects who have completed the study in contrast to 65 subjects who were included in the first interim analysis. The subjects treated with placebo had an annual rate of decline of -2.06 g/L/year and when switched over to receive CE1226 (Delayed start group), the annual rate of decline was -1.31 g/L/year. This is similar to the value seen in study CE1226_4001 where the annual rate of decline was -1.37 for subjects treated with CE1226 (Early start group). The annual rate of decline is -1.08 g/L/year treatment year 3-4 in the subjects who received CE1226 from the beginning (including year 1-2; Early start group). Overall, the new interim analysis data for study CE1226_3001 support the results observed in study CE1226_4001.

In the study CE1226_4001 study the A₁-PI concentrations were measured at the end of a dosing period and are trough concentrations. The mean trough concentrations in the CE1226 group in the CE1226_4001 was approximately 16 µM (11-23 µM, 90 % prediction interval). In addition, the Applicant has developed a population pharmacokinetic (PK) model and estimated the average serum A₁-PI concentration throughout a dosing interval to be in the order of 19 to 20 µM in study CE1226_4001 which is in the lower range of normal.

To summarise, the pre-specified primary endpoint (TLC/FRC combined) did not reach statistical significance, however, was close to doing so. The analysis of CT in TLC, the full inspiration state, demonstrated a statistically significant difference to placebo, accompanied by a consistent result in FRC at resting expiration. The Applicant provides published evidence that TLC is the less variable and therefore most robust inspiration state to follow changes in lung tissue, and more sensitive to detect small changes. It is therefore regarded acceptable to consider the results of CT measurements at TLC state as the primarily relevant ones. Thus, a decline in lung loss, measured via whole lung CT densitometry using TLC state, is observed for the CE1226 treated arm compared to the placebo arm.

The mean trough A₁-PI concentrations in the CE1226 group in the CE1226_4001 was approximately 16 µM (11-23 µM, 90 % prediction interval) and the estimated average serum A₁-PI concentration throughout a dosing interval is in the order of 19 to 20 µM which is in the lower range of normal.

In the performed pivotal study, the mean trough A₁-PI concentrations in subjects receiving Respreeza was approximately 16 µM (11-23 µM, 90 % prediction interval) and the estimated average serum A₁-PI concentration throughout a dosing interval is in the order of 19 to 20 µM which is in the lower range of normal.

Thus, it has been shown that treatment increases serum levels but it should be noted that the relationship between achieved serum level and clinical effect on lung density is currently not known.

Furthermore, CHMP has agreed on a randomized, long-term PAES as recommended by the expert panel to study the dose-relationship if the higher API levels achieved in the blood might influence the rate of lung density decline and whether that would support an increased dose of 120mg/kg based on scientific observation of the population treated that previous efficacy evaluations might not have covered in population with higher rate of exacerbations.

The Applicant has in response to a raised question regarding the initially proposed post authorisation study committed to conduct a randomized, long term, high/low dose study that will evaluate the effect of a high dose (120 mg/kg) as both a routine therapy as well as an up-titration regimen for those subjects whose lung density decline persists above 2 g/L/y following administration of 60 mg/kg therapy as a post authorisation commitment. The preliminary outlined study begins with a run-in period followed by a randomized treatment period (60 mg/kg, 120 mg/kg) with the aim to evaluate the efficacy and safety profile of the two doses. This is strongly endorsed. The Applicant proposes that following the treatment period, subjects who are persistent fast decliners, will be up-titrated in a blinded manner. All aspects of the study need to be thoroughly discussed and a centralised scientific advice regarding the study design is recommended. The CHMP endorses the Applicant's commitment to seek centralised scientific advice regarding the study design.

Additional expert consultation

An ad hoc expert group meeting was convened in the context of the ongoing assessment of the Respreeza(human alpha1-proteinase inhibitor) application for marketing authorisation in the EU as requested by the CHMP during the November 2014 plenary meeting and took place on the 14 January 2015. The conclusions were the following:

Question 1.

What is the strength of the available evidence (e.g. data from registries, published clinical trial data, Cochrane review from 2010) supporting efficacy of alpha 1 proteinase inhibitor (A1-PI) replacement therapy in slowing the destruction of lung tissue that leads to emphysema in adults with alpha1-proteinase inhibitor deficiency and clinically evident lung disease?

The experts agreed that there is a consistent effect of i.v. A1-PI(H) augmentation therapy on lung density demonstrated across clinical trials; however, there is a lack of robust evidence that this translates into a clinically relevant effect.

Published clinical studies on the efficacy are overall non-conclusive of the overall efficacy. The experts referred to several publications, including a prospective study from Wencker et al. in 1998 showing that the decline in FEV1 was slowed by i.v. A1-PI treatment compared to historical data, and a study from Stockley et al in 2013, in which pooling the results of two previous small trials on replacement therapy showed a statistically significant reduction in the loss of CT but with no difference in the FEV1 favouring the treatment. In 2010 a Cochrane report [Gotsche, 2010] recommend against A1-PI therapy on the grounds of lack evidence of clinical benefit.

Correlation of CT-measured lung density with functional and patient-reported outcomes in A1-PI deficiency was reviewed in several studies, with exercise capacity [Dowson 2001], lung function measures, including FEV1, FEV1/FVC, and DLCO [Gould 1991, Kinsella 1990], and health status indices [Dowson, 2001] correlating variably with CT density. Dirksen in 2009 showed a longitudinal correlation between decline in lung density and

decline in FEV1, but not with DLCO or SGRQ, over a period of 30 months. The variability of the correlation of functional endpoints with CT in baseline conditions and as parameters of progression of the disease is due to a number of reasons including the different pathogenetic drivers of the changes in indices of airflow limitation (FEV1) vs. indices of emphysema, the latter better reflected by CT densitometry (ref). The measurement of gas transfer parameters such as DLCO is subject to large longitudinal variability.

In conclusion, the expert panel agreed that there remains uncertainty how lung density decline rate translates into clinically relevant effect. This is compounded by the fact that individuals with severe A1 deficiency decline at different rates, with some developing significant and progressive lung disease and others not.

It is likely though that augmentation therapy has an effect on emphysema. Experts expressed also the view that this uncertainty is to remain as it is not possible to solve the question through feasible clinical trials particularly due to high variability of clinical outcome measures, as discussed above. The experts noted that the impact on the beneficial clinical effect might be influenced due to the late diagnosis of patients. On the other hand there might be an opportunity on the assessment of relevant clinical benefit in specific subpopulations, such as fast decliners (in density and/or lung function) vs. slow decliners.

Question 2.

What is the strength of the available evidence that A1-PI concentration in the serum is a surrogate for clinical efficacy? Is a A1-PI concentration threshold of 11 µM sufficiently justified considering that the normal range for healthy subjects is between 20-53 µM?

The expert panel concurred serum A1-PI concentration is being used as a surrogate endpoint (biological) of efficacy. This is not demonstrated directly in relation to levels of A1-PI reached by replacement treatment but on the published literature that has shown a higher risk of developing emphysema due to A1-PI deficiency with lower A1-PI serum levels and genotype PiZZ.

The experts noted that the 11 µM threshold is primarily based on publications by Eriksson that showed individuals with endogenous serum A1-PI concentrations below 11 µM manifest a significantly increased risk for development of emphysema above the general population background risk [Eriksson 1964, Eriksson 1965]. There is no further significant support for this threshold. As not all subjects with lower than average A1-PI serum levels will develop emphysema, current recommendations from the ATS/ERS 2003 and the CTS 2012 recommend treatment with A1-PI augmentation therapy to individuals with A1-PI serum concentrations <11 µM presenting with clinical signs of lung function decline.

Historically this target has been translated into a dosing of 60 mg/kg BW. However, the experts unanimously agreed that there would be a benefit to conduct further clinical studies to investigate whether some patients would benefit from higher doses.

Question 3.

What is the clinical relevance of lung density measurements as a parameter of clinical efficacy? Do the efficacy results in studies CE1226_4001 and 3001 with respect to lung density measurements (taking into account imbalances between the two treatment groups in the lung density at baseline) establish a clinically relevant effect?

The experts panel agreed that lung density measurements by CT scan have been used since the 1980s and is the most sensitive-to-change endpoint in emphysema and uniquely suitable as a clinical study endpoint due to its direct and validated representation and quantification of the anatomical changes underlying this condition.

The Applicant has undertaken a randomised, double-blind, placebo controlled study (CE1226_4001 and 3001) to assess the impact of A1-PI augmentation therapy over 24 (to 48 in the extended trial) months in subjects with emphysema secondary to severe A1-PI deficiency. In this study, the expert panel agreed that A1-PI augmentation showed slowing the decline in lung density as a surrogate of progressive destruction of the lung parenchyma in emphysema, measured by the CT lung density decline. The expert panel agreed the data includes heterogeneous population mixing rapid decliners in lung density compared to slow decliners and therefore the evidence of clinical emphysema lung density decline rate in non-smokers might not be clear, which is not unexpected. However, from the clinical trials indirect conclusions can be drawn on clinical benefit on emphysema through the lung density measurements.

The expert panel also confirmed the validity of the CT density measurements performed at TLC (Total Lung capacity) since they ensure a much lower variability than the scans taken at FRC (Functional residual capacity). In this respect, the experts also confirmed the plausibility of the changes in primary endpoint from the density measured at TLC and FRC scans to the density measured on scans acquired at TLC.

Question 4.

In study 4001, no beneficial effect was documented for clinical endpoints (e.g. effect on the functional lung parameters and clinical symptoms like exacerbations). Is demonstration of effect on such endpoints required to establish a clinically relevant effect of the treatment in question?

The expert panel agreed that the pivotal trial design (with regards to size and duration) was not powered to detect an effect on either lung function or the rate and severity of exacerbations.

The expert panel point of view is that assessment of lung function, i.e., FEV1, FEV1 % predicted, FVC, FEV1/FVC and Dico, as well as exacerbations are not evidence in the degree/decline of lung tissue.

Overall however, the view expressed by several experts was that no further data would be required to be convinced that at least some selected patients would derive clinical relevant effects from the treatment. For details of such patient population see response to question 6.

Question 5.

On which of the endpoints discussed in questions 2 – 4 above an effect would have to be demonstrated, as a minimum, to conclude that the effect provided by treatment in question is clinically relevant.

The expert panel agreed that clinically relevant effect of augmentation therapy would have to demonstrate an elevation of the mean trough serum A1 PI level in subjects to above 11 μ M and a reduction of the rate of lung density decline as measured by CT scan. Physiological measures such as 6 min walking test as well as health status indices with the SGQR (St George's Respiratory Questionnaire and Short Form-36) [Dowson 2001b] could be considered as secondary endpoints.

No minimum pre-defined lung density decline rate by g/l/yr measured by CT scan was considered as endpoints to demonstrate a clinical relevant effect. Mortality-related endpoints have been proven non-realistic even in trials non- A1 PI deficient COPD with thousands of patients, and are therefore even less an option in a disease as rare as A1 PI deficiency.

Question 6.

What would be the appropriate target population in clinical practice for alpha 1 proteinase inhibitor replacement therapy, especially regarding the patient's phenotype, severity of the disease and level of lung obstruction?

The expert panel agreed that the appropriate target population in clinical practice for alpha 1 proteinase inhibitor replacement therapy would be patients presenting with a combination of risk factors:

- Significant lung density decline,
- severity of emphysema,
- deficient/low level of A1PI concentration, below 11 μM
- phenotype/genotype.at risk

The expert panel agreed not to be too restrictive on lung function (FEV1) in the target population and specifically not to define a lower cut-off; the treatment recommendations from the Canadian Thoracic Society in 2012 recommending treatment for patients whose FEV1 is between 25 and 80 percent of predicted and/or a diffusing capacity below 70% of predicted were noted.

The expert panel concurred that specialist centres should establish the treatment of an individual patient as the decision on treatment needs to be individual and currently it is not possible to define any exact criteria. It is necessary to identify factors predicting natural course and outcome of treatment that could be used in future clinical practice.

The experts suggested that the patients assumed to benefit from the treatment, i.e. the therapeutic indication population should be defined by both the threshold of serum A1-PI <11 μM AND having a phenotype/genotype associated with severe deficiency, risk of progression based on phenotype, decline when non smoking severity of emphysema at diagnosis, presence of other co-morbidities affecting longevity and symptoms

Additional comments from the ad-hoc expert group:

The expert panel strongly supported the need to conduct further studies e.g. using also data from national registries of A1-AP deficiency and the AIR international registry. The scope of post-authorization studies includes establishing whether the serum levels of API have an influence in the lung density decline, and establish a dose-relationship if the higher API levels achieved in the blood might influence the rate of lung density decline and whether that would support an increased dose.

Furthermore, using the existing study data for the product the experts recommended to perform sensitivity analysis to identify potential confounding factors for clinical response (like fast vs. slow decliners, A1-PI pharmacokinetics, severity of emphysema).

2.5.4. Conclusions on the clinical efficacy

Overall, it is agreed that augmentation therapy increases the plasma A₁-PI concentrations above 11 μM as intended in subjects with emphysema with evidence of progressive lung disease. The achieved A₁-PI through level in the study CE1226_4001 were 16 μM and the average serum A₁-PI concentration throughout a dosing interval was estimated to be in the order of 19 to 20 μM which is in the lower range of normal.

A statistical significant decline in lung loss, measured via whole lung CT densitometry using "TLC" state, is observed for the CE1226 treated arm compared to the placebo arm.

The clinical relevance of the magnitude of the effect on lung density seen with CE1226, difference of 0.74 g/L/year compared to placebo, was thoroughly discussed at an ad hoc expert meeting (14 January 2015). The experts concluded that it is considered likely that augmentation therapy has an effect on emphysema, although, uncertainty remains how lung density decline rate translates into clinically relevant effect. Experts expressed also the view that this uncertainty is to remain as it is not possible to solve the question through feasible clinical trials particularly due to high variability of clinical outcome measures, as discussed above. The experts noted that the impact on the beneficial clinical effect might be influenced due to the late diagnosis of patients. On the other hand there might be an opportunity on the assessment of relevant clinical benefit in specific subpopulations, such as fast decliners (in density and/or lung function) vs. slow decliners.

At the ad hoc expert meeting the expert panel concurred serum A1-PI concentration is being used as a surrogate endpoint (biological) of efficacy. This is not demonstrated directly in relation to levels of A1-PI reached by replacement treatment but on the published literature that has shown a higher risk of developing emphysema due to A1-PI deficiency with lower A1-PI serum levels and genotype PiZZ. The expert panel agreed that clinically relevant effect of augmentation therapy would have to demonstrate an elevation of the mean trough serum A1 PI level in subjects to above 11 μ M and a reduction of the rate of lung density decline as measured by CT scan.

In this respect the results in the CE1226_4001 and CE1226_3001 extension studies have provided these two requisites since reassuring level of A₁-PI concentrations were achieved and a statistically significant difference in lung density decline between CE1226 and placebo treatment, measured at full inspiration, was observed. The magnitude of the effect on lung density seen with CE1226, difference of 0.74 g/L/year compared to placebo, is of the same magnitude as reported in other studies (Dirksen 1999, 2009).

The Applicant has made several attempts to address the possible clinical relevance of the observed effects in the pivotal study. The Applicant has conducted a new post-hoc analysis to evaluate longitudinal Pearson's correlations between lung density decline and FEV₁ decline based on the preliminary 4-year data from studies CE1226_4001 and CE1226_3001 extension (analyses performed with data available in January 2015). The results indicate a moderate correlation between the change in lung density and the change in FEV₁ at 48 months. The potential correlation of CT-measured lung density with functional and patient-reported outcomes in A1-PI deficiency has been reviewed in several studies. In two studies (Dirksen in 2009, Parr 2006) a correlation between decline in lung density and decline in FEV₁ over a period of 30-36 months was observed. Thus, there is some support for a clinical relevant effect expressed as a reduced worsening of FEV₁ in connection with reduced decline in lung density.

The Applicant has moreover discussed the correlation between mortality and decline in lung-density. The results from both the NHLBI registry (Dawkins 2009), and UK registry studies (Stockley, to be published) are presented again. Overall these data indicate that the rate of lung density decline measured by CT densitometry is strongly associated with mortality risk among those patients with FEV₁ values between 30% and 50% of predicted. This unpublished data has to be interpreted carefully, but a more rapid regression of lung density is detrimental for the patient. This is also supported in a publication by Dawkins 2009. Although, the data is not providing any direct evidence with respect to the beneficial effect of the magnitude of the effect on lung density seen with treatment with CE1226.

Furthermore, the Applicant has made an attempt to provide a clinical context of this magnitude of difference, by projected the length of time that it would take patients starting with the average lung density observed in study CE1226_4001 (approximately 45 g/L) to reach a theoretical terminal lung density level, which in this study corresponded to approximately 20 g/L based on whether they received augmentation therapy or not. This hypothetical calculation suggests that the difference approached approximately 6 years longer until patients

receiving CE1226 reached this level of lung density compared to those who received placebo. However, there are limitations with the performed extrapolation as also acknowledged by the Applicant.

To conclude, the efficacy of the treatment has been demonstrated as far as it possibly can be achieved. Furthermore, CHMP has agreed on a randomized, long-term PAES as an Annex II condition as recommended by the expert panel to study the dose-relationship if the higher API levels achieved in the blood might influence the rate of lung density decline and whether that would support an increased dose of 120mg/kg based on scientific observation of the population treated that previous efficacy evaluations might not have covered in population with higher rate of exacerbations.

The Applicant has in response to a raised question regarding the initially proposed post authorisation study committed to conduct a randomized, long term, high/low dose study as an Annex II condition that will evaluate the effect of a high dose (120 mg/kg) as both a routine therapy as well as an up-titration regimen for those subjects whose lung density decline persists above 2 g/L/y following administration of 60 mg/kg therapy as a post authorisation commitment. The preliminary outlined study begins with a run-in period followed by a randomized treatment period (60 mg/kg, 120 mg/kg) with the aim to evaluate the efficacy and safety profile of the two doses. This is strongly endorsed. The Applicant proposes that following the treatment period, subjects who are persistent fast decliners, will be up-titrated in a blinded manner. All aspects of the study need to be thoroughly discussed and a centralised scientific advice regarding the study design is recommended. The CHMP endorses the Applicant's commitment to seek centralised scientific advice regarding the study design.

2.6. Clinical safety

The safety evaluation is based on the 6 clinical studies presented: studies 101 (RPR118635-101), 1002 (CE1226/2-1002), 201 (RPR118635-201), 2002 (CE1226/2-2002) and the pivotal clinical study (CE1226_4001; performed in subjects with A1-PI deficiency and clinical evidence of emphysema) with its extension (CE1226_3001).

Patient exposure

Across the program a total of 221 unique subjects were treated with A1-PI at a dose of 60 mg/kg or more (6 patients received 120 mg/kg and 87 received placebo). The demographics of the safety population are appropriate to allow for conclusions of safety profile for the population to be treated. Over 90% of subjects had the severe ZZ genotype, and most subjects had FEV1 % predicted values of $\leq 70\%$, indicating that the population comprised moderately to severely affected subjects with A1-PI deficiency. They were in average 52 years old (only 2 were > 65 in the A1-PI treated group). They were predominantly men (58 %) with a normal weight span (54 % $> \text{BMI } 25$ and 86 % < 30). All were non-smokers.

The duration of exposure varies between studies. Counted as years of exposure the database is completely dominated by the pivotal study CE1226_4001 (2 years) with its extension CE1226_3001 (with a duration of 2 years at data lock point for the interim analysis). However, the latter does not add information in comparison to placebo, as it was single armed. Of the 221 patients totally enrolled, 93 participated in CE1226_4001 and an additional 63 (previously treated with placebo) participated in CE1226_3001.

In an attempt to summarise data from all studies, the applicant has compared the exposure-adjusted incidence rates (EAIR) between treatment groups. This EAIR was calculated as the total number of events that occurred during the subject exposure time divided by the subject exposure time (in years), which was defined as the sum of the total exposure time of all subjects in a treatment group.

Adverse events

Overall, there were 2709 adverse reactions reported in the 221 subjects in the A1-PI group, 1071 in the 87 subjects in the placebo group. The exposure-adjusted incidence rate was 6.35 (95% confidence interval [CI]: 6.11, 6.59) with A1-PI and 7.18 (95% CI: 6.76, 7.62) with placebo, thus non-overlapping. The apparent difference in EAIR in favour of placebo was however not confirmed by the data from the largest placebo controlled study (CE1226_4001). In this study the overall frequency of adverse reactions were comparable between groups. The frequency is higher in the A1-PI (CE1226 in the table) group for the most frequent events but the numerical difference is small.

Table 29

Preferred term	CE1226 (N=93, SY ^a =171.14)		Placebo (N=87, SY ^a =147.75)	
	Number (% ^b) of subjects	Number (rate ^c) of events	Number (% ^b) of subjects	Number (rate ^c) of events
Any event	86 (92.5)	702 (4.10)	83 (95.4)	560 (3.79)
Headache	29 (31.2)	65 (0.38)	20 (23.0)	48 (0.32)
Chronic obstructive pulmonary disease	21 (22.6)	54 (0.32)	15 (17.2)	28 (0.19)
Condition aggravated	19 (20.4)	36 (0.21)	12 (13.8)	25 (0.17)
Nasopharyngitis	18 (19.4)	30 (0.18)	15 (17.2)	23 (0.16)
Lower respiratory tract infection	14 (15.1)	42 (0.25)	15 (17.2)	34 (0.23)
Dyspnea	12 (12.9)	16 (0.09)	4 (4.6)	4 (0.03)
Oropharyngeal pain	11 (11.8)	12 (0.07)	6 (6.9)	6 (0.04)
Upper respiratory tract infection	10 (10.8)	14 (0.08)	12 (13.8)	17 (0.12)
Bronchitis	7 (7.5)	13 (0.08)	9 (10.3)	10 (0.07)
Pneumonia	6 (6.5)	9 (0.05)	9 (10.3)	13 (0.09)
Edema peripheral	5 (5.4)	5 (0.03)	9 (10.3)	10 (0.07)

N = number of subjects in the population; SY = subject years.

^a Sum of treatment duration over all subjects within the treatment group.

^b Percentage of subjects who experienced an event based on the Safety population.

^c Number of treatment-emergent adverse events/subject year.

Data from the extension study CE1226_3001 does not allow for comparison with placebo as the study is singled armed. Instead the data are presented as a comparison between subjects who received A1-PI in the initial study CE1226_4001 (so called "early start") and those who received placebo in that study (so called "delayed start"). Active treatment is thus delayed 2 years in the latter group.

Table 30 - Proportion of subjects with TEAEs (reported by $\geq 10\%$ of subjects in either group) and exposure adjusted incidence rates by preferred term

Preferred term	Early Start (N=76, SY ^a =120.1)		Delayed Start (N=64, SY ^a =106.0)		Overall (N=140, SY ^a =226.1)	
	Number (% ^b) of subjects	Number (rate ^c) of events	Number (% ^b) of subjects	Number (rate ^c) of events	Number (% ^b) of subjects	Number (rate ^c) of events
Any event	72 (94.7)	599 (4.99)	61 (95.3)	532 (5.02)	133 (95.0)	1131 (5.00)
COPD	31 (40.8)	73 (0.61)	19 (29.7)	69 (0.65)	50 (35.7)	142 (0.63)
Nasopharyngitis	23 (30.3)	31 (0.26)	16 (25.0)	32 (0.30)	39 (27.9)	63 (0.28)
Condition aggravated	16 (21.1)	33 (0.27)	12 (18.8)	33 (0.31)	28 (20.0)	66 (0.29)
Headache	14 (18.4)	19 (0.16)	10 (15.6)	23 (0.22)	24 (17.1)	42 (0.19)
Lower respiratory tract infection	11 (14.5)	49 (0.41)	9 (14.1)	43 (0.41)	20 (14.3)	92 (0.41)

Upper respiratory tract infection	10 (13.2)	18 (0.15)	5 (7.8)	14 (0.13)	15 (10.7)	32 (0.14)
Pharyngolaryngeal pain	9 (11.8)	9 (0.07)	5 (7.8)	5 (0.05)	14 (10.0)	14 (0.06)
Pneumonia	7 (9.2)	12 (0.10)	7 (10.9)	10 (0.09)	14 (10.0)	22 (0.10)
Cough	8 (10.5)	15 (0.12)	5 (7.8)	8 (0.08)	13 (9.3)	23 (0.10)
Influenza	3 (3.9)	4 (0.03)	9 (14.1)	10 (0.09)	12 (8.6)	14 (0.06)
Oral candidiasis	4 (5.3)	12 (0.10)	8 (12.5)	20 (0.19)	12 (8.6)	32 (0.14)

^a. Sum of treatment duration over all subjects within the treatment group.

^b. Percentage of subjects who experienced an event based on the Safety population.

^c. Number of TEAEs/subject year.

Events are sorted by decreasing number of subjects based on the overall number of subjects with TEAEs.

Adverse reactions of exploratory interest

The applicant has defined a number of adverse reactions as of exploratory interest as they are related to the drug formulation as such (hypersensitivity events including anaphylactic reaction and hypersensitivity and viral transmission).

For hypersensitivity events the following MedDRA categories (SMQs) were considered: anaphylactic reactions, anaphylactic shock and hypersensitivity. There were 180 events recorded in the A1-PI group (0.25 events per patient year) and 51 in the placebo group (0.15 events per patient year). During the first 6 months of treatment 24 % of the patients experience a hypersensitivity reaction in the A1-PI group compared to 16 % in the placebo group. These figures include the PTs "cough" and dyspnoea" and thus it is difficult to distinguish between symptoms linked to the disease progress as such as adverse reactions from treatment. Upon request, the applicant further discussed hypersensitivity. A new search using the criteria SMQs anaphylactic/anaphylactoid shock conditions – narrow, anaphylactic reaction – narrow and hypersensitivity - narrow was performed. Data were provided expressed as percentage of patients affected for A1-PI and placebo for 6 month and 24 months.

Table 31 Hypersensitivity events study CE1226_4001

Table 51 Hypersensitivity events that occurred during 24 months of treatment in both treatment arms (study CE1226_4001)

Preferred term	CE1226 (N=93, TSEY=170.62, NIN=8405)					Placebo (N=87, TSEY=147.28, NIN=7195)				
	E	n	%	EAIR	IAIR	E	n	%	EAIR	IAIR
Any hypersensitivity event	27	15	16.1	0.158	0.321	22	17	19.5	0.149	0.306
Injection site urticaria	8	1	1.1	0.047	0.095	0	0	0	0	0
Urticaria	4	4	4.3	0.023	0.048	5	3	3.4	0.034	0.069
Hot flush	3	1	1.1	0.018	0.036	0	0	0	0	0
Dermatitis contact	2	2	2.2	0.012	0.024	1	1	1.1	0.007	0.014
Rash	2	2	2.2	0.012	0.024	3	3	3.4	0.020	0.042
Eczema	2	2	2.2	0.012	0.024	2	2	2.3	0.014	0.028
Dermatitis allergic	2	2	2.2	0.012	0.024	0	0	0	0	0
Dermatitis	1	1	1.1	0.006	0.012	3	2	2.3	0.020	0.042
Anaphylactic reaction	1	1	1.1	0.006	0.012	0	0	0	0	0
Eye allergy	1	1	1.1	0.006	0.012	0	0	0	0	0
Rhinitis allergic	1	1	1.1	0.006	0.012	0	0	0	0	0
Drug hypersensitivity	0	0	0	0	0	2	2	2.3	0.014	0.028
Eye swelling	0	0	0	0	0	2	2	2.3	0.014	0.028
Hypersensitivity	0	0	0	0	0	2	2	2.3	0.014	0.028
Lip swelling	0	0	0	0	0	1	1	1.1	0.007	0.014
Pharyngeal oedema	0	0	0	0	0	1	1	1.1	0.007	0.014

E = number of TEAEs; EAIR = exposure adjusted incidence rate; IAIR = infusion adjusted incidence rate; n = number of subjects with preferred term; NIN = total number of infusions in the treatment; TSEY = total subject exposure years.

Note: Preferred terms are sorted by decreasing EAIR based on CE1226. The percentages are only based on the first 6 months of treatment. They are calculated as n/N where n is the number of subjects who has TEAE in the first 6 months. At each level of summarization, a subject is counted once if the subject reported 1 or more events. Adverse events were coded according to MedDRA 15.1.

Source: Q92 Attachment 01.

Table 32 Hypersensitivity events study CE1226_3001**Table 53** Hypersensitivity events that occurred during 24 months of treatment (study CE1226_3001)

Preferred Term	Early Start (N=76,TSEY=138.06,NIN=6841)					Delayed Start (N=64,TSEY=117.97,NIN=5789)				
	E	n	%	EAIR	IAIR	E	n	%	EAIR	IAIR
Any hypersensitivity event	14	8	10.5	0.101	0.205	10	9	14.1	0.085	0.173
Eczema	4	4	5.3	0.029	0.058	2	2	3.1	0.017	0.035
Rash	4	3	3.9	0.029	0.058	0	0	0	0	0
Hypersensitivity	2	2	2.6	0.015	0.029	1	1	1.6	0.009	0.017
Dermatitis allergic	1	1	1.3	0.007	0.015	0	0	0	0	0
Skin reaction	1	1	1.3	0.007	0.015	0	0	0	0	0
Rhinitis allergic	1	1	1.3	0.007	0.015	0	0	0	0	0
Urticaria	1	1	1.3	0.007	0.015	0	0	0	0	0
Blood IgE increased	0	0	0	0	0	1	1	1.6	0.009	0.017
Drug hypersensitivity	0	0	0	0	0	1	1	1.6	0.009	0.017
Hot flush	0	0	0	0	0	2	2	3.1	0.017	0.035
Injection site rash	0	0	0	0	0	1	1	1.6	0.009	0.017
Pruritus allergic	0	0	0	0	0	1	1	1.6	0.009	0.017
Rash papulo-macular	0	0	0	0	0	1	1	1.6	0.009	0.017

E = number of TEAEs; EAIR = exposure adjusted incidence rate; IAIR = infusion adjusted incidence rate; n = number of subjects with preferred term; NIN = total number of infusions in the treatment; TSEY = total subject exposure years.

Note: Preferred terms are sorted by decreasing EAIR based on CE1226. The percentages are only based on the first 6 months of treatment. They are calculated as n/N where n is the number of subjects who has TEAE in the first 6 months. At each level of summarization, a subject is counted once if the subject reported 1 or more events. Adverse events were coded according to MedDRA 15.1.

Source: Q92 Attachment 02.

The relevant texts in section 4.4 and 4.8 of the SmPC have been updated with regards to the results from this summary. Hypersensitivity remains the most important identified risks and the applicant made further efforts to distinguish, to the extent possible, hypersensitivity reactions manifested in the airways from symptoms of the disease to be treated. No signals of such mix were found.

A1-PI is a human plasma-derived product and therefore inherits the theoretical risk of transmission of blood-borne pathogens. There was however no viral safety concern in any of the 6 clinical studies with A1-PI. The tests performed included hepatitis A antibody, hepatitis C antibody, HBsAg, hepatitis B surface antibody, hepatitis B core antibody, human immunodeficiency virus type-1/type-2 (HIV-1/-2) antibodies, and sampling for potential polymerase chain reaction testing.

In all 6 clinical studies with A1-PI, subjects were evaluated for A1-PI antibody and immunoglobulin A, and immune complex profile C1q binding assay was also evaluated in studies 101, 1002, 201, and 2002. No immune complexes or A1-PI antibodies were detected in any subject in any of the clinical studies.

Chronic obstructive pulmonary disease

Exacerbation of COPD was recorded in 40 out of 221 patients (18.1 %) during the first 6 month of treatment. The corresponding figure for placebo is 11/149 (12.6 %). The overall incidence rate was 0.59 and 0.36 events per patient year respectively. Based on incidence rate this was the most common adverse reaction in the test group with an odds ratio versus placebo of 1.66 (95% CI: 1.24, 2.23). The definition of COPD exacerbation and serious COPD exacerbation differs between the safety and the efficacy part of the dossier. Due to these findings, the Applicant was asked to justify their assessment that there would be no increased risk of COPD exacerbations with CE1226 treatment. In response, the applicant presented their data as "COPD composite" events thereby linking COPD as an adverse reaction with clinical exacerbations. Consistent with the observation in the efficacy-part of the dossier it was concluded that the number of COPD exacerbations was not lowered following treatment. As COPD is an end stage of the disease to be treated it was unexpected to note that the incidence rate

was significantly higher than in the placebo group (0.59 and 0.36 events per patient year respectively; odds ratio 1.66 (95% CI: 1.24, 2.23)). This finding is directly linked also to the efficacy of the product.

Serious adverse events and deaths

The incidence rate for serious adverse reactions was similar between groups (0.37 events/patient-year for A1-PI and 0.40 for placebo). The most common organ system affected in the test group was respiratory, thoracic and mediastinal disorders (0.12 events/patient year in the A1-PI group, and 0.06 in the placebo group, COPD being the most prevalent PT. No relevant differences between treatment groups in any other PTs with at least 2 adverse reactions could be shown. The remaining severe adverse reactions were single occurrences in either treatment group.

Six deaths occurred during the course of the clinical program. Three of the deaths occurred in the placebo group (breast cancer metastatic, sepsis, and pneumonia) and 1 in the Prolastin group (respiratory arrest). The two deaths that occurred in the CE1226 group were due to respiratory arrest and COPD.

There were altogether 14 events of neoplasms in the A1-PI group and 7 in the placebo group. The incidence rate was similar. Of these 14, 7 were lung neoplasms and the rest a variety of different types. All lung neoplasms were benign.

For cardiac events the incidence rate was higher for A1-PI than for placebo (0.07 and 0.02 events/patient year respectively). The risk ratio was 3.26 [95 % CI: 0.99-10.72). The number of events was (28/437 and 3/149 events/patient years respectively). A variety of different PTs were recorded. There were 3 records of cardiac failure in the A1-PI treated group and none in the placebo group. A search on "Embolic and thrombotic events", found 9 TEAEs in subjects with an exposure duration of at least 6 months (7 events in CE1226, 2 events in placebo). All of these TEAEs were causally unrelated apart from 1 TEAE of thrombosis in the CE1226 group. Subjects with exposure durations of at least 3 months had 7 thrombotic events in CE1226, 3 thrombotic events in placebo group, and with at least 12 months 5 thrombotic events in CE1226, 2 thrombotic events in placebo group.

Laboratory findings

No integrated analysis of clinical laboratory safety was performed. There were no clinically significant findings for haematology, serum chemistry, urinalysis or coagulation parameters in either of the single-dose studies. In the multiple-dose studies (201 and 2002), A1-PI was similar to Prolastin with respect to the incidence and type of test results for these parameters. Since the findings on clinical laboratory safety were minor in the earlier studies, haematology, serum chemistry, urinalysis, and coagulation parameters were not analyzed in studies CE1226_4001 and CE1226_3001. A justification was provided for not investigating clinical laboratory safety in the long-term study versus placebo.

Safety in special populations

The potential effect of intrinsic and extrinsic factors of interest on the safety of A1-PI treatment was assessed by examining similarities and differences for incidence rate ratios of A1-PI versus placebo for each subgroup. A number of subgroups were analysed (sex, age, genotype, BMI, FEV₁ % predicted, A1-PI concentration and adjusted P15. No firm conclusions could be drawn from this subgroup analysis.

Immunological events

In all 6 clinical studies with A1-PI, subjects were evaluated for A1-PI antibody and immunoglobulin A, and immune complex profile C1q binding assay was also evaluated in studies 101, 1002, 201, and 2002. No immune complexes or A1-PI antibodies were detected in any subject in any of the clinical studies.

Safety related to drug-drug interactions and other interactions

The proportion of subjects with concomitant medications was 96.4% during treatment with A1-PI, 98.9% during treatment with placebo, and 87.5% during treatment with Prolastin. The most frequent concomitant medications (ie, given to more than 40% of CE1226 subjects) were anilides, glucocorticoids, influenza vaccines, and selective beta-2- adrenoreceptor agonists.

Discontinuation due to adverse events

There were 3 adverse reactions that led to discontinuation of treatment in the CE1226 group and 12 in the placebo group. All TEAEs leading to treatment discontinuation were single occurrences of each PT; the 3 events in the CE1226 group were back pain, COPD, and lung transplant.

Post marketing experience

Cumulatively, since US in July 2003 until July 2013, CSL Behring Global Pharmacovigilance received a total of 321 reports of AEs spontaneously reported. The majority of reports originated from the US market. The cumulative subject exposure in the market setting is estimated as 400,549 doses.

Overall, 18 fatal reports were received. No causal relationship to the application of A1-PI was reported for these cases. In each of the cases, the subject's underlying disease provided a plausible alternative explanation.

Of the total 321 reports received, 120 cases were identified using the search criteria to identify potential hypersensitivity/allergic/anaphylactic reaction cases.

Cumulatively, 12 case reports of suspected transmission of infectious agents were received. These cases included PTs of influenza, viral upper respiratory tract infection, gastroenteritis viral, viral infection, infectious mononucleosis, nosocomial infection, and hepatitis C. The causality to A1-PI for the hepatitis C case was assessed as unlikely.

Table 33 Post-Marketing reports

System organ class	Number of case reports per primary PT	Most frequent PTs by number of cases (if > 10 reports were received for this SOC)
Infections and infestations	55	Pneumonia 9, Upper respiratory tract infection 8
General disorders and administration site conditions	41	Death 9, Fatigue 9
Nervous system disorders	34	Headache 17
Skin and subcutaneous tissue disorders	32	Rash 12
Respiratory, thoracic and mediastinal disorders	22	Dyspnea 11
Gastrointestinal disorders	18	Diarrhea 4, Vomiting 4
Musculoskeletal disorders	15	Arthralgia 5, Pain in extremity 5
Vascular disorders	8	
Immune system disorders	7	
Investigations	6	
Eye disorders	4	

Injury, poisoning and procedural complications	4	
Psychiatric disorders	4	
Surgical and medical procedures	4	
Metabolism and nutrition disorders	2	
Cardiac disorders	1	
Ear and labyrinth disorders	1	
Hepatobiliary disorders	1	
Neoplasm, benign, malignant and unspecified	1	
Pregnancy, puerperium and perinatal conditions	1	
Renal and urinary disorders	1	
Reproductive and breast disorders	1	

2.6.1. Discussion on clinical safety

As A1-PI is intended to replace a human protein in deficient patients prominent safety concerns are not expected besides possibly reactions related to the infusion itself, hypersensitivity reactions and viral/prion safety and a warning to patients is reflected in section 4.4 of the SmPC. The studies were relatively small with a total safety database of only 221 exposed patients. The applicant has presented a summary analysis of data from all studies but due to different treatment durations in different groups and the fact that the extension study CE1226_2003 included patients who had been placebo treated for two years following diagnosis the figures in this summary analysis are uncertain. Anyway, overall it appears as if the overall safety pattern is acceptable with similar rates of adverse reactions in the A1-PI treated patients and placebo treated controls. As expected there were cases of hypersensitivity reaction, e.g. urticaria at the injections sites (8 cases vs zero in the placebo group). In response to the LoQ, the applicant has recalculated their figures but nevertheless a further update was needed to describe how often a particular patient is likely to experience hypersensitivity in section 4.8 of the SmPC. To the extent possible there should be an attempt to distinguish hypersensitivity reaction manifested in the airways from the ongoing disease. The number of cardiovascular events appears somewhat higher in the A1-PI treated patients but there are no mechanistic rationale for this finding and most events occurred in one single patient. Thrombotic and embolic events have been reported as TEAEs, but mainly assessed as causally unrelated to treatment. A clearer presentation of the data was presented in response to LoQ showing that there was no increased risk.

Haematology, serum chemistry, urinalysis, and coagulation parameters were only analysed in single dose studies and in studies 201 and 2001, both 6 months treatments without comparator or with comparison to Prolastin, respectively. The justification provided by the applicant for not investigating clinical laboratory safety in the long-term study CE1226_4001 versus placebo was regarded as satisfactory by the CHMP.

As COPD is an end stage of the disease to be treated it was unexpected to note that the incidence rate was significantly higher than in the placebo group (0.59 and 0.36 events per patient year respectively; odds ratio 1.66 (95% CI: 1.24, 2.23)). This finding is directly linked also to the efficacy of the product.

Post-marketing data from US does not indicate any specific safety concerns. The table with adverse reactions in the SmPC section 4.8 was further discussed with regard to choice of denominator for frequency. CHMP concluded that the denominator should be number of subjects and not number of infusions given.

2.6.2. Conclusions on the clinical safety

The safety profile for A1-PI was found as expected based on the character of the treatment and the known properties of A1-PI. The main concern as known with this kind of product is hypersensitivity/anaphylactoid reactions. No specific concerns were raised for severe adverse reactions and deaths.

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

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 2.2 is acceptable. The PRAC endorsed PRAC Rapporteur assessment report is attached.

Safety concerns

Table 34: Safety concerns

Important Identified Risks	Hypersensitivity/anaphylactic reactions
Important Potential Risks	Transmission of infectious agents
	Increased or unknown risks with home based self-administration
	Medication error
Missing information	Limited experience in pregnancy/lactation
	Limited experience in geriatric population
	No experience in in patients who have undergone lung transplantation or volume reduction surgery
	No experience in in patients with hepatic impairment
	Limited experience in patients with FEV ₁ <35%
	Limited experience in long term safety

Pharmacovigilance plan

Table 35: on-going and planned studies in the Post-authorisation Pharmacovigilance Development 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)
CE1226_3001:	To collect long-	1) Hypersensitivity/	Started	Interim safety data

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)
An Open, Non- Controlled, Multicenter, Multinational Study to evaluate the Efficacy and Safety of CE1226 Administration in Chronic Augmentation and Maintenance Therapy in Subjects with Emphysema due to Alpha1- Proteinase Inhibitor Deficiency who completed Clinical Study CE1226_4001 (Category 3)	term data for the safety and efficacy of chronic augmentation and maintenance therapy with CE1226 given iv at a dosage of 60 mg/kg body weight weekly in subjects with emphysema due to A1-PI deficiency.	Anaphylactic reactions 2) Transmission of infectious agents 3) Limited experience in geriatric population		to be submitted with PSUR. Final report to be completed September 2015.

Risk minimisation measures

Table 36: Proposal from MAH for risk minimisation measures (copy from V.2.2 of RMP)

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Hypersensitivity/anaphylactic reactions	Text in SmPC: 4.3 Contraindications Hypersensitivity to the active substance or to any of the excipients listed in section 6.1 (see also section 4.4). IgA deficient patients with known antibodies against IgA, due to the risk of severe hypersensitivity and anaphylactic reactions. 4.4 Special warnings and precautions for use	None proposed

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	<p>The recommended infusion rate given under section 4.2 should be adhered. During the first infusions, patient's clinical state, including vital signs, should be closely monitored throughout the infusion period. If any reaction takes place that might be related to the administration of Respreeza, the rate of infusion should be decreased or the administration should be stopped, as required by the clinical condition of the patient. If symptoms subside promptly after stopping, the infusion may be resumed at a lower rate that is comfortable for the patient.</p> <p><u>Hypersensitivity</u></p> <p>Hypersensitivity reactions may occur, including in patients who have tolerated previous treatment with human alpha1-proteinase inhibitor.</p> <p>Suspected allergic or anaphylactic type reactions may require immediate discontinuation of the infusion, depending on the nature and severity of the reaction. In case of shock, emergency medical treatment should be administered.</p>	
Transmission of infectious agents	<p>Text in SmPC:</p> <p>4.4 Special warnings and precautions for use</p> <p><u>Transmissible agents</u></p> <p>Standard measures to prevent infections resulting from the use of medicinal products prepared from human blood or plasma include selection of donors, screening of individual donations and plasma pools for specific markers of infection and the inclusion of effective manufacturing steps for the inactivation/removal of viruses. Despite this, when medicinal products prepared</p>	None proposed

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	<p>from human blood or plasma are administered, the possibility of transmitting infective agents cannot be totally excluded. This also applies to unknown or emerging viruses and other pathogens.</p> <p>The measures taken are considered effective for enveloped viruses such as human immunodeficiency virus (HIV), hepatitis B virus (HBV) and hepatitis C virus (HCV) and for the non-enveloped hepatitis A (HAV) and parvovirus B19 virus.</p> <p>Appropriate vaccination (hepatitis A and B) should be considered for patients in regular/repeated receipt of human plasma-derived proteinase inhibitors.</p> <p>It is strongly recommended that every time that Respreeza is administered to a patient, the name and batch number of the product are recorded in order to maintain a link between the patient and the batch of the product</p>	
Increased or unknown risks with home based self-administration	<p>Text in SmPC Section 4.4: Special warnings and precautions for use:</p> <p><u>Home-treatment/self- administration</u></p> <p>There are limited data regarding the use of this medicinal product in home-treatment/self- administration.</p> <p>Potential risks associated with home-treatment/ self-administration are related to the handling and administration of the medicinal product as well as to the handling of adverse reactions, particularly hypersensitivity. Patients should be informed of signs of hypersensitivity reactions.</p> <p>The decision of whether a patient is suitable for home-treatment /</p>	None proposed

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	<p>self-administration is made by the treating doctor, who should ensure appropriate training is provided (e.g. regarding reconstitution, use of transfer device or filter, assembly of intravenous tubing, infusion techniques, maintenance of a treatment diary, identification of adverse reactions and measures to be taken in case such reactions occur) and the use is reviewed at regular intervals.</p>	
Medication error	<p>Text in SmPC Section 6.6: Special precautions for disposal and other handling was updated.</p> <p>Text in package leaflet was updated including more detailed instructions for administration.</p>	None proposed
Limited experience in pregnancy/lactation	<p>Text in SmPC section 4.6 Fertility, pregnancy and lactation:</p> <p><u>Pregnancy</u></p> <p>No animal reproduction studies have been conducted with Respreeza and its safety for use in human pregnancy has not been established in controlled clinical trials. Since alpha1-proteinase inhibitor is an endogenous human protein, it is considered unlikely that Respreeza will cause harm to the foetus when given at recommended doses. However, Respreeza should be given with caution to pregnant women.</p> <p><u>Breast-feeding</u></p> <p>It is unknown whether Respreeza/metabolites are excreted in human milk. The excretion of Human alpha1-proteinase inhibitor in milk has not been studied in animals. A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with Respreeza should be made, taking into account the benefit of</p>	None proposed

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	<p>breast-feeding to the child and the benefit of Human alpha1-proteinase inhibitor therapy to the woman.</p> <p><u>Fertility</u></p> <p>No animal fertility studies have been conducted with Respreeza and its effect on human fertility has not been established in controlled clinical trials. Since human alpha1-proteinase inhibitor is an endogenous human protein, no adverse effects on fertility are expected when given at recommended doses.</p>	
Limited experience in geriatric population	<p>Text in SmPC section 4.2 Posology and method of administration:</p> <p><u>Elderly Population</u></p> <p>The safety and efficacy of Respreeza in elderly patients (65 years of age or older) have not been established in specific clinical trials.</p>	None proposed
No experience in patients with lung transplantation or volume reduction surgery	No text in SmPC	None proposed
No experience in patients with hepatic impairment	<p>Text in SmPC section 4.2 Posology and method of administration:</p> <p><u>Patients with renal or hepatic impairment</u></p> <p>No special investigations have been performed. No alternative dose regimen can be recommended in those patients.</p>	None proposed
Limited experience with FEV ₁ <35%	<p>Text in SmPC section 4.1 Therapeutic indication:</p> <p>Respreeza is indicated for maintenance treatment, to slow the progression of emphysema in adults with documented severe alpha1-proteinase inhibitor deficiency (e.g. genotypes PiZZ, PiZ(null), Pi(null,null), PiSZ). Patients are to be under optimal pharmacologic and non-pharmacologic treatment and show</p>	None proposed

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	evidence of progressive lung disease (e.g. lower forced expiratory volume per second (FEV1) predicted, impaired walking capacity or increased number of exacerbations) as evaluated by a healthcare professional experienced in the treatment of alpha1-proteinase inhibitor deficiency.	
Limited experience in long term safety	No text in SmPC	None proposed

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

Alpha1-proteinase inhibitor (A1-PI) deficiency, also known as alpha1-antitrypsin deficiency is a genetic rare disorder that manifests as pulmonary emphysema and is characterized by low serum levels of A1-PI, the main protease inhibitor (PI) in human serum.

Respreeza contains human alpha-1 proteinase inhibitor, powder and solvent for solution for infusion, 1000 mg, and the recommended dose is 60 mg/kg body weight administered intravenously once a week.

The efficacy of human alpha-1 proteinase inhibitor for the proposed indication of “*maintenance treatment, to slow the progression of emphysema in adults with documented severe alpha₁-proteinase inhibitor deficiency (e.g. genotypes PiZZ, PiZ(null), Pi(null,null), PiSZ). Patients are to be under optimal pharmacologic and non-pharmacologic treatment and show evidence of progressive lung disease (e.g. lower forced expiratory volume per second (FEV₁) predicted, impaired walking capacity or increased number of exacerbations) as evaluated by a healthcare professional experienced in the treatment of alpha₁-proteinase inhibitor deficiency*” was evaluated for 2-4 years in the pivotal phase III study CE1226_4001 and the extension study CE1226_3001 (expected Final CSR to be submitted in September 2015). Subjects (non-smokers) with A1-PI deficiency (serum A1-PI levels < 11 µM, or < 50 mg/dL as determined by nephelometry) with emphysema and reduced lung function, with forced expiratory volume in 1 second (FEV1) ≥ 35% and ≤ 70% predicted were eligible for enrolment into the pivotal study.

Lung loss measured at total lung capacity (TLC) via whole lung CT densitometry, i.e. the 15th percentile point, is considered a relevant endpoint to use as it measures the physiological change in the organ which is affected

of the disease. The documented difference in study CE1226_4001 in decline of the lung density between CE1226 and placebo treatment (TLC inspiration state: -1.45 g/L/year, -2.19 g/L/year; difference between arms 0.74 g/L/year ($p=0.017$, one sided p -value)) show that CE1226 has an effect on this parameter. The results of the second interim analysis of study CE1226_3001 with a cut-off date of 31 December 2013 support the effect observed in study CE1226_4001. The observed value is slightly lower but is of the same magnitude as the observed value of 0.86 g/L/year measured at "TLC state" in the EXACTLE study (Dirksen et al, 1999).

Uncertainty in the knowledge about the beneficial effects

The results of the functional and patient reported endpoints in study CE1226_4001 showed no clear beneficial effects for the patients in the CE1226 arm in comparison to the patients in the placebo arm. The results are not unexpected since the study CE1226_4001 was not large enough or long enough, and will be completed with the ongoing long-term CE1226_3001 in the RMP and Post authorisation efficacy study in Annex II. The subjects were further permitted to use concomitant respiratory medications without any restriction and there were some differences between the two arms. Further information on the long-term use will be provided with the submission of the

The mean trough A₁-PI concentrations in the CE1226 group in the CE1226_4001 was approximately 16 μ M (11-23 μ M, 90 % prediction interval) and the estimated average serum A₁-PI concentration throughout a dosing interval is in the order of 19 to 20 μ M which is in the lower range of normal. However, the relationship between achieved serum level and effect on lung density is not known.

The Applicant has committed to conduct a randomized, long term, high/low dose study that will evaluate the effect of a high dose (120 mg/kg) as both a routine therapy as well as an up-titration regimen for those subjects whose lung density decline persists above 2 g/L/y following administration of 60 mg/kg therapy as a post authorisation commitment. The preliminary outlined study begins with a run-in period followed by a randomized treatment period (60 mg/kg, 120 mg/kg) with the aim to evaluate the efficacy and safety profile of the two doses. The Applicant also commits that following the treatment period, subjects who are persistent fast decliners, will be up-titrated in a blinded manner. All aspects of the study need to be thoroughly discussed and a centralised scientific advice regarding the study design is recommended. The CHMP endorses the Applicant's commitment to seek centralised scientific advice regarding the study design. Furthermore the CHMP agreed to the final report of CE1226_3001 to be completed September 2015.

Risks

Unfavourable effects

The aim of the treatment is to substitute A₁-PI deficient patients and as the level of exposure is not exceeding the endogenous level in healthy subjects no adverse reactions related to the protein itself is expected. With regard to the general pattern of adverse reactions no specific concerns are raised. The most common adverse reactions recorded are either common ailments such as headache (31.2/23.0) and nasopharyngitis (19.4/17.2) or symptoms related to the progression of the disease. (Figures in parentheses refer to frequencies expressed as percentage recorded in the pivotal study CE1226_4001 for A₁-PI and placebo respectively.)

The frequencies of severe adverse reactions are similar in the groups treated with A₁-PI and placebo and there are no specific signals pointing at certain areas of concern.

An important identified risk linked to the use of the product is hypersensitivity and is reflected in the RMP. In the pivotal clinical trial CE1226_4001 the overall frequency of hypersensitivity reactions appears rather high (16 % for the treatment group and 19 % for placebo) but similar between groups. Furthermore the risk of hypersensitivity is reflected in section 4.4 of the smPC as a special warning and health care professionals

should monitor the patient throughout the infusion rate, and there are limited data regarding the use of this medicinal product in home-treatment / self-administration. furthermore in section 4.8 of the SmPC as listed undesirable effect.

Uncertainty in the knowledge about the unfavourable effects

With regard to the disease related symptoms these were in some cases more prominent in the group treated with A1-PI: COPD exacerbations (22.6/17.2), condition aggravated (20.4/13.8), dyspnoea (12.9/4.6) and oropharyngeal pain (11.8/6.9).

The incidence rate of COPD exacerbations was significantly higher than in the placebo group (0.59 and 0.36 events per patient year respectively; odds ratio 1.66 (95% CI: 1.24, 2.23).

The database is relatively small with only 221 exposed subjects. Thus the frequency of adverse reactions other than the most common cannot be estimated with any precision. . Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in section 4.8 of the SmPC and post-authorisation studies will gather more information with regards to the precision of the undesirable effects.

Weekly intravenous infusions of a human blood product may carry risks related to the aseptic reconstitution technique and the administration technique especially if the product is to be given by self-administration, nevertheless this risk is adequately mitigated by information in the product information.

Benefit-risk balance

Importance of favourable and unfavourable effects

Alpha1-proteinase inhibitor deficiency is a genetic rare disorder that can manifest in symptoms from different organs, e.g as pulmonary emphysema. The pathogenesis of the disease is reduced serum levels of A1-PI, the main protease inhibitor in human serum. Human alpha1-proteinase inhibitor has been developed for maintenance treatment with the intention to slow the underlying destruction of lung tissue leading to emphysema in adults with alpha1-proteinase inhibitor (A1 PI) deficiency with clinically evident lung disease.

A statistically significant decline in lung loss, measured via whole lung CT densitometry using "TLC" state, is observed for the Respreeza treated arm compared to the placebo arm. The magnitude of the effect is similar to previous studies of substitution therapy. It has not been fully documented in clinical studies that a slower rate of decline in lung loss translates into clinically relevant outcomes. The clinical relevance of the magnitude of the effect on lung density seen with Respreeza was thoroughly discussed at an ad hoc expert meeting and it was concluded that in patients with severe disease and high risk of progression of emphysema it is expected that treatment with Respreeza will have a beneficial effect.

The beneficial effect of Respreeza -treated subjects demonstrated a consistent pattern of slower lung density decline than those receiving placebo. The annual rate of lung density decline, as measured by CT scan at total lung capacity (TLC) over 2 years was lower with Respreeza (-1.45 g/L) as compared with placebo (-2.19 g/L), reflecting a 34% reduction ($p = 0.017$, 1-sided) as described in section 5.1 of the SmPC.

The main safety concerns are hypersensitivity or allergic reactions have been observed during the treatment. In the most serious cases, allergic reactions may progress to severe anaphylactic reactions even when the patient has shown no hypersensitivity to previous administrations as described in section 4.4 of the SmPC.

In the performed pivotal study, the mean trough A₁-PI concentrations in subjects receiving Respreeza was approximately 16 µM (11-23 µM, 90 % prediction interval) and the estimated average serum A₁-PI

concentration throughout a dosing interval is in the order of 19 to 20 µM which is in the lower range of normal. Thus, it has been shown that treatment increases serum levels but it should be noted that the relationship between achieved serum level and clinical effect on lung density is currently not known. A randomized, long-term PAES as an Annex II condition as recommended by the expert panel to study the dose-relationship if the higher API levels achieved in the blood might influence the rate of lung density decline and whether that would support an increased dose of 120mg/kg based on scientific observation of the population treated that previous efficacy evaluations might not have covered in population with higher rate of exacerbations

No specific safety concerns have arisen in the clinical studies.

Symptoms related to the progression of the disease (e.g. COPD, condition aggravated and dyspnoea) were somewhat more common in patients treated with Respreeza. However, as the subjects in the arm treated with Respreeza also had a more severe disease when compared to the subjects in the placebo arm at base line, the apparently more rapid progression of the disease in patients treated with Respreeza could be due to imbalance at study inclusion. It is also noted that the rate of severe exacerbations appears similar independent of treatment.

Benefit-risk balance

The effect of human alpha-1 proteinase inhibitor treatment on slowing the decline in lung density in adults with documented severe alpha1-proteinase inhibitor deficiency is considered to outweigh the few safety issues identified. The benefit risk balance is therefore considered to be positive.

Discussion on the benefit-risk balance

Respreeza is approved by the FDA since 2003. The pivotal studies (4001 and 3001) for the current EU application was also submitted to the FDA as an efficacy supplement along with an application for an extended indication. In this context, the FDA performed a GCP inspection of 4 study sites. The inspection report (July 2014) identified some GCP departures which was communicated to the company September 2014 and the FDA concluded that the studies were not adequate to consider for supporting the requested new application.

The Applicant has acknowledged that during the course of the CE1226_4001 study, there were GCP departures. Many of the issues identified by the FDA inspectors were identified by CSLB/contract research organizations (CROs) during routine study monitoring, review of monitoring reports, and/or during CSLB quality assurance audits. In addition, an independent clinical quality assurance has been performed. Following identification of issues, related corrective measures/actions were implemented, including process updates, training, and site communications. For those topics that could have potentially impacted the integrity of the clinical data, the Applicant has demonstrated that the corrective actions applied during the course of the studies did positively impact the overall GCP compliance. The main concerns were inability to verify that subjects received the correct active or placebo investigational medicinal product and issues referring to dosing irregularities as well as issues related to blinding of the IMP.

The Applicant's has submitted their responses to the inspection findings in the response to the Day 180 outstanding issues and has provided additional clarifications in subsequent responses. During an oral explanation at the CHMP, the applicant clearly justified, from a GCP perspective that the pivotal studies for the MAA, inspected by the FDA in July 2014 and previously for one site by the Irish medicines Board 2011 are adequate to support an approval. The CHMP concluded that the GCP findings would not influence the results of the studies in a way that the B/R of the product could be affected.

The Applicant has committed to perform, as agreed with the CHMP ,a randomized, long-term PAES as

recommended by the expert panel to study the dose-relationship if the higher API levels achieved in the blood might influence the rate of lung density decline and whether that would support an increased dose of 120mg/kg based on scientific observation of the population treated that previous efficacy evaluations might not have covered in particular in populations with frequent exacerbations as described in Annex II.

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 Respreeza is indicated for maintenance treatment, to slow the progression of emphysema in adults with documented severe α_1 -proteinase inhibitor deficiency (e.g. genotypes PiZZ, PiZ(null), Pi(null,null), PiSZ). Patients are to be under optimal pharmacologic and non-pharmacologic treatment and show evidence of progressive lung disease (e.g. lower forced expiratory volume per second (FEV₁) predicted, impaired walking capacity or increased number of exacerbations) as evaluated by a healthcare professional experienced in the treatment of α_1 -proteinase inhibitor deficiency 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 restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates 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.
- **Obligation to complete post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
Post authorisation efficacy study (PAES): A randomized, long-term PAES has been agreed to study the dose-relationship if the higher API levels achieved in the blood might influence the rate of lung density decline and whether that would support an increased dose of 120mg/kg the MAH should conduct and submit the results of a randomized, long term, efficacy study conducted according to an agreed protocol.	Submission of final clinical study report by 31 March 2025

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.

New Active Substance Status

Not applicable.

Paediatric Data

Not applicable.