23 March 2017
EMA/398059/2017
Committee for Medicinal Products for Human Use (CHMP)

Withdrawal Assessment report

Infinia

International non-proprietary name: alpha-1-antitrypsin

Procedure No. EMEA/H/C/003934/0000

Note

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

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

Table of contents

List of abbreviations

AAT(API)	Alpha-1 Antitrypsin (Alpha-1-Proteinase inhibitor)
AATD(APID)	Alpha-1 Antitrypsin Deficiency (Alpha-1-Proteinase inhibitor deficiency)
AATD-TEAE	Treatment - Emergent Adverse Event associated with Alpha-1 Antitrypsin Deficiency underlying disease
ADA	Anti-Drug Antibody
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine Aminotransferase
API	Alpha-1 Proteinase Inhibitor (other name for Alpha-1 Antitrypsin)
AST	Aspartate Aminotransferase
AUC_{0-t}	Area under the plasma concentration curve from zero to the time of the last quantifiable sample
BAL	Broncho-Alveolar Lavage
BMI	Body Mass Index
BUN	Blood Urea Nitrogen
C_{max}	Peak Plasma Concentration
CBC	Complete Blood Count
CBG	Cortisol (or Corticosteroid) Binding Globulin
CD	Circular dicroism
CF	Cystic Fibrosis
CI	Confidence Interval
CM	Carboxymethyl
CoA	Certificate of Analysis
COPD	Chronic Obstructive Pulmonary Disease
CRP	C-Reactive Protein
CSR	Clinical Study Report
CT	Computed Tomography
DB	Double-Blind
DLCO	Diffusing Capacity of the Lung for Carbon Monoxide
DEAE	Diethyl amino ethyl
ECG	Electrocardiogram
ELF	Epithelial Lining Fluid
ES-MS	Electron spray (ionisation)-mass spectrometry
FEV1	Forced Expiration Volume in 1 Second
FEV1%	Forced Expiration Volume in 1 Second, Percent of Predicted Value
FVC	Forced vital Capacity
GLP	Good Laboratory Practice
GMP	Good manufacturing practice
HPLC	High performance liquid chromatography
IEF	Isoelectric focussing
IL-8	Interleukin 8
IPC	In process control
IV	Intravenous
IT	Intratracheal
J2R	Jump to references
Kamada-AAT for inhalation	Company's working name for Infinia
LC	Liquid chromatography

MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed Model for Repeated Measures
NAT	Nucleic Acid Testing
NE	Neutrophil elastase
NF	Nanofiltration
NLT	Not less than
NMT	Not more than
NZW	New Zealand White
OLE	Open-Label Extension
PE	Polyethylene
PEG	Polyethylene glycol
PFT	Pulmonary function test
PI	Protease inhibitor
PK	Pharmacokinetics
PMF	Plasma master file
PT	Preferred term
QA	Quality assurance
QC	Quality control
RHS	Reference house standard
SAE	Serious Adverse Event
SD	Standard deviation
SE-HPLC	Size exclusion HPLC
SmPC	Summary of Product Characteristics
SOC	System Organ Class
SOP	Standard operating procedure
SVC	Slow Vital Capacity
TEAE	Treatment-emergent Adverse Event
TnBP	tri-n-butylphosphate
T_{max}	Time to reach the peak concentration
UF/DF	Ultrafiltration/diafiltration
WB	Western blot
WBC	White Blood Count

1. Recommendation

Based on the review of the data on quality, safety and efficacy, the CHMP considers that the application for Infinia (Kamada-AAT for Inhalation), for the applied indication of *"treatment and maintenance therapy of adult patients with congenital deficiency of alpha-1 antitrypsin and lung disease with clinical evidence of emphysema and airway obstruction (FEV1/SVC<70%)."* **is still not approvable** since "major objections" in clinical efficacy, safety and RMP have not been solved, which preclude a recommendation for marketing authorisation.

The major objections precluding a recommendation of marketing authorisation pertain to the following principal deficiencies regarding efficacy and safety:

- Efficacy of Infinia in alpha-1 antitrypsin deficient patients has not been demonstrated. None of the predefined endpoints in the pivotal trial 007 reveal any signs of benefit of the treatment. Most of the endpoints reveal even disadvantages for the AAT treated patients. Results of post-hoc analysis are compromised by different types of issues/deficiencies precluding a positive conclusion on the results of lung function parameters.
- Tolerability of AAT via the inhalation route of administration is still questioned based on the safety profile of the total study population. The safety profile of the subpopulation with possible less severe disease of the pivotal study is not considered convincingly improved compared to the total study population. Even though a subpopulation of Study 007 with possible less severe disease might show a better safety profile, this is not confirmed in Study 006, or any other clinical trial.
- The high frequency of ADAs (64%) in AAT treated patients as well as the sustained antibody response in most of these patients (83%) is still considered to be a major safety concern, since the occurrence of ADAs is associated with higher frequencies of TEAEs, including hypersensitivity reactions. Moreover, long term safety aspects have not been clarified. A potential risk for severe immunogenicity adverse events in ADA positive patients starting with IV-AAT after discontinuation of Kamada-AAT for Inhalation could not be excluded.
- Use of this product is associated with a number of important risks including hypersensitivity, a high frequency of anti-drug antibodies that is sustained in many patients, and also a high frequency of respiratory disorders including dyspnoea, COPD and pneumonia. The proposed open label phase IV study is unlikely to provide a clearer understanding of the safety profile or further inform the best approach to risk minimisation and may even be unethical. Consequently, the RMP is not acceptable since the proposed pharmacovigilance and risk minimisation activities are not sufficient to ensure that the benefit risk balance is favourable in the proposed indication.

Questions to be posed to additional experts

N/A

Inspection issues

GMP inspection

A request for EU-GMP inspection has been adopted for the following site in order to verify the GMP compliance status. The outcome of this inspection is required for the Committee to complete its examination of the application and will be needed by Day 181.

Kamada Ltd.
Kibbutz Beit Kama
M.P. Negev 8532500
Israel

GCP inspection

None.

New active Substance status

The active substance Alpha-1-Antitrypsin (also known as Alpha-1-Proteinase inhibitor) contained in the medicinal product Infinia (Kamada-AAT for Inhalation), is not to be qualified as a new active substance.

2. Executive summary

2.1. Problem statement

Alpha 1-antitrypsin (AAT) deficiency (AATD), also known as Alpha1-proteinase inhibitor (API) deficiency, is a hereditary condition in which a reduced level of functional AAT is associated with early onset of progressive lung emphysema. This serious and life-threatening, chronic pulmonary disease becomes clinically apparent by the third to fourth decade of life, and usually progresses to severe respiratory insufficiency and premature death. AATD is inherited as an autosomal recessive disorder with a high number of different genetic variants recognized. By far the most prevalent type of clinically important AAT deficiency is the Z variant, which can be homo- and heterozygous. Homozygotes of Pi type Z have only 10 to 20 percent of the normal serum AAT concentration.

AAT is a 52 kDa single polypeptide glycoprotein produced by hepatocytes and mononuclear phagocytes. AAT 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. If NE is present in the lung and not regulated by its naturally occurring inhibitor AAT, which is the case in AATD, 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.

The most common method for augmenting the lung's anti-protease and anti-inflammatory defences in AATD is by administering exogenous AAT by IV infusion of purified human plasma AAT on a once-weekly basis.

Inhalation therapy as intended with Infinia may represent an alternative therapeutic option to the IV route.

2.2. About the product

The active substance of Infinia is a plasma-derived serine protease inhibitor (serpin) which is produced in the liver, and acts on a number of proteolytic enzymes. In the body, AAT is thought to protect tissues from the action of proteolytic enzymes secreted by inflammatory cells. A major physiological target enzyme is neutrophil elastase (NE). Lack of AAT in the blood leaves neutrophil elastase free to act in various tissues, for example in the lungs, where the resulting loss of elastin can lead to severe respiratory complications. In addition to its role as an anti-protease, AAT has important anti-inflammatory properties. These effects are unrelated to protease inhibition and include blocking the pro-inflammatory effects of human neutrophil peptide and regulating expression of pro-inflammatory cytokines like TNFα, IL-6, IL-8, monocyte chemoattractant protein 1, and IL-1β.

Infinia is supplied as a ready to use sterile solution for nebulisation. The nebulizer solution is presented in vials containing 4 ml solution. The product is provided as a multipack comprising 56 (4 packs of 14) vials and a replacement Vespera® nebuliser handset.

The solution is clear and colorless to yellow-green and may contain a few protein particles. Infinia is supplied as a 2% solution of AAT in a buffered solution. Sodium hydroxide is added as required for pH adjustment.

2.3. The development programme/compliance with CHMP guidance/scientific advice

Between June 2006 and February 2014, Kamada obtained Protocol Assistance and follow-up advice from the CHMP/SAWP on 7 occasions regarding the development of Kamada-AAT for Inhalation in the claimed indication. National scientific advice was obtained from the BASG/Austria (December 2013), the MPA/Sweden (November 2010 and December 2013) and the PEI/Germany (April 2008 and December 2013).

The initial SAWP/CHMP protocol assistance included advice on the development of the Phase I study (Kamada-AAT (inhaled)-001; Study 001), and initial discussions of the design of the Phase II/III protocol (Study 007). SAWP/CHMP also advised that a lung deposition study would not be required for Marketing Authorisation, although it might be useful to confirm that Kamada-AAT for Inhalation was satisfactorily delivered to the site of action. Notwithstanding these recommendations, the Applicant conducted a lung deposition study (Kamada-AAT (inhaled)-005; Study 005) and demonstrated that the distribution of radio-labelled Kamada-AAT for Inhalation in the airways, using the inhalation device intended for marketing purposes, is satisfactory.

SAWP/CHMP recommended that both Phase I and Phase II/III protocols should include a thorough investigation of the immunogenic potential of Kamada-AAT for Inhalation since this is the first administration of the plasma-derived product by the inhalation route. This was implemented in the Phase Ib study (Kamada-AAT (inhaled)-002; Study 002) and in Study 007, where the development of antibody to human plasma-derived AAT was evaluated throughout the study.

Other SAWP/CHMP recommendations that were all implemented in the design of the Phase II/III Study 007 included the performance of a CT scan at baseline and study termination visits to evaluate lung density and the exclusion of subjects who were smokers or who had a history of smoking in the previous 12 months.

During subsequent Protocol Assistance, SAWP/CHMP considered that the Applicant's primary endpoint (i.e. time to the first moderate or severe exacerbation) may not be considered acceptable on the grounds that the timing of a first event does not give information on subsequent events, i.e. recurrence. The CHMP recommended that the Applicant used ‘rate of exacerbations’, as in COPD trials, or ‘severity of exacerbations’ as a primary endpoint. The Applicant understood and acknowledged the SAWP/CHMP’s comments concerning the choice of the primary efficacy endpoint for this study. However, time to the first moderate or severe exacerbation for Study 007 was retained as the primary endpoint by the Applicant, after extensive consultation with expert investigators.

The original protocol for Study 007 consisted of a DB randomised phase only, and planned to recruit 200 subjects. However, as a result of the extreme difficulty in recruiting subjects into the study, a decision was taken in 2012 to reduce the sample size from 200 to approximately 150. An OLE phase was later added to the study to ensure that sufficient safety data was collected to satisfy the recommendation of ICH Guidance E1 on the Extent of Population Exposure to Assess Clinical Safety for Drugs intended for Long-term Treatment of Non-Life-Threatening Conditions. This change was discussed and agreed with SAWP/CHMP prior to implementation.

Regarding Quality aspects the Applicant followed the Scientific Advices received from the competent authorities of Austria, Germany, and Sweden.

2.4. General comments on compliance with GMP, GLP, GCP

GMP

GMP compliance of the Infinia (Kamada-AAT for Inhalation) manufacturing site is demonstrated by a respective manufacturing license and a national GMP certificate valid until June 2016. A pre-authorisation EU-GMP inspection has been adopted by CHMP in May 2016.

GLP

The safety pharmacology studies as well as the studies on toxicokinetics and most of the toxicological studies (except one repeated dose toxicity study), have been performed under GLP conditions. The pharmacodynamics and the pharmacokinetics studies have been performed under non-GLP conditions.

GCP

All studies submitted in this MAA conducted inside and outside the European Union (Canada, USA and Israel) were performed in full compliance with Good Clinical Practice (GCP) and are consistent with the International Conference on Harmonisation (ICH) guidelines on drug development. All studies were closely monitored by the study sponsor's personnel or a contract research organisation for compliance to the protocol and the procedures described in it. Further, the Applicant confirms that all clinical trials carried out outside the European Union meet the ethical requirements of Directive 2001/20/EC.

2.5. Type of application and other comments on the submitted dossier

- Legal basis

This application follows a centralized procedure according to Regulation (EC) No 726/2004 based upon Article 3(1) –Annex 4 – orphan designated medicinal product. The application is also submitted in accordance to Article 8(3) of Directive 2001/83/EC.

- Accelerated procedure

  N/A

- Conditional approval

  N/A

- Exceptional circumstances

  N/A

- Biosimilar application

  N/A

- 1 year data exclusivity

  N/A

- Significance of paediatric studies

A product-specific waiver for conducting paediatric studies for the "treatment of emphysema secondary to congenital deficiency of alpha-1 antitrypsin has been granted for all subsets of the paediatric population for the use of Kamada-AAT for Inhalation on the grounds that the disease or condition for which the specific medicinal product is intended occurs only in the adult population (EMEA-001525-PIP01-13, Decision number: P/0318/2013).

The SmPC will state that the safety and efficacy of Infinia in the paediatric population (below 18 years) has not been established as no data are available.

3. Scientific overview and discussion

3.1. Introduction

Infinia (formerly Kamada-AAT), Nebuliser Solution, is a sterile, liquid preparation of highly purified, human plasma-derived alpha-1 antitrypsin.

The Nebuliser Solution comprises a sterile solution of AAT (20 mg/ml) supplied in glass vials containing 4 ml of solution (80 mg of AAT) for administration by inhalation.

3.2. Quality aspects

3.2.1. Active Substance

General Information

Kamada-AAT active substance (AS) is a clear and colourless to yellow green, non-sterile buffered solution containing active Alpha 1-anti-trypsine or Alpha 1-Proteinase Inhibitor (AAT).

Kamda-AAT is a serine protease inhibitor (serpin) that acts on a number of proteolytic enzymes. It is a single chain glycoprotein consisting of 394 amino acids in the mature form (without the signal peptide) with an apparent molecular weight of 51-54 kDa. It has one Cysteine residue at position 232 and three N-glycosylation sites at Asn-46, Asn-83 and Asn-247. Cys-232 is found to be covalently linked to a free single Cysteine by a disulfide bridge. The three N-linked glycosylation sites contain either diantennary or triantennary N-glycans.

Manufacture, process controls and characterisation

Description of manufacturing process and process controls

The starting material for the production of Kamada-AAT AS (active substance) is pooled human plasma that complies with the Ph. Eur. monograph 0853 for “Human plasma for fractionation” and for which European Plasma Master Files (PMF) are available.

The manufacturing process of Kamada-AAT AS starts from Cohn Fraction IV/IV-1 paste. Kamada-AAT is purified from either Fraction IV-1 paste or Fraction IV paste by Kamada, using respectively the ‘established process’ or the ‘variant process’. These processes are basically similar, but differ in operational limits for the pre-treatment and chromatography steps.

The manufacturing process of Kamada-AAT AS consists of eight major steps in both, the established and the variant process.

The plasma is initially processed by the Cohn/Oncley alcohol fractionation. The by-product of this fractionation is Fraction IV-1/Fraction IV paste containing AAT (intermediate material).

The manufacturing process by Kamada starts with the introduction of these intermediates into the process. The description of the manufacturing process in flow charts and narrative is sufficiently detailed to understand the process variants. Limitations for use and reuse of columns, or column lifetimes, have been designated for each column in the AAT manufacturing process. The currently specified life times were established in small scale and confirmed in full scale. Extension of lifetime may be possible, depending on ongoing life time studies. The currently established lifetimes have been successfully validated. The approach to extend the life time of columns, if justified by data, can be accepted.

Adequate control of the starting materials and the raw materials used in the manufacture of Kamada-AAT has been demonstrated. The starting material for commercial production of Kamada-AAT is human plasma for fractionation certified by European Plasma Master File (PMF). PMF Certificates have been included. In general there is no concern regarding the quality of the starting material of the Kamada-AAT commercial manufacturing process, pooled Plasma for Fractionation acc. Ph. Eur. All relevant information on this material is laid down in the approved PMFs. The use of intermediate from plasma of non-EU, but FDA-approved blood and plasma collection centers for product lots of early clinical study seems acceptable, as these lots will not be marketed in the EU.

Control of critical steps and intermediates

Intermediate Fraction IV-1 and Fraction IV manufacture

The most critical intermediates are the Fraction IV-1/IV pastes that are used as the starting material in the AAT manufacturing process at Kamada. Separate sections in the eCTD dossier briefly summarize the manufacture and control of these intermediates.

It is considered necessary that Kamada has detailed knowledge not only about the underlying plasma, but also about the entire manufacturing process and its control, as well as the quality of the intermediate. The level of details presented in the Module 3 Active Substance sections relating to the intermediate is considered in line with the Plasma-derived medicinal products guideline (EMA/CHMP/BWP/706271/2010). Since the Fraction IV-1/IV serves as starting material for the manufacture of the AS, the full documentation on quality has to be included into Module 3 of the CTD.

Quality control of the Fraction IV paste and Fraction IV-1 paste consists of a verification that test requirements were complied with (Certificates of Analysis), review of shipment records, visual inspection, and laboratory release tests (identification, potency, and purity). The acceptance criteria for potency and purity are based on stability data and/or measurements in Fraction IV and Fraction IV-1 paste stored for various periods of time. As potency and specific activity decrease during storage, this approach is not agreed. The Applicant is requested to further justify and/or revise the testing strategy for incoming Fraction IV/IV-1 paste. If testing is not performed just prior to further manufacturing, it should be demonstrated how the potential effect of further storage is taken into account in setting acceptance criteria. Also, it should be clearly indicated which limit (release or shelf life) is applied to the testing performed at Kamada.

Process validation

Critical operational parameters and quality attributes have been defined during process validation to control the manufacturing process at Kamada. A justification of the overall control strategy including a discussion of 1) the identification of the critical quality attributes (CQAs), 2) the selection of critical operational parameters and 3) the selection of IPCs have been provided. Acceptance limits of quality attributes for IPC samples and AS are consistently met.

The process validation followed respective guidance documents. An adequate set of process control parameters and quality attributes has been established which were all met during process verification. IPCs show consistent results of critical quality attributes and it is confirmed that impurities are reduced to low level, regardless of the origin of the Fraction IV-1/IV paste.

Although the process parameters were partially different, depending on the origin of the Fraction IV-1/IV paste, the process delivers an AS of equivalent quality, safety and efficacy. The robustness of critical process steps was investigated in validated scaled-down model systems in line with process validation guidance. These studies challenged the pre-treatment step and the chromatography steps, based on design of experiments (DoE) for planning and performing the experiments and their analysis. The results of the robustness studies support the limits for the operational parameters. It is noted that the Applicant does not claim a design space. The robustness of virus removal steps to reduce viral load

and to maintain product quality has been investigated. It is shown that slight modifications in the manufacturing process are robust for the pretreatment process and the chromatography steps at the tested operational parameters, using all types of paste as intermediate material. It can be concluded that the process steps operate in a robust way without negative effect on product quality, if operational parameters are modified in the specified range.

Mixing validation was performed in two process steps where mixing is complex. The in-process Kamada-AAT product at each production step can be kept up to 24 hours until further process. In order to establish longer hold time for specific manufacturing steps in the Kamada-AAT AS process (all at room temperature), two types of studies have been performed, laboratory scale stability studies on in process samples from production scale process and cumulative worst case hold time studies at full production scale in original vessels in the production area. In these studies, extended hold times have been validated.

A container closure comparability study was performed during product development. It could be demonstrated that the proposed container closure do not have any detectable influence on AS quality or stability.

Manufacturing process development

In general a sufficiently detailed description of the manufacturing process development has been given. From the description and from tabular overviews it is conclusive which material was used for preclinical or clinical studies. Comparability of the active substance (AS) and finished product (FP) batches of AAT manufactured from material of different origin is confirmed.

Comparability

Comparability of AS batches manufactured according to the different manufacturing processes used during development is demonstrated in several parts of the CTD: process validation, characterisation, batch analysis, and stability.

Characterisation

The full amino acid sequence of Kamada-AAT has been confirmed and conforms to the published cDNA and amino acid sequence of human plasma alpha-1 antitrypsin. Biological activity was characterised.

In general, the Applicant has presented a detailed structural characterisation of this plasma-derived inhibitor in line with ICH Q6B, forced degradation studies investigated elevated temperatures, freeze-thaw, light exposure, oxidation stress and acidic conditions on product quality. It is shown that the conformance batches show very similar physico-chemical characteristics, irrespective of the origin of the Fraction IV-1/IV paste. As well, product– and process-related impurities have been investigated and were found below the limit of detection or were only present at low residual level. For characterisation of residual plasma proteins five proteins were selected.

Specification

The AS is controlled by an adequate set of release parameters and specification limits which are mostly in line with the Ph. Eur. monograph for alpha 1 proteinase inhibitor. All test methods applied in the control of the AS are compendial or have been validated in line with ICH Q2 (R1). The limits are based on process capability and production history, as well as patient safety aspects. The release limits have in principle been sufficiently justified in line with ICH Q6B.

Reference materials

A detailed description of the reference materials used in IPC, AS and FP release testing has been presented. The data demonstrate that the reference materials are qualified for the intended use. Extensive characterisation studies confirm that the reference standards RHS#1 and RHS#2 are representative of the physico-chemical and functional characteristics of Kamada-AAT AS and FP batches, with low level of impurities.

Stability

The AS stability testing has been performed in line with ICH Q5C, investigating real time/real temperature conditions as well as accelerated conditions. The studies covered AS lots from process validation and those used in phase II/III clinical trials. The large set of AS lots also included material manufactured from Fraction IV-1 or IV paste of different age. Also both types of storage containers (type I glass or PE bags) were included. The origin of the intermediate Fraction IV-1/IV paste, or the age of the paste has no detectable influence on the AS stability. Based on the data presented, the proposed shelf life at the recommended storage conditions can be accepted.

The post-approval stability commitment gives no reason for concern. In forced degradation studies, changes in the AAT isoform were observed after light exposure, storage at elevated temperature, repeated freeze-thaw, and, mainly, exposure to acidic conditions.

3.2.2. Finished Medicinal Product

Description of the product and Pharmaceutical Development

The Kamada-AAT finished product (FP) is supplied as a ready to use sterile solution for nebulisation. The nebulizer solution is presented in vials containing 4 ml solution. The solution is clear and colourless to yellow-green and may contain a few protein particles. The FP is supplied as a 2% solution of AAT in a buffered solution comprising phosphate and sodium chloride in water for injections (WFI). Sodium hydroxide is added as required for pH adjustment.

Kamada-AAT active substance contains the same formulation as the FP but has a higher concentration of active Human Alpha-1 Antitrypsin.

Phosphate, sodium chloride, sodium hydroxide and WFI are the only excipients present in the formulated product. WFI is used as the solvent and sodium hydroxide solution is used for pH adjustment. All excipients are currently tested according to the relevant Ph. Eur. Monograph. No novel excipients are used. The formulation that was developed for the Kamada-AAT intravenous product was found to be compatible with the nebuliser delivery system.

The container is a vial (~13 ml volume) made of Type I borosilicate, clear glass (Ph. Eur./ USP). This is closed with a rubber stopper (Ph. Eur./ USP) and capped with a tear off seal fitted with a flip off cap.

Kamada-AAT is administered by inhalation using the Vespera® nebuliser handset (CE certified) used in combination with an eBase Controller. The Vespera® nebuliser handset contains a vibrating membrane that generates an aerosol. The handset is CE certified according to Directive 93/42/EEC by a Notified Body.

Pharmaceutical Development

The stability of Kamada-AAT containing 2% active AAT was studied under various conditions of temperature with different excipients. The final formulation was selected in order to provide a solution that mimics physiological pH and osmolality. The solution was found to be compatible with the nebuliser delivery system.

In order to allow safe application of at least 4 ml solution, each vial of Kamada-AAT is filled in slight excess over the labelled volume. The Applicant showed that this leads to a consistent filling of the device with at least 4 ml.

Each lot of FP is routinely tested for appearance, identity, potency, purity and impurities, safety and for general properties.

The physicochemical and biological properties of Kamada-AAT were initially determined on the FP. Following the introduction of a holding step for the AS, product characterization has been performed on the AS. The Applicant considers this justified because the manufacture of Kamada-AAT FP requires only a dilution of the AS, resulting in a slightly lower active AAT concentration in the same formulation.

As part of the finished product process development, an optimization of the filling and sterilization process was performed. Aerosol characterisation studies of three representative Kamada-AAT clinical lots were conducted in accordance with the EMA Guideline on the pharmaceutical quality of inhalation and nasal products and the current Ph. Eur. monograph 2.9.44. The aerosol particle size distribution tests were performed using the Cascade Impaction (Next Generation Pharmaceutical Impactor NGI) and by the Breath Simulator (PARI Compas II) to measure the delivered dose.

The results of the Cascade Impactor are used to calculate the Mean Mass Aerodynamic Diameter (MMAD), the Geometric Standard Deviation (GSD) and the FPF (percentage of the particles with diameter of less than 5 µm), for each clinical lot and the overall mean. The results show very good consistency between the lots.

During the development, breath simulation experiments were conducted, using two breathing patterns: healthy adult and a patient with emphysema. Results showed similar performance for the standard and emphysema breathing patterns. Therefore, the breath simulation studies with the clinical lots were conducted using the standard breathing pattern only.

The intended treatment regimen for Kamada-AAT is one month (28 days) of twice daily inhalation using the Vespera nebuliser handset. In order to cover this treatment period the aerosol characteristics were determined at the start and after 4 and 6 weeks of simulated treatment. The Applicant concluded that the nebuliser handset in-use period of 1 month (28 days) is acceptable when used for administration of Kamada-AAT solution. The quality of nebulised AAT (ratio active AAT/antigenic AAT, % monomeric AAT) was similar to that of the control (non-nebulised AAT).

Container Closure System

The glass vials used for the proposed commercial Kamada-AAT FP are Type I borosilicate, clear glass vials. The vials are closed with rubber stoppers. The secondary packaging component consists of aluminium tear off seal fitted with a flip off cap. The materials are conform to the Ph. Eur. requirements and are compatible with the finished product. The tests for leachables and extractables did only show very low results which are all well below the acceptance limits. However, the use of ultrapure water for the leachable/extractable studies is not acceptable. Therefore, the Applicant provided data from studies performed with the Kamada AAT dilution buffer.

The delivery device used for the nebulisation of the Kamada-AAT formulation is the Vespera nebuliser handset used in combination with an eBase Controller. The Vespera nebuliser handset is CE certified according to Directive 93/42/EEC by a Notified Body. The EC Declaration of Conformity for medical devices in accordance with Annex II (excluding section 4) of Directive 93/42/EEC has been provided. In the case of Vespera nebulizer handset, no components are in contact with the finished product formulation during storage. Thus, an extractable study is not applicable. All plastic materials have been tested for biocompatibility as required for CE certified medical devices.

Kamada-AAT is a sterile, preservative free ready to use solution. No antimicrobial preservative is added during the Kamada-AAT manufacturing process. The active substance solution is tested for microbial limits and endotoxins. The finished product is sterilised through 0.2 µm filters, which are validated for the purpose by the manufacturers. The integrity of the primary packaging is tested as part of the stability studies. Environmental monitoring and aseptic processing are also performed and controlled.

Manufacture of the product and process controls

The manufacturer's facilities are clearly described. The active substance is used to formulate the FP to the required pH and protein concentration by dilution with the buffer. The resulting solution is sterile-filtered twice and is aseptically filled into washed, sterilized, and depyrogenated, 10 ml Type I glass vials (4 ml final product are filled into 10 ml vials). Following visual inspection, the vials are labelled and stored. The packed FP vials undergo a review by the Quality Unit and is approved for dispatch. The samples from the lot are tested for release in an authorized EU laboratory.

The critical steps of the manufacturing process and in process controls (IPC) have been defined. A process validation for Kamada-AAT was performed at production scale to qualify the routine production process. The process conformance was designed to demonstrate that the process, when operated within the defined ranges, produces Kamada-AAT FP that consistently meets all in-process controls, in-process acceptance criteria and release specifications.

The validation of following processes was shown in the dossier: facility, utility, and equipment qualification; cleaning validation; raw materials and components qualification; formulation step; mixing; the sterilisation process; and the filling process.

For the sterile filtration, the Applicant introduced an additional sterile filtration system by an alternative manufacturer. To qualify the material from the alternative manufacturer, studies on extractables from both manufacturers were compared.

The studies on extractables for the filters were performed by the manufacturers of the filter systems.

The Applicant provided a thorough risk assessment based on the expected concentrations of the impurities as well as on their structure.

Moreover, the Applicant also provided data on the extractables from the filters used.

In the study on comparability and consistency, different lots of the finished product manufactured from three different active substance sources have been compared. It would also be relevant to compare the activities of the lots stemming from the different starting materials. However, these data are provided in the stability studies. According to the stability data, the activity is not dependent on the starting material.

The excipients phosphate, sodium chloride and sodium hydroxide, and water for injections are all stated to be of Ph. Eur. Quality. The Applicant explains that all of the raw materials used as excipients in the manufacturing process are released by Quality Control (QC) after testing according to the current relevant Ph. Eur. monograph to confirm product identity and quality, as defined by the pharmacopoeia. Water for Injections (WFI) is produced at Kamada. No excipients of animal or human origin are used, no novel excipients are used.

Product specification

The FP is tested for release for appearance, identification, potency, purity and impurities, safety and pH. The analytical methods used in the analysis of the FP are mostly clearly described and validation for the methods has been provided.

The batch analyses provided by the Applicant all comply with the corresponding specifications. Some of the specifications were modified during the product development process. The justification of FP specifications for appearance, identity, and potency provided by the Applicant can be accepted. The justification of specifications has been provided, however, some specifications at the end of shelf life need further justification.

The reference house standards used are the same already discussed in the active substance part of the dossier.

The primary container closure system for Kamada-AAT finished product consists of ~13 ml glass vials, classified as Type I glass, closed with rubber stoppers. Each vial is filled with 4 ml (labelled fill volume) Kamada-AAT FP.

The primary packaging material is of Ph.Eur. quality and hence appropriate for the considered use.

Stability of the product

The stability of the finished product was tested under the following conditions: long term testing at 5±3ºC; Accelerated testing at 25±2ºC; Combined temperature testing involving long term storage at 5±3ºC until the end of the proposed shelf life; stress testing; container closure comparability by long term (5±3ºC) and accelerated (25±2ºC) storage of vials with different types of container closures.

Based on the stability studies of Kamada-AAT the Applicant concluded that the product is stable when stored at 5±3°C. The product is sensitive to light and therefore the product should be protected from light during storage.

Adventitious agents

Testing of plasma is considered adequate including exclusion criteria for donors with risk for (v)CJD. All plasma donations are screened by NAT-minipool testing strategy for HIV-1 RNA, HBV-DNA, HCV-RNA and HAV-RNA, and B19V. Plasma pools are additionally tested by NAT for HIV-1 RNA, HBV-DNA, HCV-RNA and HAV-RNA, and high titer B19V DNA.

The manufacturing process has been sufficiently investigated for virus reduction. Enveloped viruses and non-enveloped viruses including parvoviruses are efficiently inactivated and removed. Regarding HEV a dedicated risk analysis should be provided according to the "Reflection paper on viral safety of plasma-derived medicinal products with respect to hepatitis E virus" EMA/CHMP/BWP/723009/2014. Regarding the viral risk assessment, the calculation for the worst case virus loads in plasma pools presented by Kamada is not considered correct. A revised risk assessment should be presented.

3.2.3. Discussion on chemical, pharmaceutical and biological aspects

Active Substance

General aspects

The general information provided on the active substance of Kamada-AAT is acceptable.

Manufacturing process

The Applicant has in general sufficiently described the manufacturing process and its control. Flow diagrams for the manufacturing processes from plasma to Fraction IV and Fraction IV-1 and from Fraction IV/Fraction IV-1 to active substance have been provided, including information on operational parameters and intermediates. Upon request, additional information was provided on the operational parameters used for Ultrafiltration/Diafiltration.

The Applicant confirmed that the manufacturers of Fraction IV and Fraction IV-1 will notify the Applicant in case of changes to the Fraction manufacturing process and, if required, a variation to the dossier of Kamada-AAT will be submitted to the competent authorities accordingly.

Two separate manufacturing processes are defined for Fraction IV-1 paste (the 'established process) and Fraction IV paste (the 'variant process'). These processes are basically similar, but differ in operational limits for the pre-treatment and chromatography steps. This approach was sufficiently justified for the first purification steps. The remaining differences in the operational limits at the steps are minor and can be accepted.

Control of critical steps

Critical steps, critical process parameters, and IPCs have been defined. Upon request, a justification of the overall control strategy including a discussion of 1) the identification of the critical quality attributes (CQAs), 2) the selection of critical operational parameters and 3) the selection of IPCs was provided.

The hold-times for the in-process intermediates have been sufficiently justified. Additional validation data are provided that support the proposed maximum hold time for the S/D treatment.

Intermediates

Two intermediates are defined in the AS process: Fraction IV-1 and Fraction IV paste. A linear decrease in AAT activity in Fraction IV and IV-1 paste is observed during storage at -20°C. The storage period from date of paste manufacturing until the date of AS production was limited based on stability data and characterisation of AAT activity in batches of Fraction IV and IV-1 paste, and on AS and FP stability data.

The testing strategy and acceptance criteria for potency and purity for the incoming pastes should be further justified as potency and specific activity decrease during storage. The Certificates of Analysis in general ensure that the Fraction IV and Fraction IV-1 paste comply with the information provided in the Kamada-AAT dossier.

The information on the starting material 'plasma for fractionation' that is used to manufacture the Fraction IV-1 and IV Intermediates is considered acceptable. Full access of Kamada to the PMFs of the Fraction IV-1 and IV manufacturers is assured by respective agreements. However, only a summary dossier has been presented to describe the manufacture and control of Fraction IV-1/Fraction IV. This is considered not in line with the plasma-derived medicinal products Guideline (EMA/CHMP/BWP/706271/2010). Full dossier sections should be presented.

Process validation

In general, the validation ('consistency') studies demonstrate consistent manufacturing process performance. The process derived impurities were reduced to levels below the proposed specification in all validation batches.

The results of the process validation support comparability of AS batches manufactured according to the different manufacturing processes or using different Fraction IV-1/Fraction IV pastes.

The general approach for the robustness (DoE) studies, using qualified linear scaled down models, and assessing the impact of operational parameters at high, low, and setpoint values on selected output parameters is acceptable. The results of the robustness studies support the limits for the operational parameters. It is noted that the Applicant does not claim a design space.

Manufacturing process development and comparability

The manufacturing process development has been sufficiently described. Comparative historical data (ranges) provided in the process validation section support comparability of AS batches manufactured according to the current and previous manufacturing processes with respect to specific activity, residual plasma derived proteins, and percentage of monomers and polymers. The evaluation of plasma-derived impurities, batch analysis and stability data further support comparability.

Characterisation data in general support comparability of RHS#1 and batches manufactured according to the current manufacturing processes. However, the carbohydrate analysis should be discussed in more detail and any differences observed between batches manufactured according to different manufacturing processes justified.

Characterisation

Structural, physicochemical and biological characterisation was performed for all validation batches and reference standard RHS #1. The results give no reason for concern. Forced degradation studies have been performed at the finished product level. The study conditions include elevated temperatures, freeze-thaw, light exposure, oxidation stress and acidic conditions. Aggregation, desialylation, proteolytic degradation and photolytic degradation were identified as possible degradation pathways.

For characterisation of residual plasma proteins five proteins were selected. Upon request, this choice has been further justified, and additional data were provided on a number of additional protein impurities that were not part of the routine monitoring program. Overall results of the studies show that the levels of the studied plasma-derived impurities are acceptably low.

Specification

The proposed test panel for AS release is acceptable. Upon request, the acceptance criteria for endotoxin were tightened in line with Ph. Eur. requirements.

Stability

The results of the stability studies support the proposed AS shelf life at the recommended storage conditions. The post-approval stability commitment gives no reason for concern. However, as requested, the Applicant revised the stability protocol based on the results of the forced degradation studies.

Finished Product

Description of the product and Pharmaceutical Development

The composition of the nebuliser solution is clearly stated. The excipients are well known and comply with the Ph. Eur. No preservative is needed as the entire content of one vial is sterile and is administered as one dose.

Conform the EMA Guideline on the pharmaceutical quality of inhalation and nasal products and the Ph. Eur. monograph for preparations for inhalation (01/2012:0617), the Applicant has provided data of the aerosol particle size distribution of three clinical lots using the Cascade Impaction and data on the drug delivery rate and total drug delivered of three clinical lots using a breathing simulator. These studies were conducted in accordance with the European Pharmacopoeia chapter 2.9.44, preparation for nebulisation: characterisation. Three clinical batches were used, covering the major Fraction IV-1/Fraction IV paste manufacturing processes of Kamada AS.

The data of the particles size distribution tests show good consistency between lots. The data of the breath simulator test show consistency between the clinical lots with regard to the drug delivery rate and total drug delivered. The life time studies of the nebuliser handset are considered adequate. Results are also reasonably in line with those of clinical studies batches.

Particle size of nebulised solutions is dependent on the physicochemical properties of the nebulised fluids, particularly the surface tension and viscosity. The primary component of the FP formulation that affects both parameters is the protein concentration. It was sufficiently demonstrated that the size distribution and drug delivery rate are not significantly affected by the protein concentration in the proposed range.

Manufacture of the product and process controls

The FP manufacturing process of the sterile solution for nebulisation in vials is very similar to the preparation of a solution for injection in vials and is relatively straightforward. It consists of six major operations and has been adequately described.

Product specification

According to the specification the product may contain a few visible protein particles. The presence of a substantial number of vials with a high number of visible proteinaceous particles within a batch should be considered atypically for Kamada-AAT FP and, therefore, it is not acceptable to only monitor for proteinaceous particles. The proposed alert limit should be tightened and an acceptable quality level (AQL) should be defined for the second inspection that is performed according to ISO 2859. The approach should be laid down in the dossier (i.e., control of critical steps and intermediates).

Stability

The general approach of the Applicant to support the shelf life of the finished product is acceptable. Photostability studies indicate that the product is sensitive for light, which is properly reflected in the labelling of the product. Freeze-thaw studies are not conclusive, which is also properly reflected in the labelling of the product.

Comparability exercise for Finished Medicinal Drug Product

Commercial manufacturing of the FP will utilize the same manufacturer and FP formulation as used for Phase II/III studies. Some minor changes were introduced after manufacturing phase II/III clinical batches. These changes are validated and it is unlikely that they adversely affect the quality of the product.

Adventitious agents

The Applicant has sufficiently addressed the risk of potential contamination with non-viral adventitious agents. With respect to viral adventitious agents, it has been demonstrated that the manufacturing process of Kamada-AAT contains two distinct effective steps which complement each other in their mode of action and one of which is effective against non-enveloped viruses. Virus validation studies for the virus inactivation and removal steps were performed. Robustness of these steps was appropriately addressed.

Despite some comments on the calculation of the residual risk estimate, the currently available information suggests that the safety margin of Kamada-AAT with respect to HIV, HBV, HCV, and HAV will be acceptable. Overall, the provided information shows that the manufacturing process of Kamada-AAT contains a step that can be considered effective against non-enveloped viruses including Parvovirus B19 and that fractionation, and possibly other manufacturing steps will further contribute to its removal.

3.2.4. Conclusions on the chemical, pharmaceutical and biological aspects

The overall standard of the Module 3 Quality dossier presented in support of this application for Infinia is reasonable, with the descriptions of the manufacture and control of the active substance and finished product containing sufficient detail to permit an in depth assessment of the marketing authorization application.

The marketing authorisation application for Infinia could be approvable from the quality point of view provided that the Applicant gives satisfactory responses to the list of outstanding issues.

3.3. Non clinical aspects

3.3.1. Pharmacology

No primary pharmacology studies have been conducted with Infinia; however, AAT and its role in emphysema are described in the literature and have been understood for many years.
The anti-bacterial and anti-inflammatory properties of Kamada-AAT were evaluated in a model of chronic P. aeruginosa lung infection in rats in comparison to antibiotic (enrofloxacine, Baytril) treatment.
Since Kamada-AAT is a plasma derived product that is administered to AAT-deficient patients to restore and maintain normal AAT levels, no safety pharmacology studies specific to the central nervous and cardiovascular systems were performed. Nevertheless, three safety pharmacology studies have been performed specific to the respiratory system.

Table 1: Overview of pharmacological studies

Type of Study	Test System	Test Article	Method of Administration	Testing Facility	Study No. / Literature Citation	Location eCTD Section
Primary Pharmacodynamics (Literature)						
AAT effect on elastase-induced emphysema	Syrian male hamsters	Human AAT	Intratracheal Single dose	Not applicable	Stone et al., 1990	4.3
AAT effect on papain- and elastase-induced emphysema	Syrian male hamsters	Human AAT	Intratracheal and intracardiac Single dose	Not applicable	Martorana and Share, 1976	4.3
AAT effect on smoke-induced emphysema	Human API transgenic CD-1 mice	Prolastin®	Intraperitoneal 6-month repeat-dose	Not applicable	Churg et al., 2003	4.3
AAT effect on smoke-induced emphysema	A/J female mice	Recombinant AAT	Inhalation 6-month repeat-dose	Not applicable	Pemberton et al., 2006	4.3
Secondary Pharmacodynamics						
Kamada-AAT effect in rat model of chronic *pseudomonas aeruginosa* lung infection	Sprague Dawley rats	Kamada-AAT	Intratracheal	EUPROTEC Ltd.	Euprotec WO041008	4.2.1.2
Safety Pharmacology						
Respiratory- cytotoxicity effect	human lung sub-bronchial gland adenocarcinoma Calu-3 cell line	Kamada-AAT	*In vitro*	Across Barriers	C-13003-118-0905	4.2.1.3
Respiratory- cytotoxicity effect [1]	normal, human-derived tracheal/ bronchial epithelial cell EpiAirway model	Kamada-AAT	*In vitro*	Harlan Biotech Israel	KAM/117/CTX	4.2.1.3
Respiratory Safety Pharmacology Study in Rats [1]	Sprague-Dawley Rats, male	Kamada-AAT	Inhalation	Huntigdon Life Sciences	KAM0003	4.2.1.3
Pharmacodynamic Drug Interactions						
No studies were conducted						

[1] Report contains a GLP compliance statement

3.3.2. Pharmacokinetics

Five toxicokinetic studies were conducted during the toxicology programme of Kamada-AAT that assessed exposure of animals to Kamada-AAT using inhalation, intratracheal (IT) and intravenous (IV) routes of administration. During the Protocol Assistance meeting on February 2014, the CHMP agreed that the PK data from the intravenous Kamada-AAT in addition to PK information from the Phase II/ III (at T_0, 20 weeks and 50 weeks) would be sufficient and that no separate PK studies were needed with the inhaled product.

Table 2: Overview of pharmacokinetic studies

				Test Article: Kamada-AAT	
Type of Study	**Test System**	**Method of Administration[1]**	**Testing Facility**	**Study Number**	**Location eCTD Section**
Absorption					
Pharmacokinetics	Rabbits	Intravenous	American Red Cross, USA	405	4.2.2.2
Toxicokinetics[2]	Rats	Inhalation	Huntingdon Life Sciences, UK	KAM0002	4.2.3.1
Toxicokinetics[2]	Rats	Inhalation, Intratracheal	Charles River Laboratories, Canada	79997	4.2.3.1
Toxicokinetics[2]	Rats	Inhalation, 28-day	Huntingdon Life Sciences, UK	KAM0001	4.2.3.2
Toxicokinetics[2]	Rats	Intratracheal, 15 days	Charles River Laboratories, Canada	79999	4.2.3.2
Toxicokinetics[2]	Rats	Intratracheal, 15 days	Charles River Laboratories, Canada	7300094	4.2.3.2
Distribution					
No studies were conducted					
Metabolism					
No studies were conducted					
Excretion					
No studies were conducted					
Pharmacokinetic drug interactions					
No studies were conducted					

[1] Single dose, unless otherwise stated
[2] Report contains a GLP compliance statement

3.3.3. Toxicology

Four single dose and five repeat-dose toxicology studies in rats and rabbits as well as one neoantigenicity study in rabbits using the inhalation, intratracheal, intravenous (IV), intradermal, intramuscular and subcutaneous routes have been undertaken. All but two studies conducted were in compliant with GLP guidelines.

Two *in vitro* cytotoxicity studies in pulmonary cells have been conducted and are relevant to the evaluation of the local tolerance of Kamada-AAT. Finally, the effects of the viral inactivation manufacturing process on potential neoantigenicity of Kamada-AAT have been tested.

Table 3: Overview of toxicology studies

Type of Study	Species and strain	Method of administration	Duration of Dosing	GLP	Testing Facility	Study Number	eCTD Section
Single Dose Toxicity							
	Rats, Sprague Dawley	Inhalation	Single dose	Yes	Huntingdon Life Sciences UK	KAM0002	4.2.3.1
	Rats, Sprague Dawley	Inhalation Intratracheal	Single dose	Yes	Charles River Laboratories Canada	79997	4.2.3.1
	Rats, Sprague Dawley	IV bolus	Single dose	Yes[1]	Harlan Biotech Israel	KAM/029/AIT	4.2.3.1
	Rabbits, New Zealand White	IV bolus	Single dose	Yes[1]	Harlan Biotech Israel	KAM/030/AIT	4.2.3.1
Repeated Dose Toxicity							
	Rats, Sprague Dawley	Inhalation	daily, 5 days	No	Huntingdon Life Sciences UK	KAM0012	4.2.3.2
	Rats, Sprague Dawley	Inhalation	Phase 1: daily, 5 days Phase 2: daily, 28 days	Yes	Huntingdon Life Sciences UK	KAM0001	4.2.3.2
	Rats, Sprague Dawley	Intratracheal	15-days, every other day	Yes	Charles River Laboratories Canada	79999	4.2.3.2
	Rats, Sprague Dawley	Intratracheal	15-days, every other day	Yes	Charles River Laboratories Canada	7300094	4.2.3.2
	Rabbits, New Zealand White	IV bolus	daily, 5 days	Yes[1]	Harlan Biotech Israel	KAM/031/RIT	4.2.3.2
Genotoxicity							
No studies were conducted							
Carcinogenicity							
No studies were conducted							
Reproductive and developmental toxicity							
No studies were conducted							
Local tolerance							
	Calu-3 cell monolayers	*in vitro*	single dose	No	Across Barriers GmbH Germany	C-13003-118-0905	4.2.1.3
	EpiAirway NHBE layers	*in vitro*	single dose	Yes	Harlan Biotech Israel	KAM/117/CTX	4.2.1.3
Other toxicity: Neoantigenicity							
	Rabbits, New Zealand White	ID, IM or SC	25 weeks immunisation	Yes	American Red Cross USA	ARC071902	4.2.3.7.1

[1]: Partly GLP compliant: no formulation analysis and toxicokinetics; histopathological assessment performed in a non GLP laboratory.
Underlined dose denotes the NOAEL

3.3.4. Ecotoxicity / environmental risk assessment

Kamada-AAT is a protein extracted from human plasma and purified by chromatography and two viral elimination procedures. Therefore, the active substance is a naturally occuring substance, the use of which will not alter the concentration or distribution of the substance in the environment. As Kamada-AAT is not expected to pose a risk to the environment, no ERA studies have been performed.

3.3.5. Discussion on non-clinical aspects

Pharmacology

No studies on pharmacodynamics have been conducted with Kamada-AAT, but it is referred to literature in which AAT application has been proven beneficial in different preclinical models. So, human plasma purified AAT and/or recombinant human AAT have been shown to significantly reduce lung lesions associated with papain- and elastase-induced emphysema in hamsters and cigarette smoke-induced emphysema in mice. In addition, AAT protects the lungs from neutrophil and macrophage infiltration and reduces the concentrations of inflammatory component LTB4 and lung matrix breakdown products hydroxyproline and desmosine almost back to baseline levels.

In general, every AAT product should demonstrate its ability to provide the anticipated benefit in appropriate preclinical pharmacodynamic models. However, Kamada-AAT is no novel product but has already a large clinical experience either administered IV as well as per inhalation. In this context and with regard to the whole preclinical data package (PK and toxicity studies) demonstrating AAT levels in the lung which are expected to provide beneficial effects, the omission of own pharmacodynamic studies is considered acceptable.

Concerning safety pharmacology the single-dose respiratory study showed that Kamada-AAT, administered by inhalation, had no physiological or toxicological significant effect on respiration rate, tidal volume or minute volume up to 6 hours from initiation of dosing. In the *in vitro* studies, Kamada-AAT concentrations up to 20 mg/ml had no effect on the growth of cultured human bronchial cells (Calu-3 cells) or the multi-layered, highly differentiated human-derived tracheal/broncheal epithelial EpiAirway model, indicating that Kamada-AAT is not cytotoxic. Based on these findings inhalation of Kamada-AAT to humans is expected to be well-tolerated and not to produce any overt pulmonary adverse effects.

Pharmacokinetics

Kamada-AAT absorption was evaluated by toxicokinetic assessment performed during single dose and repeat-dose toxicology studies via inhalation and intratracheal administration to rats. The PK of Kamada-AAT was determined following a single IV administration to rabbits in comparison to Prolastin.

No dedicated preclinical study was performed to evaluate Kamada-AAT distribution but non-clinical literature has been provided that aerosolized AAT is distributed from the alveolar epithelial surface through the lung interstitum into the circulation.

After a single administration by inhalation to rats, Kamada-AAT was absorbed slowly,. C_{max} and AUC_{0-t} increased with doses, although not proportionally.

In order to select the administration route for systemic absorption, a comparison of inhalation and intratracheal administration was performed in rats. Therefore, the IT route was selected for the pivotal toxicity study.

Further, the accumulation ratios, based on AUC_{24} values corrected for the estimated doses on each sampling day, were generally greater than one, indicating that accumulation occurred after repeated inhalation exposure to Kamada-AAT. Nevertheless, accumulation of Kamada-AAT is not expectedin patients as the intended clinical dose of 160 mg/day is significantly lower than the high dose administered in the above mentioned toxicity study. The study also provided evidence that in general there were no differences in the systemic exposure of male and female rats to Kamada-AAT, except at the highest estimated achieved dose level where the systemic exposure of female rats to Kamada-AAT was higher than that of males.

IV administration of 1 mg Kamada-AAT to male and female rabbits resulted in a two-compartment PK profile with an initial $t_{1/2}$ of 16 hours and a terminal $t_{1/2}$ of 68 hours. The C_{max} observed at the first sampling time (10 minutes) was 42,264 ng/mL. No sex differences were observed in these parameters.

Overall, Kamada-AAT is absorbed systemically following administration via inhalation or via the intratracheal route. Systemic absorption is less than dose-proportional and accumulation occurs with repeated administrations. The results of the studies demonstrated that the drug, locally applied into the lungs (alveolar deposition of the aerosolized drug) slowly diffuse across the respiratory epithelium into the lung interstitial lymph until reaching the systemic circulation.

Toxicology

Concerning toxicology the results of three single and four repeat dose toxicity studies have been provided. Single dose studies were performed in Sprague Dawley rats following inhalation administration and one in Sprague Dawley rats and one in NZW rabbits following IV administration (NOAEL 650 mg/kg or 600 mg/kg, respectively). Local tolerance was investigated within single as well as repeat-dose toxicity inhalation studies and in the respiratory safety pharmacology study. Both *in vitro* cytotoxicity studies have demonstrated the absence of cytotoxic effect of Kamada-AAT at concentrations up to 20 mg/mL on lung bronchial cells or on human-derived tracheal/bronchial epithelial cells, respectively. Furthermore, one study addressing potential neo-antigenicity to assess whether the viral inactivation procedures in the manufacturing of Kamada-AAT to reduce and inactivate viral particles, causes changes in the Kamada-AAT structure that would result in expression of new epitopes was presented. The findings suggest that the viral inactivation procedures used in the manufacturing of Kamada-AAT did not induce the generation of novel antigenic epitopes in AAT.

Of note, within the repeat dose toxicity study some findings were observed, i.e. transient increases in white blood cell parameters, the presence of anti-Kamada-AAT antibodies in the blood of some animals, reversible enlargement of the bronchial lymph nodes, reversible microscopic changes in the lymphoid tissues of the nose and lungs and a toxicokinetic profile of lower systemic Kamada-AAT concentrations in the high-dose males after repeated exposure. However, it is agreed to the Applicant that these findings are consistent with a mild immunological response and reveal no safety concerns.

In view of the already existing clinical experience with inhaled Kamada-AAT, type and amount of toxicity studies are considered sufficient to support marketing authorisation. The results of toxicity studies reveal no safety concerns.

3.3.6. Conclusion on non-clinical aspects

In general, type and amount of pharmacodynamic, safety pharmacology, pharmacokinetic and toxicology studies performed with Infinia are considered sufficient and appropriate to support marketing authorisation.

3.4. Clinical aspects

The clinical development programme for Infinia comprises 6 controlled and uncontrolled studies conducted in Israel, in Europe and in Canada (Table 4).

Table 4: Overview on clinical studies conducted with Kamada-AAT for inhalation

Study/ Protocol # Country	Study Design and Objectives	Treatment Regimen	Study Population	Number of Subjects
Phase 1 studies				
Kamada-AAT (inhaled)-001 [Study 001] Phase 1 Israel	Randomised, single-blind, placebo-controlled, single-dose, dose escalation study to assess the safety and tolerability of single administration of Kamada-AAT for Inhalation in healthy subjects	40, 80, 160 mg, single dose	Healthy subjects	Randomised: 24 Dosed: 18 Kamada-AAT for Inhalation 6 placebo
Kamada-AAT (inhaled)-002 [Study 002] Phase 1 Israel	Randomised, single-blind, placebo-controlled, parallel group, dose-ranging study to assess the safety and tolerability of repeated administration of Kamada-AAT for Inhalation in healthy subjects.	80, 160 mg per day for 14 days	Healthy subjects	Randomised: 15 Dosed: 10 Kamada-AAT for Inhalation 5 placebo
Phase 2 studies				
Kamada-AAT (inhaled)-003 [Study 003] Phase 2 Israel	Double-blind, randomised, placebo-controlled study to assess the safety and efficacy of Kamada-AAT for Inhalation in CF patients.	80 mg per day for 28 days	Subjects with CF	Randomised: 21 Dosed: 14 Kamada-AAT for Inhalation 7 placebo
Kamada-AAT (inhaled)-004 [Study 004] Phase 2 Israel	Double-blind, randomised, placebo-controlled study to explore the safety and efficacy of Kamada-AAT for Inhalation in bronchiectasis patients	80 mg twice a day for 12 weeks	Subjects with bronchiectasis	Randomised: 21 Dosed: 14 Kamada-AAT for Inhalation 7 placebo
Kamada-AAT (inhaled)-005 [Study 005] Phase 2 Israel	Single dose, open-label study to investigate the intrapulmonary distribution of radiolabelled Kamada-AAT for Inhalation in the lungs of the study subjects	40 mg labelled with 99m-Tc-DTPA (Technetium-labelled Diethylene-Triamine-Penta Acetate), single dose	Healthy subjects Subjects with COPD Subjects with CF	Randomised: 21 Dosed: 15 Kamada-AAT for Inhalation: 2 healthy 7 COPD 6 CF
Phase 2/3 study				
Kamada-AAT (inhaled)-007 [Study 007] Phase 2/3 EU, Canada	Randomised, double-blind, placebo-controlled multicenter, international study followed by an open-label extension period evaluating the safety and efficacy of Kamada-AAT for Inhalation	Double-blind period: 160 mg per day (80 mg twice a day) for 50 wk Open-label extension period: 160 mg per day (80 mg twice a day) for 50 wk	Subjects with AATD	Double-blind period: Randomised: 168 Dosed: 87 Kamada-AAT for Inhalation 81 placebo Open-label period: Previous AAT: 33 Previous placebo: 47

Kamada-AAT (inhaled)-006 (Phase 2), VS	Randomised , double-blind, placebo-controlled study , to assess the levels of AAT and other analytes in epithelial lining fluid (ELF) and plasma and to assess the safety of the treatment in subjects with alpha-1 antitrypsin (AAT) deficiency	80 mg/day and 160 mg/day for 12 wk	subjects with AATD	Randomised: 36 Dosed: 12 Kamada –AAT 80 mg/day 12 Kamada –AAT 160 mg/day 12 placebo

3.4.1. Pharmacokinetics

PK of Kamada-AAT for Inhalation in AATD patients has been evaluated in the phase II study Kamada-AAT (inhaled)-006 (Study 006) in USA. This study evaluated the AAT concentrations in Epithelial Lining Fluid (ELF) and plasma following two different doses of Kamada AAT for Inhalation in AATD subjects (80 mg/day and 160 mg/day). Study 006 showed that the antigenic AAT ELF level change from baseline achieved with 160 mg/day Kamada-AAT for Inhalation was about 17.6 µM, which is significantly higher than that observed with the IV route of administration (~2.4 µM, see Study IV-002) and the normal AAT ELF levels in healthy subjects (1-5 µM) (Hubbard et al., 1990). Furthermore, the antigenic AAT ELF level change from baseline achieved with 80 mg/day Kamada-AAT for Inhalation was 5.0 µM.

For its primary indication treatment and maintenance therapy of adult patients with congenital deficiency of alpha-1 antitrypsin and lung disease with clinical evidence of emphysema and airway obstruction (FEV1/SVC<70%), Kamada-AAT for Inhalation is not intended to be absorbed systemically. Treatment with Kamada-AAT for Inhalation increases the local levels of alpha-1 antitrypsin (AAT) in the lung, particularly in the airways. Levels of AAT are null or greatly reduced in the airways of patients with AATD. However, systemic absorption of AAT after inhalation was determined in Study 007 by measurement of PiM (the normal M-type AAT protein). Study 007 was performed in two parts. During the DB part of the study, subjects with AATD received 80 mg (4 mL) twice daily (160 mg daily) of Kamada-AAT for Inhalation or twice daily 4 mL inhaled placebo for 50 weeks. Plasma levels of PiM, the phenotype symbol of the normal human AAT protein, were determined with a plasma assay. For this analysis, blood samples were drawn at baseline/randomisation visit, week 20 and week 50, and at the early discontinuation visit, if applicable. Plasma PiM levels were not determined during the OLE part of the study.

A statistically significant increase of PiM levels was observed in the Kamada-AAT for Inhalation treatment arm after 20 and 50 weeks of treatment, while no increase was observed in the placebo treatment arm ($p < 0.001$). For the 'complete ITT population', at week 50, the median plasma AAT level change from baseline was 130 nM.

The in vivo bioavailability of Kamada-AAT for Inhalation was estimated, based on the steady state PiM levels (130 nM at 50 weeks after a daily dose of 160 mg Kamada-AAT for Inhalation) and compared with the plasma levels following intravenous (IV) administration (10.5 µM at 12 weeks after administration of 60 mg/kg/week of Kamada-AAT Intravenous). An absolute bioavailability of 5% of the total daily drug inhaled was found.

Distribution of Kamada-AAT for Inhalation in lung tissues has been determined in a supportive study (005) in non-AATD subjects, i.e. some healthy, some with chronic pulmonary obstructive disease (COPD) with severe emphysema comparable to that developed by AATD patients, and some with cystic fibrosis (CF). This study is considered supportive as it was not conducted in the indication claimed for Kamada-AAT for Inhalation. The objective of this study was to investigate the pattern of the intrapulmonary deposition of radiolabelled Kamada-AAT for Inhalation using planar gamma-scintigraphy.

In brief, this lung deposition study demonstrated that the aerosol particles were sufficiently small to penetrate into the peripheral lung zone. In COPD patients, 40% of the initial dose was deposited in the lungs. So, for an individual dose of 80 mg of Kamada-AAT for Inhalation, approximately 30 mg reach the lung.

Further, two studies were submitted in which the single dose PK parameters and steady state concentrations of IV- administered Kamada AAT have been evaluated (IV-001 and IV-002). In these studies has been shown that Kamada AAT has a volume of distribution of 3.2L and that AAT has a terminal half-live of about 94 hours and a clearance of 0.7 L/day.

The Applicant provided the intra- and inter-individual variability in study 006 and 007. The intra-individual variability of the plasma PiM levels at steady state ranged from 46 to 59% for the AAT formulation and from 42 to 49% for the placebo formulation. In Study 006, the inter-individual variability of the plasma PiM levels at steady state ranged from 44 to 71% for the AAT formulation and 31 to 57% for the placebo formulation. The intra- and inter-individual variability is similar across the AAT and placebo groups. In study 007, the inter-individual variability of the plasma PiM levels at steady state was very large (>100%).

3.4.2. Pharmacodynamics

The effect of Kamada-AAT for Inhalation on pulmonary markers of airway inflammation has been investigated in one study in healthy subjects (002) and in two studies in patients with respiratory diseases (CF in study Kamada-AAT inhaled-003, and bronchiectasis in study Kamada-AAT inhaled-004).

Further, PD of Kamada-AAT for Inhalation in patients with AATD has been investigated in the currently submitted Study 006, which will determine AAT-NE complexes, NE concentration, neutrophil count and inflammatory markers in the ELF. Results of Study 006 are determined.

3.4.3. Discussion on clinical pharmacology

The provided description of the analytical methodology of study inhaled 007, IV-001 and IV-002 is insufficient. The analytical reports for study inhaled 007, IV-001 and IV-002, including all within study validation steps (like collection of ISR data) have not been submitted. The method validation reports for the analytical methods used to determine antigenic AAT and functional AAT levels in studies IV-001 and IV-002 have been submitted.

The suitability of method A1RP-MVR-MET-012 is questioned as the validation report mentions that the method is validated for serum samples while AAT levels were estimated in plasma in study 007. The measured concentrations were ranging from 15-1500nM.

Plasma and ELF AAT levels after IV administration and after inhalation are very different. Plasma levels after IV administration are in the µM range while ELF levels are in the nM range; after inhalation the AAT plasma levels are in the nM range while ELF concentrations are yet unknown. No cross validation was performed. Therefore, caution should be used when comparing cross studies. The results within one study are reliable.

The assay for the detection of AAT-reactive IgG Antibodies is considered acceptable and appropriately validated. The method seems to have an acceptable assay sensitivity and drug tolerance.

The Applicant provided information on an assay of the neutralizing antibody-assay the results of the different studies and the interpretation of the results of the anti-AAT antibody positive patients are further discussed in the safety part of this document.

In terms of pharmacokinetic data (PK), no full PK has been evaluated in clinical studies as Kamada-AAT for Inhalation is not intended to be absorbed systemically. However, systemic absorption levels of normal active AAT protein (PiM) were measured in patients' plasma in the pivotal study 007 at single time-points, i.e. at baseline/randomisation visit, at week 20 and 50, and at the early discontinuation visit. Taken all values together, a statistically significant increase of PiM levels was observed in the Kamada-AAT for Inhalation treatment arm after 20 and 50 weeks of treatment, while no increase was observed in the placebo treatment arm. However, there are some doubts concerning the meaning and the validity of these data. First of all, the baseline values are very high in some patients though in theory they should be below the limit of quantification. Further, looking at the raw data one might get the impression that in most of the patients the values from week 20 to week 50 distinctly decline and often reach baseline values again.

Systemic concentrations of AAT after multiple doses of inhaled and IV Kamada AAT have both been analysed. However, as concentrations are much lower after inhalation and considerable differences have been found in the formation of antibodies it is not clear if IV data on elimination, dose proportionality and time dependency can be extrapolated to the inhalation formulation.

The variability of AAT PK after inhalation is high and it is not clear what causes the different inter-individual variability between study 007 and 006. According to the Applicant it is unlikely that the large variability is associated with the concomitant use of drugs against COPD. However, no analysis was performed by the Applicant to substantiate this conclusion. It is therefore unknown if concomitant COPD medication may lead to an increase in plasma exposure.

Kamada-AAT for Inhalation is intended to act locally by increase of the local levels of AAT in the airways and interstitium. The observed systemic exposure will presumable not contribute to the effect of the drug product on the treatment of obstructive lung disease as they are much lower than the AAT levels following IV administration. All AAT treated patients achieved a statistical significant increase in epithelial lining fluid AAT level, The Applicant discussed the influence of covariates (gender, body weight, age, race, lung function, renal function and effect of antibodies) on the systemic concentrations of AAT. All patients were Caucasian and therefore no conclusions can be drawn on the effect of race of the systemic concentrations of AAT. BMI and gender were not found to be significant covariates. Age, FEV1% and creatinine clearance appear to influence plasma PiM levels. Creatinine clearance and FEV1% seem to be correlated with age, but the underlying mechanism of this correlation remains unknown (exposure in moderate creatinine clearance is lower than in mild renal impairment).

As hepatic degradation is not an important elimination pathway for AAT there is no need to study hepatic impairment.

The *in vivo* bioavailability of Kamada-AAT for Inhalation was estimated to be 5%, based on the steady state PiM levels compared with the plasma levels following intravenous (IV) administration. Taken into account the high inter-individual variability this estimate value has to be regarded as rough, only. And further, it has to be noted that steady state concentration at different time points have been compared.

Distribution of Kamada-AAT for Inhalation in lung tissues has been determined in a supportive study in non-AATD subjects, i.e. some healthy, some with chronic pulmonary obstructive disease (COPD) with severe emphysema comparable to that developed by AATD patients, and some with cystic fibrosis

(CF). This lung deposition study demonstrated that the aerosol particles were sufficiently small to penetrate into the peripheral lung zone, and the drug was evenly distributed between the right and left regions of the lungs. In COPD patients, around 40% of the initial dose was deposited in the lungs. Of note, there was a wide variability in the amount of drug reaching the lungs in the COPD and CF groups with individual percent ranged from 26.7% to 60.1%. This variation may be explained by subject-related factors such as pulmonary function, excess of sputum production that blocked the airways and low inspiration flow rate as well as altered breathing patterns. Overall, these findings raise concerns whether AAT application via inhalation per se is able to provide a stable and defined amount of AAT in the lung tissue in every single patient.

In terms of pharmacodynamics, the effect of Kamada-AAT for Inhalation on airway inflammation was investigated in subjects with respiratory diseases, i.e. cystic fibrosis (CF) and bronchiectasis. In Study 003, the assessment of inflammatory markers in sputum of CF subjects indicated a beneficial effect of Kamada-AAT for Inhalation on airway inflammation, as demonstrated by a trend towards reduction of neutrophil count and NE levels in the active treatment group, which was not apparent in the placebo group. However, there was no indication of a significant effect of Kamada-AAT for Inhalation on IL-8 concentration or Pseudomonas aeruginosa bacterial colonisation in the sputum, or on serum CRP level. Results in bronchiectasis patients (Study 004) were inconclusive probably due to the variability of the disease severity of the subject population. Overall, the results from these two studies do not provide a clear picture upon the effect of Infinia on the chosen airway inflammation markers. In consequence, these investigations cannot serve as proof of the anticipated pharmacodynamic action of inhaled Kamada-AAT in the lungs.

3.4.4. Conclusions on clinical pharmacology

Overall, in terms of PK the Applicant did perform three studies, one study to assess the AAT levels in ELF and plasma, one absorption and one distribution study. This proceeding has been agreed with EMA. Limited PK data have been generated for inhaled Kamada AAT. It appears that the systemic bioavailability of Kamada AAT for inhalation is low, which is appropriate as the product is intended to act locally. IV Kamada AAT has a long terminal half-life, but it is unclear if these IV data can be extrapolated to the inhalation formulation due to the lack of appropriate PK characterisation of the inhalation formulation, as concentrations are much lower after inhalation than after IV administration and if (neutralising) antibodies may affect dose elimination or proportionality.

The number of patients in the pharmacodynamic studies is low, hindering a clear interpretation. The use of other patients (cystic fibrosis, bronchiectasis) instead of the intended AATD patient population in the proof of concept study raises concerns whether these studies can be used in support of the intended patient population. The quantitative difference between patients with bronchiectasis and AATD patients in responses to inflammation and infection may hamper the comparison. Overall, the results of these studies are inconclusive.

3.4.5. Clinical efficacy

Main clinical study

Data derived from the single Phase II/III Study 007 comprise the efficacy data base for the marketing authorisation application of Kamada-AAT for Inhalation for the treatment and maintenance therapy of adult patients with congenital AATD and lung disease with clinical evidence of emphysema and airway obstruction. There are no other controlled trials in AATD conducted with Kamada-AAT for Inhalation that support the efficacy assessment for the proposed indication.

The Investigational Medicinal Product, Kamada-AAT for Inhalation, was administered as two daily inhalations of 80 mg (4 mL) each. Inhalation was performed using the Vespera® electronic nebuliser, based on the eFlow® technology (PARI Pharma GmbH, Germany). Each inhalation session lasted approximately 10-15 minutes. For subjects who received placebo during the DB part of the study, the same volume (4 mL) of buffer solution was administered twice daily using the Vespera® nebuliser.

The primary objective of this study was to assess the rate and severity of exacerbations in AATD patients when treated with Kamada-AAT for Inhalation or placebo during a 50-week DB treatment period. The secondary objectives in this study were to evaluate the safety profile of Kamada-AAT for Inhalation versus placebo and to explore additional parameters that may demonstrate the effect of Kamada-AAT for Inhalation on the rate and severity of exacerbations in AATD patients during the 50-week double-blind (DB) treatment period. In addition, the secondary objectives of the study were to evaluate the safety, tolerability of Kamada-AAT for Inhalation during the 50-week open-label-extension (OLE) treatment period. Tertiary objectives, defined for the DB period of the study only, were exploratory in nature.

Primary efficacy endpoint:

Time from Randomisation to the First Event-Based Exacerbation with a Severity of Moderate or Severe

Analysis of the time to first moderate/severe exacerbation according to the initial SAP did not reveal any significant difference between the AAT (112 days) and Placebo groups (140 days), p = 0.0952 (ITT population). No difference between the Placebo and the AAT treatment arms was noted in any of the study populations analysed. Thus, the primary efficacy parameter in this study was not met.

In light of the baseline differences between the treatment arms that may have affected their response, a sensitivity analysis, in which patients with poor prognosis were excluded, was conducted to evaluate the impact of baseline differences between the AAT and Placebo arms. Patients having the following baseline covariate values were considered as a subgroup associated with poor prognosis and were excluded (censored): Age ≥ 60 years old, BMI < 20 kg/m^2, Oxygen users (at study entry). However, the results of the subgroup sensitivity analyses did not show significant difference between the AAT and Placebo arms with respect to the time to the first moderate/severe exacerbation in any of the study populations analysed.

Secondary endpoints

(a) Time to First Event-Based Exacerbation with a Severity of Mild, Moderate or Severe

No advantage of AAT treatment was demonstrated in regarding the time from randomisation to the first event-based exacerbation of mild, moderate or severe intensity (76 days for AAT, 133 days for placebo). Similarly, no difference was seen between the study groups when sensitivity subgroup analysis was performed using the same baseline covariates as for the primary endpoint. The p value between treatments adjusted for country for the ITT population was 0.0091 for all subjects and 0.3678 after sensitivity analysis.

(b) Rate of Event Based Exacerbations

Overall the rate of exacerbation was higher in the AAT group compared to placebo. The rate of severe exacerbations was significantly higher in the AAT compared to placebo group (p = 0.0450); this significance disappeared after sensitivity analysis.

(c) Severity of the First Event-Based Exacerbation and Symptom-Based Exacerbation

No difference was seen when all types of exacerbations were compared in the ITT population. Similar results were obtained after the subgroup sensitivity analysis.

The analysis of symptom-based exacerbation revealed that patients in the AAT arm had less type I exacerbations compared to patients in the placebo arm (18.8% versus 31.3%, p = 0.0614). However, these findings were not observed after subgroup analysis.

Tertiary Efficacy Variables

(a) Incidence of Event-Based and Symptom-Based Exacerbations by Time of Onset During Treatment Period and Severity

The incidence of all event-based and symptom-based exacerbations by severity during the whole study period were analysed for the ITT population. Incidence rates are generally similar when analysing AAT group compared with Placebo group.

(b) Duration of Event-based and Symptom-based Exacerbations by Time of Onset During the Treatment Period

The mean duration of episodes in both AAT and placebo arms were similar. More episodes were counted when symptom-based exacerbations were considered; since there are untreated episodes that are captured by the criteria for symptom-based exacerbations.

(c) Quality of Life

Patients completed a standard respiratory QoL questionnaire, the SGRQ, at baseline and 4 weeks after the end of treatment (week 54). The Symptoms component of the SGRQ, the Activity and Impact components, as well as the Total Score, did not show any improvement compared to baseline.

(d) Lung Computed Tomography Scan

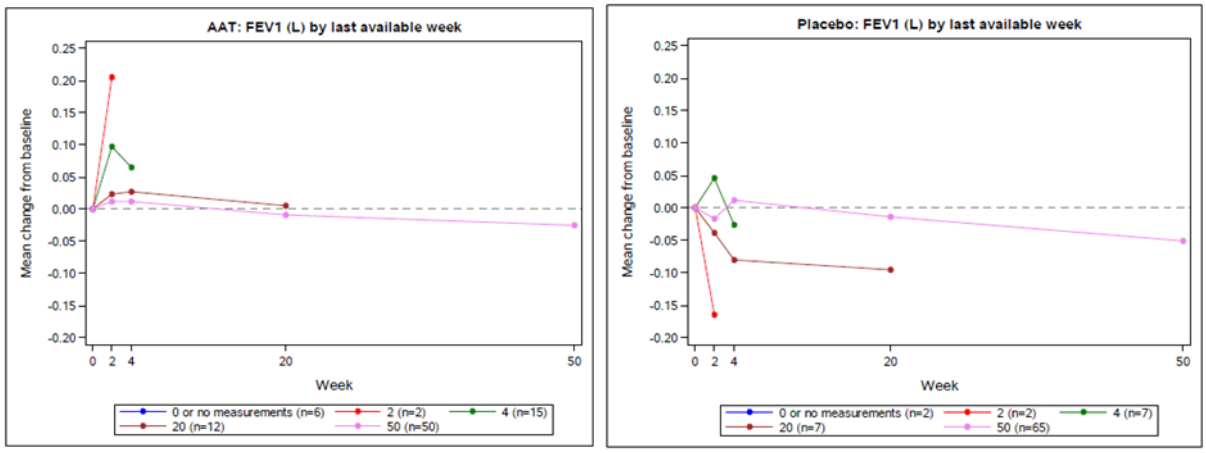
A subset of patients from the Netherlands sites were scanned for safety and lung density at two time points: baseline/randomization and termination/early termination of the DB period. All CT images were analyzed using densitometry. No statistically significant changes were observed between arms or within arms. Overall, these data are not considered to have much clinical significance because of the small sample size and the short duration of the study.

Post-hoc analysis: Pulmonary Function Test (PFT)

Looking at the overall treatment effect, using MMRM test with adjustment to baseline covariates and mixed Linear Models with implementation of different MI models for handling of missing data, patients treated with AAT had a statistically significant increase in their spirometry parameters compared to placebo, with mean FEV1 values increasing by 18.6 mL (range: -8.2 to 45.4) in the AAT group and decreasing by 29.4 mL (range: -55.3 to -3.5) in the placebo group and producing an overall treatment effect of 48.0 mL (p = 0.0124). Similarly, FEV1/SVC values increased by 0.74% in the AAT arm and decreased by 0.96% in the placebo arm (p = 0.0025) and also FEV1% of Predicted Value (%). However, no differences were found between treatment arms regarding diffusing capacity parameters.

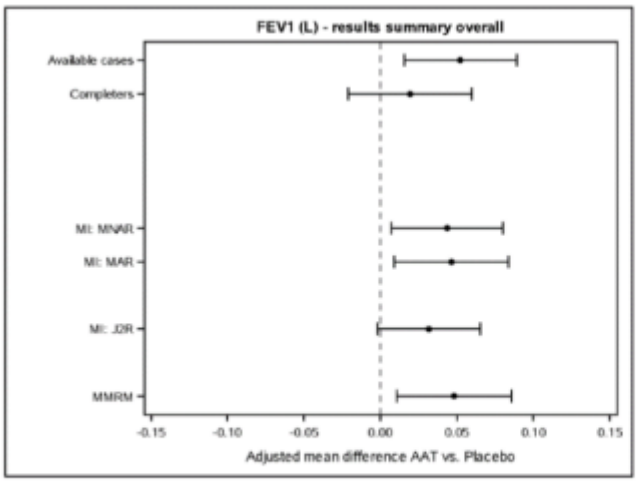
Detailed progress of FEV1 shows the influence of the early withdrawals (**Error! Reference source not found.**).

Figure 1: FEV1 (L) by last available week AAT and placebo respectively



Because of the high number of early withdrawals different imputations models were applied such as MAR, MNAR and J2R to take into account these missing data.

Figure 2: MMRM Analysis of FEV1 (L) – All Covariates*, Without Early Termination Visit (ITT Population)



*Adjusted for baseline value, age, country, BMI, SGRQ total score and oxygen use, MMRM: Mixed Models for Repeated Measures; MI: Multiple Imputations ; MAR: Missing at Random; MNAR: Missing Not at Random; J2R: Jump to Reference.

Post-Hoc Analysis: Severity of Exacerbation Measured by Symptom Scores

In order to evaluate in details the severity of the first exacerbation, post-hoc analyses were performed on each of the three cardinal symptom data separately (dyspnoea, sputum volume and sputum colour).

Mixed Model for Repeated Measures (MMRM) analysis of the average score during the 10 and 14 days of the first exacerbation shows that dyspnoea improved in the AAT arm compared to Placebo (p = 0.0243 and 0.0817, respectively). The sputum volume also improved significantly in the AAT arm compared to Placebo during the 10 days of the first exacerbation (p = 0.0334). The sputum colour scores were higher in the AAT compared with the placebo group, with a significant difference during the 14-day period of the exacerbation (p = 0.0032), which might be due to the yellowish colour of the plasma-derived drug substance inhaled.

Post-Hoc Analysis: Continuous Analysis of Symptom Scores

Post-hoc a continuous analysis of the dyspnea score over the whole duration of the study was performed for the ITT population. Throughout the study, some favourable effects of AAT treatment were observed, with subjects in the AAT arm improving continuously (i.e. decreased dyspnoea scores) in contrast with the worsening seen in placebo-treated patients (i.e. increase in dyspnoea scores).

The trend throughout the study for sputum volume showed no clear difference between AAT and placebo. Regarding sputum colour, the score was lower in the placebo group than in the AAT group, which may be associated to the yellowish colour of the drug.

Among other symptoms associated with exacerbations collected continuously on a daily basis in the eDiary, a "well-being" score was also reported by the patients throughout the DB part of the study. The overall trend for well-being matched the overall continuous trend seen in dyspnoea scores: well-being was improved (i.e. scores diminished) in the AAT arm of the ITT population, in contrast with the Placebo arm where the feeling of well-being declined throughout the study. How-ever, these findings did not reach statistical significance.

Post-Hoc Analysis: dyspnoea

Dyspnoea was analysed in two different ways.

The MMRM analysis of dyspnoea scores during the first exacerbation shows that during the 10 or 14 days of the first exacerbation respectively, dyspnoea improved significantly in the AAT arm compared to Placebo ($p = 0.0243$ and 0.0817, respectively).

The trend of the E Diary scores for dyspnoea throughout the study for the ITT population shows a favourable effect of AAT treatment, with subjects in the AAT arm improving continuously (i.e. decreased dyspnoea scores) in contrast with the decline seen in placebo-treated patients (i.e. increase in dyspnoea scores).

Post-Hoc Analysis: less severe patients

A subgroup of patients in Study 007 that is most similar to the patient population in Study 006, who have a less severe stage of disease, based on the GOLD definition (FEV1 > 50% and SGRQ ≤ 50) was analysed and compared it with the rest of the patients with severe AATD (FEV1 ≤ 50%).

Support for such a stratification scheme has been discussed recently in a review (Miravitlles et al., 2016), where a heterogeneity of exacerbation behaviour in subjects was noted, particularly in GOLD category D (the most severe disease), with respect to 50% < FEV1 <50%. These differences were based on the COPD GeneR Study, an NHLBI-funded multicenter investigation of the genetic epidemiology of smoking-related lung disease (Han et al., 2013). Highly significant differences in exacerbation rates were seen particularly for subjects in GOLD category D, depending on whether the factors responsible for placing the subject in this category were based on lung function, exacerbation history, or both.

When FEV1 was analysed according to the selected subpopulations described above, it can be seen in Table 5 that there was an advantage to AAT treatment in both the more and the less severely affected patients although there was no significant difference. The change in %DLCO was greatly improved in the less severely affected patients (median -0.29% in the AAT treated patients compared to -2.62% in the placebo group) although here too, the difference was not significant, probably because of the low numbers of patients and the high variability.

Table 5: Lung Function by Subpopulation, Study 007 (Safety Population)

Parameter	Less Sick (FEV_1 > 50, SGRQ ≤ 50)			The Rest		
	AAT	Placebo	Wilcoxon p-value	AAT	Placebo	Wilcoxon p-value
FEV_1 Change to week 50	16	11		35	53	
N						
Mean (SD)	-0.03 (0.21)	-0.07 (0.11)		-0.02 (0.11)	-0.05 (0.19)	
Median (min, max)	-0.03 (-0.34,0.51)	-0.08 (-0.22,0.09)	0.7509	-0.03 (-0.21,0.28)	-0.05 (-0.76,0.54)	0.4889
DLCO% Change to week 50						
N	16	11		34	53	
Mean (SD)	-1.38 (5.72)	-2.66 (6.59)		-1.95 (5.41)	-3.37 (6.57)	
Median (min, max)	-0.29 (-10.58,7.84)	-2.62 (-12.18,12.52)	0.298	-2.34 (-17.79,8.03)	-2.62 (-24.00,11.13)	0.2985

Analysis of symptoms was based on the e-diary, in which the patients recorded symptoms daily. The diary data show that the improvement in lung function parameters was accompanied by an improvement in the number of days without increased dyspnoea or sputum (**Table 6**).

Table 6: Symptoms by Subpopulations, Study 007 (Safety Population)

Parameter	Less Sick (FEV_1 > 50, SGRQ ≤ 50)			The Rest		
	AAT	Placebo	Wilcoxon p-value	AAT	Placebo	Wilcoxon p-value
Dyspnoea % Good days						
N	22	13		65	68	
Mean (SD)	83.10 (12.52)	76.14 (25.63)		68.77 (23.52)	76.13 (21.87)	
Median (min, max)	84.48 (44.29,99.71)	82.91 (0.00,99.72)	0.554	75.31 (6.12,99.71)	82.25 (0.28,98.88)	0.028
Sputum free % days						
N	22	13		65	68	
Mean (SD)	33.53 (35.36)	30.45 (39.80)		26.34 (33.94)	29.26 (37.70)	
Median (min, max)	20.67 (0.00,98.57)	6.57 (0.00,99.15)	0.797	5.56 (0.00,97.79)	5.30 (0.00,99.43)	0.868

In addition, inhaled AAT seems to prolong the time to 1st moderate & severe exacerbation in less sick patients compared with placebo (Table 7).

Summary of main efficacy results

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

Table 7: Summary of efficacy for Study 007

Title: A Phase II/III, Double-Blind, Randomized, Placebo-Controlled, Multicenter, International Study Evaluating the Safety and Efficacy of Inhaled, Human, Alpha-1 Antitrypsin (AAT) in Alpha-1 Antitrypsin Deficient Patients with Emphysema			
Study identifier	Kamada-ATT-007		
Design	Double blind, randomized, placebo-controlled, parallel group design		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		50 weeks not applicable 50 weeks
Hypothesis	superiority		
Treatments groups	ATT		Kamada-ATT for inhalation (80 mg twice daily) for 50 weeks, n = 85
	Placebo		Placebo for 50 weeks, n = 83
Endpoints and definitions	Primary endpoint	TE1	Time from randomization to the first event-based moderate or severe exacerbation
	Secondary endpoint	TE2	Time to first event-based exacerbation (regardless of severity)
	Secondary endpoint	SEV	Severity of first exacerbation (none, mild, moderate, severe)
Database lock	Date not provided		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat when 92 events were observed		
Descriptive statistics and estimate variability	Treatment group	ATT	Placebo
	Number of subject	85	83
	TE1 Median	112	140
	95%-CI	76 – 142	104 - 174
	TE2 - Median	76	133
	95%-CI	50 - 112	83 - 151
	SEV (Frequencies)	None: 18 (21.2%) Mild: 12 (14.1%) Moderate: 48 (56.5%) Severe: 7 (8.2%)	None: 20 (24.1%) Mild: 10 (12.0%) Moderate: 53 (63.9%) Severe: 0 (0.0%)
Effect estimate per comparison	Primary endpoint TE1	Comparison groups	AAT / Placebo
		HR[1]	1.339
		95%-CI	0.937 – 1.914
		P-value (log-rank test)	0.095
	Secondary endpoint TE2	HR[1] (covariate adjusted)	1.658
		95%-CI (covariate adjusted)	1.148 – 2.396
		P-value (log-rank test)	0.0091

	Secondary end-point SEV	p-value (CMH-Test)	0.4195
Notes	With regard to the analysis of TE1 and TE2 respectively the Company provided several sensitivity analyses based on post-hoc findings regarding baseline group imbalances. Amongst others the Company provided a sub-group analysis excluding all patients aged above 60 years and/or having a BMI < 20 and/or patients who used oxygen at study entry as well as considering these variables (plus SGRQ at baseline) as covariates in a Cox-regression. However, none of these analyses indicated an advantage for AAT over placebo regarding time to the first event-based moderate or severe exacerbation. Regarding the post-hoc analyses of pulmonary function parameters (not shown here): these analyses are to be interpreted with caution as the decision to analyse these parameters was data driven (Applicant's statement: "Some of the pulmonary function parameters showed statistical and clinically meaningful differences between the two treatment groups when analysed using appropriate statistical methods that account for missing values and for baseline imbalances. These parameters were therefore analysed post-hoc as efficacy parameters, based on the ITT population.")		

1 – HR < 1 indicates and advantage for AAT, HR > 1 indicates a disadvantage for AAT

2 - Adjusted for previous treatment with IV ATT.

3 - Adjusted for country, age (continuous), BMI (continuous), oxygen (yes/no), and SGRQ (continuous).

Clinical studies in special populations

No specific studies have been performed with Kamada-AAT for Inhalation in special populations. The omission of clinical efficacy studies in special populations has been sufficiently justified.

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

N/A

Supportive study(ies)

N/A

3.4.6. Discussion on clinical efficacy

Marketing authorisation application of Infinia for the "treatment and maintenance therapy of adult patients with congenital AATD and lung disease with clinical evidence of emphysema and airway obstruction" is based on data derived from a single pivotal Phase II/III study, i.e. study 007.

Design and conduct of clinical studies

Study 007 was performed in two parts: Part 1, a randomized, double-blind (DB), placebo-controlled multicenter, international study evaluating the safety and efficacy of Kamada-AAT for Inhalation for 50 weeks, and Part 2, an open-label extension (OLE) period of 50 weeks that was aimed to further evaluate the safety of the drug for an additional period of time for AAT arm patient and to enable drug exposure for the previous placebo arm patients. In the OLE, patients received only Kamada-AAT for Inhalation at the same dose and schedule as they received during the DB period, irrespective of their previous treatment (active drug or placebo).

A sample size of approximately 200 subjects was planned to be enrolled in the DB period, to collect a total number of exacerbation events of 92. However, it was noted that this number of events was reached after 168 subjects had been randomised to study treatment. A total of 85 subjects were thus

randomised to AAT and 83 subjects to placebo. Of note, during the DB period, many subjects withdrew early from the study: 14/83 (17%) in the Placebo arm and 34/85 (40%) in the AAT treatment arm. Overall, "only" 120 subjects (71%) completed the DB phase of the study, i.e. 51/85 in the AAT group (60%) and 69/83 (83%) in the placebo group. The main reason for discontinuation was the occurrence of AEs (n=15 in the AAT and n=6 in the placebo group). The high numbers of withdrawals as well as the difference in withdrawals between treatment groups have to be considered when assessing the validity of study results.

At the baseline/randomization visit patients who were eligible for the DB period were randomly assigned in a 1:1 ratio to receive either Kamada-AAT for Inhalation or a matching dose of placebo using a pre-determined computer-generated randomization schedule. The randomization schedule was stratified by 1) site and 2) whether or not the subjects were, at study entry, receiving AAT IV infusions. Despite randomisation three baseline parameters (age $\geqslant$ 60 years, BMI < 20 kg/m2 and use of oxygen), that are indicative of a more severe disease stage, were unevenly distributed between the two arms of the ITT study population. Of note, the SGRQ Total Score revealed an opposite situation as the Score was higher (which implies a worse clinical situation) in the placebo group.

Patients who received Kamada-AAT for Inhalation were treated with twice daily inhalation sessions of 80 mg Kamada-AAT for Inhalation each (i.e. 160 mg per day). Though the dosing regimen has been discussed within several EMA Scientific Advices and had been acknowledged, it has to be noted that the chosen dose is empirical, only, as no dose-response investigations are available - neither non-clinical nor clinical. Furthermore, results from lung distribution studies (though not performed in AATD patients but in patients with COPD and CF) revealed a high inter-individual variability of drug reaching the lungs. Thus, a stable drug delivery has to be questioned per se due to the way of application.

The primary efficacy endpoint in this study was the time from randomisation to the first event- based exacerbation with a severity of moderate or severe. Post-hoc analysis was performed on pulmonary function tests (PFT) parameters which were obtained during the DB period as safety parameters. Further, several secondary and tertiary efficacy endpoints have been investigated.

The choice of endpoints especially the primary endpoint (time to first moderate or severe exacerbation) has been discussed with the Applicant over a long time in several Scientific Advices (EMA). The choice of primary endpoint has always been regarded critical and still in the last Scientific Advice it has been stated that the chosen primary endpoint lacks justification. However, given the difficulties to conduct a randomized controlled trial of sufficient size in this rare orphan condition this proceeding had been acknowledged and CHMP conceded that finally in terms of MAA the totality of evidence will have to be taken into account.

Efficacy data and additional analyses

The primary efficacy parameter, i.e. time to first moderate/severe event-based exacerbation, was not met; even after sensitivity analyses, either excluding patients with poor prognosis or accounting for important baseline variables, no significant differences could be found as was acknowledged by the Applicant. It appears that the endpoint did not fail because of a lack of power due to a low rate of exacerbations as the exacerbation rate was in line with the expectations (2.46 in AAT group and 2.06 in the placebo group for moderate/severe exacerbations, respectively).

Post-hoc efficacy analyses were conducted for PFT parameters using different models to take into account the amount of missing data due to early withdrawals from the study and the imbalance observed at baseline between both treatment groups. These analyses revealed that patients treated with AAT had a statistically significant improvement in their spirometry parameters mean FEV1 and FEV1/SVC compared to placebo. No differences were found between treatment arms regarding diffusing capacity

parameters. In general, it has to be noted that results from post-hoc analysis might trigger further investigations but are not regarded sufficient as proof of efficacy. Further, the results per se are considered questionable. Due to the high number of drop-outs the Applicant used imputation models to account for missing data. In general the use of imputation models might be considered acceptable. However, in this case looking at the raw data doubts arise whether there is indeed a benefit for the majority of patients. In most of the patients (n=62) there seem to be no effect on FEV1 whereas only n=17 seem to positively respond to the treatment. However, these 17 patients are non-completers, thus whether or not the effect of FEV1 improvement was indeed sustained or only transient could not be demonstrated. In the placebo group most of the patients (n=65) did have a decline of FEV1 values similar as in the AAT group whereas only 9 patients had a strong decline in FEV1 values and in 15 patients there was even an improvement.

The Applicant claimed the MMRM analysis of FEV1 as the primary analysis. Notably, the graphical presentation of FEV1 showed that the difference appears to be driven by the gain in FEV1 in the first two weeks (positive in AAT group and negative in placebo group). Considering the mode of action, a fast effect is not expected. Furthermore the high early withdrawal rate of patients with a relative high FEV1 as observed in the Kamada group is not understood and may have affected the differences in mean FEV1. In the analyses, the Applicant focuses on the MMRM analysis of the FEV1 estimating an average effect over 5 measurements. However, the MMRM tends to estimate the effect of those patients able to adhere to randomised treatment and does not fully address the early drop-out that is likely differential, also in other characteristics than corrected for by the MMRM. Furthermore, the earlier endpoints (week 0, 2, 4) where a larger effect is observed, may weight more into this average. Finally, the measurements at a later time are too far apart (week 20, 50) to provide reassurance of maintenance of effect. To remove the effect of the early measurements, a new analysis using a baseline value computed as the mean of Week 0, Week 2, and Week 4 values of FEV1 resulted in the difference of approximately 20-25 mL between AAT inhaled and placebo. This difference is not considered to be relevant. Given the context of a failed trial, a post-hoc selected emphasis on observed effects in the pulmonary function parameters, and the questions about consistency (some endpoints clearly not in favour of AAT), a compelling analysis of FEV1 is needed. Therefore, the J2R analysis, as a worse case scenario is considered the most important analysis. Moreover, its assumption (the return to placebo values when data is missing) is not considered unreasonable because the last known measurement for week 20 and week 50 and therefore the last known date on treatment is at least 20-4=16 or 50-20=30 weeks earlier which leaves time to return to placebo values. This J2R sensitivity analysis showed a non-significant substantial smaller difference (only roughly half of the unadjusted effect) between AAT and placebo, which questions the clinical relevance and robustness of findings as it could have also be attributed to chance finding when depicted against the results of the different sensitivity analysis.

Unfortunately, the modest effect gained in overall effect of FEV1 is difficult to indirectly compare with other registered compounds. Inhaled AAT appears to have better results on FEV1 compared to other trials. However, comparisons are complicated by the differences between populations and relatively small patient groups. TLC and RV are not measured, although these are standard in emphysema. FEV1 as efficacy parameter has to be measured standardised according to ATS/ERS guidelines (2003). The use of bronchodilators before PFT was not standardised and protocolled. Because medication that can interfere with measurement of pulmonary function was not withheld, results could have been (unbalanced) confounded (MO).

Another AAT product (IV) was approved on base of measurements of CT density. Therefore, the validity of showing an overall effect in post-bronchodilator FEV1 needs to be justified.

In terms of secondary endpoints, a significant disadvantage of AAT treatment was demonstrated for time from randomisation to the first event-based exacerbation of mild, moderate or severe intensity

(p=0.009). Further, the overall rate of event-based exacerbation was higher in the AAT group compared to placebo; the rate of severe exacerbations was even significantly higher in the AAT compared to placebo group (p = 0.0450), however, this significance disappeared after sensitivity analysis.

In order to show a benefit in symptoms, as required by the EMA, the applicant also performed a post-hoc analysis of the symptoms during their first and second exacerbation. Analysis of severity of first exacerbation rise the impression that AAT treated patients might be less symptomatic compared to placebo treated as less type I symptom-based exacerbations were noted. However, all other symptom-based values are in disfavour for the AAT group, i.e. type II (23 vs 12) and type III (34 vs 33). Similarly, in terms of event-based exacerbation two severe exacerbations were noted in the AAT group and none in the placebo group. The decrease in number of symptoms and improvements of symptom scores during exacerbations may indicate a beneficial change in the nature of the exacerbation when receiving treatment with inhaled AAT, but these were on non-validated scores.

Nevertheless the occurrence of less type I symptom-based exacerbations was further evaluated by post-hoc analyses (using MMRM). Analyses were performed separately on each of the three cardinal symptom data, i.e. dyspnoea, sputum volume and sputum colour. These analyses reveal dyspnoea and sputum volume improved significantly in the AAT arm compared to Placebo at least during 10 days but not during 14 days. The overall significance of these findings is questionable. The Post-Hoc Analysis on Severity of Exacerbation is based on the observed data and has to be interpreted with caution as withdrawals leading to missing values are not considered. Furthermore, the putative 'benefit' in terms of dyspnoea and sputum volume is only evident when looking at a time range 0-10 days whereas at the time range 0-14 days the effect has disappeared. Of note, sputum colour was in disfavour for the AAT treated patients.

Dyspnoea as a parameter for the symptomatic benefit is also chosen post-hoc. Although the importance of dyspnoea for a COPD patient is acknowledged, dyspnoea was not primarily assigned as a parameter of interest. Moreover, the generally accepted method to measure dyspnoea and well-being is by the use of validated quality of life questionnaire such as SGRQ. This was the predefined secondary endpoint for measuring these important parameters.

The Quality of Life questionnaire, the SGRQ, did not show any improvement in the AAT treated patients. Contrariwise, the overall picture reveals a more favourable trend for the placebo treated patients. The Applicant argued that these results might be explained by the fact that the last assessment was performed 4 weeks after the last day of treatment, a period during which no drug was administered and well after the AAT/placebo had been washed out of the patient's airways, allowing a rebound of symptoms. This argumentation cannot be followed as effects of a 52 week AAT treatment period should have been visible even after a 4 week treatment interruption

Continuous analysis of the dyspnoea and well-being score over the whole duration of the study seems to demonstrate continuous improvement. However, the differences are very small and considered not clinically relevant. Furthermore, the Post-Hoc Analysis is based on the observed data and has to be interpreted with caution as withdrawals leading to missing values are not considered. These used methods for measuring dyspnoea are not validated and cannot be compared to existing MCID or statistical comparisons. Therefore, these findings cannot overrule the negative results observed with the SGRQ. Therefore, a symptomatic benefit is not substantiated.

Tertiary endpoints did not reveal any positive effects of AAT treatment. The analysis of incidence of all exacerbations does not affirm the trend seen when only first exacerbations were analysed (see above). Contrariwise type I exacerbations are the same in AAT and placebo group. Further, the overall picture reveal an unfavourable trend for the AAT treated patients, i.e. more severe and more type II and III exacerbations occur. The mean (and median) duration of episodes (in days) in both AAT and placebo

arms were overall similar. However, looking at the event-based exacerbations a trend towards shorter duration was seen in the placebo group.

Lung CT scans have been performed in a small subset of patients (n=18 AAT, n= 17 placebo), only. These investigations did not reveal any statistically significant nor clinically relevant changes.

The results of antigenic AAT ELF level in study 006 were suggestive for activity of inhaled AAT. However, confirmation is necessary in phase III trials with established efficacy parameters. However, to support clinical efficacy the period over which is measured is far too short and the number of patients studied too small for being confirmative.

The sub-analysis in 007 in patients with a less severe stage of disease (FEV1 > 50% and SGRQ ≤ 50) revealed a small numerical advantage in FEV1 for AAT treatment in both the more and the less severely affected patients. This was also observed in %DLCO in the less severely affected. In addition, inhaled AAT seems to prolong the time to 1st moderate & severe exacerbation in less sick patients compared with placebo. The sub-analysis showed that inhaled AAT seems to have a positive effect in less sick patients compared with placebo. However, the groups are very small, and the differences between the groups without statistical significance. Additionally, in study 006, where PFT parameter were exploratory measured, no treatment-related or dose-related trend was observed. At Week 12, a numerical difference in the change from baseline in FEV1 and FEV1% was observed in favour for the placebo group compared to AAT 160 mag (and AAT 80 mg). However, the differences were not statistically significant different. Thus, the claimed positive effect of FEV1 in study 007, for the total population or for the presented LESS SICK population, is not confirmed. Moreover, an opposite effect appears to be present. However, it is realised that the patient numbers are small and the period of measurements was short.

3.4.7. Conclusions on clinical efficacy

In order to support clinical efficacy the Applicant submitted data from a single pivotal trial. Thus, the requirements for a submission with a single pivotal trial as outlined in the Points to Consider on application with 1. meta-analyses; 2. one pivotal study (CPMP/EWP/2330/99) apply, i.e. the results of the single pivotal trial have to be clinically relevant and statistically compelling. But, the pivotal trial failed to show a statistically significant superiority of AAT compared to placebo with regard to its primary efficacy endpoint, time to first moderate or severe exacerbation. In order to account for imbalances regarding baseline covariates the Applicant performed sensitivity analyses which, however, did not change the outcome. The same holds true for all secondary and tertiary endpoints. Most of these reveal even disadvantages for the AAT treated patients.

Following unblinding of the data it was found that some of the pulmonary function parameters (initially considered as safety parameter) showed ‘statistical and clinically meaningful’ differences between the two treatment groups ‘when analysed using appropriate statistical methods that account for missing values and for baseline imbalances’. These parameters were therefore analysed post-hoc as efficacy parameters, based on the ITT population. However, as with any data-driven analyses, the effects seen for the pulmonary function parameters have to be interpreted critically and need further confirmation in future trials. Furthermore, in terms of pulmonary function single patient data reveal that in most of the patients there was no effect, whereas only a minority (all non-completers) showed an improvement of pulmonary function.

The results from the currently submitted study 006 reveal that inhaled AAT reach the lung ELF, but no signs of anti-inflammatory activity (or clinical efficacy) were found. The claimed effect on FEV1, i.e. a less decline when compared to placebo, is not robust, because it is based on post-hoc analyses and suffers from different methodological issues. After correction, the clinical relevance of the claimed ef-

fect diminished and the statistical significance disappeared. Moreover, the measurements of PFT were not protocolled. Finally, no other PFT measurement confirmed the observed claimed clinical effect.

Thus, a symptomatic benefit is not convincingly proven (only post-hoc analyses) and uncertainties remain for the FEV1 measurements (absence of a protocol for the measurements, low number of measurements and mainly in the beginning of the treatment, the focus on estimating an average using MMRM). A symptomatic benefit is not convincingly proven (only post-hoc analyses) and uncertainties remain for the FEV1 measurements (absence of a protocol for the measurements, low number of measurements and mainly in the beginning of the treatment, the focus on estimating an average using MMRM). The trial results are neither considered 'clinically relevant' nor 'statistically compelling'.

3.4.8. Clinical safety

Patient exposure

Overall, the clinical trials investigating Kamada-AAT for Inhalation included 264 unique subjects. There were 205 subjects exposed to Kamada-AAT for Inhalation and 106 subjects exposed to placebo (out of which 47 further received Kamada-AAT for Inhalation in the OLE part of Study 007). A total of 168 out of 264 subjects were AATD subjects (134 out of 205 exposed to Kamada-AAT for Inhalation). The majority of subjects (159 out of 205 subjects, i.e. 78%) received the final intended dosage of Kamada-AAT for Inhalation, i.e. 160 mg daily as two inhalations of 80 mg.

The clinical trials investigating Kamada-AAT Intravenous included 98 unique subjects. There were 97 exposed to Kamada-AAT Intravenous and 17 exposed to an active control (out of which 16 received Kamada-AAT Intravenous in the cross-over part of Study Kamada-API-002 [Study IV-002]). A total of 68 out of 98 subjects were AATD subjects (67 out of 97 exposed to Kamada-AAT Intravenous). The majority of subjects (85 out of 97 subjects, i.e. 88%) received the approved dosage of Kamada-AAT Intravenous, i.e. 60 mg/kg/wk.

The chronic use of Kamada-AAT for Inhalation in patients with AATD is supported by long-term safety data in 100 subjects treated for at least 6 months (including 39 subjects treated for at least 1 year).

Adverse events

Exacerbation events and all other events related to the underlying AATD disease itself (AATD-TEAEs) were reported as AEs and SAEs. Since many of the AEs were associated with the AATD underlying disease, the data was analysed, were applicable, also after removal of the AATD-TEAEs.

The analysis of subjects with AATD who received Kamada-AAT for Inhalation is based on Study 007 only. In order to compare the safety profile of Kamada-AAT for Inhalation vs. placebo, all subjects who ever received Kamada-AAT for Inhalation during Study 007 were pooled, i.e. subjects in the AAT group in the DB period (some of which continued into the OLE period) plus subjects previously in the placebo group in the DB period who received AAT in the OLE period. This constitutes the "All AAT" group and is based on 134 subjects. The "Placebo" group is based on the 81 subjects who received placebo in the DB phase.

Among subjects with AATD treated with Kamada-AAT for Inhalation in Study 007, 131 out of 134 (97.8%) reported at least 1 TEAE overall, compared with 78 out of 81 (96.3%) of subjects in the Placebo group (table 8).

Table 8: Summary of All Treatment-Emergent Adverse Events by System Organ Class and by Treatment Group (Study 007)

System Organ Class	DB Part		OLE Part		Overall AAT N=134
	AAT N=87	Placebo N=81	Previous AAT N=33	Previous Placebo N=47	
Subjects with at least 1 TEAE	**86 (98.9%)**	**78 (96.3%)**	**32 (97.0%)**	**45 (95.7%)**	**131 (97.8%)**
Number of TEAEs	**726**	**615**	**206**	**268**	**1200**
Blood and Lymphatic System Disorders	2 (2.3%)	3 (3.7%)	1 (3.0%)	0	3 (2.2%)
Cardiac Disorders	3 (3.4%)	6 (7.4%)	1 (3.0%)	6 (12.8%)	10 (7.5%)
Ear and Labyrinth Disorders	1 (1.1%)	2 (2.5%)	1 (3.0%)	3 (6.4%)	5 (3.7%)
Endocrine Disorders	1 (1.1%)	0	1 (3.0%)	0	1 (0.7%)
Eye Disorders	4 (4.6%)	1 (1.2%)	0	2 (4.3%)	6 (4.5%)
Gastrointestinal Disorders	32 (36.8%)	26 (32.1%)	7 (21.2%)	9 (19.1%)	45 (33.6%)
General Disorders and Administration Site Conditions	23 (26.4%)	26 (32.1%)	9 (27.3%)	13 (27.7%)	39 (29.1%)
Hepatobiliary Disorders	1 (1.1%)	1 (1.2%)	1 (3.0%)	4 (8.5%)	6 (4.5%)
Immune System Disorders	2 (2.3%)	1 (1.2%)	1 (3.0%)	0	3 (2.2%)
Infections and Infestations	65 (74.7%)	54 (66.7%)	18 (54.5%)	26 (55.3%)	95 (70.9%)
Injury, Poisoning and Procedural Complications	7 (8.0%)	11 (13.6%)	3 (9.1%)	6 (12.8%)	16 (11.9%)
Investigations	7 (8.0%)	6 (7.4%)	2 (6.1%)	3 (6.4%)	11 (8.2%)
Metabolism and Nutrition Disorders	3 (3.4%)	3 (3.7%)	1 (3.0%)	2 (4.3%)	6 (4.5%)
Musculoskeletal and Connective Tissue Disorders	21 (24.1%)	23 (28.4%)	8 (24.2%)	13 (27.7%)	38 (28.4%)
Neoplasms Benign, Malignant and Unspecified (Incl. Cysts and Polyps)	4 (4.6%)	2 (2.5%)	1 (3.0%)	5 (10.6%)	10 (7.5%)
Nervous System Disorders	15 (17.2%)	12 (14.8%)	8 (24.2%)	7 (14.9%)	28 (20.9%)
Psychiatric Disorders	4 (4.6%)	4 (4.9%)	1 (3.0%)	3 (6.4%)	8 (6.0%)
Renal and Urinary Disorders	2 (2.3%)	2 (2.5%)	1 (3.0%)	2 (4.3%)	5 (3.7%)
Reproductive System and Breast Disorders	0	2 (2.5%)	0	1 (2.1%)	1 (0.7%)
Respiratory, Thoracic and Mediastinal Disorders	79 (90.8%)	64 (79.0%)	27 (81.8%)	38 (80.9%)	119 (88.8%)
Skin and Subcutaneous Tissue Disorders	17 (19.5%)	11 (13.6%)	3 (9.1%)	8 (17.0%)	27 (20.1%)

TEAEs occurring in ≥ 5% of subjects receiving Kamada AAT for Inhalation, irrespective of relationship to study drug, are summarised in Table 3.4-2. Overall, the most common AEs (reported in > 10% of subjects receiving Kamada AAT for Inhalation) were COPD (59.7%), dyspnoea (40.3%), cough (22.4%), lower respiratory tract infection (14.9%), productive cough (14.2%), nasopharyngitis (13.4%), oropharyngeal pain (12.7%), headache and influenza-like illness (both 11.2%) and nausea (10.4%). Most of these AEs are considered to be associated to the underlying disease, AATD.

After removal of the AATD-TEAEs, the most common AEs were headache (11.2%), nausea (10.4%), and diarrhoea (9.0%).

Analysis by Duration of Exposure reveal that the frequency of subjects reporting TEAEs did not consistently increase with increasing duration of exposure to Kamada-AAT for Inhalation in all SOCs.

Analysis of the Annual Rates of AEs reveal the highest rates of events per subject-year by SOC in:

- Respiratory, Thoracic and Mediastinal Disorders SOC (4.20 AEs/subject-year for Kamada-AAT for Inhalation vs. 3.69 for placebo)
- Infections and Infestations SOC (2.15 AEs/subject-year for Kamada-AAT for Inhalation vs. 2.23 for placebo)
- Gastrointestinal Disorders SOC (0.62 AEs/subject-year for Kamada-AAT for Inhalation vs. 0.68 for placebo)

Most TEAEs were mild to moderate for subjects on Kamada-AAT for Inhalation (73.9%) or placebo (81.5%). The frequency of subjects reporting at least 1 severe TEAE was numerically higher in the Kamada-AAT for Inhalation overall group (23.9%) as compared to placebo (14.8%). After removing AATD-TEAEs, the frequency of subjects reporting at least 1 severe TEAE was 8.2% in the Kamada-AAT for Inhalation overall group compared to 4.9% in the placebo group.

The percentage of subjects who reported at least 1 TEAE considered by the investigator to be related to study drug (i.e. possibly or probably related) was similar in subjects receiving Kamada-AAT for Inhalation as compared to subjects receiving placebo (48.5% versus 46.9%). After removing AATD-TEAEs, the frequency of subjects reporting at least one treatment-related TEAE was 17.2% in the Kamada-AAT for Inhalation overall group compared to 13.6% in the placebo group.

The most frequently occurring related TEAEs were dyspnea (24.6% in AAT subjects and 24.7% in placebo subjects) and cough (11.9% in AAT subjects and 8.6% in placebo subjects). These AEs are considered to be associated to the underlying disease. After removal of AATD-TEAEs, the most common treatment-related AEs was headache (3.0% in AAT subjects and 2.5% in placebo subjects).

Serious adverse events and deaths

During Study 007 conducted in subjects with AATD, a total of 6 deaths have been reported in the Kamada-AAT for Inhalation group, representing an incidence of 4.5% (6/134). None of the deaths was considered by the Investigator to be related to study drug. All of these deaths were related to the effects of target organ involvement by an underlying disease, only 2 (1.5%) of them had a fatal TEAE which was not considered AATD-related. Of note, no death occurred in the placebo group.

No deaths occurred in any of the other studies with Kamada-AAT for inhalation conducted in healthy volunteers or in subjects with other respiratory disease. No deaths occurred during studies with Kamada-AAT intravenous.

In study 007, overall, there were more Kamada-AAT for Inhalation-treated subjects who reported at least 1 SAE (35.8%) compared with placebo (18.5%). After removing AATD-TEAEs, the frequency of subjects reporting at least 1 SAE was 12.6% in the Kamada-AAT for Inhalation overall group compared to 1.2% in the placebo group.

Among subjects experiencing SAEs, as expected the most frequently occurring SOCs were Respiratory, Thoracic and Mediastinal Disorders SOC (18.7% in AAT subjects and 9.9% in placebo subjects) and Infections and Infestations SOC (16.4% in AAT subjects and 9.9% in placebo subjects).

The incidence of the most frequently occurring SAEs for subjects receiving Kamada-AAT for Inhalation was higher than that in the placebo group: dyspnea (9.0% vs. 7.4%), COPD (8.2% vs. 0%), and pneumonia (6.0% vs. 3.7%). All these SAEs are considered to be associated to AATD.

After removal of the SAEs that relate to the underlying disease, the most common SAEs encountered with Kamada-AAT for Inhalation were diverticulitis (2.2%) and facial palsy (1.5%). None of these were experienced by placebo patients.

Most of the treatment-related SAEs were associated with Respiratory, Thoracic and Mediastinal Disorders SOC and Infections and Infestations SOC; no treatment-related SAE was reported in the placebo group. After removal of the SAEs that relate to underlying disease (AATD-TEAEs), only 1 case of idiopathic thrombocytopenic purpura was reported in the AAT group.

Laboratory findings

There was no notable change from baseline in mean haematology and clinical chemistry values over time in studies conducted with Kamada-AAT (AATD, healthy volunteers and in subjects with respiratory disease).

Of note, in Study 002 in healthy volunteers, changes in immunology parameters that were considered to be clinically significant were decreases in C3 and C4 that were reported three times in two subjects receiving AAT (80 mg dosage group).

In clinical studies with Kamada-AAT intravenous some findings were noted. However, none were considered to be of medical concern.

In all studies conducted with Kamada-AAT, i.e. for Inhalation and for Intravenous use, there were no changes in viral serology results as compared to baseline, i.e. no seroconversion occurred.

Safety in special populations

No specific studies have been performed with Kamada-AAT for Inhalation in special populations.

According to the Applicant, comparison of patients aged 65 years or older with younger patients did not show any statistically significant difference in the frequency of AEs relative to age, but actual data could not be found and will be requested.

Safety information for patients with signs of asthma (~20% of AATD patients) who might develop bronchoconstriction in response to inhaled protein; and for patients with previous IV-AAT use is missing and will be requested.

Immunological events

The immunogenicity of Kamada-AAT for Inhalation was evaluated during Study 007 in serum samples from individuals with AATD from the DB and the OLE periods, analysed using an assay for the detection of AAT-reactive IgG antibodies.

When considering the entire population exposed to Kamada-AAT for Inhalation, the overall immunogenicity incidence was 76/119 (64%). The majority (68/76, 89%) of the positive patients had low titres (below or equal to 16); 6 patients had a titre of 32, one had a titre of 64 and one patient had a titre of 1024.

Among the 76 subjects who developed ADAs following exposure to Kamada-AAT for Inhalation, 14 (18%) subjects had a transient response (i.e. ADA levels returned to zero at the end of the study). The remaining 62 (82%) subjects had a sustained response, i.e. ADAs were detected at the last sampling point.

Of the 76 patients who generated positive ADAs, 8 developed ADA titres of 32 and above, but none more than 1024. The examination of the immunogenic profile of these patients leads to the conclusion that there is no correlation between the occurrence of ADAs and the efficacy and safety profile of this product. However, in two subjects (out of 5 patients in whom PiM levels have been determined), ADAs were associated with a reduction by more than half of the levels of plasma PiM, suggesting a possible in vivo neutralising effect of the ADAs.

Safety related to drug-drug interactions and other interactions

The elimination of Kamada-AAT for Inhalation is as expected for proteins and consequently the potential for clinical food and drug interactions with AAT appears to be very low. No drug interaction studies were performed.

Discontinuation due to AES

The percentage of subjects who experienced at least 1 TEAE that led to withdrawal of study drug was higher for subjects receiving Kamada-AAT for Inhalation as compared to subjects receiving placebo (25.4% versus 6.2%, respectively, table 4.9-1). After removing AATD-TEAEs, the frequency of subjects reporting at least 1 TEAE that led to withdrawal of study drug was 5.2% in the Kamada-AAT for Inhalation overall group compared to 1.2% in the placebo group. In most of the study groups, subject's withdrawals due to AEs occurred mainly after 3 to 6 months of treatment.

3.4.9. Discussion on clinical safety

The safety data base of Kamada AAT for inhalation comprises 6 controlled and uncontrolled studies. The pivotal study Kamada-AAT (inhaled)-007 was conducted in the claimed indication, i.e. treatment and maintenance therapy of adult patients with congenital deficiency of alpha-1 antitrypsin and lung disease with clinical evidence of emphysema and airway obstruction (FEV1/SVC < 70%). The 5 other studies were performed in healthy volunteers, in subjects with cystic fibrosis (CF), in subjects with emphysema with chronic obstructive pulmonary disease (COPD) and in subjects with bronchiectasis. In addition, safety data are also available from 3 clinical studies where Kamada-AAT was administered intravenously.

In total, 134 individual patients have been exposed to Kamada-AAT for inhalation in the pivotal Study 007 (i.e. 87 in the double blind (DB) period and 47 previous placebo patients in the open label extension (OLE) period). An additional 33 patients that previously received AAT in the DB period received AAT in the OLE period. Main focus was on the DB period, as this is the only placebo controlled period. The number of AATD patients exposed to Kamada-AAT for Inhalation is considered limited. Even more of concern is the very limited availability of long term safety data, especially compared to other available data of IV-AAT products. Moreover, available data for continuous Kamada-AAT treatment for at least one year is very limited since almost half of the patients entering the OLE period had a lag time in AAT treatment of more than 6 months.

During the DB period, a higher frequency of severe TEAEs (25.3% AAT vs 14.8% placebo), related TEAEs (57.5% vs. 46.9%), SAEs (34.5% vs. 18.5%) and related SAEs (6.9% vs 0%) were reported with Kamada-AAT compared to placebo. Most events with Kamada-AAT for inhalation were in the respiratory, thoracic and mediastinal disorder SOC. The incidence of the most frequently occurring SAEs for subjects receiving Kamada-AAT for Inhalation was distinctly higher than that in the placebo group: dyspnea (9.0% vs. 7.4%), COPD (8.2% vs. 0%), and pneumonia (6.0% vs. 3.7%). Similarly, the percentage of subjects who experienced at least 1 TEAE that led to withdrawal of study drug was higher for subjects receiving Kamada-AAT for Inhalation as compared to subjects receiving placebo (25.4%

versus 6.2%, respectively). A conservative approach by which discontinuation due to subject decision is also considered treatment related, i.e. due to AEs, leads to a treatment related discontinuation rate of 33%. Even though small imbalances in baseline characteristics indicated a more severe disease status for the AAT arm, the high frequencies of severe TEAEs and SAEs in the AAT arm is of concern and make tolerability of the inhaled route of AAT administration questionable.

The frequency of hypersensitivity reactions was high in both arms of the DB part (global analysis 66.7% AAT vs 63.0% placebo). In a narrow analysis without disease related symptoms hypersensitivity was reported more frequently with AAT (19.5% vs 11.1%). Interpretation of this data is difficult as symptoms due to hypersensitivity reactions partly overlap with symptoms of the disease such as cough and dyspnoea. Furthermore, the high frequency of hypersensitivity in placebo patients is of concern, even when disease related symptoms are excluded. This might also indicate a-specific hyperreactivity to the inhalation liquid. The majority of patients received concomitant medications such as corticosteroids or antihistamines for systemic use, which could suppress or decrease hypersensitivity reactions. The severity of the hypersensitivity reactions and the frequency of hypersensitivity reactions separated by anti-drug antibody status is unknown. Hypersensitivity, as well as symptoms related to the respiratory, thoracic and mediastinal disorder SOCs were not included in section 4.8 of the SmPC.

The immunogenicity of Kamada-AAT for Inhalation was evaluated during Study 007 in serum samples from individuals with AATD analysed using a validated assay for the detection of AAT-reactive IgG antibodies. The overall immunogenicity incidence was 76/119 (64%). The majority (68/76, 89%) of the positive patients had low titres (below or equal to 16); 6 patients had a titre of 32, one had a titre of 64 and one patient had a titre of 1024. Among the 76 subjects who developed ADAs following exposure to Kamada-AAT for Inhalation, 14 (18%) subjects had a transient response (i.e. ADA levels returned to zero at the end of the study). The remaining 62 (82%) subjects had a sustained response.

The Applicant presented narratives of the eight patients who developed antibody titre of ≥ 32. In most of the eight patients the antibody response has to be regarded as sustained as no follow-up measures have been performed. So far, no clinical symptoms are considered attributable to AAT-inhaled, but it is unknown whether there is an association between positive ADA status and hypersensitivity reactions. In two patients (only 5 have been tested for PiM levels) a decrease in PiM level was noted suggesting a possible in vivo neutralising effect of the ADAs. And further, the Applicant did not justify why only ADA titres of ≥ 32 are considered relevant. It is questioned whether anti-AAT antibodies might reduce efficacy or cause severe immunogenicity adverse events in ADA positive patients starting with IV-AAT after discontinuation of Kamada-AAT for Inhalation.

Of note, antibody formation to human plasma-derived AAT was determined only for non-IV treated patients who had never received augmentation therapy with AAT. Thus, from the AAT all population n=134 fifteen patients were excluded. The exclusion is not plausible: the Applicant argued that no immunogenicity reactions have been reported after the IV administration of plasma-derived AAT (Baker et al., 2010; Campos et al., 2013; EMA, 2015b); and likewise Kamada-AAT Intravenous, which has the same formulation as Kamada-AAT for Inhalation, was also shown to be non-immunogenic during Study IV-002. Thus, patient who received prior therapy with IV AAT should also have been tested for the occurrence of antibodies as this phenomenon obviously only occur after inhalation therapy.

Taken together, the high percentage of patients i.e. 76/119 (64%) who develop ADAs and the observation that this antibody response was sustained in most of these patients is considered to be major safety concern. No clinical symptoms are considered attributable to the occurrence of ADAs, so far. However, decrease in PiM levels as seen in some patients suggests a possible in vivo neutralising effect of these ADAs. In addition, the possibility of cross reactivity hasn't been addressed.

With their response to LoQ the applicant presented further results and discussion on the occurrence of high percentage of patients in study 007 who developed ADAs (64%). Meanwhile the question concerning the possible neutralizing capacity of these ADAs has been addressed. Overall, there were 17 patients with measurable neutralizing ADAs (nADA) among all 75 patients confirmed positive for anti-AAT ADAs, i.e. 23%. The most common nADA titre was 1; only 1 patient had a titre of 16. In terms of 'efficacy' there was no obvious impact of the ADAs or nADAs on the PiM levels. In some patient one might get the impression that nADA do impact the PiM level in others not. As such no clear correlation could be found. According to the applicant there was also no correlation between PiM levels and ADA status in Study 006. Further, the presence of anti-AAT antibodies, whether neutralising or not, had no significant effect on the FEV1 expressed as change from baseline at weeks 20 and 50. However, that no correlation between ADA and FEV1 could be found is not surprising in relation to the great variability of the individual FEV1 values.

Similarly, safety data of Study 007 were analysed based on the ADA/nADA status of the subjects. It is of concern that a higher frequency of TEAEs was observed in the DB period for (n)ADA positive compared to (n)ADA negative patients in almost all SOCs. These TEAEs might reflect immunological events, since immunological events can be included in different SOCs. The largest differences were observed in the following SOCs: General Disorders and Administration Site Conditions (41.7% nADA+, 28.1% nADA-, 21.6% ADA-), Infections and Infestations (91.7%, 81.3%, 62.2%), Musculoskeletal and Connective Tissue Disorders (50%, 34.4%, 13.5%), Skin and Subcutaneous Tissue Disorders (33.3%, 25%, 10.8%).

Since the frequency of hypersensitivity AEs has been currently calculated with a different method compared to the original dossier, it is difficult to interpret the data regarding hypersensitivity AEs. It is unclear how many patients that reported hypersensitivity reactions in the global and narrow analysis of the original dossier (AAT arm: 66.7% and 19.5%) were (n)ADA positive or negative.

With the new third method using standardised MedDRA queries (SMQs) hypersensitivity and anaphylactic reaction, hypersensitivity AEs were presented as a function of the immunological status per visit (20 weeks, 50 weeks and week 50 of the OLE part of the study), but no cumulative frequencies could be found. Furthermore, it is questioned which preferred terms occurred more frequently in the ADA+ patients.

The data presented with the third definition of hypersensitivity indicated that patients who experienced hypersensitivity reactions tended to have higher ADA titres than those without hypersensitivity. This effect seems not related to the presence of detectable nADAs, as titres never exceeded 1 in the 17 ADA positive patients with hypersensitivity events.

Concerning the question about the clinical impact of switching the route of administration from inhaled AAT to AAT IV in ADA positive patients there is insufficient data. The applicant argued that based on the experience with other products it is expected that the switch of ADA positive subjects from Kamada-AAT for Inhalation to an IV AAT, i.e. a less immunogenic route, will result in a decrease of ADA levels. However, this remains to be elucidated.

In summary, despite the observation that the neutralizing effect of the detected nADAs seems limited in vivo, the higher frequency of AEs and especially hypersensitivity reactions in ADA positive patients is of concern. Although no anaphylaxis was reported and most of the AEs classified by MedDRA as hypersensitivity events resolved while patients continued their inhaled AAT treatment, it is of concern that 40% of hypersensitivity reactions in the AAT arm were severe). Furthermore, actual frequencies of hypersensitivity reactions might be even higher, as different methods for defining hypersensitivity reactions have been used by the applicant hampering interpretation of safety data.

Altogether, immunogenicity of Kamada AAT for inhalation is still considered a major safety concern. Furthermore, there is a potential risk for severe immunogenicity adverse events in ADA positive patients starting with IV-AAT after discontinuation of Kamada-AAT for Inhalation, as there is insufficient data regarding the clinical impact of switching the route of administration.

In the response to second safety major concern the applicant argued that the patient population included in study 007 were severe ill patients, i.e. categorised as GOLD group D. In line with this, patients who withdrew from the study had a significantly higher SGRQ score at baseline. In light of the results of study 006 where less severe ill patients were included, a subpopulation of study 007 (similar less sick) was analysed.

In this subpopulation (FEV1 > 50% and SGRQ $\leqslant$ 50), a reduction in number of withdrawals (al-so due to AEs) in patients with less severe disease is observed compared to the overall study population. There was no difference between the mean number of AEs (8.095 vs 8.077) or respiratory AEs (2.762 vs 2.769) for the "less sick" AAT and placebo groups, respectively. With respect to SAEs, there were slightly fewer SAEs in the AAT group compared to the placebo in this subpopulation (mean of 0.2857 vs 0.3846, respectively). Altogether, the safety of this subpopulation of the pivotal study is not convincingly better than safety for the total study population.

Furthermore, it was pointed out that about half of the withdrawals from Study 007 were due to adverse events that were related to the underlying disease making it difficult to distinguish any causality related to the study medication (probably masking lack of efficacy). Of note, most of the TEAEs leading to withdrawal that were considered possibly related to the study drug occurred at the start of the study, and according to the applicant, there is a possibility for the requirement of an adjustment period.

The applicant compared the safety results of the pivotal Study 007 with the Phase II supportive PK study 006. In this supportive study, only 24 patients received AAT in the DB part of the study, of which only 12 patients received the proposed dose of 160mg (the other 12 received 80mg) (vs n=87 in the pivotal study). Moreover, treatment duration was short (12 weeks maximum in the DB part vs a mean of 36 weeks in the DB part of the pivotal study). This hampers comparison of TEAE frequencies between the two studies.

Based on comparison of frequencies between the two studies, the applicant considered the safety profile in Study 006 as favourable. However, due to the different exposure time in both studies, the event rate/100 days is considered the best option to compare safety results. During the DB period, the rate of AEs/100 days, severe AEs/100 days, drug related AEs/100 days, and hypersensitivity AEs/100 days were comparable between the AAT arms of both studies, or slightly higher in study 006. The SAE rate/100 days was slightly lower in study 006. In both studies the data suggest a general reduction in AEs during the OLE part. In the OLE part of Study 006, only 26 patients received AAT, making it difficult to compare frequencies, but it seems as if a lower event rate was observed in the OLE part of Study 006 compared with Study 007.

Altogether, it is questionable whether Study 006 could be considered supportive at all, considering the very limited number of patients at the proposed posology (n=12) and short follow up (max 12 weeks). It can only be concluded that no new safety signals have been detected in Study 006. Most importantly, it is not agreed with the applicant that Study 006 showed a better safety profile of Kamada AAT compared to Study 007.

Concerning the comparison of tolerability of inhaled AAT to registered intravenous AAT the applicant provided data from the literature. In terms of the cited observational studies there were less serious adverse events and less numbers of dyspnea. Furthermore, the RAPID study is mentioned where IV AAT was compared to a placebo group. The applicant argues that the incidence of cough and pneumonia was lower than in study 007. However, the incidence of dyspnea is distinctly higher in patients treated in study 007. The number of severe TEAEs is indeed similar in study 007 (25.3%) and the RAPID trial (27%), as well as the number of SAEs. However, the number of related SAE is not cited correctly, as in the publication related serious TEAE is given with 1% (and not 23%) and further, any TEAE leading to withdrawal from study is given with 1%. As such the incidence of related SAEs and discontinuation due to AEs is distinctly higher in patients treated with AAT for inhalation than in IV treated patients.

Altogether, based on the total safety population, tolerability of AAT via the inhalation route of administration is still questioned. Even though a subpopulation of Study 007 with possible less severe disease might show a better safety profile, this is not confirmed in Study 006, or any other clinical trial.

3.4.10. Conclusions on clinical safety

The safety data base of Infinia comprises 6 controlled and uncontrolled studies. However, the information of the pivotal study-007 is considered the most relevant as this study was the only one conducted in the claimed indication. Analyses of the safety data of study 007 reveal two major safety concerns. Firstly, the high incidence of ADAs whose relevance in terms of neutralizing capacity hasn't yet elucidated, and secondly, the distinctly higher incidence of the most frequently occurring SAEs dyspnea, COPD and pneumonia in the AAT treated patients indicating a worsening of the underlying disease.

With their response to LoQ the applicant hasn't been able to solve the raised safety major issues. The high frequency of ADAs (64%) in AAT treated patients as well as the sustained antibody response in most of these patients (83%) is still considered to be a major safety concern, since the occurrence of ADAs is associated with higher frequencies of TEAEs, including hypersensitivity reactions. Moreover, long term safety aspects as well as potential immunogenic risks for patients switching back to IV AAT therapy have not been clarified. Furthermore, tolerability of AAT via the inhalation route of administration is still questioned based on the safety profile of the total study population. The safety profile of the subpopulation with possible less severe disease of the pivotal study is not considered convincingly improved compared to the total study population.

3.5. Risk management plan

Safety concerns

Summary of safety concerns

The Applicant proposed the following summary of safety concerns in the RMP:

Summary of safety concerns	
Important identified risks	• Hypersensitivity reaction in patients with selective IgA deficiencies who have known antibodies against IgA and patients hypersensitive to the product or to any of its component

Summary of safety concerns	
Important potential risks	• Long term immunogenicity • Transmission of infectious agents • Bacterial growth in the Vespera® nebuliser handset • Potential for off-label use (use in patients with cystic fibrosis) • Potential for off-label use (use in patients with bronchiectasis) • Potential for off-label use (use in patients with asthma associated with AATD) • Potential for off-label use (use in patients with COPD not associated with AATD)
Missing information	• Long term local effect in the lung • Patients with a history of lung transplant or a lung surgery within the past 2 years • Pregnancy and breast feeding

Discussion on safety specification

The Applicant identified “Hypersensitivity reaction in patients with selective IgA deficiencies who have known anti-bodies against IgA and patients hypersensitive to the product or to any of its component” as important identified risk. This estimate should be changed to “hypersensitivity including anaphylaxis” as for other AAT products covering the risk in all patients.

‘Serious respiratory disorders (including COPD, pneumonia and dyspnoea)’ should be included as an important identified risk.

Long term immunogenicity is considered by the Applicant as an important ‘potential’ risk, only. This grading is considered questionable. The Applicant anticipate that the development of ADAs do not have any impact on efficacy and safety of Kamada-AAT for Inhalation application. However, for the time being the risk should be at least updated to ‘Long term immunogenicity including lack of efficacy due to neutralising antibodies.’

Further, transmission of infectious agents is considered as an important potential risk. This grading is considered adequate. A respective warning statement has been included into the SmPC.

Bacterial growth in the Vespera® nebuliser handset was identified as an important potential risk which is considered appropriate. In the SmPC respective information are given in section 4.2 posology and section 6.6. However, a special warning should also be included in section 4.4 in order to point out that if the nebuliser is not cleaned as described in the instructions for Use/Cleaning bacterial growth might occur which may lead to infections, particularly to infections of the respiratory tract.

“Long term safety” is an important missing information in the RMP and should be included as there are important safety concerns identified and the long term experience is limited. This could be added or replace “Long term local effect”.

Conclusions on the safety specification

The information presented in the safety specification leads to the conclusion that the following issues should be addressed: (1) For the time being, the risk should be updated to 'Long term immunogenicity including lack of efficacy due to neutralising antibodies'. (2) Bacterial growth in the Vespera® nebuliser handset should be reflected as special warning in SmPC section 4.4. (3) The four risks describing potential for off label use in other indications 'potential for off label use in patients with CF, bronchiectasis, asthma associated with AATD and COPD not associated with AATD' should be justified. (4) 'Bronchospasm' should be included as an important potential risk in the RMP and as a warning in section 4.4 of the SmPC. 'Serious respiratory disorders (including COPD, pneumonia and dyspnoea)' should be included as an important identified risk. The RMP should be updated throughout to reflect this additional change.

Pharmacovigilance plan

The proposed post-authorisation PhV development plan has been updated to reflect the agreed changes to the list of safety concerns.

- Routine pharmacovigilance was proposed to address the majority of the agreed safety concerns.
- Additional pharmacovigilance activities were proposed to provide further information on the following specific safety concerns.
    - **Potential for transmission of infectious agents and hypersensitivity:** Study 006 - an ongoing 24 week Phase II, double-blind, placebo-controlled study in 36 patients to explore the ELF (epithelial lining fluid) and plasma concentration as well as safety of Kamada-AAT for Inhalation in AATD subjects. Study 006 is a PK and safety study which will also determine AAT-NE complexes, NE concentration, neutrophil count and inflammatory markers in the ELF.
    - **Hypersensitivity, long term immunogenicity, transmission of infectious agents and long term local effects in the lung:** A phase IV study (name to be agreed) which is an open label, non-controlled, multicentre, multinational study in approximately 100 subjects to evaluate the long term safety (100 weeks) of Kamada-AAT for Inhalation for the treatment and maintenance therapy of adult patients with congenital deficiency of alpha-1 antitrypsin and lung disease with clinical evidence of emphysema and airway obstruction (FEV1/SVC<70%). The study protocol has not yet been submitted for approval. Due to the imbalance of mortality observed in clinical trials, this study should also monitor "all causes mortality". This proposed PASS should only be considered as a PASS category 3 study and not a condition to marketing authorisation as, although it could provide some additional information, it will be insufficient to further characterise the risks.

The PRAC considered that use of this product is associated with a number of important risks including hypersensitivity, a high frequency of anti-drug antibodies that is sustained in many patients, and also a high frequency of respiratory disorders including dyspnoea, COPD and pneumonia. The proposed open label phase IV study is unlikely to provide clearer understanding of the safety profile or further inform the best approach to risk minimisation and may even be unethical. Consequently, **the proposed pharmacovigilance activities are <u>not</u> considered sufficient to ensure that the benefit risk balance is favourable in the proposed indication.**

The applicant has submitted a Pregnancy Outcome Form in Annex 7 of the RMP as requested. However, the following modifications are required to the form to improve data capture:

- The form is intended to be a pregnancy 'outcome' form to primarily capture adverse events related to the pregnancy and the neonate as a result of maternal medicinal product exposure prior to or during pregnancy. The proposed form appears to be divided into 2 separate sections, the first section capturing details of the mother's adverse event and the second section capturing the pregnancy/neonatal adverse event. This makes the form unnecessarily lengthy, with repetition of several questions. Also, if the mother has not experienced an adverse event, the reporter may not read further to complete the pregnancy/neonatal related information later in the form.
- The pregnancy outcome/neonatal adverse reaction questions should precede the questions capturing any maternal adverse events and consideration should be given to consolidation of questions to avoid repetition (e.g. reporter details, patient information, medicinal product exposure etc.).
- In order to capture information on previous pregnancies or other maternal history relevant to pregnancy, section D of the form should be updated to capture information on patient history and previous pregnancies only. Specific questions should be included on number, date and outcome of previous pregnancies (including stillbirth, miscarriage, birth defect, congenital abnormality, elective termination). Information on the current pregnancy should be removed from this section and combined with the information on current pregnancy outcome to create a section for pregnancy course and outcome. This new section should include a question on details and dates of adverse pregnancy outcomes (for the current pregnancy) such as stillbirth, miscarriage, birth defects etc., as well as reporter opinion on causality with the medicinal product.
- Exposure: A question should be included on whether dose of the medicinal product was adjusted. The questions should cover exposure prior to pregnancy (if relevant) and exposure during pregnancy.
- Some of the neonatal questions are taken from a general ADR form and are not appropriate e.g. 'has the patient already developed such an adverse reaction?' These questions should be removed or reviewed and updated to make them relevant to neonates.

Risk minimisation measures

Routine risk minimisation measures were proposed for each of the safety concerns. This includes labelling/instructions in the SmPC, the PIL, the EasyCare Cleaning Instructions for Use and the Nebuliser Handset Instructions for Use as well as restriction as a prescription only medicine.

The proposed risk minimisation activities have been updated to reflect agreed changes to the list of safety concerns.

As requested, the SmPC has been updated to include the following a warning in section 4.4:

- 'As with other inhalation therapy, paradoxical bronchospasm may occur with an immediate increase in wheezing after dosing. INFINIA® should be discontinued immediately, the patient assessed and alternative therapy instituted if necessary'.

In line with most other inhalation therapies, the applicant should also include the following additional information in the warning:

- 'Paradoxical bronchospasm responds to a rapid-acting bronchodilator and should be treated straightaway'

Conclusion

Use of this product is associated with a number of important risks including hypersensitivity, a high frequency of anti-drug antibodies that is sustained in many patients, and also a high frequency of respiratory disorders including dyspnoea, COPD and pneumonia. The PRAC considered that **the proposed risk minimisation activities are <u>not</u> sufficient to ensure that the benefit risk balance is favourable in the proposed indication.**

3.6. Pharmacovigilance system

The Applicant has provided the Summary of the Pharmacovigilance System (signed on 21 February 2016). The PRAC considers that the Pharmacovigilance system as described by the Applicant fulfils the requirements and provides adequate evidence that the Applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

4. Orphan medicinal products

According to the conclusion of the Commission Decision (dated 2004-11-16) the medicinal product "Alpha-1 antitrypsin (inhalation use)" was designated as an orphan medicinal product for the indication: Treatment of emphysema secondary to congenital alpha-1 antitrypsin deficiency.

The product was entered in the Community Register of Orphan Medicinal Products under No EU/3/04/244.

5. Benefit risk assessment

Benefits

Beneficial effects

The primary efficacy parameter, i.e. time to first moderate/severe event-based exacerbation, was not met. No significant differences could be found following a sensitivity analyses, by excluding patients with poor prognosis or accounting for important baseline variables.

The same holds true for the secondary and tertiary endpoints. Most of these reveal even disadvantages for AAT treated patients: a significant disadvantage of AAT treatment was demonstrated for the secondary endpoint time from randomisation to the first event-based exacerbation of mild, moderate or severe intensity (p=0.009). Further, the overall rate of event-based exacerbation was higher in the AAT group compared to placebo; and the rate of severe exacerbations was significantly higher in the AAT compared to placebo group (p = 0.0450).

Post-hoc efficacy analyses were conducted for PFT parameters using different models to take into account the amount of missing data due to early withdrawals from the study and the imbalance observed at baseline between both treatment groups. These analyses revealed that patients treated with AAT had a statistically significant improvement in their spirometry parameters mean FEV1 and FEV1/SVC compared to placebo. No differences were found between treatment arms regarding diffusing capacity parameters.

Further, dyspnoea was analysed as a symptom during the first exacerbation. For AAT, the score was 11.95 compared to 12.25 for placebo (p = 0.0243) measured over day 0-10. This statistical significance disappeared when dyspnoea was measured over day 0-14: AAT group 11.58 compared to placebo 11.78 (p= 0.0817).

Uncertainty in the knowledge about the beneficial effects

It has to be noted that results from post-hoc analysis might trigger further investigations but are not regarded sufficient as proof of efficacy. Further, the results per se are considered questionable. Due to the high number of drop-outs imputation models have been used to account for missing data. In general the use of imputation models might be considered acceptable. However, in this case looking at the raw data doubts arise whether there is indeed a benefit for the majority of patients. In most of the patients (n=62) there seems to be no effect on FEV1 whereas seem to positively respond to the treatment. However, these 17 patients are non-completers, thus whether or not the effect of FEV1 improvement was indeed sustained or only transient could not be demonstrated. In the placebo group the majority of patients (n=65) did have a decline of FEV1 values similar as in the AAT group whereas 9 patients of the placebo group had a strong decline in FEV1 values and in 15 patients there was even an improvement.

And further, post-bronchodilator FEV1 was measured. As per EMA's guideline on COPD, the pre-bronchodilator FEV1 is the preferred measure in the development of a new product for maintenance treatment. However, another lung function parameter (e.g. post-bronchodilator FEV1) could be the parameter of choice if justified. The use of a bronchodilator drug during PFT measurement may cause a small increase in FEV1 depending on the reversibility. As up to 20% of the AATD patients may have asthma, a substantial portion of the included patients may have reversibility of FEV1. The Applicant should justify why the post-bronchodilator FEV1 would be the proper reflection of effect of Kamada also taken into account that the degree of reversibility may differ between the two treatment groups.

Concomitant bronchodilator medication has not been withhold before the lung function measurement. Furthermore, specific parameters for emphysema to support the FEV1 such as total lung capacity (TLC) and residual volume (RV) are not measured.

The Applicant claimed the MMRM analysis of FEV1 as the primary analysis. Notably, the graphical presentation of FEV1 showed that the difference appears to be driven by the gain in FEV1 in the first two weeks (positive in AAT group and negative in placebo group). Considering the mode of action, a fast effect is not expected. Furthermore the high early withdrawal rate of patients with a relative high FEV1 as observed in the Kamada group is not understood and may have affected the differences in mean FEV1. The J2R sensitivity analysis, the analysis with the most conservative approach of handling missing data, showed a non-significant substantial smaller difference (only roughly half of the unadjusted effect) between AAT and placebo, which questions the clinical relevance and robustness of findings.

As stipulated in the EMA guideline on COPD (EMA/CHMP/483572/2012 –corr.1), in case of a primary focus on lung function measurement, additional evidence of efficacy must be demonstrated through the use of a co-primary endpoint, either a symptom-based endpoint or a patient-related endpoint Efficacy should be demonstrated convincingly for both co-primary endpoints and improvements seen in these endpoints must be statistically significant and clinically relevant. The Applicant claims a benefit in dyspnoea as an important patient derived benefit. Dyspnoea was collected in two different ways i.e. during an exacerbation as a symptom and continuously by means of an eDiary. The clinical relevance and robustness of the symptom score analysis of dyspnoea during the first exacerbation is unclear. Differences between AAT and placebo were significant over the first 10 days but were less and nonsignificant when measured over the first 14 days ($p = 0.0243$ and 0.0817, respectively). For the E-diary score, there was a trend showing a favourable effect of AAT treatment throughout the study. In addition, reporting scales for dyspnoea and the analyses are not found and should be provided. The Applicant is also requested to discuss the clinical relevance by means of validation and MCID of the used scales.

Furthermore, positive findings in FEV1 and FEV1% predicted are not observed for DLCO, another lung function parameter affected in emphysema. However, it is known that FEV1 and DLCO are not highly correlated.

The incidence of dyspnoea was also analysed post-hoc in depth in order to show a symptom-derived benefit. A small favourable effect of AAT treatment in terms of decreased dyspnoea scores was observed in patients treated with AAT whereas a decline of dyspnoea scores was observed in placebo-treated patients. However, the reporting scales for dyspnoea are not scientifically justified (MCID) and the clinical relevance of the difference is questioned.

Finally, it is unclear whether differences in the colour of sputum between placebo and Kamada AAT might have compromised the integrity of blinding.

Risks

Unfavourable effects

Severe TEAEs occurred more frequently in the Kamada-AAT arm (DB AAT 25.3%, overall AAT 23.9% as compared to placebo (14.8%).

Drug related TEAEs were reported with a higher frequency in the AAT group (57.5%) compared to the placebo arm (46.9%) during the DB period. Most related TEAEs were in the respiratory, thoracic and mediastinal disorder SOC, but no individual related TEAEs occurred ≥ 5% more frequent in the AAT compared to the placebo arm during the DB period. During the OLE period, 28.8% of patients reported

treatment-related TEAEs, mostly being dyspnoea, cough and COPD. For these most frequently occurring SAEs the incidence was distinctly higher for subjects receiving Kamada-AAT for Inhalation than that in the placebo group: dyspnoea (9.0% vs. 7.4%), COPD (8.2% vs. 0%), and pneumonia (6.0% vs. 3.7%). Similarly, the percentage of subjects who experienced at least 1 TEAE that led to withdrawal of study drug was higher for subjects receiving Kamada-AAT for Inhalation as compared to subjects receiving placebo (25.4% versus 6.2%, respectively).

The frequency of hypersensitivity reactions was high in both arms of the DB part (global analysis 66.7% AAT vs 63.0% placebo). In a narrow analysis without disease related symptoms hypersensitivity was reported more frequently with AAT (19.5% vs 11.1%).

The immunogenicity of Kamada-AAT for Inhalation was evaluated during Study 007. The overall immunogenicity incidence was 76/119 (64%). The majority (68/76, 89%) of the positive patients had low titres (below or equal to 16); 6 patients had a titre of 32, one had a titre of 64 and one patient had a titre of 1024. Among the 76 subjects who developed ADAs following exposure to Kamada-AAT for Inhalation, 14 (18%) subjects had a transient response (i.e. ADA levels returned to zero at the end of the study). The remaining 62 (82%) subjects had a sustained response.

Uncertainty in the knowledge about the unfavourable effects

Long-term safety data of treatment with Kamada-AAT and the available data for continuous Kamada-AAT treatment for at least one year are very limited. Only 39 patients received Kamada-AAT for inhalation for at least one year and almost half of the patients entering the OLE period had a lag time in AAT treatment of more than 6 months.

The frequency of hypersensitivity reactions in both the Kamada group as in the placebo arm was high, while the majority of patients received concomitant medications such as corticosteroids or antihistamines for systemic use, which should suppress or decrease hypersensitivity reactions. Interpretation of the data regarding Kamada-AAT induced hypersensitivity is complicated because symptoms due to hypersensitivity reactions partly overlap with symptoms of the underlying disease such as cough and dyspnoea. Even after excluding probably disease related symptoms, the frequency of hypersensitivity reactions remained high, also in the placebo group. The latter may be indicative for aspecific hyperreactivity to the inhalation liquid. The severity of the hypersensitivity reactions and the frequency of hypersensitivity reactions separated by anti-drug antibody status is unknown.

Information regarding clinical consequences of the high frequency of ADAs with Kamada-AAT for inhalation is very limited. No clinical symptoms are considered attributable to the occurrence of ADAs, so far. However, decrease in PiM levels, as seen in some patients, suggests a possible in vivo neutralising effect. In addition, the possibility of cross reactivity hasn't been addressed. Whether there is an association between positive ADA status and hypersensitivity reactions has not been thoroughly investigated. And further, it is questioned whether anti-AAT antibodies might reduce efficacy or cause severe immunogenicity adverse events in ADA positive patients starting with IV-AAT after discontinuation of Kamada-AAT for Inhalation.

Safety data for patients with signs of asthma (~20% of AATD patients) who might develop bronchoconstriction in response to inhaled protein, and for patients with previous or concomitant IV-AAT, use is missing.

Table 9: Effects Table for INFINIA

Effect	Short Description	Unit	Treatment	Control / Placebo	Uncertainties / Strength of evidence	References
Favourable Effects						
Primary endpoint	Time to first event-based exacerbation Moderate and severe	Median days (range)	112 (76, 142)	140 (104, 174)	Result even in disfavour after sensitivity analysis*	Clinical documentation, MO1
Secondary endpoint	Time to first event-based exacerbation Mild, moderate, and severe	Median days (range)	76 (59, 112)	133 (83, 151)	Result even in disfavour after sensitivity analysis*	Clinical documentation, MO1
Secondary endpoint	Rate of event-base exacerbation (all types)	Yearly rate	3.12	2.67	Rate of severe exacerbations was even significantly higher in AAT group	Clinical documentation, MO1
Secondary endpoint	Severity of first exacerbation	Event-based (%)	None: 21.2 Mild: 14.1 Moderate: 56.5 Severe: 8.2	20.4 16.3 63.3 0.0	Result do not change significantly after sensitivity analysis*	Clinical documentation, MO1
	Severity of first exacerbation	Sympt om-based (%)	Type III 34 Type II 23 Type I 16	33 12 26	Result do not change significantly after sensitivity analysis*	Clinical documentation, MO1
Unfavourable Effects						
ADAs	Subjects with ADAs in pivotal study 007	%	63	0	use of confirmatory assay, possible neutralizing capacity not yet clarified	MO2
frequent respiratory SAEs	Subjects with respiratory SAEs in pivotal study 007	%	Dyspnea: 9.0 COPD: 8.2 Pneumonia: 6.0	7.4 0 3.7	imbalance in demographic baseline values	MO3

Abbreviations: ADA=anti-drug antibody, COPD= chronic obstructive pulmonary disease, SAE= serious adverse event

* patients with poor prognosis excluded

Balance

In the pivotal Study 007 no favourable effects were noted for the AATD patients treated with Infinia. None of the primary, secondary and/or tertiary endpoints revealed any benefit. Favourable effects as claimed by the Applicant due to post-hoc analysis of data are not acceptable as proof of efficacy as with any data-driven analyses, observed effects need further confirmation in future trials.

In addition to the fact that no favourable effects were noted, unfavourable effects were identified, i.e. high occurrence ADAs with possible neutralizing capacity and the high occurrence of respiratory SAEs implicating a worsening of disease.

Importance of favourable and unfavourable effects

Reduction of exacerbations is important because exacerbations are relevant for the decline of lung function as well as for quality of life. The absence of an effect on exacerbation is an important negative finding, especially in the perspective that it appears that Kamada may have a detrimental effect on exacerbation time to first exacerbation as well as on yearly rate of exacerbation.

FEV1 and FEV1/FVC are important parameters for the progression of obstructive diseases like in AATD. The extent of inflammation, fibrosis, and luminal exudates in small airways is correlated with the reduction in FEV1 and FEV1/FVC ratio, and probably with the accelerated decline in FEV1 characteristic of COPD. Although emphysema is more associated with gas exchange abnormalities than with reduced FEV1, it does contribute to gas trapping during expiration. Notably, the observed benefit in overall effect of FEV1 post-bronchodilator is only modest and the results may be confounded by other bronchodilatory medication. Comparisons with results of previous trials are hampered because of different study designs.

DLCO as measurement is a valuable measurement for gas transport that is impaired in AATD. However, as a parameters the reproducibility is lower than FEV1.

From a patient perspective a decrease in dyspnoea is important. However, dyspnoea as a parameter in clinical trials is not yet validated in the setting as the primary objective. Support of other validated patent derived measurements such as SGRQ is necessary. A small favourable effect of AAT treatment was observed compared to placebo for the occurrence of dyspnoea during an exacerbation, but was not confirmed in the SGRQ.

The tolerability of AAT via the inhalation route of administration is questioned, due to the high frequency of (S)AEs, discontinuations due to AEs, hypersensitivity reactions and the increase in ADAs when compared to placebo. It is of concern that the new route of administration seems to cause more safety concerns when indirectly compared to licensed and commercially available IV-AAT. It is furthermore of concern that information regarding clinical consequences of the high frequency of ADAs with Kamada-AAT for inhalation is very limited, especially in light of the almost absent long term safety data.

Benefit-risk balance

The benefit-risk balance is clearly negative as no favourable effects were noted, but unfavourable effects were identified. Kamada AAT failed to show a reduction of the time to first moderate-severe exacerbations compared with placebo in the primary as well as in the sensitivity analyses. Additional analyses using exacerbation as a parameter were consistent with these negative findings. For the PFTs data different types of issues/deficiencies compromise the results and preclude a positive conclusion. Regarding the symptom or patients derived outcomes, none of the endpoints could show a benefit of Kamada over placebo except for the incidence of dyspnoea. The high frequency of severe and serious adverse events and discontinuations due to adverse events, make tolerability of the inhalation route of administration questionable. In addition, the high frequency of ADAs with unknown clinical consequences is of major concern.

Discussion on the benefit-risk assessment

Efficacy of AAT for inhalation in alpha-1 antitrypsin deficient patients has not been shown: The single, pivotal trial 007 failed to show a statistically significant superiority of inhaled AAT compared to placebo with regard to its primary efficacy endpoint, time to first moderate or severe exacerbation. Even after sensitivity analyses, no positive effect of AAT on the primary efficacy endpoint could be shown. The same holds true for the secondary and tertiary endpoints. Most of these reveal even disadvantages for the AAT treated patients: a significant disadvantage of AAT treatment was demonstrated for the secondary endpoint time from randomisation to the first event-based exacerbation of mild, moderate or severe intensity (p=0.009). Further, the overall rate of event-based exacerbation was higher in the AAT group compared to placebo; and the rate of severe exacerbations was significantly higher in the AAT compared to placebo group (p = 0.0450). Effects seen after post-hoc analysis on severity of exacerbation, dyspnoea score and on some pulmonary function parameters (PFT) have to be interpreted critically: as with any data-driven analyses, observed effects need further confirmation in future trials.

The change of the purpose of the PFT is accompanied with specific deficiencies the totality of PFT data and the lack of withdrawal of concomitant medication before PFT; because medication that can interfere with measurement of pulmonary function was not withheld, results could have been (unbalanced) confounded. Further serious concerns exist regarding the used statistical MMRM analysis of the FEV1 estimating an average effect over 5 measurements. Drawbacks are that the MMRM tends to estimate the effect of those patients able to adhere to randomised treatment and does not fully address the early drop-out that is likely differential, also in other characteristics than corrected for by the MMRM, that the earlier endpoints (week 0, 2, 4) with a larger effect may weight more into this average and that the later measurements are too far apart to provide reassurance of maintenance of effect. In an additional analysis to correct the early measurements resulted in the difference of approximately 20-25 mL between AAT inhaled and placebo. This difference is not considered to be relevant.

Therefore, the claimed favourable effect in lung function test is currently disputed.

As stipulated in the EMA guideline on COPD (EMA/CHMP/483572/2012 –corr.1), evidence of efficacy in COPD must be demonstrated either by means of a symptom-based endpoint or a patient-related endpoint, the Applicant has discussed dyspnoea in depth in order to show a benefit in a symptom-based endpoint. Dyspnoea is a symptom closely associated with airflow obstruction in COPD. Dyspnoea has an adverse effect on the patient's quality of life. However, it is usual only considered as supporting evidence. Therefore the clinical importance should further be justified. Additionally, dyspnoea was post-hoc analysed as symptom in the first exacerbation or as item in the e-Diary. The clinical relevance should be justified. Altogether, an improvement in a symptom-based endpoint or a patient-related endpoint has not been established.

In addition, two major safety concerns have been identified.

During the DB treatment period, a higher frequency of severe TEAEs (25.3% vs 14.8%), related TEAEs (57.5% vs. 46.9%), SAEs (34.5% vs. 18.5%) and related SAEs (6.9% vs 0%) were reported with Kamada-AAT compared to placebo. The incidence of the most frequently occurring SAEs was distinctly higher for subjects receiving Kamada-AAT for Inhalation than that in the placebo group: dyspnoea (9.0% vs. 7.4%), COPD (8.2% vs. 0%), and pneumonia (6.0% vs. 3.7%). Similarly, the percentage of subjects who experienced at least 1 TEAE that led to withdrawal of study drug was clearly higher for subjects receiving Kamada-AAT for Inhalation as compared to subjects receiving placebo (25.4% versus 6.2%, respectively). In contrast, in the registration trials with IV-AAT the incidence rates for SAEs were comparable to the placebo group. Discontinuation due to AEs occurred in a substantially higher percentage of patients in the AAT treatment groups (DB period: AAT 19.9%) compared to placebo (6.2%). A more conservative approach by which discontinuation due to subject decision is also consid-

ered treatment related, i.e. due to AEs, leads to a treatment related discontinuation rate of 33%. Both approaches indicate a premature discontinuation rate due to AEs that is much higher as observed with IV-AAT.

Although the most frequent AEs were in the respiratory, thoracic and mediastinal disorder SOC and considered to be related to the underlying disease by the Applicant, these might also reflect local irritation due to inhalation of the human plasma protein AAT. This is supported by the observation that a high percentage of patients discontinued due to AEs. The Applicant should justify tolerability of Kamada-AAT for inhalation. The severity of AEs leading to discontinuation, and time to resolution of AEs should be presented.

Secondly, the high frequency of ADAs is a major concern. 76/119 (64%) of patients developed ADAs and this antibody response was sustained in most of these patients. Of note, no ADAs have been observed with IV-AAT. It is unknown whether the increased levels of anti-AAT antibodies with the inhalation route of administration might reduce efficacy, or cause a higher frequency and/or higher intensity of hypersensitivity reactions. Furthermore, the consequences for future treatment with IV-AAT in ADA positive patients after discontinuation of Kamada-AAT for Inhalation are unknown. The Applicant should submit data regarding possible neutralising capacity of these antibodies as soon as possible. In addition, safety information should be presented separated by ADA status (including hypersensitivity reactions and intensity of AEs), and consequences of ADA positivity for future IV-AAT treatment should be discussed.

In their response to the LoQ the applicant presented results from study 006 and further analysis of some post-hoc analysis results. In brief, results from study 006 reveal that inhaled AAT reach the lung ELF, but no signs of anti-inflammatory activity or clinical efficacy were found.

In terms of safety, the high frequency of ADAs (64%) in AAT treated patients as well as the sustained antibody response in most of these patients (83%) is still considered to be a major safety concern, since the occurrence of ADAs is associated with higher frequencies of TEAEs, including hypersensitivity reactions. Moreover, long term safety aspects as well as potential immunogenic risks for patients switching back to IV AAT therapy have not been clarified. Furthermore, tolerability of AAT via the inhalation route of administration is still questioned based on the safety profile of the total study population. The safety profile of the subpopulation with possible less severe disease of the pivotal study is not convincingly improved compared to the total study population.

Conclusions

The overall B/R of Infinia (Kamada-AAT for Inhalation) remains negative.