

**MEDICAL MID-CYCLE REVIEW MEMORANDUM OF ORIGINAL
BLA**

TO: FILE STN: 125325/0

See also: STN

SPONSOR: KAMADA

**PRODUCT: ALPHA-1 PROTEINASE INHIBITOR (HUMAN)
INTRAVENOUS**

**INDICATION: CHRONIC AUGMENTATION AND
MAINTENANCE THERAPY IN INDIVIDUALS WITH
CONGENITAL DEFICIENCY OF ALPHA-1 PKLROTEINASE
INHIBITOR AND CLINICAL EVIDENCE OF EMPHYSEMA**

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

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

CC: RPM: Cherie Ward-Peralta

**SUBJECT: MEDICAL FILING REVIEW OF ORIGINAL BLA,
REVISED**

SUBMISSION LETTER DATE: 29 May 2009

CBER RECEIPT DATE: 29 May 2009

RECOMMENDATION:

1. 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
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 ¹	ZZ	MZ
--(b)(6)- ----- ----	Kamada-API	6.51	MZ	MaltonMZ

¹ The A1-PI level was reported in the dataset as <20mg/dl.

2. 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.

3. 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

4. Please submit to the IND as soon as possible a protocol and plan to conduct and report the results of a stage 1 study that 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. The objective of the study is to estimate the magnitude of the difference in efficacy between the currently recommend dose and the higher dose. The study should ideally be initiated prior to licensure but may be completed during phase IV. 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. **[Sponsor should also be sent the same language regarding the 2 stage clinically meaningful endpoint PMC program that has been sent to Talecris for Prolastin C, to Baxter for Aralast NP, and to CSL Berhring for Zemaira.]**

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)- too 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.
6. 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 2nd 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.

REVIEW

Product

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

Kamada A1-PI undergoes 2 dedicated viral reduction steps: Solvent Detergent treatment and Nanofiltration.

The sponsor cover letter is self-contradictory, in that it states that one clinical study is submitted in support of the application, yet the BLA contains 2 studies:

<i>Presentation:</i>	50 ml vials, sterile
<i>Concentration</i>	(b)(4)
<i>Purity</i>	
<i>Activity</i>	
<i>Route of Administration</i>	Intravenous

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

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 AAT deficiency.

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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 -(b)(4)- 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

See also Clinical Pharmacology review memo.

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 A₁-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.

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

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

STUDY 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.

SUMMARY OF STUDY DESIGN

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.

This was an open label descriptive study with a sequential dose escalation and an 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).

The 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 RESULTS FROM SINGLE DOSE PK STUDY

A reported reactive HIV result on the 3-month draw for Subject -(b)(6)- 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. 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 they plan a 1nd database lock after complet virology results are available, which will result in an addendum to this report.

REVIEWER COMMENT REGARDING STUDY DESIGN

The design of this study was inadequate, in that 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 held of subjects, especially because the clinical benefit of AAT augmentation has not been conclusively established. Note that I was not involved in the design of this study. In addition, 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. The aim of the study should have been to model the single PK results to extrapolate steady-state trough levels in order to determine what dose would be likely to match the trough level of a U.S.-licensed A1-PI product given 60 mg/kg/week to steady state. Also note that "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

DESIGN AND RESULTS OF CLINICAL STUDIES

Study -(b)(4)- 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

PIVOTAL STUDY OBJECTIVES

The primary objectives of this study is to demonstrate that Kamada-API is not therapeutically inferior to the active control, Prolastin® and to determine the efficacy of Kamada-API in maintaining alpha-1 functional plasma levels in excess of 11 µM.





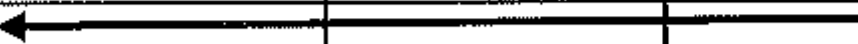
The secondary objectives are to compare the levels of antitrypsin in the ELF before and after 10-12 weeks of administrations and to assess the safety associated with Kamada-API administration.

DESIGN AND RESULTS OF STUDY API-002

SUMMARY OF STUDY DESIGN

Two period trial. Following a 5 week washout from prior AAT therapy, 50 AAT subjects with some 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 2nd part of the trial, all subjects received Kamada A1-PI through week 24. A f/u 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 2nd 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 2nd bronchoscopy at the investigator's discretion.

	-5 weeks	Day 0/Week 1	Week 2
Washout			
BAL and bronchial biopsy/brushing			
Randomization			
Kamada API or Prolastin®			
Kamada API			
AE Follow Up			
Virology Follow Up			
Resume API Standard of Care			

Reviewer comment on study design: I don't know how the "and/or" feature of the primary endpoint is intended to be interpreted. Thus, the primary endpoint should be met for both antigenic and functional A1-PI.

SAFETY ASSESSMENTS IN STUDY API-002

- Treatment-Emergent Adverse Events (TEAEs)
- Vital Signs
- CBC with differential
- Routine biochemistry including electrolytes, BUN, serum creatinine, ALT, AST, alk phosphatase, total and direct bilirubin
- Viral markers (HbsAg and antibodies to HIV1, HIV2, HCV, HBs, and HBc)
- C3 and C4 serum complement levels

- Baseline IgA level
- Physical exam
- Radiology
- Measure the frequency of pulmonary exacerbations. The criteria to define a pulmonary exacerbation in this study are:
 - Increased shortness of breath above baseline
 - Increased sputum volume above baseline
 - Change in color of sputum (increased sputum volume for at least 48 hours)

An exacerbation is defined as one or more of the above elements is present, the exacerbation is classified as ‘mild’, if only one or two all three elements are present this is classified as a ‘severe’. The medications associated with each exacerbation will be recorded.

Anticipated AEs from experience with Prolastin brand A1-PI were generally mild myalgia, arthralgia, and back pain, plus hypersensitivity reactions, including anaphylaxis.

AE Intensity was defined as:

- ***Mild:*** Awareness of signs or symptoms, but no impact on activity.
- ***Moderate:*** Event sufficient to affect usual activity (e.g., unable to work or perform usual activities).
- ***Severe:*** Inability to work or perform usual activities.

EFFICACY ASSESSMENTS IN STUDY API-002

Primary endpoint:

The primary outcome variable is the trough circulating functional API (as an average of the Weeks 7-12 results). In a non-inferiority trial the goal will be to show that the mean API during this period is no lower than 3 μ M below the control. If such, the comparison of the two treatment groups will be based on a two-sided 95% confidence interval for the difference in API. If the lower bound of this API interval is above (less negative than) the control, demonstrating a lack of inferiority will have been achieved.

Secondary Endpoints:

The levels of antigenic and/or functional API present in the ELF will be summarized for each treatment group using means and standard deviations (pre-treatment, post-treatment and change from baseline). The change from baseline in each treatment group will be compared with zero using a t-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 ELF wall by measuring Macrophages, Eosinophils, Lymphocytes in the ELF;
- Changes from baseline of the following ELF parameters (antigenic API and ANEC);

- NE; and
 - AAT-NE complexes.
- Mean ratio of the functional to antigenic API trough level Weeks 7-12 (6 infusions);
 - Ratio of mean antigenic API trough level Weeks 7-12 in the Prolastin® group to the equivalent mean value in the Kamada-API group after their crossover to Kamada-API (i.e. Week 7);
 - As above but for functional API; and
 - Frequency of pulmonary exacerbations.

STATISTICAL METHODS

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 1.0×10^4
- Ratio of [Urea]plasma over [Urea]BAL sample was > 30 and < 350

The non-inferiority procedure described above is formally null hypothesis that the difference between the average Kamada-API group and that in the Prolastin® group alternative hypothesis that the difference is $> 3 \mu\text{M}$.

The confidence interval on which the test is based will be Wilcoxon signed-rank test, stratified by center. This test the 95% confidence interval used to assess non-inferiority.

Additionally, 95% exact binomial lower confidence bound proportion of subjects in each treatment group for whom API for Weeks 7-12 is in excess of $11 \mu\text{M}$. It is a proportion of subjects in the Kamada-API group for whom exceed 80%.

The frequency of pulmonary exacerbations will be analyzed the definition of exacerbations as listed in the Note clarification 4 in section 4.2.1 of the protocol.

ADDITIONAL ASSESSMENTS IN STUDY API-002

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

SAFETY ASSESSMENTS

Physical exam

Vital signs at every visit prior to infusion, 5-10 min after start of infusion, q 30 min and prn during infusion, immediately after infusion and 1 hour after end of infusion.

EKG

CXR

Spirometry at baseline, weeks 12 and 24

HRCT in BAL substudy subjects (optionally repeated post-baseline)

CBC with differential

Routine serum chemistries including BUN, glucose, electrolytes, AST, ALT, total and direct bilirubin, alkaline phosphatase.

Virology: HbsAg, HB core Ag, HBsAb, HCV Ab, HIV! & 2 Ab at screening, baseline, weeks 12 and 28. **Note that -(b)(4)- was not done and testing for parvovirus B19 and PCR were also not done, which is not in keeping with longstanding OBRR requirements for evaluation of plasma-derived products.**

AEs

C3 and C4 at baseline, weeks 12 and 24.

Anti-A1-PI antibodies were not assessed in this study, although they were in the single dose PK study. The sponsor measured C3 and C4 complement serum levels, stating “The consumption of serum complement components C3 and C4 reflects the classic and alternate pathway activations of the complement system. Complement levels below normal range may potentially indicate occurrence of an immune complex disease (immunogenicity reaction).”

RESULTS OF PHASE 2-3 PK NON-INFERIORITY STUDY -(b)(4)- API 002:

DISPOSITION OF SUBJECTS IN PIVOTAL STUDY

The number of subjects randomized was 52. Two had withdrawn consent and were randomized in error but not dosed. Thirty-three were administered Kamada A₁-PI and 17 were administered Prolastin. Two subjects were withdrawn early due to AEs (urticaria in the Kamada A₁-PI group and pulmonary emboli in the Prolastin group). Zero Kamada A₁-PI and one Prolastin 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 A₁-PI group and 2 in the Prolastin group).

DEMOGRAPHICS IN STUDY -(b)(4)- API 002:

Demographics (ITT) (from Sponsor's Table 7)

Parameter	Statistic	Kamada-API N=33	Prolastin® 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®
(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 A₁-PI levels are normally 17 microM or above. The sponsor addressed this in Amendment 6, but questions remain.

PROTOCOL VIOLATIONS

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

One subject received exogenous A₁PI slightly less than the required 5 weeks prior to study start.

In the Kamada product group, 12 subjects missed 1 or more infusions and A₁PI levels.

In the Prolastin group, 3 subjects missed single infusions and these 3 plus another subject missed having an A₁PI 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.

EFFICACY

Serum AAT level surrogate endpoints

Mean baseline antigenic A₁PI levels were 4.8 microM in the Kamada A₁PI group and 4.3 microM in the Prolastin group. Mean baseline functional A₁PI levels were 3.1 microM in the Kamada A₁PI group and 2.3 microM in the Prolastin group.

The primary endpoint was met for both antigenic and functional serum A₁-PI levels in the sponsor's analysis. Mean antigenic and functional A₁-PI levels in the modified ITT population were greater for the Kamada A₁-PI than for Prolastin in the sponsor's analysis.

In the sponsor's analysis, The median antigenic API values for Weeks 7-12 were 14.5 μ M in the Kamada-API group (range: 11.6 to 18.5 μ M), and 12.8 μ M in the Prolastin® group (range: 10.4 – 19.2 μ M). The median functional API values were lower than the antigenic values in both groups and were 11.8 μ M in the Kamada-API group (range: 8.2 to 16.9 μ M) and 11.4 μ M in the Prolastin® group (range: 7.7 to 18.0 μ M). The lower bound of the confidence intervals were greater than – 3 μ 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 API levels exceeding 11 μ M 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 μ M was 66.7% in the Kamada-API group and 62.5% in the Prolastin® group.”

Levels of serum functional A₁-PI were notably lower in both Kamada A₁-PI and Prolastin groups than has been seen in most other pivotal trials of U.S. licensed A₁-PI products; however low levels were also seen in the pivotal study for Prolastin C. This could be due to assay or standard differences, or might reflect sub-potent lots of both products having been used in the study.

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].

SAFETY

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 A₁-PI group and pulmonary emboli in the Prolastin 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 is asked to clarify this apparent discrepancy.).

- Subject ---(b)(6)--- (Prolastin®) 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.

Six SAEs were reported for 4 subjects, all of them in the “API” group. 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 other SAEs were pneumothorax prior to dosing, ERCP, and COPD exacerbation.

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

Study Period 1 (randomized parallel period – 1st 12 weeks):

Numbers (%) of subjects reporting Related AEs – study period 1		
AE	Kamada A₁-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	Prolastin
-----------	---------------	------------------

	A ₁ -PI Randomization Group	Randomization Group
Urticaria	1 (3%)	0 (0%)
Dizziness	1 (3%)	0 (0%)
Rash	1 (3%)	0 (0%)
Joint Swelling	1 (1%)	0 (0%)
Decreased Platelet Count	9 (1%)	0 (0%)
Influenza-like illness	9 (1%)	0 (0%)
Lethargy	0 (0%)	1 (6%)

No subjects seroconverted for HBV, HCV, or HIV during the pivotal study.

Levels of C3 and C4 complement remained relatively stable in both groups.

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 subject.

DEFICIENCIES IDENTIFIED

The pivotal phase 2-3 study had only 4 weeks post-end-of-dosing viral follow-up, which is not in keeping with Div. of Hematology current thinking, which requires 6 months follow-up testing for HCV and HIV unless each subject received only a single lot of product.

The statement of the primary endpoint is unclear: “Circulating antigenic **and/or** [emphasis added] functional API trough level averaged over Weeks 7-12 (6 infusions). The goal of this study was to demonstrate that Kamada-API is not clinically inferior to Prolastin®. The definition of lack of inferiority was an average trough value no lower than 3 μ M below that of

the control product at steady state, as assessed using a 95% confidence interval for the difference in mean values.

“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-API in the BAL samples.”

The proportion of subjects having steady-state functional A₁-PI (ANEC) levels < 11 microM was greater for both Kamada A₁-PI and Prolastin arms (33.3% and 37.5%, respectively) than has been seen in other trials. The reason for this is unclear, but highlights that a substantial proportion of subjects may be underdosed using the recommended 60 mg/kg IV weekly dose, even when using the poorly-supported historical therapeutic trough target level of > 11 microM.

Based on AEs considered by the investigator to be at least possibly product related, Kamada A₁-PI may be more allergenic than Prolastin. Urticaria, rash, joint swelling, and thrombocytopenia were reported (1 case each) only in the Kamada arm. This could reflect the small size of the study and the 2:1 randomization.

The Adverse Events dataset, (ADVERS10.XPT), appears to lack a datafield to indicate to which treatment group the subject has been assigned. It also lacks data to permit calculation of the number of hours/days since the end of the last test product infusion.

The sponsor cover letter is self-contradictory, in that it states that one clinical study is submitted in support of the application, yet the BLA contains 2 studies:

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.

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 A₁-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 A₁-PI from individual sampling time points are provided with this submission.

Raw data for the primary endpoint analytes, antigenic and functional A1-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 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)--- and --(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 AI-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 AI-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 ¹	ZZ	MZ
--(b)(6)---- -----	Kamada-API	6.51	MZ	MaltonMZ

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

Reviewer Comment

It is known that the -----(b)(4)----- 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 to be 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 A₁-PI products, as recommended by the joint NHLBI-FDA Workshop held in 1985, which has formed the basis of licensure of all A₁-PI IV products to date.]