



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

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**Date:** 6/30/10

**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)  
Proprietary name: GLASSIA

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

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**Recommendation:** Approval

**Background**

Kamada submitted an original BLA application for  $\alpha_1$ -proteinase inhibitor (human) (Alpha<sub>1</sub>-PI). This is the first liquid formulation of Alpha<sub>1</sub>-PI and the first Kamada's product under review for the US market.

The product will be marketed under the proprietary name GLASSIA<sup>™</sup>.

GLASSIA<sup>™</sup> is a 2% solution of human Alpha<sub>1</sub>-PI indicated for chronic augmentation and maintenance therapy in adults with emphysema due to congenital deficiency of Alpha<sub>1</sub>-PI, also known as alpha-1-antitrypsin. GLASSIA<sup>™</sup> is formulated in -(b)(4)-sodium phosphate buffer, pH -(b)(4)-, containing -(b)(4)- sodium chloride and does not contain preservatives. GLASSIA<sup>™</sup> is filled to a 50 mL volume (1 g) in -(b)(4)- glass vials with ----(b)(4)---- rubber stoppers. The product is stable at 2 – 8 °C for up to 24 months.

GLASSIA™ is manufactured at the Beit Kama, Israel facility from human plasma --- (b)(4) --- intermediate (----- (b)(4) -----) made at the ----- (b)(4) ----- facility in ----- (b)(4) ----- . The Beit Kama, Israel facility has been inspected. Raw material testing is performed at ----- (b)(4) ----- . Microbial testing is performed by ----- (b)(4) ----- .

The starting material for GLASSIA™ is ----- (b)(4) ----- .  
----- is manufactured from either recovered or Source plasma. Recovered plasma is separated from whole blood collected at ----- (b)(4) ----- blood collection centers (U.S. license - (b)(4) -). Source plasma is collected by ----- (b)(4) ----- FDA-licensed U.S. plasma centers. Collection facilities are FDA-inspected.

GLASSIA™ is manufactured by a combination of cold ethanol fractionation of plasma, ----- (b)(4) ----- , and a series of ----- (b)(4) ----- chromatography steps.

The updated lot release specifications are listed below.

Test	Specification	Analytical Procedure
Appearance	The solution is clear and colorless to yellow-green. May contain a few protein particles.	Visual inspection
--- (b)(4) ---	--- (b)(4) ----- -----	--- (b)(4) ----- -----
- (b)(4) -	--- (b)(4) ----- ----	--- (b)(4) -----
Total Active API Content	--- (b)(4) -----	--- (b)(4) -----
Active API Content	--- (b)(4) -----	--- (b)(4) -----
Specific Activity	--- (b)(4) -----	--- (b)(4) ----- ----- -----
Sodium	--- (b)(4) -----	--- (b)(4) -----
Chloride (as NaCl)	-- (b)(4) --	--- (b)(4) -----
Phosphate	--- (b)(4) -----	--- (b)(4) -----
----- (b)(4) ----- -----	--- (b)(4) ----- ----- --- (b)(4) ----- -----	--- (b)(4) ---
Residual TnBP <sup>1</sup>	--- (b)(4) -----	--- (b)(4) -----
Residual Tween 80 <sub>1</sub>	--- (b)(4) -----	--- (b)(4) ----- -----
--- (b)(4) -----	--- (b)(4) -----	--- (b)(4) ----- -----

Bacterial Endotoxin	---(b)(4)-----	---(b)(4)-----
Pyrogenicity	Pass	Rabbit pyrogen test
Sterility	Pass	Membrane filtration
General Safety Test	Meets Requirements	Mice and guinea pigs toxicity (21 CFR 610.11)
pH	--(b)(4)-	---(b)(4)----- -----
Extractable Volume	---(b)(4)----	---(b)(4)----- -----

(b)(4)-----  
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Major issues discussed during the review of this submission included:

Presence of protein particulates in the product – Glassia may contain small amount of visible protein particles. With this respect Glassia is not unique; other protein products also contain protein particles. Since there are no established methods for protein particulates counting, -----(b)(4)-----  
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----- Also, CBER will perform visual inspection of the vials submitted to the Product review Branch in support of the lots submitted for release. In addition, Kamada will perform phase IV clinical study required by CBER to further assess the safety of the product. Also, they agreed to perform 6 postmarketing studies in order to 1) obtain additional safety data based on adverse events reporting 2) -----(b)(4)-----  
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- Immunogenicity testing (immunogenicity assay) – Kamada made progress in the assay development and they will submit an assay validation report by November 1, 2010 and they will finalize the study by February 1, 2011.
- Final container specifications and process quality attributes – the TNBP final container specification was tightened to be consistent with historical results; the bacterial endotoxin specification was tightened at the -----(b)(4)-----  
---- to be consistent with the specification for the final container product.
- -----(b)(4)----- – Data available at this time were found insufficient to support this operation. Kamada withdrew their request and will submit a PAS when sufficient data are acquired.
- Recommended product storage conditions – Proposed storage conditions, 24 months at 2 – 8 °C and -----(b)(4)-----, were not supported with sufficient data for the -----(b)(4)----- The approved storage temperature is 2 – 8 °C and allows for short term temperature excursions that may occur during the normal handling of the product.

- Correction factor for an in-house potency standard calibrated against the WHO standard – a correction factor was implemented to ensure that the dose of the product is not less than that used in the clinical trials.
- Out of specification investigations -----(b)(4)-----  
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This review memo discusses Kamada's responses to the CMC IRs dated 12/9/0, Items 38, 42, 44 - 56. The remaining CMC items were reviewed by the CMC reviewers Jennifer Reed, Lilin Zhong, Maria L. Virata-Theimer, Douglas Frazier and Pei Zhang. The responses to the items mentioned above were provided in Amendments 12 and 14, CBER comments are in italics and are followed with a discussion of Kamada's response in normal font.

## **Review**

### Amendment 12

This amendment contains a response to items 38, 42, 44 – 56 dated 12/9/09.

38. *Please change the upper limit for TnBP -----(b)(4)----- from -----(b)(4)-----*  
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Kamada changed the upper limit for TnBP in the -----(b)(4)----- and drug product from -----(b)(4)-----.

*Reviewer's comment:* The response is satisfactory.

42. *Please provide a list of raw materials used in the Kamada-API purification process and indicate the quality of each material and testing that is performed.*

Kamada stated that details regarding the quality and testing of -----(b)(4)----- were provided in the original BLA. In this amendment, Kamada provided a list of remaining raw materials with their grade (see Attachments, Table 42-1) and detailed information on testing. All non active raw materials used in the manufacturing of Kamada-API are of --- (b)(4) --- except for tri(n-butyl) phosphate (TNBP), which is of --(b)(4)-- as no --(b)(4)-- monograph is available. Raw material release specifications are based on the relevant pharmacopoeial monograph. In Tables 42-2 through Table 42-10 Kamada detailed the testing that is performed by QC or an approved contract laboratory on each of the non active raw materials listed in Table 42-1.

Some of the tests are part of routine raw material batch release and are performed on -----(b)(4)----- of non active raw material. Testing according to the complete monograph is performed as part of the approval of a new non active raw material

supplier and for approved suppliers, -----(b)(4)----- of the non active raw material is tested.

Water for Injection (WFI) is produced by Kamada. The routine test program for WFI testing of -----(b)(4)----- was described in the original submission in Chapter 3.2.A.1 Section 2.10.3. The chemical and microbial attributes for WFI were initially based on -----(b)(4)---- and the -----(b)(4)----- for WFI. Some of the limits were adjusted (lowered) in the course of the performance qualification study based on data trends. Tests performed for WFI with specifications are provided in Table 42-10 (see Attachments). In addition to the tests required by the -(b)(4)-, Kamada also performs tests required by the -----(b)(4)-----.

*Reviewer's comment:* The response is satisfactory.

43. *Please provide a table with all process control parameters (not only critical) and all quality attributes. Please note that all process parameter ranges should have two-sided limits. In the table, please include time of each operation.*

Kamada stated that this information will be provided in a separate submission by 1/18/10 and subsequently provided this information.

*Reviewer's comment:* The response is satisfactory.

44. *Please provide a table similar to Table S.2.5-55 containing operating parameters for the manufacture of the drug substance and drug product for the clinical lots, lots manufactured during product comparability study (recovered plasma vs. Source Plasma) and for the conformance lots. For the clinical lots, please provide observed parameter ranges, for the comparability and conformance lots, please provide individual results. Also, please provide a table with all in-process product quality attributes observed for the lots mentioned above with product quality attributes ranges for the clinical lots and individual results for the comparability and conformance lots.*

Kamada provided the observed ranges of the operating parameters for the manufacture of the drug substance and drug product clinical lots in Table 44-1 and quality attributes ranges for the clinical lots in Table 44-2 (see Attachments).

Kamada stated that a table containing individual results of operating parameters for the manufacture of the drug substance and drug product for lots manufactured during product comparability study and for the conformance lots was provided in Table S.2.5-2 of the original submission and a table with all in-process product quality attributes with individual results for the comparability and conformance lots were provided in Table S.2.5-14 and Table S.2.5-15 of the original BLA submission.

*Reviewer's comment:* The response is satisfactory. Current operating limits are consistent with the limits observed during the manufacture of the clinical lots.



----- (b)(4) -----  
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Reviewer's comment: The response is satisfactory.

48. ----- (b)(4) -----  
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----- (b)(4) -----  
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*Reviewer's comment:* The response is satisfactory.

49. ----- (b)(4) -----  
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 ----- (b)(4) -----  
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*Reviewer's comment:* The response is satisfactory.

50. ----- (b)(4) -----  
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----- (b)(4) -----  
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*Reviewer's comment:* The response is satisfactory.

51. ----- (b)(4) -----  
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----- (b)(4) -----  
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52. *Please provide equipment flow diagram with indication of sampling points and all tests performed at each sampling point.*

Kamada provided equipment flow diagram in Figure 52-1, indicated the tests performed at each sampling point for one sub-batch in Figure 52-2 (the second sub-batch is tested in an identical manner). They also showed drug product equipment flow diagram with indication of all tests performed at each sampling point in Figure 52-3 (see Attachments).

*Reviewer's comment:* The response is satisfactory.

53. *Please clarify whether ----- (b)(4) ----- that is proposed in this submission was validated in the full scale manufacture. Please note that --- (b)(4) --- should be validated in the full scale and the --- (b)(4) --- lots should be placed on stability.*

Kamada stated that the ----- (b)(4) ----- proposed in the BLA submission was performed at laboratory scale and not full scale manufacture. Kamada proposed to validate the --- (b)(4) --- process by performing one full scale production run. Recently, Kamada produced a full scale lot to support --- (b)(4) ---; however, we advised Kamada to withdraw a --- (b)(4) --- request and submit it in a PAS when sufficient data is available to support this operation, including at least 6 months of stability data under normal and accelerated conditions. Kamada withdrew --- (b)(4) --- request in Amendment 32.

54. *Please clarify what amount of ----- (b)(4) ----- was used in the pilot scale. Section 3.2S.2.5 p.166 and Section 2.3.S.2.3 p. 17 appear to provide conflicting information, - (b)(4) - of the full scale and ----- (b)(4) -----, respectively.*

Kamada clarified that the “early” pilot runs were produced at a partial manufacturing scale starting with approximately ----- (b)(4) ----- . These runs were produced as part of the technology transfer of the process from R&D to Production

and as initial scale-up from laboratory scale to “full scale”. These runs were discontinued upon completion of the scale-up process.

As of 2001, Kamada-API lots were manufactured at “full scale” by processing  
----- (b)(4) -----  
----- (b)(4) ----- . The pilot scale, - (b)(4) - of the full scale process, is  
currently in use for investigation and development purposes.

*Reviewer's comment:* The response is satisfactory.

55. Please provide a list of all pilot and full scale lots manufactured thus far and the year of their manufacture. Please include lots, manufacture of which was not completed. If such lots exist, please provide the reason for stopping the manufacturing process.

Kamada provided a list of -(b)(4)- full scale lots including Phase I clinical lot # 6112006 (Table 55-1), lots produced prior to Phase I clinical lot [full scale -(b)(4)- and pilot 4)] (Table 55-2), pilot runs -(b)(4)- related to this BLA (Table 55-3), and -(b)(4)- drug substance batches from which no drug product was formulated and which were manufactured from -----(b)(4)----- and produced for cleaning validation purposes (Table 55-4) (see Attachments).

*Reviewer's comment:* The response is satisfactory.

56. Please provide a list of deviations observed during the manufacture of paste comparability lots and conformance lots. Also, please provide summaries of the investigations.

Kamada provided lists of deviations reported during production of the drug substance, drug product and out of limit (OOL) results observed for the drug substance and drug product and subsequently provided Amendment 13 with summaries of each deviation and OOL result containing a description of the deviation/OOL result, investigation, impact of the deviation/OOL result on product quality, and recommended corrective and preventive actions.

*Reviewer's comment:* The response is satisfactory.

## Amendment 14

Amendment 14 contains a response to Item 43 from the fax dated 12/9/09.

43. Please provide a table with all process control parameters (not only critical) and all quality attributes. Please note that all process parameter ranges should have two-sided limits. In the table, please include time of each operation.

Kamada provided the requested information (see tables 43-1-1 through 43-1-8 in Attachments). In addition, they informed that they have incurred an --(b)(4)--

mechanical failure in -----(b)(4)----- vessel, -(b)(4)-. The required corrective and preventative actions necessitated making a change in the configuration of the -(b)(4)- in the vessel and their operational parameters during the -----(b)(4)---- steps. The new procedure was being validated at that time. Subsequently, new validation information was provided.

*Reviewer's comment:* The operating ranges are narrow; the process appears to be well controlled.