



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

MID CYCLE STATISTICAL REVIEW AND EVALUATION -BLA

BLA Supplement Number: STN 125350.0

Product Name: Immune Globulin Subcutaneous (Human), 20% Liquid

Indication(s): Treatment of Primary Immunodeficiency (PID)

Applicant: CSL Behring

Date(s): eCTD submission - April 30, 2009

Review Priority: Standard

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1. EXECUTIVE SUMMARY

The sponsor, CSL Behring, submitted a biologic licensure application for IgPro20, a product for subcutaneous use with the high immunoglobulin concentration of 20%. The corresponding pivotal study (ZLB04_009CR) is a phase III, open-label, prospective, multicenter study of the efficacy, tolerability, safety and pharmacokinetics of IgPro20 in subjects with Primary Immunodeficiency (PID). This statistical review covers mainly the efficacy study results for the mid-cycle statistical review memo. Analysis of primary endpoint is verified in this memo while analyses of secondary endpoints are still on-going.

2. INTRODUCTION

2.1 Overview

Primary immunodeficiencies (PID) include a variety of disorders in which there is an intrinsic defect in the immune system that renders patients more susceptible to infections. These infections may be fatal if left untreated. Immunoglobulin replacement therapy is the standard treatment for patients with primary immunodeficiencies. Providing passive immunity and maintaining consistent serum IgG levels controls serum IgG levels controls most of the recurrent infections and results in significantly improved quality of life for these subjects.

CSL Behring (Prior to 01/01/2007 ZLB Behring) performed two phase II/III clinical studies with its SCIG Vivaglobin. In a six-month phase III study conducted in Europe and Brazil (CE1200_2002), the dose of Vivaglobin was equivalent to the previous IVIG dose (100%), i.e. a mean weekly dose of 89 mg/kg body weight. In a twelve-month phase II/III study conducted in the United States and Canada (CE1200-3001, BB-IND-(b)(4)-), the Vivaglobin dose was determined by comparing the area under the curve (AUC) of an IVIG and Vivaglobin and by adjusting the dose of Vivaglobin to achieve non-inferior AUCs. The first SCIG product obtained a US license in January 2006 (BL 125115/0). IgG trough levels in both studies increased compared to the previous IVIG treatment, from 7.9 to 10.4 g/L (mean of median) in the North American study and from 7.5 to 8.7 g/L (median) in the Europe/Brazilian study.

In April 2004, the sponsor submitted BB-IND -(b)(4)- to conduct a phase III clinical trials to investigate IgPro10, a chromatographically purified IVIG. The sponsor submitted the IND -(b)(4)- in April 2006 to investigate IgPro20 through a phase III study. The IND -(b)(4)- was initiated with FDA's agreement on September 29, 2006.

IgPro20 is a liquid (ready-to-use) formulation of normal human immunoglobulin (IgG) having an IgG concentration of 20%. The active substance of IgPro20 is highly purified polyvalent human immunoglobulin G (>96%). IgPro20 is stabilized with 250 mmol/L L-proline and 10-30 mg/L Polysorbate 80. The IgPro20 product employs the same manufacturing process as IgPro10.

2.2 Data Sources

Data sources include eCTD submission located in the FDA's Electronic Document Room (EDR) at the following link:

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3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

Study Design and Endpoints

Study Objectives

The primary objective was to evaluate whether the rate of clinically documented serious bacterial infections (SBIs) per subject per year is less than 1. SBIs are defined as:

- Bacterial pneumonia
- Bacteremia and septicemia
- Osteomyelitis / septic arthritis
- Bacterial meningitis
- Visceral abscess

The primary objective of the pharmacokinetic sub-study is to show that the chosen subcutaneous dose regimen is associated with steady-state AUCs not inferior to those obtained with the previous IV dose regimen. Secondary objectives of the PK sub-study are to determine the PK parameters AUC, C_{max} and T_{max} of total IgG, and the serum concentration of IgG subclasses, specific IgGs and L-proline.

Study Design

The trial is planned as a prospective multicenter, open-label, single arm phase III study for the treatment of subjects with PID.

Study Duration

The study consisted of a 12-week wash-in/wash-out period followed by a 12-month efficacy period. During the wash-in/wash-out period the weekly dose of IgPro20 will be one fourth (for subjects with previous 4 weekly schedule) or one third (for subjects with previous 3 weekly schedule) of the average dose of the previous 3 IVIG infusion times 1.3 (130%).

The first enrollment date was 29 November 2006 and the last completed date was 27 October 2008.

Study Centers

A total of 12 centers in the USA enrolled subjects for this study.

Study Endpoints

The primary efficacy endpoint of this study was defined as the annual rate of clinically documented SBIs in the MITT population during the efficacy period (starting with Week 13).

Secondary efficacy endpoints include

- Rates of SBIs in the ITT and PPE population
- Number of infection episodes
- Day out of work / school / kindergarten / day care or unable to perform normal activities
- Days of hospitalization due to infections
- Use of antibiotics for infection prophylaxis and treatment

Patient Disposition, Demographic and Baseline Characteristics

Analysis Population

The intent-to-treat (ITT) safety data comprises all subjects treated with the study drug during any study period, including both the wash-in/wash-out period and the efficacy period.

The modified intention to treat (MITT) data set comprises all subjects treated with the study drug during the efficacy period, and having the disease under study. The 12-month efficacy period starts with Week 13 and ends after the completion visit.

The per protocol efficacy (PPE) data set consists of all subjects who complete the 12-month efficacy period.

The following table shows the number of subjects in each population:

Planned enrollment	50
Actual enrollment	49
ITT population	49
MITT population	38
PPE population	25
Discontinued	21

There were 11 subjects discontinued the study during the wash-in/wash-out period and 10 subjects discontinued the study during the efficacy period. There were 3 subjects completed the study but not included in the PPE population analysis due to the major protocol deviation. The following table categorizes the discontinuation reasons:

Withdrawn Reason	Withdrawn Period	Total number of subjects	Subject ID
Withdrawn of consent	Wash-in/wash-out	8	----- (b)(6) ----- ----- ----- -----
AE	Wash-in/wash-out	2	----- (b)(6) -----
Disqualifying laboratory results	Wash-in/wash-out	1	-(b)(6)-
Withdrawn of consent	Efficacy	6	----- (b)(6) ----- ----- -----
Multiple violations of the protocol	Efficacy	1	-(b)(6)-
Lost to follow-up	Efficacy	1	-(b)(6)-
Non-compliance	Efficacy	1	-(b)(6)-
Termination of the study site	Efficacy	1	-(b)(6)-

A total of 11 subjects in the ITT population who were treated during the wash-in/wash-out period only were excluded for the MITT population. A total of 13 subjects (10 discontinued and 3 completed treatments) in the MITT population were excluded from the PPE population because of protocol deviations. Major protocol deviations include “deviation of > 10% overall from the planned number of infusions during efficacy period” (9 subjects), “deviation of >10% overall from planned adjusted dose during efficacy period” (2 subjects), “subject did not obtain IgPro20 infusions on 3 consecutive weeks during efficacy period” (2 subjects). The sponsor summarized protocol deviations from MITT in Table 4 (Clinical Study Report, page 68) and all protocol deviations in Table 14.1.1.4 (Clinical Study Report, page 69).

Statistical Methodologies

The primary efficacy endpoint was defined as the infection rate of clinically documented SBIs per person year in the MITT population during the efficacy period. The null hypothesis is $H_0: \lambda_1 \geq 1.0$ versus $H_a: \lambda_1 < 1.0$, where λ_1 represents the parameter of a Poisson distribution,

i.e., the number of SBIs in the IgPro20 group per subject through the 12-month efficacy period was tested by providing the upper 1-sided 99% confidence limit. Secondary efficacy endpoints and safety variables were analyzed descriptively.

The 12-month rate λ_1 was estimated as:

$$\lambda_t = 365 \frac{y}{t},$$

where y represents the total number of SBIs observed and t is the total number of observed days. In this study the estimate of λ_t was zero, for MITT, ITT and PPE population respectively.

Its upper one-sided 99% confidence limit (λ_{upper}) was calculated by the sponsor as:

$$\lambda_{upper} = \frac{365}{t} \times 0.5 \chi_{0.99, 2y+2}^2$$

The sponsor's estimation of the 99% confidence limit was 0.132, which was confirmed by this statistical reviewer. The estimation of λ_{upper} of ITT and PPE population is 0.117, which was also verified by this statistical reviewer.

Results and Conclusions

The infection rate of SBIs per person year of the MITT population was zero because none of subjects in this study has an SBI. The primary objective of this study met the study success criterion. The following table summarizes the results:

Population	Number of SBIs	Rate	Number of study days	Upper 99% confidence limit
MITT	0	0	12697	0.132
ITT	0	0	16234	0.104
PEE	0	0	9543	0.176

NOTE: The following table summarizes the primary efficacy analyses with imputation methods conducted by the sponsor:

Imputation method	Number of SBIS	Rate	Number of study days	Upper 99% confidence limit
None	0	0	12697	0.132
Worst case approach	0	0	14329	0.117
Worst case approach for drop outs according to drop out reason	0	0	14329	0.117
Extrapolation approach	0	0	14329	0.117
Mean number approach	0	0	14329	0.117
Best case approach	0	0	14329	0.117

This statistical review memo serves the mid-cycle review commitment. There will be an extensive internal discussion about the imputation methods. Any internal consensus

about the imputation methods will be included in the final review memo. Analyses of secondary endpoints are still on-going.

3.2 Evaluation of Safety

In this study the sponsor evaluate the safety of IgPro20 in ITT population (49 subjects). A total of 2264 IgPro20 infusions were administered. The sponsor also investigated the safety of IgPro20 through ZLB06_003CR and ZLB04_008CR study.

All subjects in the ITT population experienced at least one AE and all subjects had at least one AE that was at least possibly related to study drug and temporally associated with an infusion (i.e., during or within 72 hour of infusion). Excluding local reactions, 45 subjects has AEs, of which 25 subjects had at least possibly related AEs, 41 subjects had AEs that were temporally associated with an infusion, and 23 subjects had at least possibly related AEs that were also temporally associated with an infusion.

The overall AE rate per infusion was 0.773, and the rate of AEs that were temporally associated with study drug was 0.692. The most common AE was injection site reaction, which was experienced at least once by all subjects and occurred at a rate of 0.580. Most AEs (99%) were mild or moderate in intensity.

Safety analyses are on going and a combination of all 3 safety studies will be provided in the final review memo.

3.3 Gender, Race, Age and Other Special/Subgroup Populations

All of the 49 subjects enrolled in the study were treated with IgPro20 and included in the ITT population. The MITT population includes all 38 subjects who were treated during the efficacy period and the PPE population included 25 subjects who completed the study per protocol. In the MITT population, 21 subjects were female and 17 subjects were male. The mean age was 36.3 years (6 children <16 years of age); mean weight was 70.0 kg. The sponsor did not implement the subgroup analyses of efficacy in the PPE population because the numbers of subjects were too small to allow firm conclusions in some subgroups.

4. SUMMARY AND CONCLUSIONS

4.1 Statistical Issues and Collective Evidence

The primary efficacy endpoint met the study success criterion for the primary objective. I investigated/confirmed the primary efficacy/safety analysis.

Since there were no SBIs during the study period regardless of the population types, the one-sided upper 99% confidence interval limit for the PEE population is greater than that of thee ITT/MITT population.

Missing data will be imputed according to the clinical reviewer's assessment and the primary efficacy analysis will be re-analyzed for the ITT, MITT, and PEE population.

4.2 Conclusions and Recommendations

This statistical reviewer confirmed that the rate of SBI per subject per year on MITT population is zero with the upper 99% confidence limit as 0.132. Using the sponsor's imputation methods for the missing data of the MITT population, the upper 99% confidence limit drops to 0.117. The rates of SBI per subject per year on ITT population and on PPE population are zero too. The upper 99% confidence limits are 0.104 and 0.176, respectively. The rate of SBI per subject per year as well as its upper 99% confidence limit met the study success criterion.

This statistical review memo serves the mid-cycle review commitment.

Sensitivity analysis using various imputation methods and the secondary safety analyses are still on-going.

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