

**MEDICAL FINAL REVIEW MEMORANDUM OF ORIGINAL BLA**

**[See also “MEDICAL FINAL REVIEW MEMORANDUM OF ORIGINAL BLA – REVISION #2 [Revision to 03 March 2010 memo]”]**

**TO: FILE STN: 125325/0, IND -(b)(4)-**

**SPONSOR: KAMADA**

**PRODUCT: ALPHA-1 PROTEINASE INHIBITOR  
(HUMAN) INTRAVENOUS [LIQUID];  
GLASSIA**

**INDICATION: CHRONIC AUGMENTATION AND  
MAINTENANCE THERAPY IN  
INDIVIDUALS WITH CONGENITAL  
DEFICIENCY OF ALPHA-1 PROTEINASE  
INHIBITOR AND CLINICAL EVIDENCE  
OF EMPHYSEMA [Wording as presented in  
original BLA prior to amendment of draft  
labeling]**

**FROM: L. ROSS PIERCE, M.D., HFM-392**

**THROUGH: NISHA JAIN, M.D., CHIEF, CRB, HFM-392**

**RPM: Cherie Ward-Peralta**

**RECEIPT DATE: 29 May 2009**

**ADD: July 1, 2010**

---

**RECOMMENDATION:**

The review of the safety and efficacy data from the single dose, dose-ranging PK trial and the 24-week multidose randomized Prolastin-controlled, parallel arm pivotal clinical trial supports a favorable conclusion to recommend licensure of the product for the indication sought.

## EXECUTIVE SUMMARY:

Kamada Alpha<sub>1</sub>-Proteinase Inhibitor (A1-PI IV, Alpha<sub>1</sub>-PI, API, alpha<sub>1</sub>-antitrypsin, AAT, Glassia) was concluded to have demonstrated non-inferiority to the licensed Prolastin Alpha<sub>1</sub>-PI comparator in a single 50 subject randomized (2:1 test: control), double-blind, parallel, active control partial crossover clinical trial (API-002) conducted at 2 centers in the U.S. Steady-state blood antigenic and functional A1-PI levels were notably lower for both Kamada A1-PI and Prolastin control subjects compared to results seen in older studies conducted by other sponsors, although Talecris also found lower functional A1-PI levels with both Prolastin and Prolastin C than had been reported in prior studies sponsored by Bayer (now Talecris) and Alpha Therapeutics (now Baxter). The clinical significance of the reduced levels of functional A1-PI in the Kamada and recent Talecris studies in comparison to the findings in prior studies is unknown. Current class labeling and the draft Kamada A1-PI package insert adequately discuss the limitations of available clinical data with respect to understanding the clinically effective dose and/or blood level of A1-PI during A1-PI augmentation therapy in patients with emphysema due to congenital A1-PI deficiency.

The pivotal trial API-002 was a 24 week, 2 period, partial cross-over study in which subjects were randomized 2:1 to an initial 12 week double-blind treatment period with weekly infusions of 60 mg/kg/week of the test product or Prolastin<sup>®</sup> as a concurrent control. All Prolastin<sup>®</sup> subjects were switched to the Kamada product during the 2<sup>nd</sup> half of the study. While the efficacy endpoint of the study was met in terms of demonstrating non-inferiority to Prolastin<sup>®</sup> in serum antigenic “and/or” functional A1-PI levels, many subjects on both products had low serum steady-state ANEC levels below the historical 11 microM “threshold.” However, as reviewed during the 2009 Blood Products Advisory Committee (BPAC) meeting, there is no credible epidemiologic evidence that the latter historically-cited cutpoint is necessarily clinically meaningful. Lung epithelial lining fluid (ELF) Antigenic A1-PI values rose from baseline after 10-12 weeks dosing with Kamada A1-PI (n = 7) and after dosing with Prolastin<sup>®</sup> (n = 2) in a bronchoalveolar lavage (BAL) sub-study. Samples for assaying Anti-neutrophil elastase capacity (ANEC, a measure of functional A1-PI), required by protocol, in the BAL sub-study were lost in a lab accident. The sponsor has agreed to conduct another BAL study in phase IV as well as a 2-

stage investigation of 1 or more clinically meaningful endpoints, as is required of all sponsors of A1-PI products.

Kamada A1-PI IV was also studied in a single dose PK study (API-001) in 18 (planned) subjects, reviewed separately by Dr. Iftekhar. I reviewed the safety data from the single dose, 3 dose level (30, 60, and 120 mg/kg) study and found no safety signals of concern.

CBER's current thinking is that this is the last A1-PI product for which FDA will accept surrogate endpoints of serum A1-PI levels. Following the BPAC recommendation earlier this year, it is expected that sponsors of new A1-PI products will be required to establish efficacy using clinically meaningful endpoint(s) pre-licensure in the future.

No significant safety signals have been detected in the clinical studies, although the test product was associated with more frequent rashes than Prolastin and 3 cases (5% incidence) of urticaria were observed for the test product, of which 1 was considered by the investigator to be related to Kamada API administration. The CMC reviewer has concerns regarding protein aggregates in the product and it cannot presently be excluded that this could potentially prove to be a safety concern as larger numbers of individuals are exposed to the product post-licensure. The sponsor as agreed to conduct a post-marketing requirement (PMR) study to help further evaluate this potential safety concern.

The FDA biostatistician validated the sponsor's analyses for the primary endpoint.

Notwithstanding clinical data quality issues evident from 3 BioResearch Monitoring (BiMo) inspections summarized below, the available data from the multidose pivotal trial and the single dose PK study are judged adequate to support a conclusion of a favorable risk: benefit balance suggesting promise for efficacy and adequate safety for licensure.

#### **REVIEW RESPONSIBILITIES:**

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

**PRODUCT:**

Kamada A1-PI is purified from -----(b)(4)----- provided by the -----(b)(4)-----

Kamada A1-PI undergoes two dedicated viral reduction steps: Solvent Detergent treatment and Nanofiltration.

GLASSIA is the first liquid Alpha<sub>1</sub>-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 °C for up to 24 months

**TRADE NAME:**

The trade name GLASSIA was found to be acceptable.

**ORPHAN DRUG STATUS:** N/A

**PREA (Pediatric Research and Equity Act) STATUS and PeRC RECOMMENDATION**

This submission triggers PREA as GLASSIA will have a new indication, dosage and route of administration. The sponsor has requested a full waiver of pediatric studies and a waiver was granted because A1-PI deficient patients do not manifest emphysema during the pediatric years. The PeRC agreed with the Division's decision to grant a waiver.

**FINANCIAL DISCLOSURE:**

The sponsor has included FDA Form 3454, which states that no investigator had a reportable financial interest in the outcome of the study and that the sponsor entered into no such agreements with the sponsor. During the BiMo inspection, -----Information withheld per the privacy act-----

----- I  
did not conclude that this necessarily compromised the data from ---  
Information withheld per the privacy act-- site of the pivotal study.

## BACKGROUND

Congenital Alpha<sub>1</sub>-Antitrypsin Deficiency (AATD) is an autosomal co-dominant condition characterized by a reduction in serum AAT levels and an increased risk of emphysema and, to a lesser extent, liver disease. Among AAT deficient patients with emphysema, a significant minority also have a reversible component to their airways obstruction indicative of a hypersensitivity or asthmatic component. Smokers with severe AAT deficiency, may develop emphysema by the 3<sup>rd</sup> to 4<sup>th</sup> decade, whereas non-smokers may develop emphysema in the 5<sup>th</sup> to 6<sup>th</sup> decades.

The AAT Z mutation involves a single amino acid substitution (glutamine for lysine) at position 342, resulting in abnormal folding and polymerization of the molecule within hepatocytes, the main site of synthesis of AAT in the human body. The intracellular polymerization of Z type AAT interferes with AAT's normal secretion into the circulation, resulting in reduced serum AAT levels. The S allele is a single amino acid substitution (valine for glutamine) at position 264, conferring instability to the protein and accelerated breakdown outside the hepatocyte.

AAT is one of several anti-proteases present in the lungs and one of its principal targets is the irreversible inhibition of neutrophil elastase (NE). There are many other proteases in the lungs but NE appears to be the most important. Normal lungs contain only small amounts of neutrophil elastase, but the concentration increases during infections. Among persons with severe AAT deficiency, there are increased levels of NE in the lungs even during quiescent periods and in those severely AAT deficient levels with normal pulmonary function as judged by spirometry (FEV<sub>1</sub>).

The diagnosis of AAT deficiency is established by detection of low serum levels of AAT and isoelectric focusing of serum. The normal AAT phenotype is designated PI\*MM. The most common deficiency alleles are Z and S. While over 100 allelic variants have been described, the most prevalent phenotype among AAT deficient patients with severe emphysema is PI\*ZZ. The estimated number of individuals in the U.S. with severe AAT deficiencies is ~60,000 – 120,000, but the vast majority of these individuals are undiagnosed. Physicians in the U.S. generally do not routinely screen for AAT deficiency when they have diagnosed an individual with chronic obstructive pulmonary disease (COPD).

The table shows example ranges for several AAT phenotypes:

**Serum AAT Concentrations by Phenotype**

Phenotype	Prevalence	Risk of Emphysema	Serum A1-PI Levels MicroM
<b>PI*MM (normal)</b>		<b>Low</b>	<b>20-53</b>
PI*ZZ <sup>2</sup>	1/2500- 1/5000	High	2 -7
PI*SZ <sup>2</sup>		Intermediate <sup>1</sup>	9 – 23
PI*MZ		Low, but > normal	17 – 33
PI*MM		Normal (Low)	20 - 53

<sup>1</sup> increased risk of emphysema in smokers.

<sup>2</sup> An unknown but substantial proportion of Pi\*ZZ and PI\*SZ patients do not develop clinically manifest emphysema during their lifetimes

Approximately 80% of PI\*ZZ patients followed in a large U.S. registry study were current or former smokers. PI\*SZ patients appear to be at increased risk of emphysema regardless of whether their native serum AAT levels are more or less than the historically postulated 11 microM therapeutic threshold. It is controversial whether PI\*MZ heterozygotes, (17 to 33 microM), have an increased risk of emphysema. One study found a statistically significant increased risk of airways obstruction among 12 of

193 (6%) of MZ patients compared to zero out of 73 MM control patients ( $p = 0.04$ ).

### **Management of patients with AA deficiency**

In addition to intravenous augmentation therapy with exogenous A<sub>1</sub>-PI (recommendation not based on randomized clinical trials), the management of patients with established airflow obstruction includes strong advice to avoid smoking, the use of inhaled bronchodilators, influenza and pneumococcal vaccination, supplemental oxygen when indicated, pulmonary rehabilitation for individuals with functional impairment, management of acute exacerbations of COPD including, as needed, brief courses of systemic corticosteroids, early antibiotic therapy for purulent exacerbations, and ventilatory support as needed. Selected individuals with severe functional impairment and airflow obstruction are considered for lung transplantation.

## **OVERVIEW OF THE CLINICAL STUDIES**

**Study API 001:** The pharmacokinetics and safety of an Alpha -1 proteinase inhibitor (ARC-API) in subjects with congenital API deficiencies: A dose-escalation clinical trial (Phase 1). N = 18 (See also Clinical Pharmacology review memo.)

This study was an open-label single dose escalation safety and PK study testing 30, 60, and 120 mg/kg IV of the test product in subjects with congenital anti-alpha<sub>1</sub>-antitrypsin (AAT, alpha<sub>1</sub>-PI, A<sub>1</sub>-PI) deficiency.

### **Sites**

**Robert A. Sandhaus**, MD, PhD, FCCP, Clinical Professor of Medicine, Director, Alpha1-Antitrypsin Deficiency Program, National Jewish Medical and Research Center, 1400 Jackson Street, Denver, CO 80206

**James. M. Stocks**, MD, Professor of Medicine, The University of Texas Health Center at Tyler, Department of Medical Specialties, 11937 US Highway 271, Tyler, TX 75708-3154

**Mark Brantly, MD**, Professor of Medicine, Molecular Genetics and Microbiology, Alpha One Foundation Research Professor, University of Florida School of Medicine, 1600 SW Archer Road, Room 452 Medical Science Building, Gainesville, FL 32610225

**Gerard Turino, MD**, Senior Professor of Medicine, St. Luke's/Roosevelt Hospital, Department of Medicine, 1000 Tenth Avenue, Suite 3A55, New York, NY 10019

**Study API 002:** Phase 2/3 Randomized Double-Blind Comparison of Alpha-1 Proteinase Inhibitor (Kamada-API) with Prolastin® in Individuals with Alpha-1 Antitrypsin Deficiency (Phase 2-3) N = 50

This study was a 2:1 randomized (test to Prolastin control) 2-arm, randomized, active controlled, double-masked multicenter PK non-inferiority study with a partial crossover. Test and control products were administered IV at 60 mg/kg weekly to subjects with congenital AAT deficiency for 12 weeks. Subjects were then dosed another 12 weeks with Kamada A<sub>1</sub>-PI test product only. Lung Epithelial Lining Fluid (ELF) analytes from bronchoalveolar lavage (BAL) that was performed on a subset of subjects at 2 centers were compared between products.

**Sites:**

**Principal Investigator:** Dr Robert Sandhaus

**Other Investigators:** Dr James Stocks, Dr Mark Brantly

**Study Centers:** National Jewish Medical and Research Center (Denver, CO), The University of Texas Health Center at Tyler (Tyler, Texas), and University of Florida School of Medicine (Gainesville, FL).

Study Dates: 7 March 2007 to 27 March 2008

**DETAILED REVIEW OF CLINICAL STUDIES:**

**Study -(b)(4)- API 001:**

The pharmacokinetics and safety of an Alpha -1 proteinase inhibitor -(b)(4)-API) in subjects with congenital API deficiencies: A dose-escalation clinical trial (Phase 1) N = 18

**Objectives:**

The primary objective of this study was to determine the pharmacokinetics of -(b)(4)-API at three different dose levels (30mg/kg, 60mg/kg and 120 mg/kg) in subjects with API deficiency. The secondary objective was to establish that -(b)(4)-API is safe and therefore allow for a Phase III clinical trial to be conducted.



**Design Synopsis:**

This was a pharmacokinetic dose-escalation study of -(b)(4)-API designed to provide data to determine the dose at which -(b)(4)-API can maintain a plasma trough level of API > 11µM/L. Clinical efficacy was not assessed. Open sequential assignment to dose groups was utilized. Comparisons between dose levels were therefore potentially subject to selection bias.

The planned enrollment was six study subjects sequentially assigned to each dose group, to allow for 5 evaluable subjects per group, thus assuring that the 18 subjects were enrolled. There were six (6) naïve subjects, with at least one in each group, which met the requirement of the protocol to enroll 1 out of 5 naïve subjects.

Subjects received a single dose (30, 60, or 120 mg/kg) of -(b)(4)-API via IV drip at a rate of 0.08ml/Kg/min. These doses were designed to allow for dosing below and above the current, typical dose used for Prolastin® administration (60 mg/kg).

**Pharmacokinetic endpoints:**

- Area under the time-concentration curve (AUTCC) – The area between this curve and a horizontal line drawn through the baseline concentration.
- Half- life ( $t_{1/2}$ ) – derived from the terminal rate constant.
- Volume of distribution – the estimated volume of plasma into which -(b)(4)-API has been dispersed.
- Clearance – the average clearance of API over the study period.

Safety endpoints included AEs through the day 14 f/u visit, vital signs, EKG, viral serology for parvovirus B19, HIV 1 & 2, HCV, HBs, HBc, and HbsAg performed at baseline with antibodies for Parvovirus B19, HBV, HDV, and HIV tested at months 3 and 6, baseline, day 1 and day 7 routine hematology (CBC and differential), routine chemistries including BUN,



Musculoskeletal/connective			
Tissue			1
CNS		1	
Respiratory/thoracic/mediastinal	2	2	3
Skin/subcutaneous tissue	1	2	
Surgical/medical procedure			1

A reported reactive HIV result on the 3-month draw for Subject S1102 occurred. Further investigation uncovered that the sample was contaminated due to the Central Laboratory personnel not following standard procedures. This was verified in writing from the Central Laboratory Quality Assurance Director. A second sample was obtained from the subject and retested. The confirmatory testing was negative.

No HCV seroconversions occurred.

All subjects except 1 had received prior HBV vaccination. That subject had been vaccinated prior to the first infusion and seroconverted by month 6.

Five of 18 subjects were not immune to Parvovirus B19 at baseline and they remained sero-negative at day 7 and at 4 weeks. Antibody titers in the sero-positive subjects did not show clinically significant rises at days 7 or at 4 weeks.

The original submission contained post therapy viral follow-up data through the 4-week post-dosing f/u visit and any available data from 3 and 6 month f/u visits. Six month viral f/u data were missing for the 2 highest dose groups and 3 month data were missing for 5 of the high dose group. The sponsor states in the study report that they plan a 2nd database lock after complete virology results are available, which will result in an addendum to this report. In response to an information request, the sponsor later stated that viral follow-up data through the 6 month f/u visit were included in the original BLA submission.

No worrisome patterns of vital sign changes were evident.

No clinically significant EKG changes were seen.

**Reviewer comment regarding study design:**

The design of this study could have been improved in several respects: a) PK sampling was carried out only through 7 days, which is a duration < 3 half-lives reported for other A1-PI products. Given that non-naïve subjects were required to not have received any AAT augmentation for 5 weeks prior to participation, delay of restarting augmentation therapy by another week or so would be unlikely to materially adversely affect the health of subjects, especially because the clinical benefit of AAT augmentation has not been conclusively established. b) the protocol's discussion of the procedure to "predict for each dose studied [using average values of derived PK parameters] how long it would be expected to take for the plasma concentration in such a subject to fall to 11 microM/L" is vague c) "Statistical considerations were not employed in the selection of the size of the subject groups." The requirement that only 1/5 subject be naïve may have biased the trial in terms of the safety assessment, because non-naïve subjects who have intolerable AEs from AAT therapy would not be expected to participate in the study. The sponsor attempted modeling to use the single PK results to extrapolate steady-state trough levels in order to determine what dose would match the trough level of a U.S.-licensed A1-PI product given 60 mg/kg/week to steady state. According to the CBER review team clinical pharmacologist, the sponsor's modeling methodology may not be reliable.

### **DESIGN AND RESULTS OF PIVOTAL CLINICAL STUDY:**

#### **Study API 002: Phase 2/3 Randomized Double-Blind Comparison of Alpha-1 Proteinase Inhibitor (Kamada-API) with Prolastin® in Individuals with Alpha-1 Antitrypsin Deficiency (Phase 2-3) N = 50**

##### **Objectives:**

"The primary objectives of this study were to demonstrate that Kamada-API is not therapeutically inferior to active control, Prolastin® (Talecris Biotherapeutics), and to determine the efficacy of Kamada-API in maintaining average trough antigenic and/or functional plasma levels in excess of 11 microM."

"The secondary objectives are to compare the levels of antigenic and/or functional API in the ELF before and after 10-12 weeks of administrations of Kamada-API, and to assess the safety associated with Kamada-API administration."

[Reviewer Comment: The study was not designed to determine whether Kamada Alpha<sub>1</sub>-PI was *therapeutically* inferior to the active control, Prolastin<sup>®</sup>, because no true efficacy endpoints were the subject of hypothesis testing.]

### **Design Synopsis:**

This study consisted of a two period trial. Following a 5 week washout from prior AAT therapy, 50 AAT subjects with evidence of COPD as noted below were randomized 2:1 to Kamada A1-PI or Prolastin, 60 mg/kg weekly x 12 weeks. In the 2<sup>nd</sup> part of the trial, all subjects received Kamada A1-PI through week 24. A follow-up visit occurred at week 28 and included viral serology, but not viral NAT. Trough antigenic and functional AAT levels were obtained from weeks 7-12, as well as during the 2<sup>nd</sup> period of the trial.

The primary endpoint was based on individual subject's mean antigenic and/or functional A1-PI serum levels from weeks 7-12. The study included a BAL substudy targeting a subset of 15 subjects. These subjects were to have undergone HRCT, BAL collection, and bronchial brushing/biopsy at days -12 to -2 and again between weeks 10 and 12 at one of 3 centers. The HRCT could be repeated prior to the 2<sup>nd</sup> bronchoscopy at the investigator's discretion. HRCT may have been included in the study design in case subjects had AEs from the bronchoscopy procedures. One would not expect meaningful changes in HRCT lung density over the 24 weeks of the study. The study design is outlined in the Table below:

	-5 weeks	Day 0/Week 1	Week 2 to 12	Week 13 to 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					←→

### Endpoints:

### Efficacy:

The primary efficacy endpoint of the study was to assess the circulating antigenic and/or functional Alpha<sub>1</sub>-PI trough level averaged over weeks 7-12 (6 infusions). The goal of this study was to demonstrate that GLASSIA was not clinically inferior to Prolastin®. The definition of lack of inferiority was an average 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<sub>1</sub>-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<sub>1</sub>-PI levels.

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<sub>1</sub>-PI Antibodies as taken at baseline and at weeks 12 and 24 (these had not been assayed as of the time of BLA submission and will be submitted as a Post Marketing Commitment following validation of the 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<sub>1</sub>-PI and Anti-Neutrophil Elastase Capacity (ANEC)):

- Neutrophil Elastase (NE)
  - Alpha<sub>1</sub>-PI-NE complexes
- Measurement of Alpha<sub>1</sub>-PI trough levels:
  - The mean ratio of functional to antigenic Alpha<sub>1</sub>-PI trough levels over weeks 7-12 (six infusions).
  - The ratio of mean antigenic Alpha<sub>1</sub>-PI trough level over weeks 7-12 (six infusions) for the Prolastin<sup>®</sup> group to the equivalent mean value for the same treatment group after their crossover to GLASSIA (i.e. weeks 19 to 24).
  - The ratio of mean functional Alpha<sub>1</sub>-PI trough level over weeks 7-12 (six infusions) for the Prolastin<sup>®</sup> group to the equivalent mean value for the same treatment group after their crossover to GLASSIA (i.e. Weeks 19 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<sub>1</sub>-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<sub>1</sub> < 80% predicted (post Bronchodilator); or
  - Loss of lung function over a one year period of greater than 35 mL in FEV<sub>1</sub>; or
  - HRCT evidence of pulmonary emphysema;
- For actively treated subjects, agreement to not receive any exogenous Alpha<sub>1</sub>-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:

- $FEV_1 < 45\%$  predicted (post-BD);
- Inability to undergo bronchoscopy;
- Allergy to lidocaine;
- Exacerbation of COPD in the previous six weeks.

### **Statistical Considerations:**

### **Efficacy Assessments**

#### **Primary endpoint:**

The primary outcome variable was the trough circulating level of antigenic and/or functional Alpha<sub>1</sub>-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  $\mu$ M 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<sup>®</sup>). If the lower bound of this Alpha<sub>1</sub>-PI interval was greater than -3  $\mu$ M, then the goal of demonstrating non-inferiority was considered to have been achieved.

#### **Secondary Endpoints:**

The levels of antigenic and/or functional API present in the BAL fluid will be summarized for each treatment group using means and standard deviations (both pre-treatment, post-treatment and change from baseline). The mean change from baseline in each treatment group will be compared with zero using a Wilcoxon signed-rank test, stratified by center.

### Tertiary Endpoints:

- Reduction of pro-inflammatory factor IL-8 in the ELF;
- Reduction in inflammatory cells, total and individual, in the bronchial wall by measuring Macrophages, Eosinophils, Neutrophils and Lymphocytes in the ELF;
- Changes from baseline of the following ELF analytes (other than antigenic API and ANEC);
  - o NE; and
  - o AAT-NE complexes.
- Mean ratio of the functional to antigenic API trough levels over Weeks 7-12 (6 infusions)
- Ratio of mean antigenic API trough level Weeks 7-12 (6 infusions) for the Prolastin® group to the equivalent mean value for the same treatment group after their crossover to Kamada API (i.e. Weeks 19 to 24);
- As above but for functional API; and
- Frequency of pulmonary exacerbations.

## STATISTICAL METHODS

Sample size: n = 50 (2:1 randomization Kamada A1-PI: Prolastin control)

### Analysis Populations

#### Intent-to-Treat Analysis Population

The Intent-to-Treat (ITT) analysis population included all randomized subjects regardless of the treatment and amount of treatment actually received.

#### Safety Analysis Population

The Safety analysis population included all subjects who were administered at least one dose of study medication.

#### Pharmacokinetic Evaluable Analysis Population

The Pharmacokinetic Evaluable (PE) population included all subjects in the ITT population who received the full dose of study medication at each dose administration and had at least one evaluable trough level beyond Week 6.

**Per-Protocol Analysis Population**

The Per-Protocol (PP) analysis population included all subjects in the PE population who received 12 full doses of study medication and had evaluable trough levels from Week 7 to Week 12 in the absence of a major protocol violation.

**Bronchoalveolar Lavage and Bronchial Biopsy/Brushing Analysis Population**

The bronchoalveolar lavage (BAL) analysis population included all subjects in the Safety population who underwent a Baseline and Week 12 BAL procedure and who met the following criteria for both samples:

- Return  $\geq$  20% recovered BAL fluid per lobe
- Cells/mL  $\geq$   $1.0 \times 10^4$
- Ratio of [Urea]/plasma over [Urea]BAL sample was  $> 30$  and  $< 350$

As noted above the primary outcome variable was the trough circulating level of antigenic and/or functional Alpha<sub>1</sub>-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  $\mu$ M 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<sup>®</sup>). If the lower bound of this Alpha<sub>1</sub>-PI interval was greater than -3  $\mu$ M, 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, 95% exact binomial lower confidence bounds were estimated for the proportion of subjects in each treatment group for whom the mean trough antigenic Alpha<sub>1</sub>-PI for weeks 7-12 was in excess of 11  $\mu$ M. It was expected that the observed proportion of subjects in the Glassia for whom this goal was achieved would exceed 80%. This 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.

The frequency of pulmonary exacerbations was to be analyzed descriptively, based on the definition of exacerbations listed in the note clarifying BAL exclusion number 4 in protocol section 4.2.1.

### **Additional assessments**

- Genotype/phenotype of AATD
- Baseline antigenic and functional A1-PI levels

## **RESULTS**

### **Disposition of subjects**

The number of subjects randomized was 52. Two had withdrawn consent and were randomized in error but not dosed. Thirty-three were administered Kamada A<sub>1</sub>-PI and 17 were administered Prolastin<sup>®</sup>. Two subjects were withdrawn early due to AEs (urticaria in the Kamada A<sub>1</sub>-PI group and pulmonary emboli in the Prolastin group). Zero Kamada A<sub>1</sub>-PI and one Prolastin<sup>®</sup> subject discontinued prior to week 12 (end of randomized, double-blind period).

The number of subjects who completed the 28 week study was 48.

Enrollment was balanced by randomized treatment group across centers with a ~ 2:1 ratio of subjects randomized to the Kamada test product compared to Prolastin at each site.

Thirteen of planned 15 subjects underwent BAL sampling. Of these only 11 had evaluable samples (9 in the Kamada A<sub>1</sub>-PI group and 2 in the Prolastin<sup>®</sup> group).

### **Demographics**

Parameter	GLASSIA N=33	Prolastin <sup>®</sup> N=17
Age (years)		
Mean (SD)	55.4 (7.7)	55.7 (9.2)
Median	55	55
Min, Max	42, 72	42, 74
Gender (n, %)		

Male	17 (51.5%)	8 (47.1%)
Female	16 (48.5%)	9 (52.9%)
Race (n, %)		
Caucasian	33 (100%)	16 (94.1%)
Hispanic	0	1 (5.9%)
Height (cm)		
Mean (SD)	171.8 (11.0)	172.3 (8.7)
Median	173	174
Min, Max	147, 191	154, 188
Weight (kg)		
Mean (SD)	82.3 (23.1)	85.7 (17.7)
Median	81.4	83.6
Min, Max	40, 162	55, 113

Phenotype (from Sponsor's Table 9)

Phenotype	Kamada-API	Prolastin <sup>®</sup>
(n, %)	N=33	N=17
ZZ	28 (84.8%)	15 (88.2%)
MZ	2 (6.1%)	0
SZ	2 (6.1%)	0
Unknown	1 (3.0%)	2 (11.8%)

It is unclear why 2 subjects with phenotype MZ were enrolled in the study, as their serum A<sub>1</sub>-PI levels are normally 17 microM or above. The sponsor addressed this in Amendment 6 and 12 (See appendices to this review).

**Good clinical practice deficiencies in the conduct of the study identified during the review process:**

- -----Information withheld per the privacy act-----  
-----

1 page determined not releaseable: Information withheld per the privacy act

Information withheld per  
the privacy act

Additional good clinical practice (GCP) deficiencies in the conduct of the pivotal study were identified during BiMo inspections (see BiMO review)

### Protocol Violations:

Two subjects (1 per randomization group) were randomized in error.

One subject received exogenous A<sub>1</sub>PI slightly less than the required 5 weeks prior to study start.

In the Kamada product group, 12 subjects missed 1 or more infusions and A<sub>1</sub>PI levels.

In the Prolastin group, 3 subjects missed single infusions and these 3 plus another subject missed having an A<sub>1</sub>PI level drawn.

A list of protocol violations was reviewed by the sponsor prior to database lock to determine if major violations had occurred which would exclude subjects from an analysis dataset.

### Additional Protocol Violations Noted during BiMo Inspections:

3 pages determined not to be releasable: Information withheld per privacy act



- a. -----Information withheld per privacy act-----  
 -----  
 -----  
 -----
- b. ----- Information withheld per privacy act -----  
 -----  
 -----  
 -----  
 -----.
- c. -----Information withheld per privacy act-----  
 -----.
- d. -----Information withheld per privacy act-----  
 -----  
 -----

**FDA's assessment of impact of Good Clinical Practice (GCP) deficiencies:**

Even after eliminating the safety data from the largest study site which had the most numerous GCP deficiencies, the review team concluded that the safety data from the remaining sites was sufficient to support the licensure of the product. Sufficient vital-sign and laboratory-safety data were available collectively from all sites to support the safety evaluation, and there was no evidence from the inspections of under-reporting of adverse experiences. Although there was a question of premature unblinding at two of the three sites, there was no evidence from the inspections that the key surrogate efficacy endpoint parameters (blood antigenic and functional Alpha<sub>1</sub>-PI levels and ELF antigenic Alpha<sub>1</sub>-PI levels calculated from BAL specimens) were compromised. At the largest site, subjects became inadvertently unblinded to study staff when each subject began the open-label portion of the study because their study drug infusion volume changed if they had originally been randomized to receive the control product, Prolastin<sup>®</sup>. However, it was not clear whether the study home-infusion nurses responsible for making many incompletely documented changes to study data were necessarily unblinded through this mechanism. At site 1, FDA could not eliminate the possibility that unblinding of study site personnel

may have occurred. However, there was no reason to believe that technicians performing surrogate “efficacy” endpoint laboratory tests (done at a different location from site (1) had knowledge of the randomization assignments while analyzing and reporting results. Technician error resulted in the loss of BAL specimens for functional Alpha<sub>1</sub>-PI levels in ELF for all trial subjects.

## **Efficacy results:**

### **Primary Endpoint: Serum AAT level (surrogate) endpoints**

The primary endpoint was met for both antigenic and functional serum A<sub>1</sub>-PI levels in the sponsor’s analysis. Mean antigenic and functional A<sub>1</sub>-PI levels in the modified ITT population were greater for the Kamada A<sub>1</sub>-PI than for Prolastin in the sponsor’s analysis. The FDA Biostatistician verified the accuracy of the sponsor’s analysis of the primary endpoint.

Mean baseline antigenic A<sub>1</sub>PI levels were 4.8 microM in the Kamada A<sub>1</sub>PI group and 4.3 microM in the Prolastin group after the 5 week washout. Mean baseline functional A<sub>1</sub>PI levels were 3.1 microM in the Kamada A<sub>1</sub>PI group and 2.3 microM in the Prolastin group.

In the sponsor’s analysis, the median antigenic API values for Weeks 7-12 were 14.5 µM in the Kamada-API group (range: 11.6 to 18.5 µM), and 12.8 µM in the Prolastin® group (range: 10.4 – 19.2 µM). The median functional API values were lower than the antigenic values in both groups and were 11.8 µM in the Kamada-API 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 intervals were greater than – 3 µM for both antigenic and functional API levels thereby demonstrating the non-inferiority of Kamada-API to Prolastin®.

“The proportion of subjects with mean trough antigenic API levels exceeding 11 µM during Weeks 7 to 12 was 100% for subjects in the Kamada-API group and 81.3% for subjects in the Prolastin® group. Similarly, the proportion of subjects with mean functional API levels > 11 µM was 66.7% in the Kamada-API group and 62.5% in the Prolastin® group.”

Levels of serum functional A<sub>1</sub>-PI were notably lower in both Kamada A<sub>1</sub>-PI and Prolastin groups than has been seen in most other pivotal trials of U.S. licensed A<sub>1</sub>-PI products; however low levels of functional A1-PI were also seen in the pivotal study for Prolastin C. This could be due to assay or standard differences. However, dosing is routinely based on vial content of functional A1-PI, not on vial content of total functional plus inactive A1-PI.

### **BAL surrogate endpoints and other BAL endpoints**

“The BAL subset was used to evaluate the effect of API treatment on the lung epithelial lining. This subset contained fewer subjects than anticipated; results were available for only 7 subjects in the Kamada-API group and 2 subjects in the Prolastin® group. Furthermore, due to a technical error, results of functional API in the ELF were not obtained and are not presented in this report. The small sample size along with the high degree of inter-subject variability in results limits the ability to interpret the BAL parameters. However, increases from Baseline in antigenic API levels in the ELF at Week 10-12 were observed in both treatment groups, and an increase from Baseline in API-NE complexes (an indication to functional API levels) was evident in the Left and Right Lung samples of the Kamada-API group at Week 10-12. This suggests that treatment with Kamada-API increased the API level in the target organ (lung) and was able to complex with NE and reduce the free concentration available to damage the lung tissue.”

Reviewer Comment: Dr. Mark Brantley has stated that rises in A1-PI:NE complexes do not necessarily reflect a reduction in free neutrophil elastase [personal communication with this reviewer– date not available].

No consistent trends were seen in pro-inflammatory ELF IL-8, ELF neutrophil elastase, or ELF neutrophil cell count changes from baseline in either test or control groups.

### **Additional Exploratory Endpoints.**

The mean ratio of functional to antigenic A1-PI trough levels during weeks 7-12 did not differ between products ( $p = 0.08$ ; ratio values of 0.82 for Kamada API and 0.87 for Prolastin®).

In the group randomized to Prolastin®, the mean values for antigenic and functional API levels were similar between Weeks 7-12 (when the subjects were treated with Prolastin®) and Weeks 19-24 (when subjects were treated with Kamada-API) with a ratio of 0.89 for antigenic API and 0.99 for

functional API. The confidence interval for the ratio indicates that the slightly higher antigenic trough levels after crossover to Kamada API were statistically significantly different in comparison to the antigenic levels during period 1 while the subjects in that randomization group were receiving Prolastin (no adjustment for multiple comparisons).

The design of the electronic case report forms made application of the protocol diagnostic criteria for pulmonary exacerbations of COPD problematic. Thus, the sponsor analyzed exacerbations of COPD by reviewing medications prescribed for COPD exacerbations. Note that not all pulmonary exacerbations identified by this analysis were reported as exacerbations of COPD by the investigators. Exacerbation of COPD was coded by the sponsor using the preferred term, "COPD." This is not particularly helpful, since all subjects were required to have evidence of COPD for trial participation.

## **SAFETY**

There were no deaths on study.

Forty-nine of 50 subjects reported at least 1 AE (32/33 in the Kamada A1-PI group and 17/17 in the Prolastin group).

The most commonly reported AEs were cough, COPD exacerbation, URI/nasopharyngitis.

Two subjects were withdrawn prematurely from the study due to adverse events (urticaria in the Kamada A<sub>1</sub>-PI group and pulmonary emboli in the Prolastin<sup>®</sup> group, according to the study report. However, the raw SAE dataset indicated that the subject with pulmonary emboli was in group "A1-PI." The sponsor was asked to clarify this apparent discrepancy and confirmed that the PE occurred in a Prolastin<sup>®</sup> subject.).

- Subject ---(b)(6)----- (Prolastin<sup>®</sup>) discontinued following one dose of study medication due to acute and chronic pulmonary emboli.
- Subject ---(b)(6)----- (Kamada-API) discontinued following the Week 12 infusion due to urticaria.

Four SAEs were reported for 4 subjects, but only 3 were treatment-emergent. The treatment-emergent SAEs reported were cholangiopancreatography (ERCP) for a common duct stone leading to reversible cholangitis and jaundice which began 33 days following the start of dosing with the test product, a COPD exacerbation which began 76 days after the start of dosing with the test product, and acute and chronic pulmonary emboli recognized the day following the start of dosing with Prolastin<sup>®</sup>. Because pulmonary emboli should be considered a serious AE, it is not clear why this AE which led to premature discontinuation is not listed among the SAEs reported in the trial in dataset, “SERIOU18.” The sponsor was asked to explain this. No SAEs were attributed by the investigator to administration of study product.

The non-treatment-emergent SAE was pneumothorax following baseline BAL, recognized prior to dosing. One additional COPD exacerbation was not reported to the sponsor as a SAE, but required an ER visit.

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

- Subject ---(b)(6)----- (Prolastin<sup>®</sup>) discontinued following one dose of study medication due to acute and chronic pulmonary emboli.
- Subject ---(b)(6)----- (GLASSIA) discontinued following the week 12 infusion due to urticaria.

Sponsor’s Table 26 shows that 6 subjects in reach randomization group during period 1 had at least 1 drug-related AE (corresponding to an incidence of 18% in the Kamada API group and 35% in the Prolastin group.

Study Period 1 Number and (%) of subjects by treatment group with at least 1 AE of the noted intensity (from Sponsor’s Table 26)

AE Intensity	Kamada API (n = 33)	Prolastin (n – 17)
Mild	24 (73%)	14 (82%)
Moderate	14 (42%)	7 (41%)
Severe	2 (6%)	2 (12%)

Sponsor’s Table 31: AEs of Severe Intensity

Treatment Period	Preferred Term	Kamada-API	Prolastin®
One	Headache	1 (3%)	1 (6%)
	Cholangitis	1 (3%)	0
	Chronic obstructive pulmonary disease	0	1 (6%) <sup>2</sup>
	Hypoxia	0	1 (6%) <sup>2</sup>
	Nausea	0	1 (6%) <sup>1</sup>
Two	Headache	0	1 (6%)

<sup>1</sup> Subject ---(b)(6)---- experienced headache and nausea

<sup>2</sup> Subject ---(b)(6)---- experienced COPD and hypoxia

Sponsor's Table 27: Overall AEs experienced during treatment (12-week randomized, double-masked period one) by treatment group, irrespective of the causality

Preferred Term	GLASSIA	Prolastin®
Cohort size	N=33	N=17
Any event	27 (82%)	16 (94%)
Cough	5 (15%)	4 (24%)
Upper respiratory tract infection	4 (12%)	0
Headache	3 (9%)	4 (24%)
COPD exacerbation	2 (6%)	2 (12%)
Productive cough	1 (3 %)	2 (12%)
Nausea	1 (3%)	2 (12%)
Fatigue	1 (3%)	2 (12%)
Epistaxis	0	2 (12%)
Sinusitis	2 (6%)	1
Bronchitis	0	1 (6%)
Chest discomfort	2 (6%)	0
Dyspnea	2 (6%)	0
Hemoptysis	2 (6%)	0
Nasopharyngitis	2 (6%)	0
Pharolayngeal Pain	3 (9%)	1 (6%)
Gastroenteritis	2 (6%)	0
Cholangitis	1 (3%)	0
Herpes Simplex	1 (3%)	0
Influenza	2 (6%)	0

Hepatic Enzyme Increased	2 (6%)	0
Dizziness	2 (6%)	0
UTI	2 (6%)	0
Contact Dermatitis	1 (3%)	0
Pruritis	1 (3%)	0

Note that (URI + Nasopharyngitis + influenza) total 8 for Kamada and 0 for Prolastin.

Sponsor's Table 28: Adverse Events Experienced During Treatment Period 2 Occurring in  $\geq 10\%$  of Subjects in a Treatment Group

<b>Preferred Term</b>	<b>Kamada-API N=33</b>	<b>Prolastin<sup>®a</sup> N=17</b>
Any event	27 (82%)	15 (88%)
Upper respiratory tract infection	8 (24%)	2 (12%)
Nasopharyngitis	4 (12%)	2 (12%)
Pharyngolaryngeal pain	4 (12%)	0
Rash	4 (12%)	0
Urticaria	1 (3%)	2 (12%)
Hypersensitivity	0	2 (12%)

<sup>a</sup> The data are presented by ITT randomization group; For the "Prolastin<sup>®</sup>" group, all subjects received Kamada A1-PI during period 2; AEs occurring during period 2 in this group might have been due to prior Prolastin<sup>®</sup> treatment, recent Kamada A1-PI treatment, both, or neither.

Note that rash is more frequent with the Kamada product (incidence of 12% vs. 0 for Prolastin<sup>®</sup> during period 2, although 2 cases of urticaria were reported for Prolastin<sup>®</sup> (period 1)/Kamada (period 2) and 1 for the Kamada/Kamada product. In addition, 1 case of contact dermatitis was reported for the Kamada product and none for Prolastin during period 1.

During period 2, COPD was reported as an AE for 3 Kamada product subjects and for 1 subject randomized to Prolastin<sup>®</sup> (during the prior period 1). One case of pneumonia in the Kamada group and none in the Prolastin<sup>®</sup> randomization group occurred during period 2. "Hypersensitivity" was reported for zero Kamada API and for 2 Prolastin<sup>®</sup> subjects during period 2. One thrombocytopenia was reported for Kamada API and none for Prolastin<sup>®</sup> randomization group during period 2. Dizziness was reported for

2 Kamada API and zero Prolastin<sup>®</sup> subjects during period 2. Eczema was reported for 1 Kamada subject and zero Prolastin<sup>®</sup> subject during period 2.

Sponsor's Table 14.3.1.2b: Treatment Emergent Adverse Events Experienced During Treatment Period 1 Occurring within 24 Hours of Last Infusion (source: Amendment 06)

System Organ Class Preferred Term	Kamada-API (N=33) N (%) / Events	Prolastin) (N=17) N (%) / Events
ANY EVENT	19 (58%)/ 35	13 (76%)/ 29
Blood and lymphatic system disorders		
Any event	1 (3%)/ 1	0 (0%)/ 0
Anemia	1 (3%)/ 1	0 (0%)/ 0
Gastrointestinal disorders		
Any event	4 (12%)/ 4	1 (6%)/ 1
Abdominal mass	1 (3%)/ 1	0 (0%)/ 0
Abdominal pain upper	1 (3%)/ 1	0 (0%)/ 0
Gastroenteritis	1 (3%)/ 1	0 (0%)/ 0
Nausea	1 (3%)/ 1	1 (6%)/ 1
General disorders and administration site conditions		
Any event	3 (9%)/ 3	5 (29%)/ 5
Fatigue	1 (3%)/ 1	2 (12%)/ 2
Influenza like illness	0 (0%)/ 0	1 (6%)/ 1
Edema	1 (3%)/ 1	1 (6%)/ 1
Edema peripheral	1 (3%)/ 1	1 (6%)/ 1
Infections and infestations		
Any event	3 (9%)/ 3	1 (6%)/ 1
Candidiasis	1 (3%)/ 1	0 (0%)/ 0
Herpes simplex	1 (3%)/ 1	0 (0%)/ 0
Influenza	1 (3%)/ 1	0 (0%)/ 0
Oral candidiasis	0 (0%)/ 0	1 (6%)/ 1
Injury poisoning and procedural complications		
Any event	0 (0%)/ 0	1 (6%)/ 1
Infusion site pruritus	0 (0%)/ 0	1 (6%)/ 1
Investigations		



Any event	3 (9%)/ 3	2 (12%)/ 2
Blood glucose increased	1 (3%)/ 1	0 (0%)/ 0
Blood sodium decreased	0 (0%)/ 0	1 (6%)/ 1
Hepatic enzyme increased	2 (6%)/ 2	0 (0%)/ 0
White blood cell count increased	0 (0%)/ 0	1 (6%)/ 1

#### Musculoskeletal and connective tissue disorders

Any event	2 (6%)/ 2	2 (12%)/ 2
Osteoporosis	0 (0%)/ 0	1 (6%)/ 1
Pain in extremity	1 (3%)/ 1	0 (0%)/ 0
Restless legs syndrome	0 (0%)/ 0	1 (6%)/ 1
Nervous system disorders		
Any event	4 (12%)/ 4	3 (18%)/ 3
Dizziness	1 (3%)/ 1	0 (0%)/ 0
Headache	3 (9%)/ 3	3 (18%)/ 3

#### Respiratory thoracic and mediastinal disorders

Any event	9 (27%)/ 12	7 (41%)/ 11
Chest discomfort	2 (6%)/ 2	0 (0%)/ 0
COPD	1 (3%)/ 1	1 (6%)/ 1
Cough	2 (6%)/ 2	3 (18%)/ 3
Dyspnea	1 (3%)/ 1	0 (0%)/ 0
Epistaxis	0 (0%)/ 0	1 (6%)/ 1
Hypoxia	0 (0%)/ 0	1 (6%)/ 1
Nasal Edema	0 (0%)/ 0	1 (6%)/ 1
Nasopharyngitis	1 (3%)/ 1	0 (0%)/ 0
Pulmonary mass	0 (0%)/ 0	1 (6%)/ 1
Sinusitis	2 (6%)/ 2	1 (6%)/ 1
Upper respiratory tract infection	3 (9%)/ 3	0 (0%)/ 0

#### Skin and subcutaneous tissue disorders

Any event	2 (6%)/ 2	1 (6%)/ 1
Pruritus	1 (3%)/ 1	0 (0%)/ 0
Sunburn	1 (3%)/ 1	0 (0%)/ 0
Urticaria	0 (0%)/ 0	1 (6%)/ 1

#### Surgical and medical procedures

Any event	0 (0%)/ 0	1 (6%)/ 1
Skin neoplasm excision	0 (0%)/ 0	1 (6%)/ 1

### Vascular disorders

Any event	1 (3%)/ 1	1 (6%)/ 1
Hypertension	1 (3%)/ 1	1 (6%)/ 1

Includes all adverse events that occurred on or after the first infusion date until the day prior to Week 13 visit. An AE that began on either the day of an infusion or the day following an infusion were classified as occurring within 24 hours of last infusion.

AEs considered at least possibly related to the test articles included:

Study Period 1 (randomized parallel period – 1<sup>st</sup> 12 weeks):

Numbers (%) of subjects reporting Related AEs – study period 1

AE	Kamada A <sub>1</sub> -PI	Prolastin
Headache	3 (9%)	1 (6%)
Hypertension	1 (3%)	1 (6%)

Study Period 2 (Open-label weeks 13 – 26):

Numbers (%) of subjects reporting Related AEs – study period 2,  
during which subjects received only Kamada A1-PI

AE	Kamada A <sub>1</sub> -PI Randomization Group (N=33)	Prolastin Randomization Group (Received Kamada A1-PI during Period 2) (N=17)
Urticaria	1 (3%)	0 (0%)
Dizziness	1 (3%)	0 (0%)
Rash	1 (3%)	0 (0%)
Joint Swelling	1 (1%)	0 (0%)
Decreased Platelet Count	1 (3%)	0 (0%)
Influenza-like illness	1 (3%)	0 (0%)
Lethargy	0 (0%)	1 (6%)

The data are presented by ITT randomization group; For the “Prolastin<sup>®</sup>” group, all subjects received Kamada A1-PI during period 2; AEs occurring during period 2 in this group might have been due to prior Prolastin<sup>®</sup> treatment, recent Kamada A1-PI treatment, both, or neither.

No subjects seroconverted for HBV, HCV, or HIV during the pivotal study. As noted above, PCR for the above viruses and parvovirus B19 were not performed.

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

Samples for A1-PI Antibodies were taken at baseline and at weeks 12 and 24 but had not been assayed as of the time of BLA submission. These data were promised to be submitted by 01 January 2010, but as of 02 March 2010 had not been received.

Routine hematology studies showed variability but no consistent pattern unique to the Kamada product. One Kamada subject (---(b)(6)-----) had a decrease in platelet count to 64K that resolved.

Several subjects in both groups had normal glucose at baseline and increased values over the study.

No abnormal chemistry values were regarded by the investigators as related to study drug. Most Abnormal aminotransferase values were considered to be likely due to A1-PI related liver disease. Kamada Subject --(b)(6)--- had a treatment-emergent ALT value during period 1 of 54 (normal 8-48) and AST of 103 (ULN 55) which resolved.

Three Kamada A1-PI and 4 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 1 Kamada A1-PI subject and 1 mild/intermediate hypertension, resolved at study termination in 1 Prolastin<sup>®</sup> subject. No subject was reported to have clinically significant hypotension.

As expected for such a short study, group mean PFTs were not meaningfully changing over the study.

One Prolastin subject had a normal CXR at baseline and an abnormal CXR at week 24, not considered clinically significant.

**Discussion of key issues identified during the clinical review and FDA's assessment:**

1. -----  
-----  
-----Information withheld per privacy act-----  
-----  
-----  
-----:  
  - a. -----Information withheld per privacy act-----  
-----  
-----.
  - b. -----Information withheld per privacy act-----  
-----  
-----.
  - c. -----Information withheld per privacy act-----  
-----  
-----  
-----  
-----  
-----  
-----.
2. Consistent finding of visible protein aggregates in the liquid product (CMC issue with possible clinical implications). -----  
------(b)(4)----- The FDA assessment of the above findings is as follows:
  - a. Visible particulates have been observed in licensed Alpha<sub>1</sub>-PI products and are mentioned in the products' package inserts. -----

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

----- The package insert recommends use of one 5 microM filter in pooling vials, and a 2<sup>nd</sup> in-line 5 microM filter is recommended during administration. -----

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

- 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<sup>®</sup> 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<sub>1</sub>-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<sub>1</sub>-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<sub>1</sub>-PI in the BAL samples.” In addition, BAL samples were obtained from only 2 of 5 planned Prolastin<sup>®</sup> control subjects. FDA assessment of the above findings is:
  - a. Available data from the completed BAL sub-study demonstrate an appropriate rise from baseline in antigenic Alpha<sub>1</sub>-PI levels in ELF.
  - b. Because functional ELF Alpha<sub>1</sub>-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<sub>1</sub>-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<sup>®</sup>. 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<sub>1</sub>-PI of  $\geq 11 \mu\text{M}$  (however 100% of patients receiving the GLASSIA product achieved trough levels of antigenic Alpha<sub>1</sub>-PI  $\geq 11 \mu\text{M}$ ). This finding raises the question of optimal dosing. Like other licensed manufacturers of Alpha<sub>1</sub>-PI, Kamada will conduct a post-marketing trial (see below) to answer this question.

#### **MEDICAL REVIEW CONCLUSIONS:**

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

**Post Marketing Requirement:**

A clinical trial to further assess the 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 which 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<sub>1</sub>-PI antibodies using an appropriately validated assay. We note that the planned study will also explore potential adverse events associated with immunogenicity, viral safety, and epithelial lining fluid analytes following the use of Kamada's Intravenous, Human Alpha<sub>1</sub>-PI (GLASSIA) and another commercial, Alpha<sub>1</sub>-PI, in Alpha<sub>1</sub>-Antitrypsin [Alpha<sub>1</sub>-PI] Deficient Patients.

Final Protocol Submission: 01 March 2011

Trial initiation Date: 05 September 2011

Trial Completion Date: 20 March 2013

Final Report Submission: 18 March 2014



**Postmarketing commitments**

1. Submission, as a supplement to the BLA STN BL 125325, of the final report of the results of anti-Alpha<sub>1</sub>-PI antibody testing from all stored clinical samples from clinical trial API-002, including all raw data. Kamada has committed to submit as a supplement to the BLA the final anti-Alpha<sub>1</sub>-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: 18 September 2007

Study/trial completion date: 27 March 2008

Submission of Assay Validation Report: 01 November 2010

Final Report Submission date: 01 February 2011

2. A Phase IV, open-label or double-blind, multicenter study investigating Epithelial Lining Fluid of Alpha<sub>1</sub>-Antitrypsin Deficient Patients for Alpha<sub>1</sub>-PI and analyte levels following augmentation therapy with GLASSIA.

Kamada has 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<sub>1</sub>-PI levels in Epithelial Lining Fluid after 10-12 weeks of treatment.

Final protocol submission date: 01 March 2011

Trial initiation Date: 05 September 2011

Study/trial completion date: 20 March 2013

Final Report Submission date: 18 March 2014

3. 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<sub>1</sub>-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<sub>CO</sub> measurements, and mortality.

Final protocol submission date: 01 March 2011

Trial initiation Date: 03 September 2012

Study/trial completion date: 03 March 2017

Final Report Submission date: 05 March 2018

- b. Trial 2: An adequately-powered study of a 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 GLASSIA Alpha-1-Proteinase Inhibitor (Human).

The study will be randomized and double-blind.

Final protocol submission date: 8 January 2018

Trial initiation Date: 07 January 2019

Study/trial completion date: 8 July 2024

Final Report Submission date: 7 July 2025

## **APPENDICES:**

Amendment 1 contains the Certification of Compliance (Form FDA 3674) for compliance with requirements of ClinicalTrials.gov.

Amendment 2 contains the response to the FDA info request dated 16 July 2009. This included responses to FDA-identified problems with the clinical databases.

Amendment 3 contains the response to the FDA info request made 9 September 2009 regarding deficiencies identified by the Clinical Pharmacology reviewer.

Amendment 4 dated 02 October 2009 is a request for proprietary name review. Proposed trade names are APIKAM (primary) and GLASSIA (alternate). I have no objection to either proposed trade name.

Amendment 5 dated 15 October 2009 only contains a letter stating that the firm does not plan to submit a 120 day safety update “since no additional safety data has been collected with intravenously administered Kamada-API since the data cutoff for the Integrated Summary of Safety (Section 2.7.4).” Reviewer Comment: The sponsor’s statement that no additional clinical data has been collected is puzzling, given the statement in the study report for API-001 which states that the original submission contained viral f/u data through the 4-week post-therapy f/u and any available data from 3 and 6 month f/u visits. The sponsor states in the study report that they plan a 2nd database lock after complete virology results are available, which will result in an addendum to this report.

This information conflicts with the cover letter to Amendment 5, which states “Complete safety and efficacy data from Studies API-OOI and API-002 were submitted in the BLA, and no additional subjects have been dosed or followed-up for safety.”

Amendment 6 dated 23 October 2009 contains the sponsor’s responses to FDA’s information request dated 31 July 2009 concerning clinical questions.

Amendment 7 dated 9 November 2009 is in response to FDA fax dated 23 October 2009 and repeats the sponsor’s responses to 3 clinical items contained in Amendment 6, as well as containing responses to CMC questions, a statement that immunogenicity data should be submitted by 01

January 2010, and an administrative matter concerning the sponsor's US representative.

Amendment 8 dated 13 Nov 2009 contains additional CMC data as agreed during the 29 January 2009 pre-BLA meeting.

Amendment 9 dated 16 November is in response to an information request conveyed during a telecon held 5 November 2009 with Dr. I. Mahmood the Division pharmacokineticist, as well as telecon minutes.

Included is the following:

A calculation conversion for converting *microM* to mg/dL [for A<sub>1</sub>-PI] and a theoretical calculation of the 60 mg/kg to */LM* is provided below.

$microM / 0.1923 = mg/dL$  OR  $mg/dL \times 0.1923 = /microM$   
(based historically on a common agreement for a 52 KDa as the molecular weight of the protein)

For example, a ZZ individual at 5 *microM* plasma AAT has  $5/0.1923 = 26.00$  mg/dL plasma AAT.

When considering a 70 kg individual receiving 60mg/Kg, he or she will receive 4200 mg total product. As you can see, this value has no volume associated with it. Therefore, we can not summarize it as a concentration unless we consider the complete system volume (individual's blood volume) to reach a theoretical system concentration. Hypothetically speaking, an individual of 70 Kg has about 5 Liter of blood. When infusing 4200 mg, he or she theoretically (not considering; the **IV** volume going in) should have an increase of 84 mg/dL or 16.15 I-LM AAT beside the ZZ AAT (around 5 I-LM) they already have in their system at the steady state.

[Reviewer's note. If we postulate distribution initially only in the plasma, and assuming instantaneous infusion, this would correspond to a peak A1PI plasma concentration of about 32 *microM*, assuming a Hct of 50.]

Amendment 10 dated 28 December 2009, provided in partial response to FDA's 23 October 2009 information request, contains the sponsor's



2010) for providing the study synopses due to the Season's Holidays that made it impossible to consult the potential study investigators.

b) Two questions (Q25 and 078) that require data from ---(b)(4)-----  
----- are partially delayed due to the Season's Holidays. Since --(b)(4)-- may prefer to submit some of the information directly to the Agency, we will contact the FDA to follow up how it should be arranged.

c) An answer for question # 33a is provided. As explained in the answer to the other three sub-questions (Q33 b, c, and d):

1. Additional work is required for a complete answer to these items.
2. The number of retention samples remaining from the clinical trials is limited and in order to be able to coordinate the use of these vials Kamada would appreciate if the agency could let us know as soon as possible if there are any additional studies/tests that the Agency would like us to perform with these lots.
3. In case there is no further studies to be performed with these lots (see item 2 above) Kamada anticipates that the data will be available by the time of the pre-approval inspection scheduled for the first week of February.

d) For question # 56 the list of deviations for the lots requested is provided. However, since all their investigation reports are in Hebrew the summaries of the investigations will be submitted in a separate submission by January 18, 2010.

e) The answer to question # 43 involves detailed review of all manufacturing records and procedures and will also be submitted in the next submission by January 18, 2010.

Amendment 13 dated 19 January 2010 consists of a complete response to question 56 from FDA's 9 December 2009 information request and includes the list of deviations observed during the manufacture of paste comparability lots and conformance lots and the summaries of their investigations.

Amendment 14 dated 26 January 2010 consists of a complete response to question 56 from FDA's 9 December 2009 information request and includes

the list of all process control parameters and all quality attributes for the manufacturing of Kamada-API drug substance and drug product.

Amendment 15 dated 5 March 2010 (Received 8 March 2010) includes revised labeling in response to revisions requested by FDA.

Amendment 16 dated 11 March 2010 contains a partial response to FDA request for additional information regarding the GMP inspection and to question 1 of FDA's 03 March 2010 letter.

Amendment 17 dated 15 March 2010 contains protocol outlines for Phase 4, PMC clinical studies as requested in FDA's 09 Dec 2009 fax info request items 12, 13, and 14.

Amendment 18 dated 18 March 2010 contains the final portion of Kamada's response to FDA's information request letter dated 3 March 2020 regarding the facility inspection

Amendment 19 dated 01 April 2010 responded to FDA information request faxes dated 18 and 19 March 2010. The 18 March 2010 fax included 8 clinical questions. The sponsor provided a revised synopsis for the Phase 4 study API-004-3a. Revised package insert is also included.

Amendment 20 dated 08 April 2010 contains response to items 2 and 3b-c of FDA's 23 March 2010 fax request for additional information regarding viral testing during the manufacturing process.

Amendment 21 dated 04 May 2010 contains responses to questions 48 and 78 of FDA's information request fax dated 9 December 2009 (concerning nanofiltration and critical operation parameters and process quality attributes for ----(b)(4)----), plus answers to all 4 questions in FDA's fax dated 20 April 2010. The latter includes an update on immunogenicity assay development, a discussion of filaments seen in the product, a question about the hold time of the BDS, and a response to a request concerning the mixing speed and time and --(b)(4)--- contact time during -----(b)(4)-----  
-----.

Amendment 22 dated 13 May 2010 contains a response to FDA's fax dated 3 May 2010 (CMC questions and comments on draft carton and vial labels) and revised draft labeling.

Amendment 23 dated 14 May 2010 contains a revised clinical study report for study Kamada-API-002 (v. 3). An outlier value for A1-PI levels was removed and results recalculated. The resulting analysis continues to indicate that Kamada A<sub>1</sub>-PI is not pharmacokinetically inferior to Prolastin in terms of both steady-state trough functional and antigenic A<sub>1</sub>-PI levels.

Amendment 24 dated 24 May 2010 contains responses to FDA's information request email dated 20 May 2010 and telecon with FDA held the same day concerning the PMR/PMC commitment letter and includes PMR/PMC milestones with revised calendar dates.

Amendment 25 dated 27 May 2010 contains responses to FDA's information request email dated 25 May 2010 concerning the PMR/PMC commitment letter and includes PMR/PMC milestones with revised calendar dates. It states the clinical [phase IV] plans will be revised per FDA's info request and will be submitted by 02 June 2010.

Amendment 26 dated 02 June 2010 contains responses to FDA's information requests faxed 19 May 2010 (CMC issues), emailed 20 May 2010 (draft protocol plans for Q12, 13, and 14 of the 09 Dec 2009 info request fax), and a follow-up relating to PPV clearance by nanofiltration to the information request fax sent 09 December 2009.

## **FURTHER DETAILS OF SELECTED SPONSOR RESPONSES TO CLINICAL INFORMATION REQUESTS**

The following deficiencies were communicated to the sponsor by fax dated 16 July 2009. The sponsor's responses from their amendment 02 dated 27 July 2009 are listed in *italics* below each FDA question, together with my reviewer comments on their reply in **bold**:

1. Please redo and resubmit prior to the filing date your adverse events (AE) datasets to include fields for:
  - Randomized treatment group
  - Product given during the most recent infusion
  - Date and start and ending time of most recent infusion
  - Date and start time of AE



- Hours elapsed since the end of the most recent infusion (use a value of zero if the AE began during the infusion).

Please include only treatment-emergent AEs in the revised datasets.

*Sponsor Reply:*

*Kamada has updated the existing pivotal study analysis dataset for AEs (i.e., der\_AE) to include fields for those requested by FDA and Treatment Emergent AEs.*

*Since AE start and stop times were not part of the raw database, the following assumption is being made for these values. If an AE began on the day of the infusion and it is not known whether the AE began before or after the start of the infusion, it is assumed that the AE began after the start of the infusion ("worst case") and a value of zero is entered for the number of days from the start of most recent infusion to the onset of the AE.*

**Reviewer Comment:**

Noted. None of the .xpt datasets open by double clicking on them, due to sponsor error in setting up the path. The dataset was opened with help from Mr. Jeff Smith by manually navigating to the corrected location in Microsoft Explorer and then dragging and dropping the datasets one by one into JMP 7.0. The revised dataset appears acceptable, but it is noted that the sponsor did not capture the starting time of AEs. The sponsor has included a field for the number of days elapsed since the last infusion. If the AE was reported on the day of an infusion, a zero value is given for this variable and it is assumed, conservatively, that the AE began during or after the infusion.

2. Your define.pdf data definition table for the raw data sets is inadequate in that it does not provide complete and unambiguous definitions of all data fields. Please submit revised definition tables to prior to the filing date to correct this deficiency.

*Sponsor Reply:*

*Revised definition tables for the raw and derived data from the pivotal study (API-002) are included in this submission. An extensive review was*

*performed on the raw datasets to incorporate FDA comments and to provide as much clarity on these fields as possible. Many of the variables have had the labels updated (see file "[List of label changes.xls](#)"). Additionally, several columns were removed from the raw datasets (see file "[List of removed columns.xls](#)") as they existed within the datasets solely for the data collection system purpose and were not utilized for the analysis (examples include a system generated unique ID number and fields that were used for back-end edit check processing). These changes were applied to the datasets as well as to the Define.PDF. Please note that all the raw and derived data for the pivotal study (API-002) and the SAS program files (including a WORD file "SAS Program Documentation (API-002)" which provided each program description) are being resubmitted with this submission, including those that remained unchanged.*

Reviewer Comment:

Noted.

3. Neither your raw nor your analysis datasets appear to contain raw data for the primary endpoint analytes, antigenic and functional A<sub>1</sub>-PI from individual sampling time points for either the pivotal trial or the single-dose PK/safety study. Please submit these data prior to the filing date. PK data from each sampling time should be submitted for each subject.

*Sponsor Reply:*

*PK study raw and derived data for the primary endpoint analytes, antigenic and functional A<sub>1</sub>-PI from individual sampling time points are provided with this submission.  
Raw data for the primary endpoint analytes, antigenic and functional A<sub>1</sub>-PI from individual sampling time points for the pivotal study are provided with this submission  
(for pivotal study API-002 see files "AAT-ANEC WEEK 13-24 V1 9-26-08.xls" and "AAT-ANEC WEEK1-12 V4.xls"; for PK study API-001 see files "pklabdata.xpt ;pkantigenic.xpt ;pkfunctional.xpt").*

*In addition, excel files have been included in the analysis datasets to provide the laboratory data that was collected for the pivotal study. Descriptions for each of these files have been provided within a new defined document (see file "Lab\_XL\_Define.PDF"). Additionally the Derived Define PDF has been linked to this document to provide an easy path for the reviewer to determine how the files were used in the analysis datasets.*

*The raw define.pdf has been updated to reflect this new data. Antigenic and functional API derived data from the pivotal study was previously provided with the original BLA*

**Reviewer Comment:**

Noted. None of the .xpt SAS transport files open when double clicking them from within Global Submit or from within Microsoft Explorer. The sponsor needs to correct this within 3 business days. The sponsor does not provide in its response the location of the raw A1-PI antigenic and functional serum level data from the single dose PK study. This has been submitted only in .xpt format. The dataset lacks an elapsed time since infusion field, but gives clock times of each sample.

4. A spot check of your raw datasets indicates that they are inadequate in that, when right mouse clicking on the field names, the column information dialog box does not provide any additional definition beyond just repeating the field name. The column information for the analysis datasets also appears to be inadequate. For example, "Treatment Number" values of "1" and "2" are not defined and "MAAT" (mean aat") does not indicate over which weeks trough levels are averaged for this derived variable in dataset "AATP1ITT." Please re-do and resubmit your datasets by the date mentioned above to correct this deficiency.

***Sponsor Reply:***

*Raw datasets for the pivotal study have been updated to include additional definition information in the column information dialog box.*

*An extensive review was performed on the raw and derived datasets to incorporate FDA comments and to provide as much clarity on these fields as possible. Many of the variables have had the column information for the analysis updated. Additionally, several columns were removed from the raw datasets as explained above in answer to question #2.*

*These changes were applied to the datasets as well as the Define.PDF.*

*Please note that all the data and program files for the pivotal study (API-002) are being resubmitted with this submission, including those that remained unchanged.*

Reviewer Comment:

Noted. As noted above, none of the .xpt datasets opens properly by double clicking on them.

5. It does not appear that you have submitted any SAS export files for the single dose PK/safety study. Please submit adequate SAS export files for this study prior to the filing date.

*Sponsor Reply:*

*Raw and derived SAS export files for the single dose PK/safety study (API-001) along with define.pdf data definition files, annotated CRF (blankcrf.pdf) and the program files are included in this submission.*

Reviewer Comment:

Noted. As noted above, none of the .xpt datasets open by double clicking on them from Global Submit. In the future, the sponsor should provide the location of all datasets.

**Filing deficiencies communicated to the sponsor by fax on 31 July 2009 together with Sponsor responses as contained in Amendment 06 received 23 October 2009 in italics and reviewer comments in bold:**

6. Please submit an analysis of the subjects in each treatment group who had the onset of their adverse event (AE) during or within 24 hours of the end of an infusion of study product. For cases in which the time of onset of the AE was not captured, assume that all AEs that began on either the day of an infusion or the day following an infusion occurred within 24 hours of the end of an infusion. Present these data (a) only for the initial 12 weeks parallel portion of the study, by treatment group and (b) for the entire duration of study, by actual treatment.

*Sponsor Response:*

*A pdf file containing the summary tables and listing for the AEs occurring within 24 hours is provided. The datasets were amended as follows to create these tables and listings:*

- 1. A flag variable indicating whether the event occurred within 24 hours of last infusion was included in the DER\_AE2 SAS dataset.*
- 2. The program ae\_bs\_24hr is a new program that created the two summary tables and listing for the AEs occurring within 24 hours.*
- 3. A code to create the .flag variable for the AEs occurring within 24 hours was included in program der\_ae.*

*A revised data description file (define pdf) and program description file (progtocpdf) are also provided. Hyperlinking is only done for new and revised dataset or program files so as to prevent broken links in the event data sets are moved outside of the eCTD structure.*

**Reviewer Comment:**

Noted.

7. Your study report for this study states on p 7 “Two subjects were withdrawn due to AEs, one subject (ID No. -----(b)(6)-----) for pulmonary emboli (Prolastin®) and one subject with urticaria (Kamada-API). The raw dataset for serious adverse events (SAEs) in study (b)(4) API 002 (“SERIOU18”) lists 6 SAEs (4 unique AE terms)

reported for 4 subjects, all in "GROUP" "API." GROUP is defined as "Static value of API for every subject." Please provide the field name in this dataset that indicates to which randomization treatment group each subject belongs.

*Sponsor Response:*

*A new dataset DER\_SAE which is a replicate of the SERJOU18 dataset with two new fields treatment and treatment number added indicating to which randomization treatment group each subject belongs. A new program der\_sae was created to derive the new DER SAE dataset.*

*Please note that the information on the SAE's for two subjects, -----(b)(6)-----, is dispensed on two lines in the raw datasets. The 6 lines in the raw datasets therefore represent 4 SAEs (4 unique AE term!') reported for 4 subjects, none of which considered related to the study drug.*

**Reviewer Comment**

Noted.

8. Why were 2 subjects with AAT phenotype MZ enrolled in study (b)(4) API 002, given that this phenotype normally is not associated with serum A1-PI levels  $< \sim 17$  microM?

*Sponsor Response:*

*Qualification of AAT deficient patients in (b)(4) - API 002 study was based on A1-PI levels in serum rather than phenotype characteristics. The study inclusion criteria in this context call for: " At-risk " alleles associated with serum AAT  $< 11$  microM including null alleles and deficiency alleles. Additionally, because of assay limitations, these MZ patients may have actually been Z/Null rather than the MZ as MZ is the result of genotyping a Z/Null individual.*

*We enclose a summary table of five different subjects in the study who had either MZ phenotype (or other) or genotype and their corresponding A1-PI levels.*

**Table 1: Subjects with MZ Phenotype or Genotypes and Their Corresponding AI-PI levels**

Subject #	Treatment Group	A1-PI Levels baseline (micro M)	Genotype	Phenotype
----- ---(b)(6)--- -----	Kamada-API	9.24	ZZ	MZ
----- ---(b)(6)--- -----	Kamada-API	9.98	MZ	PLoweliZ
----- ---(b)(6)--- -----	Kamada-API	7.5	ZZ	MZ
----- ---(b)(6)--- -----	Prolastin	<4 <sup>1</sup>	ZZ	MZ
----- ---(b)(6)--- -----	Kamada-API	6.51	MZ	MaltonMZ

<sup>1</sup> The AI-PI level was reported in the dataset as <20mg/dl.

### Reviewer Comment

**It is known that the electrophoretic or isoelectric focusing procedure for phenotyping can lead to misclassifications of AATD subjects. Nevertheless, the sponsor's response is confusing. If actual MZ subjects were enrolled, their baseline qualifying AAT levels < 11 microM may likely represent lab errors. An imbalance with greater numbers of true MZs in the Kamada- A1-PI randomization arm would tend to bias the trial results. The sponsor is asked to present additional pre-treatment serum AAT values for these subjects, if available.**

**In addition, please inform the sponsor by telephone that the path in the EDR submission for all SAS transport files (\*.xpt) is incorrect. This prevents the SAS transport files from opening when double clicking them in Global Submit. The sponsor needs to correct this by amendment within 3 business days. In addition, please ask the sponsor to provide the password to permit access to the randomization code Excel spreadsheets, or provide new randomization code Excel spreadsheets which are not password protected.**

**Additional letter-ready PMC comment which was communicated later in the review cycle:**

Please conduct a PMC BAL study because of the technical error in BAL sample processing that led to the inability to assess functional A1-PI in ELF.

[This is a very important analyte that was included among the essential endpoints to evaluate A<sub>1</sub>-PI products, as recommended by the joint NHLBI-FDA Workshop held in 1985, which has formed the basis of licensure of all A<sub>1</sub>-PI IV products to date.]

The following information request items were conveyed to the sponsor by fax on 16 December 2009 and were based on my 28 October 2009 mid-cycle review memo. Each item is followed by the sponsor's **11 JANUARY 2010 Amendment 12 response** in italics and my reviewer comment in bold.

1. (Q11) From review of medical records, please submit additional pre-augmentation therapy serum AAT levels for the following subjects whom you identified as having either MZ genotype or phenotype in your response to item 3 from our fax IR dated 31 July 2009:

**Table 1: Subjects with MZ Phenotype or Genotypes and Their Corresponding A1-PI levels**

<b>Subject #</b>	<b>Treatment Group</b>	<b>A1-PI Levels baseline (micro M)</b>	<b>Genotype</b>	<b>Phenotype</b>
-(b)(6)-	Kamada-	9.24	ZZ	MZ



-(b)(6)- -----	API			
----- (b)(6)-- -----	Kamada-API	9.98	MZ	PLoweliZ
----- (b)(6)-- -----	Kamada-API	7.5	ZZ	MZ
----- (b)(6)-- -----	Prolastin	<4 <sup>1</sup>	ZZ	MZ
----- (b)(6)-- -----	Kamada-API	6.51	MZ	MaltonMZ

<sup>1</sup> The AI-PI level was reported in the dataset as <20mg/dl.

### ***Sponsor's Response:***

*Subjects were eligible for inclusion into Study Kamada-API-002 based on evidence of lung disease related to alpha-1 antitrypsin (AAT) deficiency and 'at-risk' alleles associated with API plasma levels < 11µM. Baseline α1-PI levels were determined after a 5-week wash-out period of exogenous API. Aside of baseline levels representing levels without augmentation therapy, controlled data representing such levels prior to enrollment into the study are not available.*

*Nonetheless, in order to clarify the differences in genotype and phenotype, as presented in the table, please find attached a signed letter from Dr. Robert Sandhaus, Principal Investigator Study for the pivotal study, further clarifying these differences and rationale for inclusion of patients based on genotype, phenotype and baseline α1-PI levels.*

*From Dr. Sandhaus' letter:*

- 1) Genotyping only detects the Z or the S gene on each allele of the alpha-1 antitrypsin gene pair. All other genes whether normal (M), or abnormal but not Z or S (Plowell or Mmalton, for example) are reported out as "M".
- 2) Phenotyping (also known as Pi-typing) identifies the type of alpha-1 antitrypsin protein circulating in the blood. When a ZZ individual is receiving augmentation therapy, their Pi-typing will change from ZZ

to MZ because of the circulating M protein delivered by the augmentation therapy. Even small amounts of M protein will be detected by Pi-typing. Thus, an individual who has recently stopped their augmentation therapy will often have the MZ phenotype form many weeks after discontinuation.

3) With respect to levels, there is a simple conversion from micromoles to mg/dL. Based on the molecular weight of alpha-1 antitrypsin (52 kD), one would multiple micromoles by 5.2 to calculate mg/dL and, conversely, divide by 5.2 to convert mg/dL to micromoles. Thus, <20 mg/dL would be equivalent to <3.85 micromole which is reasonably rounded to <4 micromole.

To summarize these points with respect to the subjects above:

- ---(b)(6)---: ZZ genotype, severely deficient level, MZ phenotype == Consistent with someone who has qualifying ZZ genotype and recently (within two months) stopped their augmentation therapy.
- ---(b)(6)---: “M”Z genotype, severely deficient level, PlowellZ phenotype == Plowell is an at-risk genotype that would not be detected by genotyping but is detected by Pi-typing.
- ---(b)(6)---: ZZ genotype, severely deficient level, MZ phenotype == Consistent with someone who has qualifying ZZ genotype and recently (within two months) stopped their augmentation therapy.
- ---(b)(6)---: ZZ genotype, severely deficient level, MZ phenotype == Consistent with someone who has qualifying ZZ genotype and recently (within two months) stopped their augmentation therapy.
- ---(b)(6)---: “M”Z genotype, severely deficient level, MmaltonZ phenotype == Mmalton is an at-risk genotype that would not be detected by genotyping but is detected by Pi-typing.

### **Reviewer Comment:**

**Noted and accepted.**

2. (Q12) Please conduct a randomized BAL study to evaluate various ELF analytes (including antigenic and functional A1-PI, neutrophil count, total and free neutrophil elastase (NE), and A1-PI:NE complexes) in and adequate number of subjects to observe significant changes from pre-augmentation therapy baseline in subjects receiving (a) Kamada A1-PI and (b) another U.S.-licensed A1-PI product dosed

to steady-state. Please submit a protocol to the IND with a cross-reference letter as an amendment to the BLA at this time. Please include this study in your letter of post marketing commitments and be sure to provide estimated milestones for submission of a final protocol, start of the trial, completion of enrollment, completion of the study, and submission of the final study report to the BLA with a letter of cross reference to the IND. The data from the BAL study submitted with your BLA are insufficient because (a) satisfactory BAL samples were available pre- and post- augmentation therapy for only 2 Prolastin subjects and (b) a technical error in BAL sample processing led to the inability to assess functional A1-PI in ELF in all samples. FDA considers this to be a key BAL study analyte.

***Sponsor's Response:***

*Please find attached a letter of post marketing commitments including a table summarizing the estimated milestone schedules requested by the Agency for the randomized BAL study including submission of a final protocol, start of the trial, completion of enrollment, completion of the study, and submission of the final study report. A draft clinical protocol cross-referring to this BLA will be submitted to BB-IND --(b)(4)-- as soon as possible.*

***Contents of letter of post marketing commitments:***

*This letter contains the Post Marketing Commitments for Kamada-API (STN: BL 125325). Kamada acknowledges the request of the Agency to perform post marketing clinical studies including (Reply to comments no.'s 12, 13 & 14 of FDA letter dated Dec 9th 2009):*

- 1. Evaluation of Bronchoalveolar Epithelial Lining Fluid (ELF) analytes.*
- 2. Immunogenicity and viral seroconversion.*
- 3. Two-stage investigation to demonstrate product efficacy*

*Kamada wishes to consider a design that will join some of the studies together and will present the suggested design before the Agency. The outlines (synopses) for the proposed studies will be*

*provided to the Agency during the remaining time of the review period and not later than March 15th 2010. Kamada would like to discuss the design of the proposed studies with the Agency on that time.*

*For these post marketing commitment clinical trials, the proposed the estimated schedules is provided in the table overleaf.*

<b>Milestone</b>	<b>Estimated timeline * for ELF study</b>	<b>Estimated timeline * for Immunogenicity and viral seroconversion study</b>	<b>Estimated timeline * for stage 1- efficacy study</b>
Submission of final protocol/s	9 months from product approval [~Q1-2011]	9 months from product approval [~Q1-2011]	9 months from product approval [~Q1-2011]
Start of trial/s (screening)	12 months from FDA approval of protocol [~Q1-2012]	9 months from FDA approval of protocol [~Q4-2011]	18 months from FDA approval of protocol [~Q1-2013]
Completion of enrollment (last patient in)	Approximately 12 months from start of trial [~Q1-2013]	Approximately 6 months from start of trial [~Q3-2012]	Approximately 24 months from start of trial [~Q1-2015]
Completion of the study (last patient out)	Approximately 4 months from completion of enrollment [~Q3-2013]	Approximately 12 months from completion of enrollment [~Q3-2013]	Approximately 12 months from completion of enrollment [~Q1-2016]
Submission of final study report	Approximately 9 months from closure of data base [~Q2-2014]	Approximately 9 months from closure of data base [~Q2-2013]	Approximately 9 months from closure of data base [~Q1-2017]

\*Please kindly note that these timelines may be subject to a change as a result of changes in protocol outline, discussions with the Agency, challenges in patient recruitment, data processing, etc.

**Reviewer Comment:**

**Noted. The milestone for starting the stage-1 efficacy study by 18 months following FDA approval of the protocol seems somewhat prolonged, especially if site preparations occur in parallel with FDA consideration of the protocol. The sponsor should be asked if they can shorten this. The fact that the duration of subject participation in the stage-1 efficacy study is only 12 months suggests that the sponsor is considering to use pulmonary exacerbations as the primary endpoint of their clinical efficacy phase IV program.**

3. (Q13) Please submit to the IND and cross-reference the BLA with an amendment for a clinical protocol to evaluate the immunogenicity and to further evaluate the viral safety of your product following multiple repeat exposures over a period of at least 6 months of regular weekly administration. Please include this study in your letter of post marketing commitments and be sure to provide estimated milestones for submission of a final protocol, start of the trial, completion of enrollment, completion of the study, and submission of the final study report to the BLA with a letter of cross reference to the IND. The protocol should include provision for measuring inhibitory antibodies in any subjects who have treatment-emergent positive antibody samples. Viral safety should be assessed by baseline and follow-up (in subjects testing negative at baseline) measurements *by both antibody and PCR* for parvovirus B19, HIV, HBV, HCV, and hepatitis A. The following testing schedule is recommended if each subject receives the same lot of product throughout the study. If the same subject receives more than one lot, 3 and 6 month testing following the end of the 6 month period of dosing should be performed.

### Viral Markers and Testing Frequency for a 6 Month Dosing Study

Virus	Baseline	3-month	6-month	3 & 6 months* post-final administration
HIV-I & II	Serology & NAT	Serology & NAT	Serology & NAT	Serology & NAT
HCV	Serology & NAT	Serology & NAT	Serology & NAT	Serology & NAT
HBV	Serology (& NAT)	Serology (& NAT)	Serology (& NAT)	Serology (& NAT)
B19**	Serology & NAT	NAT	NAT	NAT
HAV**	Serology & NAT	NAT	NAT	NAT

\* To establish the viral safety of the doses given at the end of the trial

\*\* To be performed only if the subjects are negative at the baseline

#### ***Sponsor's Response:***

- Please find attached a *letter of post marketing commitments* including a table summarizing the estimated milestone schedules requested by the Agency for the clinical study to evaluate the immunogenicity and viral safety of Kamada-API following multiple repeat exposures over a period of at least 6 months of regular weekly administration, including submission of a final protocol, start of the trial, completion of enrollment, completion of the study, and submission of the final study report. A draft clinical protocol cross-referring to this BLA will be submitted to BB-IND ---(b)(4)--- as soon as possible.

#### **Reviewer Comment:**

**Noted.**

- 4. FDA has requested and received commitments from all licensed manufacturers of  $\alpha$ 1-PI, that they perform a Phase IV investigation to demonstrate product efficacy. Design elements and considerations are outlined, below. You may propose an alternative approach if that approach satisfies the goal of the**

**Phase IV commitment.** Please submit to the IND as soon as possible a protocol and plan to conduct and report the results of your Stage 1 study designed to fulfill this commitment. Please include the Phase IV study(ies) in your letter of post marketing commitments and be sure to provide estimated milestones for submission of a final protocol, start of the trial, completion of enrollment, completion of the study, and submission of the final study report to the BLA with a letter of cross reference to the IND.

### **Recommended design of Phase IV studies:**

#### ***Stage 1***

**This study will be part of a two stage investigation as described below. The conduct of the second stage will be contingent on the outcome and results of the first stage. Briefly, the Stage 1 study examines the proposed dose plus a dose at least 2-fold higher using one or more clinically meaningful endpoints, such as pulmonary exacerbations of COPD, high resolution CT lung density, mortality, and/or serial pulmonary function testing. A key objective of the study is to estimate the magnitude of the difference in efficacy between the currently recommended dose and the higher dose. Phase 1 should be a pilot trial of clinically meaningful endpoint(s). Examples of acceptable endpoints include pulmonary exacerbations, serial pulmonary functions, mortality, and serial quantitative computerized axial tomographic (CT) lung scans.**

#### **Details include:**

- **A randomized, controlled, parallel, masked design.**
- **A minimum enrollment of 60 subjects (30 subjects per treatment group) in the pilot study.**
- **The control group(s) should include a different dose of the test product (i.e., higher, such as 120 mg/kg/week or 240 mg/kg/2 weeks) in comparison to the labeled dosing regimen of the test product**



- The trial duration would depend on the primary endpoint chosen; for pulmonary exacerbations, it will be a minimum of one-year's duration to avoid seasonal bias.
- The trial design will include measurement of baseline and steady-state antigenic and functional  $\alpha$ 1-PI blood levels.
- The trial may include a post-trial follow-up assessment by intent-to-treat.
- A draft protocol should be submitted as soon as possible to the IND, with a letter of cross-reference to the pending BLA submitted as an amendment. A final protocol will be filed to the IND with a letter of cross-reference to the BLA within 6-9 months after product approval.
- The trial will be initiated within 6-9 months after protocol acceptance by the FDA.
- Please provide milestones for the estimated times for completion of enrollment and completion of the study.
- The final study report will be submitted to the IND with a letter of cross-reference to the BLA within 9 months following completion the last study visit of the last subject.

## *Stage 2*

**Adequately-powered study of clinically meaningful endpoints(s).**

- Based on the results of the pilot study and the available scientific data at the time that this study is being designed, Kamada will design and conduct an adequately-powered study of a clinically meaningful endpoint(s). FDA suggests that Kamada work with entities maintaining registries of patients and consider working with NIH to enable recruitment. The study design could involve a single product or could potentially involve a cooperative simultaneous study of multiple products in parallel arms, using a factorial design. In the event that the study involves more than one product, Kamada commits to provide sufficient product to administer to an equal proportion of subjects as are being provided any of the other products. The design/conduct of the study may be contingent upon:
  - o The number of available subjects.

- o The number of subject-years necessary to attain an adequately powered study based on the results of the previous study and current scientific data.
- o The participation of other manufacturer(s) of this product class.
- A strong positive outcome in the pilot study may obviate the need for a follow-up study.
- The trial may include one or more post-trial follow-up assessment(s).
- The final protocol for this study will be filed to the IND and BLA within one year of the filing of the final report of the pilot study.
- You will initiate the trial within 6-9 months after protocol acceptance by the FDA.
- Please provide milestones for the estimated times for completion of enrollment and completion of the study.
- The final study report will be submitted to the IND with a letter of cross-reference to the BLA within 12 months following completion the last study visit of the last subject.

***Sponsor's Response:***

*Please find attached a letter of post marketing commitments including a table summarizing the estimated milestone schedules requested by the Agency for a Phase IV study to demonstrate product efficacy, including submission of a final protocol, start of the trial, completion of enrollment, completion of the study, and submission of the final study report.*

*A draft clinical protocol cross-referring to this BLA will be submitted to BB-IND ---(b)(4)---- as soon as possible.*

**Reviewer Comment:**

**Noted.**

5. Please modify your Adverse Event (AE) databases for study --(b)(4)-- API-001 and package insert to reflect the headache for which subject -(b)(6)- took acetaminophen (see Note to file No. 01). FDA considers

this to be a treatment-emergent AE notwithstanding the fact that the subject experienced headaches prior to the start of the study.

***Sponsor's Response:***

*The database for study -(b)(4)-API-001 (ae) and the listing (AEListing) were modified as per the Agency's comments, i.e. the headache for which subject --(b)(6)-- took acetaminophen was considered to be a treatment-emergent AE. The package insert was changed accordingly (see Kamada-API-draft-labeling, a pdf file with track changes and the Structured Product Label (SPL) Kamada-API).*

**Reviewer Comment:**

**Noted.**

6. Q 16) Please submit the addendum to clinical study API-001 containing complete viral safety follow-up data from the 3 and 6 month follow-up visits. Your study report for API-001 states that the original submission contained viral f/u data [primarily] through the 4-week post-therapy f/u and “any available data” from 3 and 6 month f/u visits. You state in the study report that you plan a 2<sup>nd</sup> database lock for this study after complete virology results are available, which will result in an addendum to the study report. This conflicts with statements you have made in the cover letter to Amendment 5 dated 15 October 2009, in which you state that you do not plan to submit a 120 day safety update “since no additional safety data has been collected with intravenously administered Kamada-API since the data cutoff for the Integrated Summary of Safety (Section 2.7.4).” The cover letter to Amendment 5 also states “Complete safety and efficacy data from Studies API-OOI and API-002 were submitted in the BLA, and no additional subjects have been dosed or followed-up for safety.” Please correct these misleading and erroneous statements.

***Sponsor's Response:***

*Section 5.3.3.2 of the BLA contains both the clinical study report API-001 dated December 12 2003 (see Integrated Study Report) and its addendum dated May 7, 2004 (see Addendum to the Integrated*

*Clinical Study Report – Viral Serology Update). This addendum contains the complete viral serology follow up data from the 3 and 6 month follow-up visits of clinical study API-001. The complete safety and efficacy data from Studies API-001 and API-002 were therefore indeed submitted in the BLA, and no additional subjects have been dosed or followed-up for safety. Hence no misleading or erroneous statements were therefore made in this respect in BLA Amendment 5.*

### **Reviewer Comment:**

**As noted in the question, the study report for API-001 indicated that the viral f/u data included in the report were incomplete, necessitating an addendum to the report. It would have been helpful if the report had contained a footnote or hyperlink to the addendum, as the report did not indicate that the addendum was actually contained in the BLA. Included in amendment 5 is a hyperlink to the “ADDENDUM TO THE INTEGRATED CLINICAL STUDY REPORT VIRAL SEROLOGY UPDATE - Date of Original Report: 12 December 2003 - Date of Addendum: 7 May 2004. This addendum gives the date of the last subject’s first visit as 28 July 2003 and the date “Actual termination of long term follow up data” as 27 January 2004. The addendum states in part:**

*This report contains the complete viral serology follow up data from the study entitled “The pharmacokinetics and safety of an Alpha -1 proteinase inhibitor <sup>(b)(4)</sup>-API in subjects with congenital API deficiencies. A dose-escalation clinical trial”. Out of the total 18 patients enrolled, the final study report dated 12 December 2003 included viral serology data on 18 patients at Baseline, 18 patients at the Day 7 follow up, 18 patients at the Week 4 follow up, 13 patients at the 3-month follow up (6 patients from the 30 mg/kg dose group, 6 patients from the 60 mg/kg dose group, and 1 patient from the 120 mg/kg dose group) and 6 patients at the 6-month follow up (6 patients from the 30 mg/kg dose group).*

*All patients were to be assessed serologically for antibodies to HIV 1 and 2 by enzyme immunoassay (EIA), Hepatitis C antibody (HCV Ab), Hepatitis B surface (HBsAb), Hepatitis B core (HBcAb), and*

*Hepatitis B surface antigens (HBsAg) at Baseline prior to the one time infusion of ARCAPI, 3 months after infusion, and 6 months after infusion. Parvovirus B19 antibody was tested at Baseline, Day 7 and Week 4.*

*Complete specimen collection kits for each time point listed above were provided to the site and the------(b)(4)-----  
-----), for sample collection by -----  
(b)(4)-----.*

*All patients tested negative at Baseline for HCV Ab, HBsAg and HBcAb. Patients ------(b)(6)----- tested positive for HBsAb at Baseline and remained positive at 3 and 6 months; all other patients tested negative at Baseline for HBsAb. All patients who had a non-reactive Parvovirus B19 test at Baseline remained non-reactive at  
Day 7 and Week 4 testing.*

*The table below illustrates the remaining data to be reported since the Integrated Clinical Study Report was issued on 12 December 2003. Anomalous data and follow up data from previous anomalous results for patients ------(b)(6)----- are also discussed below.*

**Table 1: Number of subject for whom data is reported since original report.**

**[This table shows that 6 subjects in the 60 mg/kg group had 6 month vital safety data and 5 subjects in the 120 mg/kg group had 3 month and 6 subjects in the 120 mg/kg group had 6 month viral f/u data newly reported in the addendum.]**

**2.3.1 Patient ----(b)(6)---**

*Patient ----(b)(6)---, who was previously reported to have tested negative for HBsAb at Baseline and positive at 3 months, also tested positive at 6 months. It is noted that this subject was vaccinated within 6 weeks prior to Baseline. After review by the Medical Monitor, it was decided that this recent vaccination resulted in an increased level of antibody to the level of detection of the assay from the recent vaccine. See Attachment*

*7 for Hepatitis B vaccination guidelines and interpretation of results. No further testing was required.*

### *2.3.2 Patient ---(b)(6)----*

*Despite testing negative for HBcAb at Baseline and 3 months, patient ---(b)(6)---- tested positive at 6 months. As a result, the patient was re-bled and results were negative for HBcAb. In addition, the 3 month sample was re-tested for HBcAb, which yielded negative results.*

*The medical monitor and the site's principal investigator agreed that the 6 month (b)(4) HBcAb result that was taken on 17 December 2003, was a false positive as confirmed by the negative (b)(4) HBcAb results of the repeat testing of the subject that took place on 14 January 2004. The Centers for Disease Control lists four interpretations for a positive HBcAb when HBsAg and HBsAb are negative as follows:*

- 1. may be recovering from acute HBV infection,*
- 2. may be distantly immune and test not sensitive enough to detect very low level of HBsAb in serum,*
- 3. may be susceptible with a false positive HBcAb, or 4. may be detectable level of HBsAg present in the serum and the person is actually a Please see Attachment 7 for more information.*

### *2.3.3 Patient --(b)(6)---*

*The 6 month HIV 1 and 2 results for patient S1102 were non-reactive. **Results for patient (b)(6) as stated in 9.5.1 of the CSR incorrectly described that a re-test of the 3 month sample yielded negative results when they were actually positive for ---(b)(4)---- and reactive for HIV 1 and 2 [emphasis added.]** However, as stated in 9.5.1 of the CSR, the patient was re-bled for HIV 1 and 2 on 20 June 2003 and these results were negative for -----(b)(4)---- and non-reactive for HIV 1 and 2 so, in effect, the 3 month results were still negative. See Table 4 for complete results. Additionally, the PCR test result of the investigational product was negative... It was determined by -----(b)(4)---- that the result of the positive 3 month sample*

*was caused by pre-analytical contamination prior to clinical testing. ---(b)(4)---- determined that the ----(b)(4)----- antibody testing yielded low reactive results and the Western Blot showed strong positive results, which is consistent with contamination. A junior staff member released these results without review by a laboratory manager. -(b)(4) amended the 3 month results to read “test results not conclusive” and submitted a letter to -----(b)(4)---- in response to the validity of the result being questioned.*

#### **2.4 General Overall Virology Summary**

*Results for all patients at all time points confirmed there were no seroconversions for HIV 1 & 2, HCV, HBV, or Parvovirus B19. All anomalous results from the study are summarized below.*

**Table 3: Summary of anomalous results (results in italics indicate previously unreported results)**

*[See Table on p 990 of 1033]*

*...patients -----(b)(6)----- received the first 2 Hepatitis B vaccinations within 6 weeks prior to infusion of investigational product, as reported on the Prior Medication History page of the Case Report Forms. Patient --(b)(6) tested positive for HBsAb at 6 months despite a negative result at Baseline.*

*As stated previously, patient -(b)(6)-- tested positive for HBsAb at 3 months and 6 months. This is shown in the table below along with infusion date and dose group. These positive HBsAb results for ---(b)(6)----- were most likely due to antibodies made to the Hepatitis B virus (HBV) as a result of receiving the first two Hepatitis B vaccinations within 6 weeks prior to infusion. The change does not represent a seroconversion due to infection because the subjects who tested positive for HBsAb also tested positive at -subsequent time points, where tested; additionally, HBsAg and HBcAb remained negative during these time points.*

#### **Reviewer Comment:**

**Subject --(b)(6)-- was negative for HBsAb at baseline and 3 months and positive a 6 months. The sponsor attributes this to vaccination within 6 weeks prior to baseline. It seems odd that antibodies would not be present due to vaccination at 3 months, but would be detectable at 6 months. However the lack of positive HBsAg and HBcAb results lends credence to the sponsor's hypothesis. Note that the sponsor has committed to a phase IV study to further confirm the viral safety of the product using both serology and PCR. It has been the "current thinking" for several years that sponsor's of plasma-derived products need to perform PCR in addition to serologic testing to confirm the viral safety of their products pre-licensure. Note that the sponsor's study was also deficient in that the vital safety testing time points specified by the protocol presumed that all KAMADA-API subjects would each receive a single lot of the product throughout the study, but as noted below this requirement of the protocol was not always respected.**

**Q17**

**Please explain the "Listing of Subjects receiving test drug(s) investigational" (Section 5.3.5.1.3, Appendix 16.1.6). Lot assignment appears to be inconsistent with the study protocol. Some patients appear to receive exclusively Prolastin. Some patients are stated to be on Prolastin; however, the number of lot assigned indicates that Kamada-API was used.**

***Sponsor's Response:***

*Please find the corrected Table 17-1 below:*

**Table 17-1 Listing of Subjects receiving test drug(s) investigational [See sponsor's table on p 33 of 298.]**

**Reviewer Comment:**

**The table shows 2 subjects to have received KAMADA-API and 6 subjects to have received PROLASTIN. Whereas the protocol required each subject to receive only a single lot throughout the study, all PROLASTIN subjects each received either 2 or 3**



different lots, according to table 17-1 on p 33 of 298 of BLA amendment 5. The first page of table shows each KAMADA-API subject to have received only a single lot of the product; yet, according to the FDA BiMo inspection Form 483 issued by Investigator Dianna Richards on 01/02/2010, at -----  
-----Information withheld per the privacy act-----  
(6115006A, as listed in the sponsor's Table 17-1, and lot 6126004A, not listed in Table 17-1). The 2<sup>nd</sup> page of Table 17-1 shows 22 subjects to have received KAMADA-API and 12 subjects to have received PROLASTIN. Among the KAMADA-API subjects on p 2 of the table, KAMADA-API subjects --(b)(6)-- and ----(b)(6)----- each received 2 different lots of KAMADA-API.

**Q18**

**Please submit a summary of postmarketing adverse events reported through pharmacovigilance in countries where the product is commercially available.**

***Sponsor's Response:***

Kamada-API is approved in Mexico and Brazil, although marketing has not yet commenced in these countries.

Kamada-API has been used on a "named patient" basis in Israel, Brazil and Slovenia. To date, more than (b)(4) vials were sold whereby no reports of AEs and no safety concerns have been identified.

Kamada-API has not been withdrawn from investigation or marketing in any country.

**Reviewer Comment:**

**Noted.**

**PHARMACOVIGILANCE:****Q19**

**Please submit in a BLA amendment and implement a post-licensure pharmacovigilance plan, per the ICH E2E Pharmacovigilance Planning guidance, to monitor long-term safety with the use of Kamada-API. The major components of a pharmacovigilance plan for Kamada-API should include routine pharmacovigilance (i.e., compliance with applicable post-market reporting requirements under FDA regulations) and possibly additional postmarket actions to address any potential adverse events that may be identified, particularly in view of the relatively small number of patients studied thus far, with adverse event ascertainment procedures to track allergic reaction, disease transmission, or any other unexpected side effects, especially serious ones that may emerge through systematic monitoring of larger numbers of treated patients. Routine post-marketing safety surveillance would be an integral part of your pharmacovigilance plan, as outlined in Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment ([www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126834.pdf](http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126834.pdf)).**

***Sponsor's Response:***

*Kamada's post-licensure pharmacovigilance plan is provided in the revised Chapter 1.16. In addition, Kamada commits to perform three Phase IV studies as detailed in the letter of post marketing commitments and the answers to the Agency's comments 12, 13 and 14.*

**Reviewer Comment:**

**Noted. Aside from the PMC Phase IV studies, for which protocol synopses have yet to be provided (promised by 15 March 2010), the sponsor's PVP appears to comprise routine pharmacovigilance. See review by Dr. Faith Barish of CBER/DBE.**

**Review of Amendment 17 dated 15 March 2010 contains protocol outlines for Phase 4, PMC clinical studies as requested in FDA's 09 Dec 2009 fax info request items 12, 13, and 14.**

Changes were made to the original brief PMC study outlines following consultations with A1PI field specialists.

**A Phase IV, open label, multicenter study, exploring potential immunogenicity and viral safety following the use of Kamada's Intravenous, Human, A1PI in Alpha-1 Antitrypsin Deficient Patients.**

Suggested modification	Rationale
Addition of a comparator arm	The study aims at investigating immunogenicity. A second arm of patients using a comparator drug will provide adequate counter in case of positive or false positive results for antibodies or inhibitory antibodies detected.
Adding secondary endpoint : levels of functional and antigenic A1PI	It is considered that there could be a relationship between levels of functional and antigenic A1PI and AAT antibodies and/or inhibitory antibodies.  It is important to learn the impact of antibody presence on these levels.

**Table 1-2 Suggested Changes in Protocol Outline (Synopsis) for ELF:**

**A Phase IV, open label, multicenter study, investigating Epithelial Lining Fluid of Alpha-1 Antitrypsin Deficient Patients for A1PI and analytes levels following augmentation therapy with Kamada-API.**

Suggested modification	Rationale
Omission of a comparator arm	The study is purposed to evaluate the ELF levels of Kamada-API product. Adding a comparator arm for which ELF data is already in place from past developments, is expected to negatively influence the enrollment target and challenge the performance of the study while providing relatively negligible added value to the study and Kamada-API product development.

**Table 1-3 Suggested Changes in Protocol Outline (Synopsis) for Efficacy:**

**A Phase IV, Randomized, Placebo-Controlled, Double-Blind, Multicenter Study investigating the Safety and Efficacy of Kamada-API I.V. vs placebo and another (higher) dose of Kamada API I.V by Weekly Administration in Alpha-1 Antitrypsin Deficient Patients with emphysema.**

<b>Suggested modification</b>	<b>Rationale</b>
Addition of a placebo arm to the study on top of the 60mg/kg dose vs. 120mg/kg dose	There is no controlled clinical efficacy data established for the dose of 60mg/kg. Therefore, a placebo arm is necessary. The efficacy gap difference the company expects between 60mg/kg to 120mg/kg is expected to be considerably smaller than the difference between placebo and treatment group. Therefore, it is essential to measure these differences prior to powering a study for achievement of a statistical significant efficacy result.

## **REVIEWER COMMENT ON CHANGES TO PMC STUDY OUTLINES**

- **For the immunogenicity and viral safety study:**
  - Please justify or omit the use of a 5-week washout period. Given that you have added a positive control group to this study we recommend that the study be masked rather than open-label if possible.
  - We recommend a single licensed comparator rather than multiple comparators be used.
  - Please clarify which type of viral safety tests will be performed at which time points.
  - Please clarify why each subject will participate in the study for ~ 64 weeks given that the planned treatment period is 12 weeks (p 4 of protocol outline).
- **For the BAL study, FDA recommends:**
  - Inclusion of a small number of control subjects in who have received a licensed A<sub>1</sub>-PI product. Should anomalous/unexpected results of any analytes be observed, the inclusion of a control will help to determine whether there was a problem with the assay or sample handling, as opposed to being indicative of a problem with the investigational product.
  - You may consider offering BAL study subjects simultaneous participation in the immunogenicity/viral

- safety/safety study. If this is not done, we recommend addition of antibody testing to the BAL study.**
- **The primary endpoint should be both antigenic and functional A<sub>1</sub>-PI levels in ELF after 10-12 weeks of treatment, not antigenic or functional A<sub>1</sub>-PI levels.**
  - **Depending on the size of the comparator group, in addition to changes in ELF analytes from baseline to 10-12 weeks, we recommend you analyze as an exploratory analysis the difference between treatment groups in 10-12 week values using the baseline value as a co-variate.**
- **For the dose-ranging, placebo controlled stage-one efficacy study:**
    - **We recommend the duration of the study be substantially extended. Given your choice of lung density assessed by serial quantitative computerized tomography of the lungs as the primary endpoint, the one year study duration you propose is insufficient to expect to see efficacy, based on results seen in studies with other members of this product class. [wording of this comment is superseded by Amendment 19 – see Letter-Ready Comments]**
    - **Please justify the performance of CT scans 8 and 10 weeks apart as proposed. [wording of this comment is superseded by Amendment 19 – see Letter-Ready Comments]**

**Review of Amendment 19 dated 01 April 2010 responded to FDA information request faxes dated 18 and 19 March 2010.**

The 18 March 2010 fax included 8 clinical questions. These are reproduced below with the sponsor's responses and my Reviewer Comments in bold italics.

**Q1**

**Based on the FDA BioResearch Monitoring (BiMO) inspection of study**  
**----- Information Withheld Per Privacy Act -----**  
**-----**

**-----Information withheld per the privacy act-----**  
**-----**

5 pages determined not to be releasable: Information withheld per the privacy act.

-----Information withheld per the privacy act-----

-----Information withheld per the privacy act-----

*Noted and accepted.*

**Q5**

**In study site 03 of the pivotal study, the week 12 sample for serum AI-PI levels (ANEC value of 49.8, compared to values of 11.1 and 9.77 for weeks 10 and 11, respectively) appears to be an outlier. Please re-analyze the primary endpoint for serum antigenic and functional AI-PI levels excluding this value.**

We have re-analyzed the data as per the Agency request and attach the new listing sided to a summary of the data analysis that will be incorporated in the amended CSR (see [Attachment 5-1, “Primary endpoint analysis -Outliers Removed”](#)).

To summarize, the median antigenic API values for Weeks 7-12 (Intent –To-Treat) were 14.7  $\mu\text{M}$  in the Kamada-API group (range: 11.6 to 18.5  $\mu\text{M}$ ), and 12.6  $\mu\text{M}$  in the Prolastin® group (range: 10.4 – 19.2  $\mu\text{M}$ ).

The median functional API values for Weeks 7-12 were lower than the antigenic values in both groups and were 11.9  $\mu\text{M}$  in the Kamada-API group (range: 8.2 to 16.9  $\mu\text{M}$ ) and 11.2 $\mu\text{M}$  in the Prolastin® group (range: 7.7 to 18.0  $\mu\text{M}$ ). Results for antigenic and functional API levels were similar between the two groups.

The lower bounds of the confidence intervals were greater than – 3 $\mu\text{M}$  for both antigenic and functional API levels thereby demonstrating the non-inferiority of Kamada-API to Prolastin®.

The proportion of subjects with mean trough antigenic and functional API were also recalculated. The proportion of subjects with mean trough antigenic API levels exceeding 11  $\mu\text{M}$  during Weeks 7 to 12 was 100% for subjects in the Kamada-API group and 75% for subjects in the Prolastin® group. Similarly, the proportion of subjects with mean functional API levels > 11  $\mu\text{M}$  was 66.7% in the Kamada-API group and 62.5% in the Prolastin® group.

In conclusion the removal of the noted outlier did not change the successful outcome of the study as demonstrated in the results if the primary endpoint in both antigenic and functional API values.

Kamada commits to update the CSR in accordance with the new analyses and submit it to the Agency not later than May 15th 2010.

***Reviewer Comment:***

***Noted. The results excluding this outlier value should be those used for the package insert. It is interesting that nearly 2/5 subjects treated with Prolastin at the standard 60 mg/kg/week dose had functional A1-PI levels below the historical target 11 microM value. As noted in my original BLA review, this is lower than has been seen in other studies using Prolastin.***

**Q6**

**Whereas the protocol required each subject to receive only a single lot throughout the study, all PROLASTIN subjects each received either 2**



or 3 different lots, according to the first page of table 17-1 on p 33 of 298 of BLA amendment 5. The table shows each KAMADA-API subject to have received only a single lot of the product; yet, according to the FDA BiMO inspection Form 483 issued by Investigator Dianna Richards on 01/02/2010,

at Dr. Sandhaus' site KAMADA-API subject ----(b)(6)---- received 2 different lots (6115006A, as listed in the sponsor's Table 17-1, and lot 6126004A, not listed in Table 17-1). The 2<sup>nd</sup> page of Table 17-1 shows that KAMADA-API subjects ----(b)(6)--- and ---(b)(6)--- each received 2 different lots of KAMADA-API. Please comment.

### **Sponsor's Response:**

The Agency is correct to state that the protocol calls for allocation of one lot of Kamada-API per subject and that subjects -----(b)(6) and ---(b)(6)----- received more than one lot of Kamada API during the study, as per the following table. We take this opportunity to add another correction for site number 1, for subject ----(b)(6)----- who for the same reason listed below received more than one lot, as presented in the following table:

<b>Subject</b>	<b>Lot Numbers Received</b>
---(b)(6)--	6115006A 6126004A
---(b)(6)--	6115006A 6126004A
---(b)(6)--	6115005A 6126004A 6115006A

The reason for using a second lot was due to the expiration of lots 6115005A and 6115006A during the course of the study. Kamada, therefore, supplied lot 6126004A to be administered to subjects who continued to participant in the study.

Please also note that:

□ In sites #2 and 3 there were few patients for whom another lot was allocated for the same reason. (See [Attachment 6-1 “lot numbers updated”](#) with a list of lot numbers and their allocations, following latest revision).

□ Prolastin subjects received only one lot of Prolastin 26N7LK1. Yet, due to the design of the study, these subjects must have received more than one lot of study drug (overall), since they were crossed over to Kamada-API on the second period of the study.

However, there was one subject who during the second period of the study received two lots of Kamada-API for the same reason stated

Subject	Lot Numbers Received
----(b)(6)---	6115006A
	6126004A
---(b)(6)---	6115006A
	6126004A
---(b)(6)---	6115005A
	6126004A
	6115006A

before expiration of lot 6115006A.

***Reviewer Comment:***

***Noted. The purpose of requiring 1 lot per subject was to obviate the need for 6 viral follow-up testing 6 months following the end of dosing. The sponsor has agreed to do a phase IV viral safety/immunogenicity study.***

**1 page determined not to be releasable: Information withheld per the privacy act**

-----  
-----  
-----Information withheld per the privacy act-----  
-----  
-----.

-----Information withheld per the privacy act-----  
-----.

***Reviewer Comment:***

***Noted and accepted.***

**Q8**

**Please correct the erroneous statements in your draft package insert regarding the number of subjects in each randomization group of the pivotal study who completed All 12 infusions during the double-blind portion of the study and all 24 infusions of the entire study. Our analysis shows that**

- ☐ **Four subjects out of 17 randomized to treatment 1 (Prolastin) had fewer than 12 infusions during period 1 (weeks 1-12).**
- ☐ **Three out of 33 subjects randomized to treatment 2 (Kamada A1-PI) had fewer than 12 infusions during period 1.**
- ☐ **During period 2 (weeks 13-26), 16 subjects randomized initially to Prolastin had all 12 infusions (of Kamada A1-PI) and 1 had no infusions during period 2.**
- ☐ **During period 2, 8 of 32 subjects initially randomized to Kamada A1-PI had fewer than 12 infusions during period 2, and 1 subject had no infusions during period 2.**

**Sponsor's Response:**

Changes in the Product Insert were made in accordance with the Agency's request and are submitted in this Amendment under 1.14.1.

***Reviewer Comment:***

***Noted.***

**Q9**

**We have a preliminary comment with respect to the submitted (15 Mar 2010) outline for "A Phase IV, Randomized, Placebo-Controlled, Double-Blind, Multicenter Study investigating the Safety and Efficacy of Kamada-API I.V. vs placebo and another (higher) dose of Kamada API I.V. by Weekly Administration in Alpha-1 Antitrypsin Deficient Patients with emphysema:"**

**The proposed duration of 12 months is not adequate to meet the study objectives with respect to the proposed primary endpoint of HRCT lung density change. You need to propose an appropriate longer timeframe of study drug administration and evaluation if they want to use HRCT as the primary endpoint.**

**Sponsor's Response:**

Following the agency's comment regarding the duration of the phase 4 part A efficacy study, Kamada has consulted medical experts and has amended the outline of the trial to consist duration of 18 months. The revised [Kamada-API-004-3a-Protocol-Synopsis \(ver002\)](#) for the Phase 4 Efficacy study is provided.

***Reviewer Comment:***

***By way of comparison, the EXACTLE CT study involved a total of 77 subjects randomized to Prolastin or placebo studied for 2-2.5 years.***

***Please submit statements from your consultants discussing the proposed study duration of 18 months.***

***Please submit the power calculations used to determine the proposed sample size for the study.***

***Please justify the proposed schedule of CT exams.***

**REVIEW OF CLINICAL PORTIONS OF AMENDMENT 26  
SUBMITTED 02 JUNE 2010**

Amendment 26 dated 02 June 2010 contains responses to FDA's information requests faxed 19 May 2010 (CMC issues), emailed 20 May 2010 (draft protocol plans for Q12, 13, and 14 of the 09 Dec 2009 info request fax), and a follow-up relating to PPV clearance by nanofiltration to the information request fax sent 09 December 2009.

The sponsor has elected to merge the PMR study (described by the sponsor in its cover letter as the immunogenicity study) and the BAL PMC study. Outlines for this as well as the Phase 4 Stage 1 efficacy study are included.

**PMR/BAL study title:**

A Phase IV, open label, double-blind, multicenter study exploring potential adverse events associated with particulates, immunogenicity, viral safety and ELF analytes following the use of Kamada's Intravenous, Human A1PI (Glassia™) vs. Another Commercial, A1PI in Alpha-1 Antitrypsin Deficient Patients.

Note: Kamada will consider masking the study.

Sample size: ~ 20 to be enrolled.

At least 15 will undergo BAL, of which ~ 5 will receive reference product.

Sites: 3-4

A single licensed comparator will be used.

Dose: 60 mg/kg q week

**Objectives:**

1. To evaluate immunogenicity response following the use of Kamada's A1PI intravenous formulation
2. Detection of adverse events that may possibly be related to potential presence of particulates in the product.
3. To compare levels of API (antigenic and functional) in ELF.

4. To compare neutrophil count, total and free neutrophil elastase (NE), API:NE complexes in ELF.

Pre-study washout: 5 weeks

Treatment duration per subject: 25 weeks.

### **Primary endpoints:**

Level of human antibodies against Kamada-API product (absence and false positive limit is defined within protocol)

- Level of human inhibitory antibodies against Kamada-API product (absence and false positive limit is defined within protocol)
- Adverse events that may be possibly related to potential presence of particulates in the product.

### **Secondary**

- Safety and adverse events
- Levels of functional and antigenic A1PI in ELF
- Neutrophil count, total and free neutrophil elastase (NE) levels, API:NE complexes levels in ELF
- Viral Safety testing – exploration of seroconversion of HIV, HBV, HCV and B19 (B19 limits are defined within the protocol).

Levels of functional and antigenic A1PI in serum

- Difference of ELF analytes between the two treatment groups in 10-12 week values using the baseline value as a covariate

The viral testing appears to conform to the table provided by Dr. Mahmood Farshid of this Division.

### **Stage 1 Efficacy PMC Clinical Trial Title:**

**A Phase IV, Randomized, Placebo-Controlled, Double-Blind, Multicenter Study investigating the Safety and Efficacy of Kamada-API I.V. vs placebo and a new, higher dose of Kamada API I.V by Weekly Administration in Alpha-1 Antitrypsin Deficient Patients with emphysema. (stage 1)**

Sites: 20-45

Placebo: Saline in volumes equivalent to the 2 active groups

Doses: 60 and 120 mg/kg/week Kamada A<sub>1</sub>-PI or placebo in opaque bag.

Objective:

A pilot trial to estimate the magnitude of the difference between placebo, the currently recommended dose of 60mg/kg/week and a higher dose of 120mg/kg/week. The pilot trial aims to:

1. To identify trends of drug efficacy as may be expressed in lung density and/or pulmonary exacerbations characteristics (rate, duration, severity and time to next event).

To explore the difference of the steady state levels of functional and antigenic A1PI in serum in the different study groups.

**Primary Endpoint:**

Lung density by CT

Secondary endpoints:

1. Frequency, severity, duration and time to the next exacerbation event.
2. Lung function (FEV<sub>1</sub>, DLco)
3. Steady state levels of functional and antigenic API levels

Tertiary endpoint

1. Quality of Life (measured by St George questionnaire)

Pertinent Inclusion Criteria: FEV<sub>1</sub> 30 to 80% inclusive.

Pertinent Exclusion Criterion: Exacerbation of COPD in previous 4 weeks, history of lung transplant.

Visits: baseline, weeks 8, 35, 70, 78 and telephone f/u week 80.





2 pages determined not to be releasable: Information withheld per the privacy act.