

## **Final Review Memorandum**

Subject: BLA STN: 125325  
Kamada-API [Alpha 1 Proteinase Inhibitor (Human) Intravenous]

Indication: Treatment of Alpha 1 Antitrypsin deficiency

Purpose: OBE/DE Final Review for Pharmacovigilance Planning

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### **Introduction**

OBE has completed a review of BLA 125325 for Kamada-API [Alpha-1 Proteinase Inhibitor (Human) Intravenous]. The purpose of this review is to identify potential safety issues that may need to be addressed through post market monitoring, studies, or other pharmacovigilance actions, should this product be licensed.

### **Product Background**

Alpha-1 Proteinase Inhibitor (API) deficiency is a chronic, hereditary disorder characterized by low serum and lung levels of alpha-1 proteinase inhibitor. Alpha-1 proteinase inhibitor deficiency has autosomal, co-dominant inheritance, with each allele contributing to the patient's phenotype. Approximately 100 different proteinase inhibitor alleles have been identified, several of which result in reduced serum levels of API. The M allele has a frequency of greater than 95% in the United States population and is associated with normal API levels. The homozygous S allele is associated with slightly reduced levels of API. Genetic deficiency states are associated with characteristic decreases in serum concentrations of API. Three previously licensed products for this indication are Prolastin, Aralast, and Zemaira.

API deficiency is found in almost all populations but is most prevalent in Caucasians of northern European and western European descent. It is rare in Mediterranean, Asian, and African populations. Recent estimates suggest that approximately 120 million people worldwide have a phenotype that increases their risk of emphysema. The prevalence in Caucasians is approximately 1 in 2,500 – 5,000 for those who are homozygous for the deficient variant. The most common allele associated with deficiency is present in about 1% of individuals of Northern European descent. A large majority of individuals with severe API deficiency are homozygous. A small percentage of patients inherit two “null” alleles, which leads to the absence of any API production. In patients with a mutation, there is either insufficient production of the API protein, or there is production of abnormal protein molecules that polymerize and are retained in the endoplasmic reticulum of the hepatocytes. This aggregation may lead to cirrhosis in addition to decreased levels of serum and lung API.

Emphysema associated with API deficiency is most frequently diagnosed in the third to fourth decade of life. It is manifested by chronic lung inflammation, poor lung function, and frequent exacerbations of chronic bronchitis. It is associated with significantly reduced life expectancy, and the condition is aggravated in smokers, who present early with progressive airflow obstruction.

Kamada-API is prepared by a modified cold ethanol fractionation process from human plasma obtained by licensed US plasma collection centers. API is then isolated and purified by a series of -----(b)(4)---- chromatographic procedures. As with all human plasma derived products, API concentrates carry a potential risk of transmission of viral infections. The risk is reduced by careful selection of donors and testing of plasma, as well as specific steps in the manufacturing process to inactivate or eliminate viruses. The first step uses a 15 nanometer filter, which can remove both enveloped and non-enveloped viral agents. The second is solvent/detergent treatment which inactivates enveloped viral agents such as HIV, HBV and HCV. Viral serology was assessed during clinical studies, and no seroconversion was noted.

When a new product is marketed, the exposed population may differ from the population studied in pre-approval trials. For most products, routine pharmacovigilance (i.e., compliance with applicable postmarket reporting requirements under FDA regulations) is sufficient for post-marketing risk assessment. As outlined in Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment (<http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126834.pdf>), pharmacovigilance plans may be appropriate when: 1) Serious safety risks have been identified pre- or post-approval, or 2) at risk populations have not been adequately studied. The ICH E2E Pharmacovigilance Planning guidance (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073107.pdf>) indicates that for products with important identified risks, important potential risks, or missing information, additional actions designed to address these concerns should be considered as part of the pharmacovigilance plan. The pharmacovigilance plan is developed by a product’s sponsor and is specifically focused on detecting new safety risks and/or evaluating already identified safety risks.

## **Clinical Studies**

The pivotal study is the Phase 2/3 Randomized Double-Blind Comparison of Alpha-1 Proteinase Inhibitor (Kamada-API) with Prolastin in Individuals with Alpha-1 Antitrypsin Deficiency. The Study Period was March 2007 to March 2008.

### **Primary Objectives:**

- To demonstrate that the pharmacokinetics of antigenic and/or functional Kamada-API were not inferior to those of Prolastin, the active comparator.
- To measure the efficacy of Kamada-API in maintaining antigenic and/or functional plasma levels of at least 11 uM (57 mg/dL)
- To compare alpha-1 protease inhibitor (API) trough levels (antigenic and functional) over weeks 7-12 (6 infusions).

### **Secondary Objectives:**

- 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.

### **Tertiary Exploratory Objectives:**

- To investigate whether Kamada-API reduced the concentration of pro-inflammatory factor, Interleukin 8 (IL-8) in the ELF.
- To investigate whether Kamada-API reduced lower respiratory tract inflammation in the airways as assayed by the number of inflammatory cells (specifically neutrophils) in the ELF.
- To investigate the changes of selected ELF analytes over baseline.
- To compare the frequency of pulmonary exacerbations.

This study was a double-blind, randomized, controlled, two-arm study with partial cross-over. Subjects received 60 mg/kg weekly for 12 weeks with either Kamada-API or Prolastin and for another 12 weeks with Kamada-API only. Fifty subjects were enrolled and treated, and 48 subjects completed to Week 28. Subjects with evidence of lung disease related to alpha-1 antitrypsin deficiency and “at risk” alleles associated with API plasma levels < 11 uM were eligible for inclusion. Subjects were required to have a 5-week wash-out period of exogenous API prior to dosing and to not have uncontrolled hypertension or allergy to plasma proteins.

## **Safety**

Safety was assessed by recording adverse events, laboratory evaluations, vital signs, electrocardiograms, chest x-rays, physical examinations, and post-bronchodilator spirometry, including forced expiratory volume in 1 second, and forced vital capacity.

Of the 50 subjects who participated in the study, 49 experienced at least one adverse event. There were 32 (97%) from the Kamada-API group, and 17 (100%) from the Prolastin group who experienced adverse events. The most common were respiratory, including cough, URI, exacerbation of COPD, and nasopharyngitis. The majority of events were mild or moderate in intensity, and there were no clinically meaningful differences in adverse events between the groups.

The incidence of adverse events thought to be related to the study drug was low in both groups. During treatment period 1, the most common adverse event related to the study drug was headache, 9% in the Kamada-API group and 6% in the Prolastin group. In treatment period 2, there were 5 subjects in the Kamada-API group with adverse events: 1 subject each with urticaria, flu-like symptoms, thrombocytopenia, joint swelling, dizziness, and rash. In the Prolastin group, there was 1 subject with lethargy.

Four serious adverse events were reported during the course of the study. One occurred prior to dosing (pneumothorax), and three occurred after dosing (cholangio-pancreatitis, exacerbation of COPD, and pulmonary emboli). All 4 were considered to be unrelated to the study drug. Two subjects were withdrawn secondary to adverse events; one with pulmonary emboli from the Prolastin group, and one with urticaria from the Kamada-API group. There were four subjects with clinically significant changes in hematology values during the study. One subject had decreased platelet count in the Kamada-API group, and one subject had an increased white cell count in the Prolastin group. Both events were mild and resolved prior to the end of the study. No patient had seroconversion for hepatitis B, C, or HIV during the study.

The study met stated objectives. The incidence of adverse events was low. The drug seems to be safe and well tolerated.

There is no likely potential for drug abuse with Kamada-API. Emphysema related to API deficiency manifests in the adult population. Therefore, off-label pediatric use is very unlikely.

The potential risks of allergic reactions and transmission of infectious agents can be addressed through routine pharmacovigilance. The main limitation of the safety database is the small number of patients studied during clinical trials, due to the rarity of the disease.

Previously licensed products for this indication provide some context for potential side effects that could emerge with wider population exposure after licensure. For example, adverse event reports for these products include deaths and anaphylactic or anaphylactoid reactions. One of the deaths was associated with a pulmonary embolism. On the other hand, nearly all of the fatality reports provided insufficient details for adequate assessment, and the apparent anaphylaxis and anaphylactoid reactions may not have been more than milder allergic responses.

Because so few Kamada-API patients have been monitored in clinical trials, the sponsor should consider options to gather additional information if this product is licensed in order to provide a progressively stronger basis for reassurance about its safety and to allow the earliest possible recognition of any serious risks that may not have emerged from the small preclinical experience.

## **Conclusion**

Kamada-API appears to be safe and well tolerated, with a low incidence of possible product-related adverse events. However, with so few subjects evaluated pre-licensure, post-licensure surveillance to augment the safety database and improve the likelihood for detection of important risks should be employed.

The sponsor has developed a post-marketing surveillance system based on the requirements of the ICH E2E Pharmacovigilance Planning and the Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment guidance. Included will be Periodic Adverse Event Reports and signal detection strategies. All reports on suspected ADR's will be entered into the sponsor's safety database.

If Kamada-API is approved, the sponsor should consider enhanced surveillance and submit a protocol to assess the anaphylaxis and other immunologic risks as a postmarketing commitment. The sponsor should develop an analysis and reporting plan for possibly using a registry or other method to assess risks, including an assessment of the proposed sample size specifically for the ability to detect an excess of immunogenicity in treated patients when compared to the background incidence in a similar population.

## **Letter-ready comments**

We have reviewed your post-licensure pharmacovigilance plan to monitor long-term safety with the use of Kamada-API if the FDA approves your application for a license.

In addition to routine pharmacovigilance (i.e., compliance with applicable post-market reporting requirements under FDA regulations as outlined in Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment. (<http://fda.gov/CDER/guidance/63590CC.htm>), we recommend that you consider additional post-market actions to address any potential adverse events that may be identified, particularly in view of the relatively small number of patients studied thus far.

You may submit a protocol to assess the anaphylaxis and other immunologic risks as a postmarketing commitment. It would include an analysis and reporting plan for using a registry or other method to assess risks, including an assessment of the proposed sample size specifically for the ability to detect an excess of immunogenicity in treated patients when compared to the background incidence in a similar population. Adverse event ascertainment procedures to track allergic reactions, disease transmission, or any other unexpected side effects, especially serious ones that may emerge through systematic monitoring of larger numbers of treated patients, should also be considered.

