



Food and Drug Administration
Center for Biologics Evaluation and Research
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Division of Biostatistics

MIE-CYCLE STATISTICAL REVIEW AND EVALUATION BLA

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Product Name: Kamada Human Alpha-1 Proteinase Inhibitor (Kamada-API), intravenous

Indication(s): Chronic augmentation and maintenance therapy in individuals with congenital deficiency of alpha-1-proteinase inhibitor (A1-PI) and clinical evidence of emphysema.

Applicant: Kamada

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1. EXECUTIVE SUMMARY

Kamada submits this BLA for a Human Alpha-1 Proteinase Inhibitor (Kamada API), intravenous in the treatment of chronic augmentation and maintenance therapy in individuals with congenital deficiency of alpha-1-proteinase inhibitor (A1-P1) and clinical evidence of emphysema. One randomized clinical study of efficacy (Study Kamada-API-002, NI in design) is submitted in support of the application. Primary determination of efficacy was based on pharmacokinetic evaluations and the primary outcome variables were the trough circulating level of antigenic and functional API (as an average of the week 7-12 results [6 infusions]). Results on these endpoints show comparable efficacy to Prolastin.

1.1 Conclusions and Recommendations

The conduct of the randomized study of efficacy (Study Kamada-API-002, NI in design) appears to have followed the protocol and the results appear to show comparable efficacy to Prolastin based on the specified primary study endpoints.

1.2 Brief Overview of Clinical Studies

Only one randomized clinical study of efficacy, Study Kamada-API-002, which is of non-inferiority in design, against Prolastin as an active control,) is submitted in support of the application. Primary determination of efficacy was based on pharmacokinetic evaluations and the primary outcome variable was the trough circulating level of antigenic and functional API (as an average of the week 7-12 results [6 infusions]).

1.3 Major Statistical Issues and Findings

The single efficacy study mostly followed its study protocol and its amendments. In its study report, instead of a confidence interval on the mean difference between treatments was used, a distribution-free rank test on the median was used on the primary endpoints. But this does not seem of great consequence as the data presented allowed a confidence interval on the mean difference to be calculated and this result supported the rank-based confidence interval calculation (by inverting a test.)

2. INTRODUCTION

Alpha-1-Proteinase Inhibitor (A1-PI, Human), Kamada-API is a sterile, stable, ready to use, liquid preparation of purified alpha-1-proteinase inhibitor (API), also known as alpha-1-antitrypsin (AAT), derived from human plasma. Kamada-API is indicated for chronic augmentation and maintenance therapy in individuals with congenital deficiency of alpha-1-proteinase inhibitor and clinical evidence of emphysema.

AAT deficiency is a chronic, autosomal, co-dominant, hereditary disorder characterized by low serum and pulmonary levels of API. API acts in the lungs by inhibiting serine proteases such as neutrophil elastase (NE), which is capable of digesting protein components of the alveolar walls and which is chronically present in the lung. Individuals with AAT deficiency have little or no protection against NE released by neutrophils and therefore, severe forms of the deficiency are associated with COPD, including panacinar emphysema. COPD associated with AAT deficiency is usually diagnosed in the third to fourth decades of life and results in a significantly reduced life expectancy.

A common approach to treating patients with COPD due to AAT deficiency is to augment the low protease inhibitor levels by intravenous infusion of API purified from human plasma and thus attempt to correct the imbalance in inhibition of neutrophil elastase in the lower respiratory tract. Individuals with endogenous levels of API below 11 μ M generally have a significantly increased risk for development of emphysema as compared to the general population. Therefore, the maintenance of blood serum levels of API above 11 μ M (measured antigenically) is thought to provide therapeutically relevant anti-neutrophil elastase protection.

Kamada-API is prepared from human plasma obtained from US-licensed plasma collection centers. Plasma is fractionated using a modified version of the cold ethanol fractionation process and the API is then isolated and purified by a series of ----(b)(4)---- chromatographic procedures. To reduce the risk of viral transmission, the manufacturing process for Kamada-API includes two steps specifically designed to remove or inactivate viruses. The first of these is nanofiltration (NF) through a 15 nm filter which can remove both enveloped and non-enveloped viral agents and the second is solvent/detergent (S/D) treatment with a mixture of tri-(n-butyl) phosphate (TnBP) and Polysorbate 80 (Tween 80) which inactivates enveloped viral agents such as human immunodeficiency virus (HIV), hepatitis B (HBV), and hepatitis C (HCV).

Kamada-API is formulated as a 2% solution of API in phosphate-buffered saline and is presented in single-use vials containing 50 ml of ready to use solution. The recommended dosage of Kamada-API is 60 mg/kg body weight administered once weekly by intravenous infusion.

The efficacy data for Kamada-API is derived from a single clinical study in AAT deficient patients, Study Kamada-002. In this study, 48 subjects diagnosed with AAT deficiency received an intravenous dose of 60 mg/kg weekly for up to 12 to 24 weeks. Repeat dosing was a requirement for the efficacy of A1-PI products. This review focuses on results from this study.

2.1 Data Sources

Data sources are included in the applicant electronic BLA submission.

3. STATISTICAL EVALUATION

3.1 Protocol Synopsis

This was a Phase 2/3 Randomized (2:1) Double-Blind Comparison of Alpha-1 Proteinase Inhibitor (Kamada-API) with Prolastin in Individuals with Alpha-1 Antitrypsin Deficiency. After a five-week wash-out period, Subjects were dosed weekly (60mg/kg body weight) for 12 weeks with either Kamada-API or Prolastin and for another 12 weeks with Kamada-API only. Approximately 50 subjects were planned to be enrolled to obtain 45 evaluable subjects.

Main Criteria for Inclusion: Subjects with evidence of lung disease related to alpha-1 antitrypsin (AAT) deficiency and 'at-risk' alleles associated with API plasma levels < 11 μ M were eligible for inclusion. Subjects were required to have a 5-week wash-out period of exogenous API prior to dosing, and not have uncontrolled hypertension or a known allergy to plasma proteins. Primary efficacy objectives were:

- To determine the efficacy of Kamada-API in maintaining antigenic and/or functional plasma levels of at least 11 μ M (57 mg/dL).
- To compare alpha-1 protease inhibitor (API) trough levels (antigenic and functional) over Weeks 7-12 (6 infusions). The goal 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.

Secondary objectives included:

- To compare the levels of antigenic and/or functional API in the epithelial lining fluid (ELF)
- To demonstrate that the safety profile of Kamada-API was not inferior to Prolastin.

For statistical analysis, the intent-to-treat (ITT) analysis population included all randomized subjects regardless of the treatment and amount of treatment actually received. The per-protocol analysis population included all subjects in the ITT population who received full dose of study medication at each of 12 dose administrations and had evaluable trough levels from week 7 to week 12 in the absence of a major protocol violation.

3.2 Results

A total of 50 subjects from 3 investigative sites were in fact enrolled and dosed, and 48 subjects completed the study. The ITT analysis included 49 subjects (33 on Kamada-API and 16 on Prolastin).

Baseline characteristics: The two treatment groups were generally comparable at baseline. Approximately 60% of the enrolled subjects had abnormal, but not clinically significant chest x-ray results, (11 of 33 and 10 of 17, $p=0.74$). There was a slightly higher incidence of abnormal, but deemed not clinically significant electrocardiogram results in the Prolastin group when compared with the Kamada-API group (Prolastin group 9 subjects (52.9%) versus Kamada-API group 11 subjects (33.3%), $p=0.229$).

The mean antigenic API plasma levels were 4.8 μM in the Kamada-API group and 4.3 μM in the Prolastin group, and mean functional API plasma levels were 3.1 μM in the Kamada-API group and 2.3 μM in the Prolastin group. In addition, the baseline C4 complement consumption values were statistically significantly lower in the Kamada-API group than in the Prolastin group.

Comment: *The study report states that these values were within the normal range and the difference was not of clinical significance.*

Trough Circulating Levels of Antigenic and Functional API

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 to 19.2 μM). The median functional API values for Weeks 7-12 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 two-sample Wilcoxon rank sum test, stratified by center, was inverted to provide the 95% CI to assess non-inferiority. The lower bound 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 results for the ITT Population and the per-protocol analysis are respectively summarized in the following two tables.

Trough Circulating Levels of Antigenic and Functional API (Average of Weeks 7-12, 6 Infusions) (ITT Population)				
Statistic	Antigenic API (μM)		Functional API (μM)	
	Kamada-API	Prolastin	Kamada-API	Prolastin
N	33	16	33	16
Mean (SD)	14.6 (2.0)	13.5 (2.6)	12.0 (1.8)	11.7 (2.6)
Median(range)	14.5 (11.6, 18.5)	12.8 (10.4, 19.2)	11.8 (8.2, 16.9)	11.4 (7.7, 18.0)
95% CI	(-0.08, 2.67)		(-1.04, 1.63)	

Trough Circulating Levels of Antigenic and Functional API (Average of Weeks 7-12, 6 Infusions) (Per-Protocol Population)				
Statistic	Antigenic API (µM)		Functional API (µM)	
	Kamada-API	Prolastin	Kamada-API	Prolastin
N	29	12	29	12
Mean (SD)	14.8 (2.0)	13.3 (2.8)	12.1 (1.9)	11.5 (2.5)
Median(range)	14.7 (11.6, 18.5)	12.8 (10.4, 19.2)	11.8 (8.2, 16.9)	11.4 (8.9, 18.0)
95% CI	(0.02, 3.33)		(-0.20, 1.88)	

Comment: *Instead of inverting a Wilcoxon rank sum test to derive the confidence intervals, a calculation of the 95% CI's on the mean difference using a Student's t-score provides the same conclusion: the lower bound of the confidence intervals were greater than – 3 µM for both antigenic and functional API levels.*

Comment: *The antigenic API values for Weeks 7-12 in the Kamada-API group were greater than 11 µM (target values specified in the protocol,) while in the Prolastin group they ranged 10.4 to 19.2 µM. The functional API values for Weeks 7-12 were generally lower than the antigenic values in both groups and ranged: 8.2 to 16.9 µM in the Kamada-API group and 7.7 to 18.0 µM in the Prolastin group, thus neither group reached a minimum of 11 µM on every measurement occasions during Weeks 7-12 for functional API.*

Proportion of Subjects with Mean Trough Antigenic API Exceeding 11 µM

The proportion of subjects in the ITT group 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 in the ITT group with mean functional API levels greater than 11 µM was 66.7% in the Kamada-API group and 62.5% in the Prolastin group. These results were similar between groups, and for the PP analysis. These results are summarized in the following tables.

Proportion of Subjects with Mean Trough Antigenic API Exceeding 11 µM (PP Population)				
	Antigenic API		Functional API	
	Kamada-API N=29	Prolastin N=12	Kamada-API N=29	Prolastin N=12
Yes (n, %)	29 (100%)	10 (83.3%)	20 (69%)	7 (58.3%)
No (n, %)	0 (0.0%)	2 (16.7%)	9 (31.0%)	5 (41.7%)
95% CI	(0.88, 1.00)	(0.52, 0.98)	(0.49, 0.85)	(0.28, 0.85)

Proportion of Subjects with Mean Trough Antigenic API Exceeding 11 µM (ITT Population)				
	Antigenic API		Functional API	
	Kamada-API N=33	Prolastin N=16	Kamada-API N=33	Prolastin N=16
Yes (n, %)	33 (100%)	13 (81.3%)	22 (66.7%)	10 (62.5%)
No (n, %)	0 (0.0%)	3 (18.8%)	11 (33.3%)	6 (37.5%)
95% CI	(0.89, 1.00)	(0.54, 0.96)	(0.48, 0.82)	(0.35, 0.85)

Comment: *The protocol specifies only the expectation that at least 80% of the trough levels of Kamada-API antigenic API levels exceeding 11µM during Weeks 7 to 12.*

A subset of subjects underwent Bronchoalveolar Lavage (BAL) and Bronchial Biopsy/Brushing procedure 2-10 days prior to the first infusion of study drug, and again between Weeks 10 and 12. The aim of this subset was to collect ELF samples that were analyzed for antigenic and/or functional API as well as different analytes. This was a secondary objective, and data were only available from a very small number of study subjects, 7 and 2 of the two groups respectively. No meaningful statistical analysis was presented.

3.3 Evaluation of Safety

There was no pre-specified statistical analyses plan for the safety of this product.

4. SUMMARY AND CONCLUSIONS

4.1 Statistical Issues and Collective Evidence

One randomized efficacy study was conducted for this application. In the study report, instead of a confidence interval on the mean difference between treatments was used, a distribution-free rank test on the median was used on the primary endpoints. But this does not seem of great consequence as the data presented allowed a confidence interval on the mean difference to be calculated and this result supported the rank-based confidence interval calculation. The conduct of this randomized study of efficacy (Study Kamada-API-002, NI in design) appears to have followed the protocol and the results appear to show comparable efficacy to Prolastin based on the specified primary study endpoints.

4.2 Conclusions and Recommendations

The conduct of the randomized study of efficacy (Study Kamada-API-002, NI in design) appears to have followed the protocol and the results appear to show the comparable efficacy of the products based on the specified primary study endpoints.

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