

Kamada Final Memo - GLASSIA, June 8, 2010

Date: 6/8/10

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To: File 125325

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Subject: Final Memo

Product: Alpha-1 Proteinase Inhibitor (Human) intravenous for chronic augmentation and maintenance therapy in individuals A1PI deficiency and emphysema

Submission Date: May 13, 2010

Manufacturer: Kamada, Ltd.

Recommendations:

Immunogenicity assay-

Recommended a PMR for an immunogenicity study final report to be provided no later than February 1, 2011. Recommended a validation final report to be submitted prior to testing the clinical samples.

Visual inspection for particles -

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Nanofiltration-

Recommended a down-scale study to establish differential pressure limits consistent with removal of HIV and pseudorabies viruses.

Reference standard –

Recommended that the Sponsor continue to apply the 3% correction factor based on calibration of the in house standard with the WHO international A1PI standard.

The Sponsor has committed to the following Post Marketing Requirements:

- We commit to perform **A Phase IV, randomized, double-blind, multicenter study exploring potential adverse events associated with particulates, immunogenicity and viral safety following the use of Kamada's Intravenous, Human A1PI vs. Another Commercial, A1PI in Alpha-1 Antitrypsin Deficient Patients.**

A draft of the clinical study outline will be submitted to the Agency by July 30th 2010 and study will be initiated in September 2011.

The design of this clinical study will include features which will permit the detection of possible adverse events (AEs) due to the presence of particulates in the product. This will be an additional objective of the study.

Additionally, Kamada commits to evaluate the possibility that the study will be masked rather than open-label. For this study, Kamada will submit an amendment to IND -

(b)(4)- with cross reference to BLA STN 125325/0.

The Sponsor has committed to the following Post Marketing Commitments:

- We commit to perform **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.**

A draft of the clinical study outline will be submitted to the Agency by July 30th 2010 and study will be initiated in September 2011.

The primary endpoint in this study will be both antigenic and functional A1-PI levels in ELF after 10-12 weeks of treatment.

- We commit to perform **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)

A draft of the clinical study outline will be submitted to the Agency by July 30th 2010 and study will be initiated in September 2012.

- We commit to perform **an adequately powered efficacy study with a clinical meaningful**

endpoint following the pilot study (stage 1) described above. (stage 2)

A draft of the clinical study outline will be submitted to the Agency by July 29th 2011 and study will be initiated in January 2019.

- We commit to submit the **Anti-A1-PI Antibody Assay validation report** prior to running

the stored clinical samples from the pivotal clinical trial and submit the **final results** (including all raw data) of the A1-PI antibody assay testing from stored clinical samples from the pivotal clinical trial. We commit to submit these two submissions as supplements to

BLA # STN 125325. The validation report will be submitted in November 2010 and the final results will be submitted in February 2011.

No further issues have been identified. The replies provided by the Sponsor are approvable.

Background:

Kamada-API is the first proposed liquid formulation of A1PI for intravenous delivery. Individual review memos pertaining to immunogenicity, particulates, process validation, and reference standard are attached.

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