

Addendum to Pharmacovigilance Review Memo

April 23, 2012 - Bivigam

- Office of Biostatistics and Epidemiology/Division of Epidemiology (OBE/DE)

BLA/Supplement Number: 125389/0

Product Name: Biotest- IgIV (Immune Globulin Intravenous (Human))
10%

Sponsor: Biotest Pharmaceuticals Corporation (BPC)
Indication(s): Primary immune deficiency disorders (PIDD)

Date(s): CBER receipt date: 11/3/2010; Complete Response:
9/1/2011; Re-submitted 10/26/2011; ADD: 4/26/2012

Review Priority: Routine Re-submission

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I. Background

This memorandum is an addendum to the Pharmacovigilance Memorandum for Biotest IgIV/Bivigam, STN 125389, dated 21Jun2011 and an addendum dated 2March2012. Comments from that addendum were forwarded to the sponsor as an Information Request (also dated 2March2012). The sponsor subsequently responded to this request on 12March2012 and submitted a Statistical Analysis Plan on 6April2012. This addendum addresses the sponsor's plans for a Post-Marketing Commitment study to examine the adverse effect of hypotension during and after Biotest IgIV infusion. Quotes taken directly from the BLA appear in *italics*.

II. Biotest Response to Information Request (IR) of 2March2012

The sponsor proposed a post-marketing study to examine the adverse effect of hypotension. The study will be a *multi-site, active-control, prospective, observational safety study*. (Biotest BLA, 1.11.3 PASS p.2) In the IR, OBE requested additional specifics on the study population/study design, analysis plan, data collection, and reporting.

II.A. Additional Information on the Study Population

OBE requested additional information on the inclusion and exclusion criteria for the study. As presently designed, the study will include male and female primary immune deficiency (PID) patients of any age. Study participants may be new or prevalent IgIV users. There are no specific exclusion criteria. (BLA, 1.11.3 Efficacy Information Amendment, p.2, 2March2012) The sponsor also plans to analyze the data by stratifying both the Bivigam and comparator IgIV groups into new and prevalent users.

Reviewer Comment: Enrolling both new and prevalent users will increase the number of study participants but may complicate the data analysis.

OBE requested additional information on the infusion service provider chosen for the study. As of 12March2012, this choice had not been finalized. However, the sponsor did specify several companies which could potentially be selected and stated that each potential company has a national presence, uses a variety of IgIV brands, and provides treatment for patients with a wide variety of disorders. (BLA, 1.11.3, p.2, 2March2012)

II.B. Additional Information on Study Design/Analysis Plan

The sponsor was requested to further clarify the null hypothesis and the primary endpoint of the study. The proposed study is a non-inferiority design. Thus, the null hypothesis is that the number of episodes of hypotension in Bivigam-treated patients will exceed the pre-specified non-inferiority margin when compared to the number of hypotension episodes in comparator group IgIV-treated patients. (BLA, 1.11.3, SAP, p.2-4) For details on the planned analysis, please see the review memo by Jessica Kim from the Division of Biostatistics. The primary endpoint is the *number of events of hypotension in subjects treated with Bivigam or other IGIV products under observational, standard of care conditions*. (BLA, 1.11.3 SAP p.1)

The comparator group will be patients receiving any other currently licensed IgIV, via the IV route. The specific products used as comparators may vary, depending on the infusion service provider selected and formulary considerations. (BLA, 1.11.3, Efficacy Information Amendment, p.3, 2March2012)

Reviewer Comment: Any combination of currently licensed IgIV products given via the IV route should be an adequate comparator group. Since the adverse event of interest is hypotension due to the presence of PS80 and Biotest is the only IgIV which contains PS80 in significant concentrations, any other IgIV (or a

combination of other IgIVs) would lead to a valid comparison for the purposes of this study.

In terms of attempting to ensure similarity between the Bivigam and comparator groups, the sponsor states that *[a]lthough, the study is not randomized, all efforts will be made to try to make the study as close to a randomized study as possible.* (BLA, 1.11.3 SAP, p.1) The sponsor plans to accomplish this by conducting several analyses, including:

- *No adjustment made on propensity score.*
- *Matching made on propensity score.*
- *Logistic regression including propensity score, with binary variable of subject having event(s) or not.* (BLA, 1.11.3 SAP, p.9)

In addition, the sponsor plans to conduct sub-group analyses based on gender, age, and past history of hypotension, renal or hepatic impairment. The sponsor also plans to examine data for the special populations of children, adolescent, pregnant or lactating women, and the elderly. It is anticipated that some of these special groups may be too small to yield significant data. (BLA, 1.11.3 Statistical Analysis Plan, p.9-10)

In response to the IR, the sponsor has agreed to modify the protocol and the primary endpoint to examine hypotension during and within 1 hour of infusion. In addition, the sponsor modified the definition of hypotension (which was a SBP <90mmHg and clinical symptoms of hypotension) to include a drop of 30mmHg in SBP. Currently, clinical symptoms of hypotension include dizziness or lightheadedness, and fainting. (BLA, 1.11.3 Efficacy Information Amendment, p.4, 2March2012)

Reviewer Comment: The “during and within 1 hour after” infusion time frame is acceptable. The definition of hypotension should be modified further to include the additional clinical symptoms of chest pain, diaphoresis, or a change in infusion rate.

II.C. Additional Information on Data Collection

OBE requested additional details on the study investigators, case adjudication, and the frequency of vital sign measurements. The sponsor has specified that the study will include *data collection, including a medical history, taken by health care professionals*

delivering IGIV through infusion service providers and not individual study investigators. (BLA, 1.11.3 Efficacy Information Amendment, p.4, 2March2012).

The sponsor has clarified that the [a]djudication of cases will be done in a product

blind manner, by an independent party. (BLA, 1.11.3 Efficacy Information Amendment, p.4, 2March2012).

Reviewer Comment: It remains unclear who will act as the primary study investigator. While health care providers may administer the infusion and collect the data and an independent party may conduct case adjudication, an investigator will still be needed to analyze the data and write a final report.

Regarding the frequency of vital signs, the sponsor states that this will be according to the infusion service provider's protocol. Typically, (according to the sponsor), this involves vital sign measurements within 15 minutes prior to the start of the infusion, prior to each infusion rate change, every 15 minutes for the 1st hour, every 30 minutes for the 2nd hour, at the onset of any adverse event, and *within 1 hour post infusion, if clinical symptoms of hypotension are present.* (BLA, 1.11.3 Efficacy Information Amendment, p.6, 2March2012)

Reviewer Comment: The sponsor will need to provide the protocol for vital sign measurement once an infusion service provider is selected. Also, the protocol will need to include an assessment 1 hour post-infusion. This could include vital sign measurements or simply a clinical assessment stating "no clinical signs of hypotension present, including dizziness, lightheadedness, chest pain, or diaphoresis."

II.D. Additional Information on Reporting

The sponsor has agreed to report on the study progress in the PAER, which will be quarterly for the first three years and annually thereafter. The sponsor has also agreed to submit the final study report within 6 months of the last patient completing the study. (BLA, 1.11.3 Efficacy Information Amendment, p.6, 2March2012)

III. Letter Ready Comments

Please modify the definition of hypotension to include the following additional clinical symptoms: chest pain, diaphoresis, change in the infusion rate. Thus, the definition should read "a decrease of 30mmHg **or** a SBP less than 90mmHg **and** clinical

symptoms of hypotension. The clinical symptoms of hypotension include 1 or more of the following: dizziness or lightheadedness, fainting, chest pain, diaphoresis, or a change in the infusion rate.”

The FDA acknowledges that healthcare providers will administer the infusions and that an independent party will adjudicate the cases. Please identify the principal investigator. In other words, please identify the person responsible for data analysis and writing the study reports.

Please provide the protocol for vital sign measurements once an infusion service provider is selected. Please clarify that this protocol will include an assessment of the patient at 1 hour post-infusion. This could include vital sign measurements or simply a clinical assessment stating “no clinical signs of hypotension present, including dizziness, lightheadedness, chest pain, or diaphoresis.”

Please provide a copy of the study protocol when available. It would seem reasonable to have a draft protocol within 3 months and a final protocol within 6 months. If this is not possible, please suggest an alternate schedule.