

Memorandum

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

Indication: Treatment of Alpha 1 Antitrypsin deficiency

Purpose: OBE/DE Mid-Cycle Review for Pharmacovigilance Planning

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Introduction

OBE has completed a Mid-Cycle review of the 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 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://fda.gov/CDER/guidance/63590CC.htm>), FDA believes 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 pharmacovigilance plan developed by a product’s sponsor focuses 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 11uM (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 were dosed with 60 mg/kg weekly for 12 weeks with either Kamada-API or Prolastin and for another 12 weeks with Kamada-API only.

50 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 subjects (97%) from the Kamada-API group, and 17 subjects (100%) from the Prolastin group who experienced adverse events. The most common adverse events were respiratory in nature, 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 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 an adverse event of 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 group. There were four subjects with clinically significant changes in hematology values during the study. One subject had decreased platelet count in the Kamada 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. There were no cases of seroconversion for hepatitis B, C or HIV during the study.

The study met stated objectives and demonstrated non-inferiority of Kamada-API to Prolastin. The incidence of adverse events was low. The drug seems to be safe and well tolerated.

There is no 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 systematically 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

Clinical studies have shown non-inferiority. Kamada seems to be safe and well tolerated, with a low incidence of possible product-related adverse events. However, with so few subjects evaluated pre-licensure, a post-licensure patient registry or possibly other methods may be considered to augment the safety database and improve the likelihood for detection of important risks.

Letter-ready comments

Clinical studies have shown non-inferiority to Prolastin. The product appears to be safe and well-tolerated, although very few patients were evaluated in clinical trials.

You should develop and implement a post-licensure pharmacovigilance plan, per the ICH E2E Pharmacovigilance Planning guidance, to monitor long-term safety with the use of Kamada. The major components of a pharmacovigilance plan for Kamada should include routine pharmacovigilance (i.e., compliance with applicable post-market reporting requirements under FDA regulations) and possibly additional post-market actions to address any potential adverse events that may be identified. This may include a patient registry to evaluate adverse events such as headache, allergic reaction and disease transmission or any other unexpected side effects, particularly serious ones that may emerge through systematic monitoring of larger numbers of treated patients.

Continue routine post-marketing as outlined in Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment (<http://fda.gov/CDER/guidance/63590CC.htm>).