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 (FINAL)

BLA Supplement Number:	STN 125350.136
Product Name:	Immune Globulin Subcutaneous (Human), 20% Liquid
Indication(s):	Treatment of Primary Immunodeficiency (PID)
Applicant:	CSL Behring
Date(s):	October 5, 2011
Review Priority:	Standard
Statistical Branch:	Therapeutics Evaluation Branch (TEB)
Primary Statistical Reviewer:	Jessica (Jiang) Hu, Ph.D., visiting scientist, Therapeutics Evaluation Branch, (HFM-219)
Concurring Reviewer (1):	Jessica Kim, PhD., Team Leader, Therapeutics Evaluation Branch, (HFM-219)
Concurring Reviewer (2):	Boguang Zhen, PhD., Acting Brach Chief, Therapeutics Evaluation Branch, (HFM-219)
Clinical Reviewer(s):	Yang, Ling, MD
Project Manager:	Rana, Pratibha

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1. EXECUTIVE SUMMARY

This is a BLA labeling supplement for Hizentra (internal product code: IgPro20), a product for subcutaneous use with the high immunoglobulin concentration of 20% from CSL Behring and indicated for the treatment of primary immunodeficiency. The sponsor (CSLB) submitted the clinical report of ZLB06_001CR in this supplement and a revised draft package insert. This statistical review discusses the primary efficacy analyses, secondary efficacy analyses as well as safety analyses. There is no statistical issue for this BLA supplement.

2. INTRODUCTION

2.1 Overview

Hizentra, Immune Globulin Subcutaneous (Human), 20% Liquid (company code IgPro20), is a ready-to-use, sterile 20% (0.2 g/mL) protein liquid preparation of polyvalent human immunoglobulin G (IgG) for subcutaneous administration. It was approved by the FDA on March 4, 2010 (under BLA 125350/0) and is indicated for the treatment of primary immunodeficiency (PID). Three clinical studies, including two safety studies (ZLB06_003CR and ZLB04_008CR) and one pivotal study (ZLB04_009CR), were submitted by the sponsor in the original application. The purpose of this BLA supplement is to incorporate, as supportive information, the efficacy and safety results of a study conducted in Europe (ZLB06_001CR) into the Hizentra package. This supplement provides an updated clinical overview and summaries that incorporate the results of the European study.

Study ZLB06_001CR is a prospective, open-label, multicenter, single arm, Phase 3 clinical study conducted in Europe that evaluated the efficacy, safety, tolerability, and pharmacokinetics of Hizentra in 51 adult and pediatric subjects with PID. This study is the pivotal study that was conducted for the registration of Hizentra in Europe and other countries outside of the US. This study consisted of a 12 week wash-in/wash-out period followed by a 28 week efficacy period.

CSLB has referenced the clinical study report of ZLB06_001CR to fulfill pediatric assessment requirement for subjects aged 2 to <16 under BLA STN 125350/103. The supplement 125350/103 was approved on 2/17/11 with labeling changes from the additional pediatric data.

The current supplement 125350/136 is classified as “efficacy” supplement because of clinical data. It is reviewed for appropriateness of the revisions in the draft package insert. Major revision in labeling includes changes to:

- Adverse Reactions section to include safety data of Study ZLB-06_001CR
- Clinical Studies section to incorporate efficacy data of Study ZLB06_001CR
- Postmarketing Experience Section to incorporate postmarketing pharmacovigillence data

The revisions also include:

- Additional language regarding age range in the Indications and Use section
- Update on thrombotic events associated with the subcutaneous IG use in the Warnings and Precautions section
- Correction in the steps for product administration in the Dosage and Administration and Patient Counseling Information section.

This statistical memo investigates the primary efficacy analyses, secondary efficacy analyses as well as safety analyses to confirm the proposed labeling revision.

2.2 Data Sources

Data sources include an 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 Design

The study ZLB06_001 was designed to assess the efficacy, tolerability, safety, and pharmacokinetics (PK) of IgPro20 in subjects with PID, including a health-related quality of life (HRQL) assessment.

The primary objective was to demonstrate sustained total serum IgG C_{trough} values during 6 consecutive weeks of the efficacy period that were comparable to the values measured during the previous 3 to 6 months of IgG treatment. Secondary objectives included evaluations of efficacy during the 28-week efficacy period, HRQL and safety (AEs, local tolerability, clinical laboratory parameters, vital signs, and physical examination). Steady-state serum concentrations of total IgG, IgG subclasses, specific IgGs, and L-proline were assessed at steady-state during the efficacy period.

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

The study consisted of a 12-week wash-in/wash-out period followed by a 28-week efficacy period. HRQL was assessed at screening, and after 12, 24 and 40 weeks of treatment with IgPro20. During the 28-week efficacy period, subjects visited the study sites at least every 4 weeks for efficacy and safety evaluations and additionally recorded details regarding IgPro20 dose and certain aspects of efficacy and safety in a diary.

The first enrollment date was 28 September 2007 and the last completed date was 31 August 2009.

A total of 15 centers in Europe (France, Germany, Poland, Romania, Spain, Sweden, Switzerland, and the United Kingdom) enrolled subjects for this study.

The study was conducted in 51 subjects, including 17 subjects < 12 years, 22 subjects < 16 years, and 25 subjects < 18 years of age.

The study design took into consideration the appropriate EMA guidance. In contrast to the US pivotal study ZLB04_009CR, the IgPro20 dose administrated throughout the study ZLB06_001 were generally equal to the weekly equivalent doses given during the subjects' previous IGIV or IGSC therapy. Because Europe applies lower pre-study doses in IgG, the mean doses of IgPro20 administered in study ZLB06_001CR were approximately 50% of the doses administered in study ZLB04_009CR.

Study Endpoints

The primary efficacy endpoint of this study was to descriptively compare IgG trough levels at 6 consecutive weeks at steady state within the study, i.e. IgG levels prior to infusions 12 to 17, with 3 trough levels obtained from the subject's previous treatment during the most recent 3 to 6 months prior to the study.

Secondary efficacy endpoints included:

- Serious bacterial infections (SBI)
- Number of infection episodes
- Days 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

Safety variables included:

- Adverse events
- Local tolerability
- Laboratory safety variables including hematology, serum chemistry, urinalysis, virology
- Other safety variables such as vital signs, physical examination etc.

Analysis Populations

The intent-to-treat (ITT) data comprises all subjects treated with the study drug during the efficacy period (starting with Week 13), and having the disease under study.

The per protocol efficacy (PPE) data set consists of all subjects who complete the 28-week efficacy period. Protocol compliance with regard to the disease under study and

efficacy measurements is required. Major deviations from the treatment schedule will also lead to an exclusion from the per protocol efficacy data set.

The “all treated” (AT) safety data set comprises all subjects treated with the study drug during any study period.

The Full-Analysis HRQL population (Full HRQL) comprises all subjects entered into the clinical trial who complete a baseline and at least one follow-up HRQL assessment. Missing visits will not be imputed, with the exception Europe applies lower pre-study doses that the "last observation carried forward" (LOCF) approach will be used to analyze the end of study (EOS) visit that is defined as the last observed post-baseline value for each subject.

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

Table 3.1.1 Number of subjects (Planned and analyzed)

Planned enrollment	51
Actual enrollment	51
ITT population	46
PPE population	34
Discontinued	8

A total of 5 subjects discontinued study during the wash-in/wash-out period, leaving 46 subjects who were treated in the efficacy period and included in the ITT population. The reasons for discontinuation were AEs (3 subjects) and withdrawal of consent (2 subjects). Of the 46 subjects entering the efficacy period, 3 subjects discontinued during the efficacy period (AE), leaving 43 subjects who completed the efficacy period.

Among the 46 subjects in ITT population, a total of 12 subjects (26.1%) in the ITT population had major protocol deviations and were therefore excluded from the PPE population. The table 3.1.2 shows the major protocol deviations in ITT population.

Table 3.1.2 Major protocol deviations (ITT population)

Subject with ≥ 1 major protocol deviation	12
Violation of inclusion criteria	6
Increase of > 10% overall from planned dose during efficacy period	5
Subject did not obtain IgPro20 infusions on 3 consecutive weeks during the efficacy period (including Infusion 12)	3
Deviation of > 10% overall from the planned number of infusions during efficacy period (Including Infusion 12)	3

Six subjects in the ITT population had a violation of an inclusion criterion. Five subjects did not have “at least 3 documented IgG C_{trough} values of $\geqslant$ 5 g/L during the previous 3 months on replacement therapy or during previous 6 months in case of stable dose for at

least 3 months" (for 3 subjects only 1 IgG C_{trough} value before the study was available, and for 2 subjects no C_{trough} value before the study was available). In addition to having major protocol deviations, 3 subjects were also excluded from the PPE population because they did not complete the 28-week efficacy period. A total of 34 subjects were included in the PPE population.

Patient Disposition, Demographic and Baseline Characteristics

In the ITT population, 15 subjects (32.6%) were female and 31 subjects (67.4%) were male. The mean age was 21.5 years (range: 3 to 60 years). A total of 17 subjects (37.0%) were 2 to < 12 years of age, 5 subjects (10.9%) were 12 to 16 years of age. All subjects were white. The mean body weight was 52.1 kg (2 to < 12 years: 25.4 kg; 12 to < 16 years: 57.1 kg; 16 to < 65 years: 69.9 kg), and the mean BMI was 20.6 kg/m^2.

In the AT population, 25 subjects (49.0%) had blood group A (19 subjects were Rh+), 13 subjects (25.5%) had blood group O (12 subjects were Rh+), 5 subjects (9.8%) had blood group B (all were Rh+), and 1 subject (2.0%, Rh+) had blood group AB. The blood group was not determined for 7 subjects (13.7%). Although some individual observations for hematology parameters at screening were flagged as abnormal, none were clinically significant and there were no safety concerns that affected the subjects' participation in the study.

Statistical Methodologies

The sponsor used descriptive statistics to summarize the results of this clinical study. In general descriptive (summary) statistics included the following: Continuous variables were summarized with number of subjects, mean, standard deviation (SD), 0% (minimum), 25%, 50% (median), 75%, and 100% (maximum) quantiles. Frequency distributions were given for categorical data.

The primary efficacy endpoint for ZLB06_001CR was IgG C_{trough} values. The primary efficacy analysis was to use descriptive statistics to compare IgG C_{trough} values at 6 consecutive weeks at steady-state (prior to Infusions 12 to 17), with 3 IgG C_{trough} values obtained from the subject's previous treatment during the last 3 to 6 months prior to the study. Efficacy analyses were carried out on the ITT population. In addition, analyses of IgG C_{trough} values and SBIs were also performed on the PPE population.

Analyses of safety endpoints were based on the AT data set.

The HRQL analyses were based on the full HRQL population. Descriptive statistics (i.e., mean, median, quartiles, standard deviations, minimum and maximum) for each instrument were reported separately for the screening visit, infusion 40 and the EOS visit. Missing values for single items within each scale were replaced as outlined by the instruments' authors. Missing data for an entire assessment (i.e., missing forms) was left as missing, and non-missing endpoints were analyzed by visit. Additionally, the LOCF approach was used to analyze the end of study visit.

Patients who discontinued from the study were not replaced. All available data were used for the efficacy analyses. No imputation was made.

No formal interim analysis was performed for this study.

Adjustments for covariates were not performed in the analyses of this study.

Due to the small number of subjects at most centers the data from all centers that participated in this study were pooled in analyses. No by-center analyses were conducted.

No adjustments for multiple comparisons were made.

Results and Conclusions

The primary efficacy analysis was based on the ITT population. An additional analysis was conducted on the PPE population by the sponsor.

Table 3.1.3 Mean of individual median IGIV or IGSC doses during 9 months before study (ITT population)

IgG therapy	Number of subjects	Mean (SD) weekly dose in mg/kg
IGIV	27	131.5(50.00)
IGSC	19	107.0(28.54)

During the last 9 months before enrollment into the study, 28 subjects (60.9%) in the ITT population had received IGIV (human normal immunoglobulin for intravenous administration) therapy at a mean of individual median weekly equivalent doses of 131.5 mg/kg, and 18 subjects (39.1%) had received IGSC (human immunoglobulin for subcutaneous administration) therapy at a mean of individual median weekly doses of 107.0 mg/kg. To calculate the mean of individual median weekly equivalent doses, each subject's doses were first aggregated to the median and then median values were analyzed. Immediately before the start of this study, 27 subjects (58.7%) had received IGIV therapy and 19 subjects (41.3%) had received IGSC therapy. Table 3.1.3 shows the previous IGIV or IGSC doses during 9 months before the enrollment of the study.

Table 3.1.4 and table 3.1.5 show the IgG trough levels before and during the study. According to the tables, the Mean IgG trough values were generally stable during the efficacy period. In the ITT population, the mean (as well as median) of individual median of IgG C_{trough} values increased by 8.1% (from 7.49 g/L with the previous IgG therapy to 8.10 g/L during Infusions 12 to 17). Table 3.1.6 presents an analysis of the data on IgG trough values with respects to age.

Table 3.1.4 Mean of individual median pre-study IgG trough levels (ITT population)

	IgG trough level (g/L)		
IgG therapy	N	Mean (SD)	Median(range)
Any	46	7.49 (1.570)	7.02 (5.26-11.71)
IGIV	27	6.78 (1.329)	6.48 (5.26-11.71)
IGSC	19	8.43 (1.375)	8.57 (5.36-10.30)

Table 3.1.5 Mean of individual median IgG trough levels before and during the study (ITT population)

	IgG trough level (g/L)	
Period	Mean (SD)	Median(range)
Pre-study	7.49 (1.570)	7.02 (5.3-11.7)
Infusion 12 to 17	8.10 (1.443)	7.99 (5.1-12.4)
Infusion 12 to 41	8.10 (1.340)	8.09 (5.2-11.2)

Table 3.1.6 Mean of individual Median IgG trough levels with respect to age (ITT population)

	Median IgG trough level (g/L)		
Period	2 to <12 years (N=17)(SD)	12 to < 16 years (N=5)(SD)	16 to < 65 years (N=24)(SD)
Pre-study	6.94 (1.223)	7.99(1.946)	7.81(1.666)
Infusion 12 to 17	7.86(1.720)	7.91(1.432)	8.31 (1.250)
Infusion 12 to 41	7.78(1.51)	8.14(1.390)	8.32(1.211)

In the PPE population, similar results were observed. The mean of individual median IgG C_{trough} values was 8.25 g/L at steady-state IgPro20 treatment (values were nearly equal when 6 consecutive IgG C_{trough} values before Infusions 12 to 17 or all IgG C_{trough} values during the efficacy period were considered) . Compared to IgG C_{trough} values for 3 infusions during the previous IGIV or IGSC treatment before the start of this study the mean of individual median IgG C_{trough} values increased by 7.4% (from 7.68 g/L with the previous IgG therapy to 8.25 g/L at steady-state IgPro20 treatment).

This statistical reviewer also calculated the mean (as well as median) of the within-subject median difference between the pre-study period and the efficacy period. For subjects who took IGSC treatment before, the mean of within-subject median difference of IgG trough level was -0.36, with a 95% confidence interval (-0.592, -0.133). For subjects who took IGIV treatment before, the mean of within-subject median difference of IgG trough level was 0.95, with a 95% confidence interval (0.548, 1.357). This contradiction might be explained by the fact that the IGSC group had a higher mean IgG trough level as 8.43 g/L during the pre-study period while the IGIV group's mean IgG trough level was only 6.78 g/L. Overall, the difference of within-subject median IgG trough levels had a mean value as 0.41 g/L with a 95% confidence interval (0.095, 0.724) for the ITT population.

Table 3.1.7 Mean of difference of within-subject median IgG trough levels before and during the study (ITT population)

	Difference of IgG trough level (g/L)		
IgG therapy	N	Mean (SD)	Median(range)
Any	46	0.41 (1.060)	0.14 (-1.255-2.91)
IGIV	27	0.95 (1.023)	0.845 (-0.76-2.91)
IGSC	19	-0.36 (0.476)	-0.45 (-1.255-0.755)

Analyses of secondary efficacy endpoints were based on the ITT population, except for the rate of SBIs, which was analyzed in the ITT and PPE populations. Secondary efficacy analyses were generally restricted to the efficacy period, starting at Infusion 13, and extending to the completion visit. Secondary efficacy analyses included:

- Rate of serious bacterial infections in the ITT and PPE population;
- Number of infection episodes;
- Number of days out of work/school/kindergarten/day care or unable to perform normal activities due to infections;
- Number of days hospitalized due to infections;
- Use of antibiotics for infection prophylaxis or treatment.

The sponsor applied descriptive statistics for secondary efficacy endpoints.

There were no subjects in the ITT population or the PPE population who had an SBI during the efficacy period. The annual rate of SBIs per subject in these populations were therefore 0, with upper 99% confidence limits of 0.192 for the ITT population (0.250 for the PPE population). A total of 36 subjects (78.3%) in the ITT population had at least 1 infection in the efficacy period. The total annual rate of infections was 5.18 infections/subject/year, with a 95% confidence limits as (4.305, 6.171).

Table 3.18 shows the summary of serious bacterial infections and Table 3.19 summarizes the rest of secondary endpoints.

Table 3.1.8 Summary of secondary efficacy endpoints (Efficacy period)

	Efficacy period	
Secondary efficacy endpoint	Number of subjects (%)	Number of events/days (annual rate)
Serious bacteria infections (PPE)	0	0
Serious bacteria infections (ITT)	0	0
Infection episodes	32(78.3)	124(5.18)
Days with antibiotics for infection prophylaxis or treatment	32(69.6)	1743(72.75)
Days out of work/school/kindergarten/day care or unable to perform normal activities due to infections	20(43.5)	198(8.00)
Days hospitalized due to infections	4(8.7)	86(3.48)

Table 3.1.9 Summary of secondary efficacy endpoints (Full evaluation period)

	Full evaluation period	
Secondary efficacy endpoint	Number of subjects (%)	Number of events/days (annual rate)
Serious bacteria infections (PPE)	1(2.9)	1(0.04)
Serious bacteria infections (ITT)	1(2.2)	1(0.03)
Infection episodes	41(89.1)	181(5.24)
Days with antibiotics for infection prophylaxis or treatment	37(80.4)	2464(71.34)
Days out of work/school/kindergarten/day care or unable to perform normal activities due to infections	31(67.4)	322(9.35)
Days hospitalized due to infections	4(8.7)	105(3.05)

Conclusion: The primary efficacy analysis of study outcomes confirms that in the European study the mean IgG trough levels increased by 8.1% from 759 mg/dL prior to the study to 810 mg/dL during the efficacy period. The secondary efficacy analysis of SBI confirms that none of subjects had an SBI during the efficacy period, which results in an annualized rate of 0 (upper one-sided 99% confidence limit of 0.192) SBIs per subject. The annualized rate of any infection was 5.18 infections per subject of the efficacy period.

3.2 Evaluation of Safety

The sponsor also investigated the safety of IgPro20 through ZLB06_001. All safety summaries and analyses are based on the AT population, which included 51 subjects who had received IgPro20 during any study period.

In the AT population, 50 subjects had at least 1 AE, 31 subjects has at least 1 AE that was at least possibly related to the study drug, and 48 subjects has at least 1 AE that occurred during an infusion or within 72 hour after the end of infusion. A total of 29 subjects had at least 1 AE that was considered at least possibly related to study drug and was temporally associated. 5 subjects experienced SAEs, all of which were assessed by the investigator to be unrelated to the study drug. 6 subjects experienced AEs that led to study discontinuation.

No deaths occurred during the study. There were 527 AEs and 1831 infusions in this study. The AE rate per infusion is 0.288. Among the 527 AEs, 194 were considered at least possibly related to study drug, resulting a rate as 0.106.

A total of 7 SAEs occurred in subjects who received at least 1 dose of IgPro20, all of these SAEs were unrelated to the study drug. A total of 14 AEs were classified as leading to discontinuation form the study, 7 of which were considered at least possibly related to study drug.

The following table 3.2.1 reports the adverse events.

Table 3.2.1 Summary of subjects with adverse events (AT population)

Adverse Event	Number of subjects (%) (N=51)	Number of adverse events (rate) (N=1831)
AEs	50(98.0)	527 (0.288)
At least possibly related AEs	31(60.8)	194 (0.106)
SAEs	5(9.8)	7(0.004)
AEs leading to discontinuation of the subject	6(11.8)	14(0.008)
At least possible related AEs leading to discontinuation	3(5.9)	7(0.004)

The subgroup analyses of AEs by age class, disease type, previous replacement therapy were summarized from Table 3.2.2 to 3.2.5.

Table 3.2.2 Subgroup analysis by age for incidence of subjects with adverse events (AT population)

Adverse Event	2 to < 12 years (N=18)	12 to <16 year (N=5)	16 to < 65 years (N=28)
AEs	18 (100)	5(100)	27(96.4)
At least possibly related AEs	7(38.9)	2(40.0)	22(78.6)
SAEs	3(16.7)	0	2(7.1)
AEs leading to discontinuation of the subject	2(11.1)	0	4(14.3)
At least possible related AEs leading to discontinuation	0	0	3(10.7)

Table 3.2.3 Subgroup analysis by age for adverse events (AT population)

Adverse Event	2 to < 12 years (N=678)	12 to <16 year (N=199)	16 to < 65 years (N=954)
AEs	134(0.198)	48(0.241)	345(0.362)
At least possibly related AEs	47(0.069)	11(0.055)	136(0.143)
SAEs	5(0.007)	0	2(0.002)
AEs leading to discontinuation of the subject	6(0.009)	0	8(0.008)
At least possible related AEs leading to discontinuation	0	0	7(0.007)

Table 3.2.4 Subgroup analysis by disease type for incidence of subjects with adverse events and adverse event rate (AT population)

	Number (%) of subjects		Number (rate) of events	
Adverse Event	CVID (N=30)	XLA (N=20)	CVID (N=1098)	XLA (N=693)
AEs	30(100)	19(95.0)	371(0.338)	154(0.222)
At least possibly related AEs	23(76.7)	8(40.0)	132(0.120)	52(0.089)
SAEs	5(16.7)	0	7(0.006)	0
AEs leading to discontinuation of the subject	3(10.0)	3(15.0)	6(0.005)	8(0.012)
At least possible related AEs leading to discontinuation	2(6.7)	1(5.0)	5(0.005)	2(0.003)

Table 3.2.5 Subgroup analysis by previous replacement therapy for incidence of subjects with adverse events and adverse event rate (AT population)

	Number (%) of subjects		Number (rate) of events	
Adverse Event	IGIV (N=31)	IGSC (N=20)	IGIV (N=1068)	IGSC (N=763)
AEs	30(96.8)	20(100)	278(0.260)	249(0.326)
At least possibly related AEs	18(58.1)	13(65.0)	112(0.105)	82(0.107)
SAEs	4(12.9)	1(5.0)	6(0.006)	1(0.001)
AEs leading to discontinuation of the subject	5(16.1)	1(5.0)	9(0.008)	5(0.007)
At least possible related AEs leading to discontinuation	3(9.7)	0	7(0.007)	0

Almost all subjects had AEs irrespective age. The subgroup analysis of AEs by age class showed a lower incidence of subjects and lower rates per infusion for at least possibly related AEs in younger subjects. The incidence of subjects with at least possibly related AEs was lower in subjects 2 to < 12 years (0.389) and subjects 12 to < 16 years (0.4) compared subjects in 16 to < 65 years (0.786). The rate of AEs was lower in subjects 2 to <12 years (0.198), compared to subjects 12 to < 16 years (0.241) and subjects 16 to < 65 years (0.362). The rates of SAEs and AEs leading to discontinuation were similar across different age groups.

The subgroup analysis of AEs by disease type showed a higher incidence of subjects with at least possibly related for subjects related CVID compared with subjects with XLA.

Subgroup analyses of AEs by previous replacement therapy and starting infusion rate revealed no relevant difference in the incidence of subjects with AEs or the rate of AEs.

Taken together, subgroup analyses of AEs revealed no clinically relevant or consistent trends according to age class, disease type, previous therapy in the overall incidences of subjects with AEs and rate per infusion.

Other safety variables checked by the sponsor includes:

- Local tolerability

- Laboratory safety variables including hematology, serum chemistry, urinalysis, virology
- Other safety variables such as vital signs, physical examination etc.

This memo does not cover each safety variables in detail.

Conclusion: The overall study report shows that there are no safety concerns with the use of IgPro20 in adult and pediatric subjects with PD.

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

The subgroup analysis by gender is limited due the small sample size. The enrollment was pre-dominated by white subjects. Accordingly, no conclusions can be drawn regarding subgroup-specific differences for gender and race in the treatment efficacy or safety.

The subgroup analyses by age for the primary efficacy analysis and the safety analyses were presented in Table 3.1.6, Table 3.2.2 and Table 3.2.3. These tables are not reprinted here.

4. SUMMARY AND CONCLUSIONS

4.1 Statistical Issues and Collective Evidence

In this submission the sponsor has referenced the clinical report for its European study ZLB06_001CR (previously submitted under BLA STN 125350/103) as an efficacy supplement to support section 14.2 of the new label. Therefore this supplement was reviewed for the appropriateness of labeling revisions.

Major revisions in labeling include changes in Clinical Studies section and Adverse Reactions section to incorporate efficacy data and safety data of study ZLB06_001CR. I checked the numbers and confirmed this statement. The efficacy data indicated that IgPro20 administrated at weekly doses resulted in sustained serum IgG C_{trough} values comparable to the previous IgG replacement therapy. The lack of any SBIs during the efficacy period of this study and the annual rate of 5.18 infections/subjects/year indicated that IgPro20 provided effective protection for subjects with PID. The safety data indicate that home-based therapy with IgPro20 was safe and well tolerated when administered as weekly SC infusions to adult and pediatric subjects with PID.

No statistical issues have been found in this BLA supplement.

4.2 Conclusions and Recommendations

In this statistical review, I confirmed the sponsor's conclusion of the primary efficacy analysis and secondary efficacy analyses of ZLB06_001 incorporated in the new labeling. I also conducted another statistical analysis to compare the 6 consecutive steady-state IgG trough levels within this study and the IgG trough levels obtained from the subject's

previous treatment during the last 3 to 6 months prior to the study. The confidence intervals for the changes in trough levels can be interpreted by the scientific reviewers to determine if there was adequate stability between the pre-treatment and the efficacy periods. The safety analyses were also verified to support the sponsor the revisions in the draft package insert.

I have no objection regarding the approval of this BLA supplement.

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