



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research
Office of Biostatistics and Epidemiology
Division of Biostatistics

STATISTICAL REVIEW AND EVALUATION

BLA/Supplement Number: STN 125389/0.23

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

Indication(s): Chronic (humoral) Primary Immune Deficiency Disorders (PIDD)

Applicant: Biotest Pharmaceutical Corporation (BPC)

Date(s): CBER receipt date: April 6, 2012

Review Priority: NA

Statistical Branch: CBER/OBE/DB/TEB (HFM-219)

Primary Statistical Reviewer: Jessica (Jeongsook) Kim, Ph.D.
Lead Mathematical Statistician

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EXECUTIVE SUMMARY

This submission is an amendment number 23 to the original BLA, STN 125389, from the Biotest Pharmaceuticals Corporation (BPC) dated on April 6, 2012. It includes sponsor's statistical analysis plan for the post marketing study, a multi-site, active control, prospective, observational, safety study, to assess the risk of hypotension in Primary Immune Deficiency Disorder (PIDD) patients treated with Bivigam and other immune globulin intravenous (IGIV) products administered at 3- or 4- week intervals. The sponsor's proposed statistical analysis plan (SAP) seems to be appropriate assuming CBER agrees with the assumptions being used in their SAP.

STATISTICAL EVALUATION

Study Design: The sponsor proposed a multi-site, active control, prospective, observational, non-inferiority, safety study to assess the risk of hypotension in Primary Immune Deficiency Disorder (PIDD) patients treated with Bivigam and other immune globulin intravenous (IGIV) products administered at 3- or 4- week intervals.

Aspects of the SAP may need to be revised after an infusion service provider and safety assessment-adjudication provider are chose.

***Reviewer's comments:** We strongly recommend finalizing the SAP before the initiation of the study.*

Study objective: The primary objective of the study is to evaluate the rate of hypotension in subjects treated with Bivigam and other immune globulin intravenous (IGIV) products under observational, standard of care conditions. The secondary objective is to evaluate the rates of hepatic and renal impairment events in patients.

The primary safety endpoint is the number of events of hypotension in subjects treated with Bivigam or other IGIV products under observational, standard of care conditions.

***Reviewer's comments:** I expect the clinical reviewer to comment on the appropriateness of the primary endpoint, the number of events of hypotension in PIDD patients treated with Bivigam.*

Study size: The sample size is based on a time-to-event non-inferiority two-sample type. The test statistic used for the sample size calculation is a logrank test with a significance level of 1-sided 2.5%, and a total dropout rate of 5%. Additional assumptions are that the events occur independently both between and within subjects, and that the risk for an event in the Bivigam treatment group is 1% and in the Control treatment (other IGIV products is 2%). Under these assumptions, 63 subjects per treatment group (corresponding to approximately 945 infusions per treatment group) would need to participate to produce a 90% power. Approximately 945 infusions of Bivigam and 945 infusions of other commercial IGIV administrations will be observed. The statistical expectation of number of events is 22.

| ***Reviewer's comments:** Using the statistical software, ~~----(b)(4)-----EAST5.2~~, a range of the required sample size was 56 to 64 depending on the subject accrual rate per unit time, 1 to 2 per 3.5 week respectively. It seems that the sponsor might have considered the middle number, 60, and added 5%*

of the dropout rate to get 63 subjects per treatment group, which seems to be acceptable if CBER agrees with the sponsor for the clinical assumptions (1% risk for an event in the Bivigam group and 2% in the Control group) used in the sample size calculation. Please also note that one year of the study duration has been used in the calculation that has not been explicitly stated in the protocol.

Study hypothesis:

$$H_0 : \frac{\lambda_{Bivigam}}{\lambda_{Control}} \geq 2 \quad \text{vs.} \quad H_1 : \frac{\lambda_{Bivigam}}{\lambda_{Control}} < 2, \text{ where } \lambda_{Control} \text{ is the constant hazard rate for the}$$

Control treatment and $\lambda_{Bivigam}$ is the constant hazard rate (expected percent time-to-event at a specific time) for the Bivigam treatment. The corresponding medians of the time-to-event distribution are $m_{Control} = \ln(2) / \lambda_{Control}$ for the Control and $m_{Bivigam} = \ln(2) / \lambda_{Bivigam}$ for the Bivigam treatment.

Reviewer's comments: The non-inferiority margin of 2 for the hazard ratio was suggested by the FDA.

Statistical analysis method

The Anderson-Gill model is applied to analyze recurrent event data; the hypotension events in subjects treated with Bivigam or other IGIV products under observational, standard of care conditions, over the entire study period being right-censored from the date of their last observation.

The PHREG procedure performs a stratified analysis to adjust for subpopulation differences. The PHREG procedure with the best subset selection method will be used to identify important prognostic factors.

The Anderson-Gill model will be used to analyze the primary endpoint, both without and with adjustment on propensity score. Non-inferiority of Bivigam versus Control will be assessed by inspecting the upper range of the 2-sided 95% confidence interval. If non-inferiority is established for the primary endpoint, the data will then be used for testing for evidence of a lower events rate versus Control for a possibility of superiority claim (upper two-sided 95% confidence limit < 1).

The nonparametric Kaplan-Meier method will be used to estimate the event-time-distribution of each treatment group.

Separate subgroup (gender, age, and past history events of hypotension, renal, or hepatic impairment) descriptions of the primary endpoint will be performed. Since several of the subgroups are expected to be small, the analyses should be viewed as exploratory. The Anderson-Gill regression analyses will be used to assess consistency of treatment effects across subgroups and populations, by inspection of P values for the interaction of treatment effect with subgroup and the hazard ratios and 2-sided 95% confidence intervals will be calculated for each subgroup. Similar exploratory analyses of these subgroups will be done for the secondary endpoints.

Reviewer's comments: *Regarding the primary analysis both without and with adjustment on propensity score, the sponsor should report both results and if two results doesn't show a common trend, detailed explanation about such study outcomes should be followed.*
At the post marketing study stage, the sponsor should have identified important prognostic factors before the study is being conducted.

Letter Ready Comments

- We strongly recommend finalizing the details of SAP before the initiation of your study.
- One year of the study duration has been used in the study size calculation, which has not been explicitly stated in the protocol. Please clarify the study duration.
- Please explicitly state the numerical information for subject accrual rate per unit time being used in your sample size justification. Please also provide a rational to use such accrual rate.
- Taking the low event rates (1% for the Bivigam and 2% for the Control) into consideration, we recommend exploring Poisson model to analyze the primary endpoint. Please report analyses results from both Ander-Gill and Poisson model.
- Regarding the primary analysis both without and with adjustment on propensity score, please report both results. If two results doesn't show a common trend, detailed explanation about such study outcomes should be followed. Also, please provide the detailed explanation on how the propensity scores are to be determined.
- At a post marketing study stage, you should have identified important prognostic factors before the study is being conducted.

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