



Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

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To: To File (STN 125325)

From: Ewa Marszal, PhD; CBER/OBRR/DH/LPD, HFM-345, 301-402-4368

Through: Dorothy Scott, MD; CBER/OBRR/DH/LPD, HFM-345, 301-827-3016

CC: Cherie Ward-Peralta, RPM; CBER/OBRR/DBA/RPMB, HFM-380, 301-827-9170

Applicant: Kamada

Product: Alpha-1-Proteinase Inhibitor (Human)
Trade name: not proposed

Subject: **Filing Memo:** Chronic augmentation and maintenance therapy in individuals with congenital deficiency of alpha-1 proteinase inhibitor (A1-PI) and clinical evidence of emphysema

Recommendation: This submission can be filed. Letter ready comments are at the end of this memo.

Review

This is a new BLA submission. The application is provided in the CTD format.

The product is manufactured at Kamada's ----(b)(4)--- multi-product production facility located in Kibbutz Beit Kama, Israel. The starting material, ----(b)(4)---- is manufactured by -----(b)(4)-----.

Raw materials and microbial testing is performed under contract by -----(b)(4)-----, respectively. Quality control, lot release and stability testing is performed by Kamada at MP Negev, Israel site. Pyrogen testing and general safety test are performed under contract by -----(b)(4)-----, respectively. Characterization of the drug substance was performed by -----(b)(4)-----.

Kamada submitted results from clinical Study Kamada-API-002) entitled “Phase II/III Randomized Double-Blind Comparison of Alpha-1 Proteinase Inhibitor (Kamada-API) with Prolastin® in Individuals with Alpha-1 Antitrypsin Deficiency” and Phase I clinical study (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.”

During the review cycle Kamada will submit the following information:

1. The extended process hold times will be validated in full scale. An amendment to the BLA will be submitted during the course of the review. Kamada refers to FDA letter dated February 26, 2009, FDA response to questions IA of the pre-BLA meeting package. We agreed to accept and evaluate in the course of the BLA review all small scale and full scale data generated thus far in support of the proposed process operating space. I think that hold time validation can be submitted during the review cycle.
2. Maximum peak height limit for the collection of the effluent from the -----(b)(4)----- column (-(b)(4)-) will be validated in full scale. An amendment to the BLA will be submitted during the course of the review. Kamada refers to FDA letter dated February 26, 2009, FDA response to question I-B of the pre-BLA meeting package. We did not specify when Kamada should validate the range; however, submitting validation data for collection of the effluent within the review cycle appears acceptable.
3. Kamada upgraded the ----(b)(4)---- and -----(b)(4)----- process for the final drug product glass containers. The Performance Qualification (PQ) studies for the new ----(b)(4)-- and the new -----(b)(4)----- are in the BLA. The data for the media fill simulations will be available for review at the pre-approval inspection. Kamada refers to FDA letter dated February 26, 2009, FDA response to question IV-A of the pre-BLA meeting package. This is consistent with our agreement.
4. Kamada will provide the immunogenicity data from patients treated with Kamada-API during the course of the BLA. Kamada refers to FDA letter dated January 12, 2009, FDA response to question VI-B of the pre-BLA meeting. This is consistent with one of the options suggested by CBER. Kamada is currently developing antigenicity assay. We may recommend that Kamada submits the data by January 1st in order to allow sufficient time for data review. In the meantime we should develop a strategy that we will follow if Kamada is not able to meet this deadline (see Letter Ready Comment #3).
5. The name of the third party contractor who will provide pharmacovigilance services to Kamada will be provided in the course of review of the BLA. This is acceptable.
6. Kamada stated that the BLA contains the draft text for the vial and carton labels and the package insert. Graphics or an artist rendering of the carton and container labels

and package insert will be provided as part of the submission for the evaluation of proprietary names.

Ms. Ward-Peralta informed the review team that Kamada is planning to submit the PNR application with three possible proprietary name options at the end of September. Dr. Nguyen clarified that, for biologics, the sponsor should propose at most 2 proprietary names at a time and should specify the primary name of choice. The alternate name will be evaluated only in the event the primary name is found unacceptable. See Letter Ready Comment #2.

Drug product specifications and release tests are listed in the Appendix to this memo. The possibility of the presence of particles in this product raises a major concern.

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. The manufacturing process includes two viral clearance steps, nanofiltration through a 15 nm filter and S/D treatment with tri-(n-butyl) phosphate (TnBP) and Polysorbate 80 (Tween 80).

Kamada-API is formulated as a 2% solution of API in phosphate-buffered saline and is presented in 50-ml vials of ready to use solution (all licensed products are lyophilized). The recommended dosage of Kamada-API is 60 mg/kg body weight administered intravenously once a week. A 5µm filter needle for filtering in-line is provided.

Kamada manufactured -(b)(4)- drug batches of the drug substance to support process consistency. This involved -----(b)(4)----- sourced from Recovered Plasma and -(b)(4)- sourced from -----(b)(4)----- from Source Plasma). Kamada stated that multiple aspects of the manufacturing process, -----(b)(4)-----
----- were assessed. All batches met specification and representative conformance batches were subjected to additional characterization studies. All batches were placed on stability. All drug product lots manufactured from these batches met specification and were placed on stability. Kamada stated that comparability of drug substance from the two types of --(b)(4)-- ----- source material as well as process consistency were demonstrated.

Kamada stated that a series of process robustness studies, using a Design of Experiment approach and a validated laboratory scale model to investigate the influence of the extremes of critical operational limits on process performance and product quality, were conducted. Acceptance limits were established based on historical data from full scale manufacturing batches. In-process materials from full scale manufacturing were used for these studies.

Kamada provided a description of the manufacturing process and process controls, information on control of materials, control of critical steps (critical process attributes during manufacture of the drug substance include mainly -----(b)(4)-----). The section on process validation contains information from conformance lots manufacturing, which according to the sponsor demonstrated the consistency of manufacture and from scaled

down model systems, which according to Kamada demonstrated the robustness of the process.

The submission includes protocol and report for the comparability study for API DS batches manufactured from Source and recovered plasma and conformance production of API DS batches from Source and recovered plasma.

Recommendation

This submission can be filed.

LETTER-READY COMMENTS

1. Please provide samples of the conformance lots (3 samples per lot) to the Product Release Branch, and reference this submission number.
2. Please note that you should propose at most 2 proprietary names at a time and should specify the primary name of choice. The alternate name will be evaluated only in the event the primary name is found unacceptable.
3. In order to allow sufficient time for the review of immunogenicity data, please provide these data by January 1, 2010.