



FOOD AND DRUG ADMINISTRATION
CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

MEMORANDUM

Date: 11/17/09

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To: File 125325 / 0

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Subject: Review of original BLA

Product: Alpha-1 Proteinase Inhibitor (Human) intravenous for chronic augmentation and maintenance therapy in individuals A1PI deficiency and emphysema
Submission Date: October 23, 2008
Manufacturer: Kamada, Ltd.

Recommendation:

The following letter-ready comments may be faxed to the Sponsor:

------(b)(4)-----

2) Were validation lots prepared in November – December 2007 analyzed by -(b)(4)-
-----? Please provide these data.

3) Please describe how the appearance test method was validated, and provide the SOP for visual inspection. How are light conditions controlled during execution of the visual inspection? Is a set of positive controls identified for training purposes? How is the visual health of inspectors monitored, and how is fatigue prevented? -----(b)(4)-----

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9) Please provide an SOP for calibration and stability monitoring for the in house reference standard. Since product potency assessed using RHS#1 is 3% higher compared with potency assessed with the WHO standard, a correction factor should be applied. Please establish a correction factor and corrected potency values for lots whose potency was established using RHS#1 reference standard.

Background Information:

In this electronic submission, the Sponsor introduces Kamada-API, the first liquid formulation of A1PI for intravenous administration in patients with congenital A1PI deficiency and emphysema. Kamada A1PI is prepared from human plasma, obtained from US licensed plasma collection centers. Plasma is fractionated using modified cold-ethanol fractionation process, and A1PI is further isolated and purified by a series of --- (b)(4) --- chromatographic procedures. Virus inactivation and removal is accomplished in two steps, 15 nm nanofiltration and solvent –detergent treatment (TNBP/ Polysorbate (Tween) 80). The proposed purification and pathogen removal steps for Kamada-API are not new. Kamada-API is a 2% solution in saline, presented in 50 ml single-use ready-to-use vials. Recommended dosage is 60 mg/kg body weight administered once per week,

----- (b)(4) -----

The target A1PI protein concentration (2%) is similar to Aralast and Prolastin. The ----- (b)(4) ----- test for identity is similar to Zemaira; however Kamada is the only A1PI manufacturer to use - (b)(4) - as a test for identity. In specifications for drug substance, Kamada indicates in a footnote that ----- (b)(4) ----- assay also serves as a measure of identity. Kamada is the only A1PI manufacturer to make this claim; other plasma proteins present as contaminants could conceivably inhibit ----- (b)(4) ---- in vitro. However in previous conversations with the firm, the combination of - (b)(4) -- ----- was determined to be acceptable to establish identity. Therefore the proposed tests for identity are fine.

The proposed potency range, active A1PI content, and specific activity are similar to Prolastin C, Zemaria and Aralast.

Kamada A1PI specifications feature sodium and phosphate levels which are similar to other A1PI products; - (b)(4) - levels are ----- (b)(4) ----- compared with Zemaira and Prolastin. Kamada indicates in justification of specifications that several different buffering conditions were tried before selecting this one as optimal.

Regarding impurities:

----- (b)(4) -----

Kamada notes that plasma related impurities and residual Tween 80, TnBP, - (b)(4) - are all measured in ----- (b)(4) ----- . We note that assay performance should not be influenced adversely by the composition of the drug product sample, and thus there is no important reason to omit testing for the impurities in the drug product as part of the release protocol. - (b)(4) -----

We note that the Sponsor's limit of detection for process-related impurities is - (b)(4) - compared with tests performed by other manufacturers. Residual Tween and - (b)(4) - appear similar to Aralast and ----- (b)(4) ---- . We note that the drug substance ----- (b)(4) - ----- to make the final product, so expected levels of the three impurities will be less

than the listed values. Even so, the proposed maximal TnBP level is -----(b)(4)-----
----- than listed in specifications for other A1PI and IVIG products. In justification of
the TnBP specification, the Sponsor references published non-clinical studies from the
New York Blood Center (1999) in which toxicities associated with TnBP were seen at
much higher doses than those found in the -----(b)(4)-----; this reference is solid and the
argument is well taken. However the Sponsor's actual experience in validation lots
suggests that the upper limit for TnBP could be -----(b)(4)-----
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[
---(b)(4)---
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Regarding endotoxin: the recommended dose of this product is 60 mg/kg, similar to the
other A1PI products. Since minimum A1PI content is -(b)(4)- per 50 ml vial, a
maximum volume of -(b)(4)- / kg would be administered to a patient. At -(b)(4)-
endotoxin / ml, the maximum endotoxin delivered per kg would be -(b)(4)-, which is
within the maximum allowable endotoxin per dose.

Elucidation of structure and other characteristics: Section 3.2.S.3.1

This document presents characterization of the Kamada A1PI Reference House Standard
(RHS) which is also a phase II/III clinical lot. Characterization of seven Kamada-A1PI
drug substance batches is also presented. The stated goal was “to establish consistency of
the product”. The seven lots are later referred to as both validation and conformance lots.

The Kamada-API DS batches referred to in this study were prepared -----(b)(4)-----
----- . As such these possibly do not represent consecutive
batches. In previous conversations with the firm (March 2008), it was proposed that 3
conformance lots be made from recovered plasma, to demonstrate reproducibility of the
manufacturing process. In addition, it was proposed that test results from -(b)(4)- lots

manufactured from source plasma should be provided to support comparability with A1PI prepared from recovered plasma. In response to this proposal, the Sponsor stated that (b)(4)- batches had been prepared in two campaigns. The first campaign (the validation campaign) is described in protocol VL-07378-PV. The batches prepared are the following:

----- (b)(4) -----

----- (b)(4) -----

In the March 2008 communication, the Sponsor indicated that the validation lots would be prepared ahead of a shutdown to allow facility upgrades. This may mean that the validation batches and conformance batches are consecutive, but we should still check. Also note that these drug products are now expired. We will need additional conformance lots that are not expired to do any in-house testing.

These are the results available for the (b)(4)- conformance / validation lots:

Assay	Lots tested
[(b)(4)]	

We stated in March 2008 that: “combining the comparability and conformance lot data may be enough for FDA to evaluate the acceptance for using (b)(4)-. FDA will need to look at parameter ranges covered during validation / comparability studies, especially time. The impurity profile will be looked at closely.”

Inherent in our statement was probably the idea that data from all assays would be available for all (b)(4)- lots. We note that the lots from the November / December

campaign were not subjected to -----(b)(4)----- . Individual assays are reviewed below:

-(b)(4)-----

-(b)(4)-----

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---(b)(4)---
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Eighteen (18) Pages Determined to be Non-Releasable: (b)(4)