

STN 125350/0 Information Request - Hizentra, October 23, 2009

**To: Paul Hartmann
CSL Behring AG**

Date: October 23, 2009

This is regarding your BLA submission STN 125350/0 for Immune Globulin Subcutaneous (Human), 20% Liquid, submitted to the Agency on April 30, 2009. FDA continues with the review of the referenced submission and requests CSL Behring AG to provide the following information.

Please address the following comments pertaining to Study ZLB04_009CR:

1. Itching and local pain are subjective evaluations. Please clarify why they fall under "assessment by the investigator", and how the scoring by Investigator at the study visit could accurately reflect what happens at home infusions.
2. Since the wash-in/wash-out period involved IGSC administration, this period should not be excluded from efficacy analysis. Please conduct additional exploratory analyses of the primary and secondary efficacy endpoints over the entire period of IgPro20 use, including the ITT, MITT and PPE populations. These analyses will not be used for labeling purposes.
3. Repeated filling of infusion pumps to deliver high doses of IGSC allows for more than 4 injection sites to be used consecutively at the same infusion. Please clarify whether this is considered protocol violation or not. The tolerability of such infusions should be compared with that of other infusions which followed the up-to-4-site rule.
4. It is not clear why there was a decrease from 3.9% to 0.2% for the use of ≥ 10 injection sites per infusion from the wash-in/wash-out period to the efficacy period. Please clarify whether the use of large infusion volumes and hence numerous injection sites predisposed to withdrawal from study.
5. There were five infusions with infusion rate reduction or premature cessation. Please submit details of these infusions.
6. Please submit the CRFs for Subject -(b)(6)-.
7. The concept of TLR is theoretical, and dependent on an intermediary link between hypothetical IGIV and IGSC average daily levels that yield equivalent AUC. It is uncertain that there is a linear relationship between Ctrough and "average daily level", and so the basis of the TLR concept has to be tested with actual data from the individualized dosing in the PK subjects. The basis of testing TLR applicability in non-PK subjects using an arbitrary range of $1.29 \pm 15\%$ derived from PK subjects' data appears to be unsound. In fact, you have noticed that TLR within the $1.29 \pm 15\%$ range could be associated with a wide distribution of trough levels in the non-PK subjects. Please conduct an analysis of this ratio in the PK subjects upon attainment of steady state in the efficacy period with individualized dosing.
8. Please conduct an analysis of the ratio of the number of infusions with temporally associated adverse events (from start to within 72 hours of the end of infusion) to

the total number of infusions, including point estimate and 95% confidence intervals.

9. It appears contradictory that only one infusion was associated with an injection site reaction of severe intensity (subject -(b)(6)-), and yet three injection site reaction of severe intensity were reported as adverse events (subject -(b)(6)- with two infusions and subject -(b)(6)-). Please clarify.
10. Please account for the missing content in pages 303 - 308 of the Clinical Study Report.
11. Please submit a PREA deferral request for data submission on the children and adolescent age groups (≥ 2 to 12, and ≥ 12 to 16 years of age respectively).

Please submit a response to this request as an amendment to the file by November 16, 2009.

Thank you.

Pratibha Rana