Summary Basis for Regulatory Action

Date: June 14, 2010
From: Ewa Marszal, Chair of the Review Committee
BLA/ STN#: STN 125325/0
Applicant Name: Kamada Ltd, Ness Ziona, Israel
Date of Submission: May 29, 2009
PDUFA Goal Date: July 1, 2010
Proprietary Name/ Established Name: GLASSIA / Alpha-1-Proteinase Inhibitor (Human)
Indication: Treatment of chronic augmentation and maintenance therapy in adults with emphysema due to congenital deficiency of alpha-1-proteinase inhibitor, also known as alpha-1-antitrypsin

Recommended Action: Approval

Signatory Authorities Action:

Offices Signatory Authority: Jay S. Epstein _____

☐ **I concur with the summary review.**

☐ **I concur with the summary review and include a separate review to add further analysis.**

☐ **I do not concur with the summary review and include a separate review.**

Offices Signatory Authority: Mary Malarkey _____

☐ **I concur with the summary review.**

☐ **I concur with the summary review and include a separate review to add further analysis.**

☐ **I do not concur with the summary review and include a separate review.**

Material Reviewed and Reviewer Names
Clinical Review: L. Ross Pierce
Clinical Pharmacology Review: Iftekhar Mahmood
Epidemiology Review: Faith Barash
Statistical Review: Stan Lin
CMC Review: Jennifer Reed, Douglas Frazier, Maria L. Virata-Theimer, Lilin Zhong, Pei Zhang, Ewa Marszal
Pharmacology/ Toxicology Review: Evi Struble
Biomonitoring Review: Dennis Cato
Facilities (DMPQ): David Doleski, Randa Melhem, Jennifer Schmidt
Labeling (APLB): Loan Nguyen
RPM: Cherie Ward-Peralta

1. Introduction

GLASSIA is a 2% solution of human alpha-1-proteinase inhibitor ($Alpha_1$-PI) indicated for chronic augmentation and maintenance therapy in adults with emphysema due to congenital deficiency of $Alpha_1$-PI, also known as alpha-1-antitrypsin.

GLASSIA is administered intravenously at 60 mg active $Alpha_1$-PI/kg body weight once weekly.

GLASSIA is manufactured at the Beit Kama, Israel facility (U.S. license 1826) from human plasma ----------(b)(4)---------- made at the -(b)(4)- ---------- facility in ----------(b)(4)----------. The Beit Kama, Israel facility has been inspected and licensed. Raw material testing is performed at --(b)(4)-- ----------. Microbial testing is performed by ----------(b)(4)---------- ------.

GLASSIA is manufactured from large pools of human U.S. Source or recovered plasma by a combination of cold alcohol fractionation, ----------(b)(4)---------- ---------- chromatography steps.

GLASSIA is the first liquid $Alpha_1$-PI product. It is formulated in -(b)(4)- sodium phosphate buffer, pH -(b)(4)--, containing -(b)(4)- sodium chloride and does not contain preservatives. GLASSIA is filled to a 50 mL volume (1 g) in -(b)(4)- glass vials with ----(b)(4)---- rubber stoppers. The product is stable at 2 – 8 ^{o}C for up to 24 months.

2. Background

This original Biologics License Application (BLA) from Kamada was received by CBER on June 1, 2009. In this application, the sponsor requests the U.S. licensure of Kamada Human Alpha-1-Proteinase Inhibitor product, GLASSIA The application was the subject of a standard 10 month BLA review schedule. The review cycle was extended by 3 months due to a major amendment received on March 11, 2010.

The clinical studies were conducted under IND -(b)(4)- for the indication of $Alpha_1$-PI deficiency associated with emphysema. The pivotal clinical study (Kamada-API-002) was a Phase 2/3 randomized double-blind comparison of GLASSIA with a licensed $Alpha_1$-PI product, Prolastin®. The goal of the study was to demonstrate that GLASSIA was not inferior to Prolastin® in terms of the antigenic and/or functional $Alpha_1$-PI trough level averaged over weeks 7-12.

3. Chemistry, Manufacturing and Controls (CMC)

a) Product Quality

The starting material for GLASSIA is --------------------------(b)(4)----------------------
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------------------. Collection facilities are FDA-inspected. Plasma units used for production of GLASSIA are tested using FDA-licensed serological assays for hepatitis B surface antigen (HBsAg), antibodies to hepatitis C virus (HCV) and human immunodeficiency virus types 1 and 2 (HIV-1/2). Plasma units are also screened by FDA-licensed Nucleic Acid Tests (NAT) for HCV and HIV-1. Each plasma unit must be non-reactive (negative) in all tests. Plasma is tested by in-process NAT procedures for parvovirus B19 and the limit for B19 DNA in the manufacturing pool is set to not exceed 10^4 IU per mL. To reduce the risk of viral transmission, the manufacturing process for GLASSIA includes two steps specifically designed to remove or inactivate viruses. The first of these is nanofiltration through a 15 nm filter that can remove both enveloped and non–enveloped viral agents, and the second is solvent/detergent (S/D) treatment with a mixture of tri-(n-butyl) phosphate (TNBP) and Polysorbate 80 (Tween 80), which inactivates enveloped viruses such as HIV, HBV, and HCV. No animal-derived source materials or reagents are used in the manufacture of GLASSIA.

All raw materials are obtained from qualified vendors and used in the manufacture of GLASSIA after material identity and quality is confirmed.

Manufacturing processes of GLASSIA is represented below:

(b)(4)----------------------------------

Drug Product

Specification

The final specifications established for GLASSIA are acceptable. Specifications and validation of the quality-control analytical methods have been evaluated by review personnel. The testing program was found to include appropriate measures of product quality attributes, product impurities, and safety. The specifications related to the active ingredient are consistent with the results from the clinical studies. The maximum content of chemical impurities is considered safe.

All routine methods used for the control or release testing of starting materials, process intermediates, drug product, and stability samples are validated, except for the method for estimating the number of visible protein aggregates, which was qualified.

Table 1. Lot Release Testing and Specifications

Test	Specification	Analytical Procedure
Appearance	The solution is clear and colorless to yellow-green. May contain a few protein particles.	Visual inspection
--(b)(4)-----	---(b)(4)----------	---(b)(4)----------
-(b)(4)-	---(b)(4)----------	---(b)(4)----------
Total Active API Content	---(b)(4)------- per vial	---(b)(4)----------
Active API Content	---(b)(4)-------	---(b)(4)----------
Specific Activity	---(b)(4)---- active API/mg protein	---(b)(4)----------
Sodium	---(b)(4)----------	---(b)(4)----------
Chloride (as NaCl)	-(b)(4)--	---(b)(4)----------
Phosphate	---(b)(4)-----	---(b)(4)----------
------(b)(4)---- ----------	---(b)(4)---------- ----------	---(b)(4)---
	---(b)(4)---------- ----------	
Residual TNBP[1]	---(b)(4)-------	---(b)(4)----------
Residual Tween 80[1]	---(b)(4)-------	---(b)(4)---------- -------
--(b)(4)---------	---(b)(4)-------	---(b)(4)---------- -------

Bacterial Endotoxin	---(b)(4)------------	---(b)(4)--------------- method
Pyrogenicity	Pass	Rabbit pyrogen test
Sterility	Pass	Membrane filtration
General Safety Test	Meets Requirements	Mice and guinea pigs toxicity (21 CFR 610.11)
pH	---(b)(4)---	---(b)(4)--------------------------
Extractable Volume	---(b)(4)----	---(b)(4)----------------------------------

--(b)(4)--

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[2]NMT – not more than

As with all biological products, a 100% visual inspection is performed on this product. There are upper control limits for different categories of defects as follows: critical (-(b)(4)--); major (----------(b)(4)-----------); minor (------------------(b)(4)------------------ -- ---------); and, esthetic (-(b)(4)- --------------------------). Subsequently, a second inspection is performed on a subset of vials as determined by the acceptable quality level (AQL) plan. This is used to determine the quality of the 100% visual inspection.

GLASSIA contains small amounts of visible protein particulates which are aggregates of the Alpha-1-Proteinase Inhibitor. In addition to 100% visual inspection and secondary AQL inspection, appearance testing is performed. --------------------------(b)(4)------------- --- -- --- --- ---. Visible protein aggregates were present in the clinical lots used in the pivotal study -------(b)(4)--------- --. Other biologics and other $Alpha_1$-PI products also have been shown to contain protein particulates.

During the pivotal clinical study, GLASSIA was filtered through a 5 µm filter needle. This filtration was shown not to affect the potency of the product. As an added safeguard, the GLASSIA labeling will recommend that the product be filtered twice before product administration: through a 5 µm filter needle during product pooling before infusion and a through a 5 µm in-line filter during administration. Based on studies conducted by the sponsor the filtration does not reduce the product potency. Kamada has agreed to a postmarketing requirement and a number of postmarketing commitments. These studies are intended to (i) --------------------------(b)(4)----------------------- --- -- -- -- -- ----------------------

Stability of Final Drug Product

The stability-study data provided in the BLA are deemed sufficient to support the proposed storage conditions for final-product GLASSIA of 24 months at 2 – 8 °C.

Table 2. GLASSIA Drug Product Long Term Stability Limits at 5 ± 3 ºC

Test	At Release	At End of Shelf Life:
Appearance	The solution is clear and colorless to yellow-green. May contain a few protein particles.	The solution is clear and colorless to yellow-green. May contain a few protein particles.
Active API Content	---(b)(4)-------	---(b)(4)------
----------(b)(4)----------	---(b)(4)---------- ----------	---(b)(4)---------- ----------
pH	---(b)(4)--	---(b)(4)--
Protein Concentration	For calculation of Specific Activity	For information only[1]
---(b)(4)----------	---(b)(4)----------	---(b)(4)----------
Bacterial Endotoxin	---(b)(4)----------	---(b)(4)----------
Pyrogenicity	Pass	Pass
Sterility	Sterile	Sterile
Visual Protein Particles	---(b)(4)----------	For information only[1]
--------(b)(4)-------	For information only[1]	For information only[1]
Package Integrity	Meets requirements	Meets requirements

[1]The assay is performed; however, there is no specification for this characteristic (CBER comment)

Control of Adventitious Agents

GLASSIA is manufactured from --------(b)(4)-------- which is produced from U.S. human Source Plasma and recovered plasma that are collected in U.S.-licensed collection facilities. Screening tests include a donor-suitability assessment -------(b)(4)-------- ----------.

Plasma units used for production of GLASSIA are tested using FDA-licensed serological assays for hepatitis B surface antigen (HBsAg) and for antibodies to hepatitis C virus (HCV) and human immunodeficiency virus types 1 and 2 (HIV-1/2), as well as by FDA-licensed Nucleic Acid Tests (NAT) for HCV and HIV-1. Each plasma unit must be non-reactive (negative) in all tests. Plasma is tested by in-process NAT procedures for parvovirus B19 and the limit for B19 DNA in the manufacturing pool is set not to exceed 10^4 IU per mL.

Table 3. Methods Used in Plasma Screening

Test	Test Performed on:		
	--------(b)(4)---------	--(b)(4)--- ----------	--------(b)(4)---------
HBsAg	--(b)(4)--		
HIV 1 & 2-Ab			
HCV-Ab			
HCV RNA			
HIV RNA			
B19V DNA			
Other Tests			

--(b)(4)---------	--(b)(4)--
--(b)(4)--	

----------(b)(4)----------

The manufacturing process for GLASSIA contains two steps which contribute to viral inactivation or removal: 1) Nanofiltration with -(b)(4)-- 15N filters; 2) Solvent/Detergent treatment with TNBP and Polysorbate 80. These steps are robust and have been validated to yield the following levels of viral inactivation or removal.

Table 4. Log_{10} Virus Reduction during Manufacture of GLASSIA

Process Step	Log Reduction of Enveloped Viruses				Log Reduction of Non-enveloped Viruses	
	HIV-1	PRV[1]	BVDV[2]	WNV	HAV	PPV[3]
Nanofiltration	> 5.59	> 5.57	> 5.74	ND	> 4.99	4.04
S/D treatment	> 6.41	> 6.14	> 5.61	> 6.32	N/A	N/A
Global Reduction Factor	> 12.00	> 11.71	> 11.35	> 6.32	> 4.99	4.04

N/A - Not Applicable. The S/D treatment is not effective for non-enveloped viruses.
ND - Not Done
[1]PRV (Pseudorabies virus) is a herpes virus that is used as a model for human herpes viruses (e.g. EBV, CMV and HHV6). It is also used as a model virus for hepatitis B virus.
[2]BVDV (Bovine viral diarrhea virus) is a RNA enveloped virus and it is used as a model virus for hepatitis C virus.
[3]PPV (Porcine parvovirus) is a non enveloped DNA virus. It is a model virus for human parvovirus B19.

b) CBER Lot Release

The major difference between GLASSIA and other licensed $Alpha_1$-PI products is that GLASSIA is a liquid product while all other licensed products are lyophilized. CBER does not perform routine lot-release testing for the licensed lyophilized $Alpha_1$-PI products as lot-release tests performed by the manufacturers appear to be appropriate to assure their safety and potency. During the review of GLASSIA, we learned that other products may contain visible protein particulates upon reconstitution and that in GLASSIA, small numbers of particulates appear to be fairly common. CBER lot release testing will include visual inspection of all samples submitted by Kamada.

c) Facilities review/inspection

Kamada, Ltd. is a biologics manufacturer located in Beit Kama, Israel. GLASSIA is the first BLA that has been submitted to FDA by Kamada. Also, this was FDA's first inspection of Kamada, Ltd. All manufacturing operations are performed at this location ----------(b)(4)----------.

----------(b)(4)----------

Additionally, the facility performs most quality control testing and all quality assurance functions for the manufacturing operations.

The pre-license inspection of Kamada occurred on February 3-4 and 7-11, 2010. The inspection team consisted of David Doleski and Ewa Marszal, PhD. A 13-item FDA Form 483 was issued to Kamada that outlined the inspectional observations discovered during the inspection. The 483 items included, but were not limited to, validation and qualification studies for sterilization, aseptic processing, and room qualification, testing, inventory management, handling of deviations, visual inspections, standard operating procedures, and calibration. Kamada provided a number of responses to the 483 items after the inspection. Kamada's corrective actions are acceptable and all 483 items are closed.

We are not aware of any ongoing or pending investigations or compliance actions with respect to the above facilities or their products. A compliance check was submitted, and the Office of Compliance and Biologics Quality, Division of Case Management does not object to the approval of this submission.

d) Environmental Assessment
On June 21, 2010, DMPQ recommended that Kamada be granted a categorical exclusion under 21 CFR 25.31 (c).

4. Nonclinical Pharmacology/Toxicology

Table 5 summarizes the toxicology studies Kamada performed with GLASSIA. In two GLP-compliant single-dose general toxicology studies, two formulations of 2% $Alpha_1$-PI were evaluated, one containing sodium phosphate-buffered saline solution and the other containing sodium phosphate-buffered ----(b)(4)--- solution. The current formulation of GLASSIA was evaluated in one repeat-dose toxicity study in rabbits.

Table 5. Toxicology Summary

Study type	Route of administration, regimen and dose levels	Species	GLP compliance	Study Number
Acute toxicology study in rats	Single Intravenous bolus injection 0, 60 and 640-650 mg/kg	Sprague-Dawley rats	Yes	KAM/029/AIT
Acute toxicology study in rabbits	Single Intravenous bolus injection 0, 60 and 600 mg/kg	New Zealand White rabbits	Yes	KAM/030/AIT
Repeat dose toxicology study in rabbits	Intravenous bolus injection once daily for 5 consecutive days 0 and 300 mg/kg	New Zealand White rabbits	Yes	KAM/031/RIT
Neoantigenicity study in rabbits	Intradermal, intramuscular,	New Zealand White rabbits	Yes	-(b)(4)-071902

	subcutaneous 20 mg			
In vitro cytotoxicity in ----(b)(4)---- line	Effect of GLASSIA on monolayer integrity (transepithelial electrical resistance, TEER)	---(b)(4)--- ----------	Yes	C-13303-118-0905
In vitro cytotoxicity in -(b)(4)- ---------- ---------	Effect of GLASSIA on monolayer integrity (transepithelial electrical resistance, TEER)	Normal human tracheal/bronchial epithelial cells differentiated at the air liquid interface	Yes	KAM/117/CTX
Pharmacokinetic comparison of GLASSIA versus Prolastin in rabbits	Single intravenous bolus injection 1 mg/kg	New Zealand White rabbits	Yes	-(b)(4)-405

Results:

1. There were no test article-related effects on observations, body weights, or hematology indices after single-dose IV administration of GLASSIA in rats. A statistically significant decrease in group-mean alanine aminotransferase (ALT) levels was seen on Day 15 in animals treated with low- (one times human dose) and high-dose (more than ten times human dose) GLASSIA in saline when compared to a vehicle control. This change was minor in magnitude and dose-independent, and had no microscopic correlates.

2. There were no test article-related changes in observations, body weights, body weight gains, or gross pathology after single-dose IV administration of GLASSIA in rabbits. There were no test article-related effects on serum chemistry indices after the 14-day recovery period.

3. There were small hematology and serum chemistry changes seen in the repeated-dose toxicity study in rabbits receiving 300 mg/kg, or five times human dose of GLASSIA, such as small reductions in group mean lymphocytes, small reductions in group mean creatinine phosphokinase (CPK), and minor increases in group mean neutrophils. Recovery was observed at the end of the 14-day recovery period.

4. There were no cytotoxic effects of GLASSIA observed in vitro, using either Calu-3 epithelial cell monolayers, or normal tracheal epithelial cell monolayers which had been differentiated at the air-liquid interface (----------(b)(4)----------).

5. There were no neoantigenic changes to $Alpha_1$-PI after a viral inactivation step was added in the manufacturing process of GLASSIA as measured by -(b)(4)- to detect antibodies against $Alpha_1$-PI.

Safety of Impurities

TNBP

GLASSIA contains ----------(b)(4)---------- of TNBP in the final formulation. Thus, the greatest amount of TNBP that could be administered with the highest weekly dose of 60 mg/kg GLASSIA is ----(b)(4)----.

1. Similar exposure to TNBP is obtained after intravenous use of other approved products, such as different immune globulin preparations.

2. The NOAEL (no-observed-adverse-effect-level) of TNBP in rabbits receiving 13 weeks of daily intravenous administrations was shown to be --(b)(4)-- or more than 26 times the human once weekly dose. At this dose, spleen and thymus weight increases were observed, however subsequent microscopic evaluation revealed no lesions, therefore the findings were not considered adverse.

In conclusion, the exposure to TNBP resulting from the clinical use of GLASSIA in recommended doses is considered safe.

PS80

GLASSIA contains ----------(b)(4)---------- of polysorbate 80 in the final formulation. The greatest amount of polysorbate 80 that could be administered per a 60 mg/kg dose of GLASSIA is ---(b)(4)---. This amount is less than other plasma-derived IV preparations, e.g., immune globulin preparations with a long history of safe use in the clinic.

In conclusion, the exposure of PS80 resulting from the clinical use of GLASSIA at recommended doses is considered safe.

5. Clinical Pharmacology

Title of Study: The pharmacokinetics and safety of an Alpha-1 proteinase inhibitor (-(b)(4)--API) in subjects with congenital API deficiencies. A dose-escalation clinical trial (Study Protocol # -(b)(4)--API 001)

This was a multi-center study, the primary objective of which was to determine the pharmacokinetics of GLASSIA at three different dose levels in subjects with $Alpha_1$-PI deficiency. The secondary objective was to evaluate the safety of GLASSIA.

Eighteen subjects (6 per dose group) with congenital $Alpha_1$-PI deficiency received a single dose of GLASSIA at one of the three dose levels; 30mg/kg, 60mg/kg, or 120 mg/kg. There were 11 males and 7 females in the study (ages ranged from 40 to 69 years). Each subject received a single dose of GLASSIA at an infusion rate of 0.08 mg/kg/min. Blood samples were taken prior to and within 5 minutes of completion of the infusion, and then at 1 hour, 6 hours, 12 hours, 24 hours, 3 days, and 7 days. The subjects were followed up for a further 7 days (to Day 14) for safety data. Subjects were also

followed up at 4 weeks and at 3 and 6 months for viral safety data. Plasma concentrations of $Alpha_1$-PI were determined by both antigenic and functional assay methods. Plasma concentrations vs. time data were fitted to one- or two-compartment models as found suitable. The results of the study are summarized below.

Antigenic (------(b)(4)-----) assay

Mean area under the curve ($AUC_{(0\text{-}168h)}$ and $AUC_{(0\text{-}infinity)}$) increased proportionally with dose and was linear (r^2 = 0.999 and 0.996, respectively) over the dose range of 30 to 120 mg/kg. The mean terminal half-lives varied from 81 hours (30 mg/kg group) to 111 hours (60 mg/kg group) with an overall mean of 93.4 hours. The mean volumes of distribution and clearance show similar values across the dose groups, with overall mean values of 3.18 liters and 0.59 mL/h/kg, respectively. The mean pharmacokinetics parameters of GLASSIA by antigenic assay are summarized in Table 6.

Table 6. Mean Pharmacokinetic Parameters of GLASSIA (Antigenic Assay)

Parameters	Dose (mg/kg)		
	30 mg/kg	60 mg/kg	120 mg/kg
$AUC_{(0\text{-}168\ hours)}$ mg•h/mL	52 ± 9	103 ± 15	212 ± 39
$AUC_{(0\text{-}infinity)}$ mg•h/mL	70 ± 14	156 ± 26	291 ± 40
Clearance (mL/h/kg)	0.59 ± 0.10	0.59 ± 0.09	0.58 ± 0.10
Half-life (h)	81 ± 19	111 ± 34	89 ± 23
Volume of distribution (L)	3.18 ± 0.55	3.02 ± 0.34	3.34 ± 1.13

Clearance was calculated from $AUC_{(0\text{-}168\ hours)}$ due to more than 20% contribution of tail to total AUC ($AUC_{(0\text{-}infinity)}$).

Functional (-(b)(4)-) assay

Mean area under the curve ($AUC_{(0\text{-}168h)}$ and $AUC_{(0\text{-}infinity)}$) increased proportionally with dose and was linear (r^2 = 0.999 and 0.999, respectively) over the dose range of 30 to 120 mg/kg. The mean terminal half-lives vary from 97 hours (30 mg/kg group) to 115 hours (120 mg/kg group) with an overall mean at 107.6 hours. The mean volumes of distribution and clearance show similar values across the dose groups, with overall mean values of 3.47 liters and 0.69 mL/h/kg, respectively. The mean pharmacokinetic parameters of GLASSIA by functional assay are summarized in Table 7. The pharmacokinetic parameters in the clinical pharmacology labeling are based on the PK parameters obtained from the functional assay.

Table 7. Mean Pharmacokinetic Parameters of GLASSIA (Functional Assay)

Parameters	Dose (mg/kg)		
	30 mg/kg	60 mg/kg	120 mg/kg
$AUC_{(0\text{-}168\ hours)}$ mg•h/mL	44 ± 8	89 ± 10	183 ± 28
$AUC_{(0\text{-}infinity)}$ mg•h/mL	70 ± 14	156 ± 26	291 ± 40
Clearance (mL/h/kg)	0.71 ± 0.14	0.68 ± 0.09	0.67 ± 0.10
Half-life (h)	97 ± 12	111 ± 33	115 ± 35

Volume of distribution (L)	3.64 ± 0.31	3.21 ± 0.31	3.57 ± 0.51

Clearance was calculated from $AUC_{(0\text{-}168\ hours)}$ due to more than 20% contribution of tail to total AUC ($AUC_{(0\text{-}infinity)}$).

Conclusions: The pharmacokinetics of GLASSIA is linear over the dose range of 30 to 120 mg/kg. The half-life of GLASSIA was determined, but may not be accurate due to study design issues (i.e. not enough time points in the terminal phase, and insufficient duration of blood sampling).

6. Clinical/ Statistical

The medical review focused on the outcomes of the pivotal positive control (Prolastin®) study, Kamada-API-002, entitled Phase II/III Randomized, Double-Blind Comparison of Alpha-1 Proteinase Inhibitor (Kamada-API) with Prolastin® in Individuals with Alpha-1 Antitrypsin (AAT) Deficiency. Supportive safety data were also available from the single dose pharmacokinetic study.

Pivotal Study:
Study Design:
Study -(b)(4)- API 002 was a Phase 2/3 randomized double-blind comparison of GLASSIA with Prolastin® in individuals with AAT deficiency. It was intended to study the use of GLASSIA for chronic augmentation and maintenance therapy in individuals with clinical evidence of emphysema due to congenital deficiency of $Alpha_1$-PI. The study was conducted as a two-period trial. The planned number of subjects was 50. During the first period, following a five week washout from prior $Alpha_1$-PI therapy, 50 AAT-deficient subjects with clinical evidence of emphysema were randomized 2:1 to GLASSIA or Prolastin® and received study product. All subjects received 60 mg/kg of GLASSIA or Prolastin® weekly for twelve weeks. During the second period which was the open-label part of the trial, all subjects received GLASSIA through week 24. During the last study period follow-up visit at week 28, blood samples were drawn and tested for viral serology, but did not undergo viral nucleic acid testing (NAT).

Trough antigenic and functional $Alpha_1$-PI levels were obtained during period 1 from weeks 7-12 as well as during the second period of the trial. The primary endpoint was based on individual subjects' mean antigenic and/or functional $Alpha_1$-PI serum levels from weeks 7-12. A subset of 15 subjects also provided bronchoalveolar lavage (BAL) collection. These subjects were selected on the basis of more stringent FEV_1 criteria than the overall study population, had to have been receiving inhaled corticosteroids at a stable dose for 2 weeks prior to the first bronchoscopy and throughout the dosing prior up to the final bronchoscopy, and must not have had an exacerbation of COPD during the previous 6 weeks. Separate randomization lists were used for BAL and non-BAL subjects. The BAL subset underwent both high-resolution computed tomography (HRCT) and BAL with bronchial brushing/biopsy at baseline (between days -12 to -2) and once again between weeks 10 and 12 at one of three centers. The HRCT could be repeated prior to the 2nd bronchoscopy at the investigator's discretion.

Table 8. Pivotal Study Design Schematic

	-5 weeks	Day 0/Week 1	Week 2-12	Week 13-24	Week 25-28
Washout	←	→			
BAL and bronchial biopsy/brushing		↔			
Randomization		↔			
Kamada API or Prolastin®		←	→		
Kamada API				↔	
AE Follow Up	←				→
Virology Follow Up					↔
Resume API Standard of Care					↔

Objectives of the study:
The study objectives were to demonstrate that the pharmacokinetics of antigenic and/or functional Alpha1-PI in GLASSIA were not inferior to those of the control product, to determine whether GLASSIA maintained antigenic and/or functional plasma levels of at least 11 μM (57 mg/dL) and to compare Alpha1-PI trough levels (antigenic and functional) over 6 infusion.

The secondary objectives were to compare the levels of antigenic and/or functional $Alpha_1$-PI in the epithelial lining fluid (ELF), at baseline and after 10-12 weeks of product administration and to assess the safety associated with GLASSIA (not to be inferior to that of Prolastin®).

Endpoints:
The primary efficacy endpoint of the study was to assess the **c**irculating antigenic and/or functional $Alpha_1$-PI trough level averaged over weeks 7-12 (6 infusions). The goal of this study was to demonstrate that GLASSIA was not inferior to Prolastin®. The definition of lack of inferiority was a mean trough value not lower than 3 μM below that of the control product at steady state, as assessed using a 95% confidence interval for the difference in mean values. The secondary efficacy endpoint of the study included change over baseline of antigenic and/or functional $Alpha_1$-PI in the ELF. Because of the ambiguity of the "and/or" feature of the primary endpoint, FDA required the primary endpoint be met for both antigenic and functional blood $Alpha_1$-PI levels. FDA's analysis consisted of both antigenic and functional blood $Alpha_1$-PI.

The safety endpoints of the study were to evaluate:

- Treatment-Emergent Adverse Events (TEAEs)
- Vital Signs at every visit prior to infusion, 5-10 min after start of infusion, every 30 min and as needed during infusion, immediately after infusion and one hour after end of infusion
- CBC with white blood cell differential

- Routine biochemistry including electrolytes, BUN, serum creatinine, ALT, AST, alkaline phosphatase, total and direct bilirubin
- Viral markers (HBsAg and antibodies to HIV-1, HIV-2, HCV, HBs, and HBc)
- C3 and C4 serum complement levels
- Samples for $Alpha_1$-PI Antibodies as taken at baseline and at weeks 12 and 24 (these had not been assayed as of the time of BLA submission due to continuing assay development and will be submitted as a Post Marketing Commitment following validation of the assay method).
- Baseline IgA level
- Physical exam
- Spirometry at baseline and at weeks 12 and 24
- The frequency of pulmonary exacerbations; The elements that defined a pulmonary exacerbation in this study were:
    - Increased shortness of breath above baseline, lasting at least 48 hours
    - Increased sputum volume above baseline, lasting at least 48 hours
    - Change in color of sputum (increased sputum purulence), lasting at least 48 hours

  An exacerbation was defined as one or more of the above elements. If a single element was present, the exacerbation was classified as 'mild', if two elements 'moderate', and if all three elements were present this was classified as a 'severe' exacerbation. Changes in medications associated with each exacerbation were also collected.

In the study a number of tertiary endpoints were also assessed and included the following:

- Measurement of pro-inflammatory cytokine IL-8 in the ELF.
- Measurement of the number and type of inflammatory cells (Total Cell Count, Macrophages, Eosinophils, Neutrophils and Lymphocytes (total and subsets)) total and individual, in the ELF.
- Measurement of the following ELF analytes (other than antigenic $Alpha_1$-PI and Anti-Neutrophil Elastase Capacity (ANEC):
    - Neutrophil Elastase (NE)
    - $Alpha_1$-PI-NE complexes
- Measurement of $Alpha_1$-PI trough levels:
    - The mean ratio of functional to antigenic $Alpha_1$-PI trough levels over weeks 7-12 (six infusions).
    - The ratio of mean antigenic $Alpha_1$-PI trough level over weeks 7-12 (six infusions) for the Prolastin® group to the equivalent mean value for the same treatment group after their crossover to GLASSIA (i.e. weeks 13 to 24).
    - The ratio of mean functional $Alpha_1$-PI trough level over weeks 7-12 (six infusions) for the Prolastin® group to the equivalent mean value for the same treatment group after their crossover to GLASSIA (i.e. Weeks 13 to 24).

Inclusion and Exclusion criteria

Inclusion criteria of the study were:

- Subjects at least 18 years of age who signed informed consent;
- "At-risk" alleles associated with serum $Alpha_1$-PI < 11 μM including null alleles and deficiency alleles. This must have been documented in the subject's history or laboratory tests performed at screening;
- Evidence of lung disease related to AAT deficiency, identified by at least one of the following:
    - FEV_1 < 80% predicted (post bronchodilator); ***or***
    - Loss of lung function over a one year period of greater than 35 mL in FEV_1; ***or***
    - HRCT evidence of pulmonary emphysema;
- For actively treated subjects, agreement to not receive any exogenous $Alpha_1$-PI product (i.e. washout) for five weeks prior to first study infusion;
- Subjects on the BAL, bronchial brushing/biopsy group had to be on inhaled corticosteroids at a stable dose two weeks prior the first bronchoscopy and throughout the dosing period up the final bronchoscopy.

Some of the study exclusion criteria included:

- Laboratory evidence of severe IgA deficiency (from medical history or by IgA testing at screening of at least 20% of lower range);
- Acute respiratory tract infection or COPD exacerbation which required antibiotic and/or systemic steroid treatment within the past 6 weeks. These patients could be re-evaluated for enrollment six weeks after an exacerbation.

The exclusion criteria for subjects entering into the BAL and bronchial biopsy/brushing included:

- FEV1 < 45% predicted (post-BD);
- Inability to undergo bronchoscopy;
- Allergy to lidocaine;
- Exacerbation of COPD in the previous six weeks.

Statistical analysis plan (SAP)

As noted above, the primary outcome variable was the trough circulating level of antigenic and/or functional $Alpha_1$-PI (an average of week 7-12 results). Since this was a non-inferiority trial, the goal was to show that the mean trough level with GLASSIA during this period was not lower than 3 μM below that of the control group. The comparison of the two treatment groups was based on the lower limit of a two-sided 95% confidence interval (CI) for the difference in means (GLASSIA minus Prolastin®).
If the lower bound of this $Alpha_1$-PI interval was greater than -3 μM, then the goal of demonstrating non-inferiority was considered to have been achieved. The CI on which the test was based was derived from a two-group Wilcoxon rank-sum test, stratified by center. This test was inverted to provide the 95% CI used to assess non-inferiority.

Additionally, the sponsor proposed to estimate the 95% exact-binomial lower confidence bounds for the proportion of subjects in each treatment group for whom the mean trough

antigenic Alpha$_1$-PI for weeks 7-12 was in excess of 11 μM. It was expected that the observed proportion of subjects in the GLASSIA cohort for whom this goal was achieved would exceed 80%, although this was not part of hypothesis testing for any of the study endpoints.

The primary endpoint analysis was performed on the Intent-to-Treat (ITT), Pharmacokinetic Evaluable (PE), and PP populations. The ITT population was considered for analysis by the FDA.

Results

Disposition of subjects

The number of subjects randomized was 52 and the number dosed with test or control product was 50. Enrollment was balanced by randomized treatment group across centers with a ~ 2:1 ratio of subjects randomized to GLASSIA compared to Prolastin® at each site. Two subjects had withdrawn consent and were randomized in error but not dosed. Thirty-three were administered GLASSIA and 17 were administered Prolastin®. Two subjects were withdrawn early due to adverse events (AEs), i.e., urticaria in the GLASSIA group and pulmonary emboli in the Prolastin® group. The early withdrawal in the Prolastin® group occurred prior to week 12 (end of randomized, double-blind period). Hence the total number of subjects who completed the 28-week study was 48. The median age was 55 years (range 42 to 74 years). There was an approximately equal distribution of males and females, and all but one of the subjects was of Caucasian descent. Two subjects had phenotype MZ, two had SZ and the rest of the enrolled subjects had ZZ phenotypes.

Thirteen of the planned 15 subjects underwent BAL sampling. Of these only 11 had evaluable samples, i.e., 9 in the GLASSIA group and 2 in the Prolastin® group.

Table 9. Clinical Study Sites

Study Site Number	Study Site	Location	Number of Subjects
01	National Jewish Medical and Research Center	Denver, Colorado	17
02	University of Texas Health Center at Tyler	Tyler, Texas	12
03	University of Florida School of Medicine	Gainesville, Florida	21

Efficacy:

The primary endpoint was met for both antigenic and functional serum Alpha$_1$-PI levels in the sponsor's analysis. Mean antigenic and functional Alpha$_1$-PI levels in the modified ITT population (n = 49) were greater for GLASSIA than for Prolastin® in the sponsor's analysis. Mean baseline antigenic Alpha$_1$-PI levels were 4.8 μM in the GLASSIA group and 4.3 μM in the Prolastin® group. Mean baseline functional Alpha$_1$-PI levels were 3.1 μM in the GLASSIA group and 2.3 μM in the Prolastin® group.

In the sponsor's original analysis, the median antigenic Alpha$_1$-PI values for weeks 7-12 were 14.5 μM in the GLASSIA group (range: 11.6 to 18.5 μM), and 12.8 μM in the Prolastin® group (range: 10.4 – 19.2 μM). The FDA biostatistician confirmed the sponsor's analysis. The sponsor performed an additional analysis of the primary endpoint after eliminating outlier data from one subject at one visit where it appeared from the results that the baseline and post-dose sample had been reversed. The results were similar and still met the *a priori* criteria of non-inferiority of the Kamada product to the Prolastin® control. The median functional Alpha$_1$-PI values were lower than the antigenic values in both groups and were 11.8 μM in the GLASSIA group (range: 8.2 to 16.9 μM) and 11.4 μM in the Prolastin® group (range: 7.7 to 18.0 μM). The lower bound of the confidence interval of the difference in means (GLASSIA minus Prolastin®) was greater than -3 μM for both antigenic and functional Alpha$_1$-PI levels, thereby demonstrating the non-inferiority of GLASSIA to Prolastin®.

The SAP outlined *apriori* assumed that at least 80% of subjects would have steady-state trough levels of Alpha$_1$-PI levels > 11 μM. The proportion of subjects with mean trough antigenic Alpha$_1$-PI levels exceeding 11 μM during weeks 7 to 12 was 100% for subjects in the GLASSIA group and 81.3% for subjects in the Prolastin® group. The proportion of subjects with mean functional Alpha$_1$-PI levels >11 μM was 66.7% in the GLASSIA group and 62.5% in the Prolastin® group. Thus according to the SAP, the above criterion for success was met for antigenic levels. The proportion of subjects with functional levels >11 μM were lower than expected for both the test and the comparator licensed product, Prolastin. The clinical significance of having functional Alpha$_1$-PI levels modestly below 11 μM is unknown.

BAL sub-study

The BAL subset contained fewer subjects than anticipated; results were available for only 7 subjects in the GLASSIA group and 2 subjects in the Prolastin® group. Due to a technical error, results of functional Alpha$_1$-PI in the ELF were not obtained. Increases from baseline in antigenic Alpha$_1$-PI levels in the ELF at week 10-12 were observed in both treatment groups, and an increase from baseline in Alpha$_1$-PI-NE complexes (an indication of functional Alpha$_1$-PI levels) was evident in the left- and right-lung samples of the GLASSIA group at week 10-12. This result suggests, but does not prove, that treatment with GLASSIA increased the functional Alpha$_1$-PI level in the target organ (lung) and was able to complex with NE and reduce its free concentration available to damage lung tissue.

Overall Safety:

There were no deaths reported in the pivotal (or the single dose PK) study.

A total of 65 subjects have received treatment with intravenous GLASSIA in two clinical studies, both performed in the US. Three subjects participated in both studies. However, because of the large temporal difference between studies (> 5 years) and major difference in study designs, each study was analyzed separately without excluding these three subjects who participated in both trials from either study analysis. Thus, safety and

efficacy of GLASSIA are reported on all 18 subjects in a Phase I study and all 50 subjects who received GLASSIA in a Phase II/III study, for a total of 68 subjects, representing 65 unique subjects.

In an open label, Phase I non-parallel, dose-escalation study, 18 subjects received a single infusion of GLASSIA at dosages of 30, 60 or 120 mg/kg.

In a randomized, Phase II/III double-blind, active-control study, 50 subjects were scheduled to receive weekly infusions of GLASSIA or the comparator Alpha1-PI product, Prolastin, at a dosage of 60 mg/kg for a total of 12 doses after which all subjects remaining in the study were treated for another 12 weeks with GLASSIA only. Overall, 17 subjects received 12 doses and 21 subjects received 24 doses of GLASSIA during the study. Eleven subjects received either 22 or 23 doses and one subject did not receive any treatment with GLASSIA during the last 12 weeks of the study.

For the pivotal study (both study periods), 49 of 50 subjects reported at least one AE (32/33 in the GLASSIA group and 17/17 in the Prolastin® group).

In study period 1, six subjects in each randomization group had at least one drug-related AE (corresponding to an incidence of 18% in the GLASSIA group and 35% in the Prolastin® group).

The most commonly reported AEs were cough, COPD exacerbation, and upper-respiratory tract infection (URI) / nasopharyngitis.

Two subjects were withdrawn prematurely from the study due to AEs (urticaria in the GLASSIA group and pulmonary emboli in the Prolastin® group).

- Subject ---(b)(6)--- (GLASSIA) discontinued following the week 12 infusion due to urticaria.
- Subject ---(b)(6)--- (Prolastin®) discontinued following one dose of study medication due to a diagnosis of acute and chronic pulmonary emboli (PE) diagnosed the day following the initial dose of study product.

The table below compares the adverse events reported during the initial 12 weeks (double-blind portion) of the Phase II/III study occurring in all subjects treated with GLASSIA with events in the concurrent Prolastin control group.

Table 10: Number of Subjects/Infusions/Adverse Events Occurring during the First 12 Weeks of Treatment

	GLASSIA	Prolastin
No. of subjects treated	33	17
No. of infusions	393	190
No. of subjects with adverse events regardless of causality (%)	27 (82%)	16 (94%)
No. of subjects with related adverse events according to investigator causality assessment (%)	6 (18%)	6 (35%)

No. of subjects with related serious adverse events	0	0
No. of subjects experiencing an adverse event within 24 hours of infusion, regardless of causality (%)	19 (58%)	14 (82%)
No. of adverse events regardless of causality (mean rate of adverse events per infusion)	70 (0.18)	46 (0.24)
No. of adverse events, regardless of causality, occurring within 24 hours of infusion (% of all adverse events)	35 (50%)	30 (65%)
No. of infusions associated with adverse events occurring within 24 hours of infusion, regardless of causality (% of infusions)	32 (8%)	28 (15%)

Table11. Adverse Events Occurring in > 5% of Subjects during the First 12 Weeks of Treatment *(Irrespective of Investigator Causality Assessment*)

	GLASSIA No. of subjects: 33	Prolastin No. of subjects: 17
Adverse Event (AE)	No. of subjects with AE (percentage of all subjects)	No. of subjects with AE (percentage of all subjects)
Cough	5 (15%)	4 (24%)
Upper respiratory tract infection	4 (12%)	0 (0%)
Headache	3 (9%)	4 (24%)
COPD Exacerbation	4 (12%)	5 (29%)

Table12. Adverse Event Frequency as a % of all Infusions (> 0.5%) *(Irrespective of Investigator Causality Assessment*)

	GLASSIA[a] No. of infusions: 960	Prolastin[b] No. of infusions: 190
Adverse Event (AE)	No. of AEs (percentage of all infusions)	No. of AEs (percentage of all infusions)
Upper respiratory tract infection	14 (1.5%)	0 (0.0%)
Headache	8 (0.8%)	4 (2.1%)
Nasopharyngitis	8 (0.8%)	0 (0.0%)
Cough	7 (0.7%)	4 (2.1%)
Pharyngolaryngeal pain	7 (0.7%)	1 (0.5%)
COPD	6 (0.6%)	2 (1.1%)

[a]Throughout entire 24-week double-blind plus open-label trial period

[b] Throughout initial 12-week double-blind period

Table13.Adverse Events Occurring in > 5% of Subjects during or Within 72 Hours of the End of an Infusion, in the First 12 Weeks of Treatment *(Irrespective of Investigator Causality Assessment*)

	GLASSIA No. of subjects: 33	Prolastin No. of subjects: 17
Adverse Event (AE)	No. of subjects with AE (percentage of all subjects)	No. of subjects with AE (percentage of all subjects)
Cough	3 (9%)	4 (24%)
Upper respiratory tract infection	3 (9%)	0 (0%)
Headache	3 (9%)	3 (18%)
Sinusitis	2 (6%)	1 (6%)
Chest discomfort	2 (6%)	0 (0%)
Dizziness	2 (6%)	0 (0%)
Hepatic enzyme increased	2 (6%)	0 (0%)

During the 12-week double blind portion of the Phase II/III trial, 4 subjects (12%) had a total of 7 exacerbations of chronic obstructive pulmonary disease (COPD) during GLASSIA treatment and 5 subjects (29%) had a total of 6 exacerbations of COPD during Prolastin treatment. Seventeen additional exacerbations in 14 subjects (28%) occurred during the 12-week open-label treatment period with GLASSIA. The overall rate of pulmonary exacerbations during treatment with either product was 1.3 exacerbations per subject per year.

Most adverse events were mild to moderate in severity, although two episodes of headache and one episode of cholangitis were severe. Two subjects experienced treatment emergent serious adverse events (cholangitis and infective exacerbation of COPD), both of which were considered by the investigator to be unrelated to treatment with GLASSIA.

Out of 68 subjects treated with GLASSIA during clinical studies, 14 (21%) experienced one or more adverse events that were assessed by the investigator as possibly or probably related to treatment (**Error! Reference source not found.**).

A total of 3 subjects (approximately 5%) receiving GLASSIA reported urticaria, irrespective of the investigator's opinion of cause.

Table14. Adverse Reactions Assessed by Investigator as Possibly or Probably Related to Treatment with GLASSIA (No. of subjects: 68*: combined data from single-dose PK study and 24-week clinical study)

Adverse Event (AE)	No. of subjects experiencing a related event according to investigator causality assessment (percentage of all subjects)
Any event	14 (21%)
Headache	4 (6%)

Dizziness	2 (3%)
Dysgeusia, Influenza-like illness, Lethargy, Pyrexia, Decreased platelet count, Joint swelling, Erythema marginatum, Pruritis, Rash, Urticaria, Hypertension.	1 (1.5%)

*Three (3) subjects participated in both the single-dose PK study and the 24-week trial, such that 65 unique subjects were administered GLASSIA.

Safety Laboratory Studies

Levels of C3 and C4 complement remained relatively stable in both groups, although for both groups their group means trended down during the trial.

No abnormal chemistry values were reported to be related to study drug. Most abnormal aminotransferase values were considered to be likely due to $Alpha_1$-PI related liver disease. No subject had treatment-emergent aminotransferase abnormalities exceeding 2x the upper limit of normal.

Vital signs

Three GLASSIA and four Prolastin® subjects had vital-sign changes deemed clinically significant, of which 2 were considered possibly related to study drug: mild/intermediate hypertension, unresolved at study termination in one GLASSIA subject, and one mild/intermediate hypertension, resolved at study termination in one Prolastin® subject. No subject was reported to have clinically significant hypotension.

Pulmonary function tests

As expected for such a short study, group mean pulmonary function tests (PFTs) were not found to be meaningfully changed over the study.

Discussion of key issues identified during the clinical review

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c. The sponsor has agreed to revise the draft package insert (PI) to lower the maximum recommended infusion rate by half to 0.04 mL/kg body weight per minute. Some subjects at all 3 sites in the pivotal study were infused at this lower rate. Had they been infused at 0.08 mL/kg/min, one cannot exclude the possibility they might have experienced more frequent and/or more severe adverse events. On this basis, the maximum recommended infusion rate recommended in the package insert was lowered to 0.04 mL/kg body weight per minute.

2. Consistent finding of visible protein aggregates in the liquid product with possible clinical implications. The concentration of these aggregates appears to increase during the storage period. The FDA assessment of the above findings are as follows:
    a. Visible particulates have been observed in licensed $Alpha_1$-PI products and are mentioned in the products' package inserts. Preliminary data suggest that approximately ----(b)(4)--- visible protein aggregates are removed by a single 5 μm filtration. The package insert recommends use of one 5 μm filter in pooling vials, and a 2^{nd} in-line 5 μm filter during administration. According to studies performed by the sponsor, the potency of the product was unchanged after filtration.
    b. No worrisome safety signals were detected in clinical studies. Three instances of urticaria (~5% incidence, not all necessarily product-related, but urticaria led to premature discontinuation of GLASSIA subject ---(b)(6)--- following the week 12 infusion: urticaria was not observed among 17 Prolastin® control subjects), 1 report of erythema marginatum, and additional rashes were noted. The relationship of these AEs to protein aggregates is uncertain.
    c. Purification steps in the manufacture of the product are similar to those used in the manufacture of other licensed $Alpha_1$-PI products.

3. Clinical immunogenicity data were not submitted by the sponsor. The FDA assessment of this deficiency is as follows:
    a. Immunogenicity is not a known problem with the current commercially available $Alpha_1$-PI products, which have similar methods of manufacture to that of GLASSIA. In addition, the preclinical data did not detect neoantigens; and the trough levels (antigenic and functional) did not decrease during treatment from week 7-12. In general, immunogenicity is not a primary concern with a plasma-derived product not subjected to harsh purification/manufacturing methods.

4. Viral NAT testing was not performed for the pivotal study. Only serological testing was conducted. The schedule of testing for serological markers of viral transmission used in the pivotal study was less than that recommended by CBER during the pre-IND meeting for this product. The pivotal phase 2/3 study had only 4 weeks post-end-of-dosing viral follow-up instead of the recommended 6 months follow-up testing for HCV and HIV, unless each subject received only a single lot of product. While the protocol required that each subject receive only one lot, approximately 4 subjects in

the trial received two different lots each. The FDA assessment of the above is as follows:

a. No viral seroconversions for HIV-1, HIV-2, HBV, or HCV were observed during the 24-week pivotal trial or in the single dose PK study. Viral PCR was performed in the single dose PK study and did not show evidence of viral transmission.
b. The plasma source material used for this product is collected and tested in the US for viral markers according to FDA requirements. In addition, GLASSIA undergoes two viral clearance steps, S/D treatment, and nanofiltration.
c. The sponsor has committed to conducting and reporting the results of a post marketing requirement (PMR) clinical trial which will include both serological and NAT testing for adventitious viruses according to current recommendations.

5. "Due to an irreversible technical error accidentally made by the lab technician at the time of BAL sample processing, no results were obtained for functional $Alpha_1$-PI in the BAL samples." In addition, BAL samples were obtained from only 2 of 5 planned Prolastin® control subjects. FDA assessment of the above findings are:
   a. Available data from the completed BAL sub-study demonstrate an appropriate rise from baseline in antigenic $Alpha_1$-PI levels in ELF.
   b. Because functional ELF $Alpha_1$-PI levels are considered by FDA to be an important analyte, the sponsor has committed to conduct a Phase IV PMC BAL study with measurement of appropriate analytes, including antigenic and functional ELF $Alpha_1$-PI levels.
   c. From a regulatory standpoint, requiring a Post Market Commitment (PMC) BAL study is consistent with the situation with Aralast, where the sponsor Baxter conducted a "remedial" BAL study as a Phase IV PMC because there were problems with the BAL sub-study submitted in the Aralast BLA.

6. Based on AEs considered by the investigator to be at least possibly product-related, GLASSIA may be more allergenic than Prolastin®. Urticaria, rash, joint swelling, and thrombocytopenia were reported (1 case each) only in the GLASSIA arm**.**
   a. This could easily reflect the small size of the study and the 2:1 randomization rather than a real difference between the safety profile of the two tested products.
   b. Additional data regarding AEs will be obtained in the sponsor's Post Market Requirement (PMR) study and in the two-stage investigation using clinically meaningful endpoints (HRCT). Should these Phase IV studies indicate that hypersensitivity reactions are more frequent or severe than expected, the labeling will be updated accordingly and other steps may be taken as appropriate.

7. Only 2/3 of patients achieved functional trough levels of serum functional $Alpha_1$-PI of $\geq$ 11 μM (however 100% of patients receiving the GLASSIA product achieved trough levels of antigenic $Alpha_1$-PI $\geq$ 11μM). This finding raises the question of

optimal dosing. Like other licensed manufacturers of Alpha$_1$-PI, Kamada will conduct a post-marketing trial (see below) to answer this question.

Conclusion:
Based on review of the safety and efficacy data from the PK and pivotal clinical trials, the Clinical Review Branch of the Division of Hematology recommends licensure of the product for the indication sought.

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b) Pediatrics
The Pediatrics Review Committee waived the pediatric study required for this application under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), because necessary studies are impossible or highly impracticable. $Alpha_1$-PI deficiency is not known to cause emphysema in pediatric individuals.

c) Other Special Populations
No other special populations are under consideration for the use of this product.

8. Advisory Committee Meeting

There were no issues related to this product that prompted the need for discussion by the Blood Products Advisory Committee.

9. Other Relevant Regulatory Issues

There were no other regulatory issues raised during the review of this BLA.

10. Labeling

Proprietary name was reviewed by the Advertising and Promotional Labeling Branch from a promotional and safety perspective. The first proposed proprietary name, Apikam, submitted on October 2, 2009 was found unacceptable on December 11, 2009. The second proposed name, GLASSIA, submitted on December 30, 2009, was found acceptable on March 3, 2010 and again on April 28, 2010 after re-evaluation with respect to the recently approved products.

Physician labeling: The final GLASSIA Package Insert is PLR-compliant.

Package Insert: Kamada provided a draft package insert with the original BLA submission on May 29, 2009. Kamada resubmitted the final version of the PI with incorporation of FDA comments on July 1, 2010.

Carton and immediate container label: Kamada provided language for labeling with the original BLA submission on May 29, 2009. Kamada submitted the final version of carton and container label with incorporation of FDA comments on June 24, 2010.

11. Recommendations and Risk/ Benefit Assessment

a) Recommended Regulatory Action
The review committee recommends the approval of this BLA.

b) Risk/ Benefit Assessment
Safety and surrogate efficacy endpoint data were found sufficient to make a favorable decision concerning potential benefit:risk balance.

c) Recommendation for Post-marketing Activities

POSTMARKETING REQUIREMENTS

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify an unexpected serious risk from adverse events relating to the presence of visible protein aggregates in the product.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA has not yet been established and is not sufficient to capture and assess this/these serious risk(s).

A clinical trial to further assess these potential risks is needed because the presence of visible protein aggregates in the product has been a consistent finding. The completed clinical studies, which employed filtration of the product when pooling vial contents prior to administration, are considered too small to reliably assess the potential for adverse events due to the presence of protein aggregates.

We have determined that only a clinical trial (rather than a nonclinical or observational study) will be required to identify an unexpected serious risk of adverse events relating to the presence of protein aggregates in the product.

Therefore, based on appropriate scientific data, we have determined that Kamada is required to conduct the following clinical trial:

1. A Phase IV, double-blind, controlled multicenter study exploring potential adverse events associated with protein aggregates. This study will evaluate the safety of the product following multiple repeat exposures over a period of at least 6 months of regular weekly administration. It will include design features that will permit the detection of potential adverse events (AEs) due to the presence of protein aggregates in the product. The study will also include viral nucleic acid testing (NAT) and testing for anti-$Alpha_1$-PI antibodies using an appropriately validated assay. We note that the planned study will also explore epithelial lining fluid analytes and potential adverse events associated with immunogenicity, and viral safety following the use of Kamada's Intravenous, Human $Alpha_1$-PI (GLASSIA) and another commercial $Alpha_1$-PI, in $Alpha_1$-Antitrypsin [$Alpha_1$-PI] Deficient Patients.

   We acknowledge the timetable you submitted on May 27, 2010, which states that you will conduct this clinical trial according to the following schedule:

   Final Protocol Submission: March 1, 2011
   Trial initiation Date: September 5, 2011
   Trial Completion Date: March 20, 2013
   Final Report Submission: March 18, 2014

POSTMARKETING COMMITMENTS

We acknowledge your written commitments as described in your letter of May 27, 2010, as outlined below:

Postmarketing Studies subject to reporting requirements of 21 CFR 601.70

2. Submission, as a supplement to the BLA STN BL 125325, of the final report of the results of anti-$Alpha_1$-PI antibody testing from all stored clinical samples from

clinical trial API-002, including all raw data. You have committed to submit as a supplement to the BLA the final anti-Alpha$_1$-PI antibody assay validation report and obtain FDA's concurrence with the assay procedure prior to running stored clinical samples from the clinical trial.

Final protocol submission date: September 18, 2007
Study/trial completion date: March 27, 2008
Submission of Assay Validation Report: November 1, 2010
Final Report Submission date: February 1, 2011

3. A Phase IV, open-label or double-blind, multicenter study investigating Epithelial Lining Fluid of Alpha$_1$-Antitrypsin Deficient Patients for Alpha$_1$-PI and analytes levels following augmentation therapy with GLASSIA.

   You have elected to make this PMC clinical trial a substudy of the PMR described above.

   The primary endpoint for this study will be both antigenic and functional Alpha$_1$-PI levels in Epithelial Lining Fluid after 10-12 weeks of treatment.

   Final protocol submission date: March 1, 2011
   Trial initiation Date: September 5, 2011
   Study/trial completion date: March 20, 2013
   Final Report Submission date: March 18, 2014

4. Conducting a post-marketing clinical program for GLASSIA which will be comprised of two clinical trials as described below:

   a. Trial 1: A Phase IV, Randomized, Placebo-Controlled, Double-Blind, Multicenter Study Investigating the Safety and Efficacy of GLASSIA vs. Placebo and another (Higher) dose of GLASSIA I.V. by Weekly Administration in Alpha$_1$-Antitrypsin Deficient Patients with emphysema.

      This study will have a primary endpoint consisting of change in lung density assessed by serial quantitative computerized tomography of the lungs. Additional endpoints will include incidence, duration, and severity of pulmonary exacerbations, serial pulmonary function testing, serial DL_{CO} measurements, and mortality.

      Final protocol submission date: March 1, 2011
      Trial initiation Date: September 3, 2012
      Study/trial completion date: March 3, 2017
      Final Report Submission date: March 5, 2018

   b. Trial 2: Adequately-powered study of clinically meaningful endpoint. Based on the results of Trial 1 above and the available scientific data,

Kamada will design and conduct a fully statistically powered efficacy study for augmentation therapy with Alpha-1-Proteinase Inhibitor (Human).

The study will be randomized and double-blind.

Final protocol submission date: January 8, 2018
Trial initiation Date: January 7, 2019
Study/trial completion date: July 8, 2024
Final Report Submission date: July 7, 2025

Postmarketing Studies not subject to reporting requirements of 21 CFR 601.70

We acknowledge your written commitments as described in your letters of June 20, 2010 and June 22, 2010 as outlined below:

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