



Clinical Review Memorandum

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

Date: January 20, 2011

To: To File (BLA STN 125350/103)

From: Hon-Sum Ko, Medical Officer, HFM-392

Through: Nisha Jain, Branch Chief, HFM-392

CC: Pratibha Rana, RPM, HFM-370

Applicant: CSL-Behring

Product: Immune Globulin Subcutaneous (Human), (IGSC, 20%; IgPro20)
Trade name: Hizentra®

Subject: Final Review of Labeling Supplement

Recommendation

Approval of this supplement based on fulfillment of the PMR for PREA deferral and labeling revisions as attached.

Background

CSLB's IgPro20 is an Immune Globulin Subcutaneous (Human) (IGSC) liquid product at 20% strength approved on 3/4/10 for marketing in the U.S for the treatment of primary immunodeficiency (PI) via the subcutaneous (SC) route. At the time of approval, CSLB had submitted pediatric assessment for 10 subjects aged 2 to <16 (3 children and 7 adolescents). Although CSLB had completed a study in Europe (ZLB06_001CR) with more pediatric data, these data had not been submitted to support pediatric labeling. The approval letter has included the following requirement for PREA compliance:

- a) "We are waiving the pediatric study requirement for ages 0 to < 2 years because the necessary studies are impossible or highly impracticable. It is rare for primary humoral immunodeficiency to present at this age group."
- b) "Your deferred pediatric study required under 505B(a) of the Federal Food, Drug, and Cosmetic Act is a required postmarketing study. The status of this postmarketing study must be reported according to 21 CFR 601.70 and section 505B(a)(3)(B) of the Federal Food, Drug, and Cosmetic Act. This required study is listed below:

1. Deferred pediatric study under PREA for the treatment of primary humoral immunodeficiency in pediatric patients ages 2 to <16.
Final report submission date: August 31, 2010.”

On 8/19/10, CSLB submitted this labeling supplement (STN 125350/103) to address the deferral in the above approval letter. The submission was received by CBER on 8/20/10.

Current Labeling Supplement

In the current labeling supplement, CSLB has presented the clinical study report for their European study, ZLB06_001CR, and revised draft package insert.

- The study report includes data on 23 additional pediatric subjects (18 children and 5 adolescents), but the entire study contains 51 subjects aged 3 to 60 with primary immunodeficiency (PI).
- The revised labeling includes changes to -
 - Pediatric Use subsection to address the PREA deferral data,
 - Dosage and Administration section to incorporate FDA’s request to change the calculation method for dose adjustment upon achieving steady state, and
 - Warnings and Precautions section to distinguish aseptic meningitis syndrome from other IGIV adverse reactions as having been reported in IGSC therapy.

Review of Current Supplement

Review of the current supplement will consist of:

- Review of the Clinical Study Report for “A multicenter study of the efficacy, tolerability, safety, and pharmacokinetics of Immune Globulin Subcutaneous (Human) IgPro20 in subjects with primary immunodeficiency (ZLB06_001CR)”, and
- Review of the revised draft package insert.

Comment The submission of the clinical study report for Study ZLB06_001CR in this supplement is intended to use the pediatric data to support revised labeling. This study was conducted in Europe without FDA input on 51 subjects aged 3 to 60, and CSLB has submitted an efficacy supplement to expand the information in the Adverse Reactions and Clinical Studies sections (STN 125350/136) on 12/8/10. Owing to the deadline for PREA compliance, the current pediatric labeling supplement is submitted first.

This review on ZLB06_001CR will therefore focus on the pediatric data because the regulatory decision on this supplement will be based on those data to fulfill PREA requirement, while the full review of ZLB06_001CR will form the basis of the action on CSLB’s efficacy supplement submitted on 12/8/10.

Concerning revisions on dosage adjustment at steady state and on aseptic meningitis syndrome, these are at FDA’s request to maintain consistency between the package inserts for Vivaglobin® and Hizentra®, both IGSC products from CSLB. No new data have been submitted for review.

Clinical Study Report for “A multicenter study of the efficacy, tolerability, safety, and pharmacokinetics of Immune Globulin Subcutaneous (Human) IgPro20 in subjects with primary immunodeficiency (ZLB06 001CR)”

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STUDY PERIOD: First enrolment on 28 September 2007, and last subject completed on 31 August 2009

PHASE OF DEVELOPMENT: 3

OBJECTIVES: To assess the efficacy, tolerability, safety, and pharmacokinetics (PK) of IgPro20 in subjects with primary immunodeficiency (PI), including a health-related quality of life (HRQL) assessment. As the primary objective, the IgPro20 dose should result in sustained immunoglobulin G (IgG) trough levels (C_{trough}) comparable to the previous IgG treatment.

METHODOLOGY: Prospective, open-label, multicentre, single-arm, Phase 3 study of IgPro20 in subjects with PI.

The study consisted of a 12-week wash-in/wash-out period followed by a 28-week efficacy period. In a PK substudy, PK assessments were performed during one treatment interval at steady-state (Week 28 ± 1). HRQL was assessed at screening, and after 12, 24, and 40 weeks of treatment with IgPro20. During the 28-week efficacy period, subjects visited study site at least every 4 weeks for efficacy and safety evaluations and also recorded details on dosing and other aspects of efficacy and safety in a diary.

NUMBER OF SUBJECTS (PLANNED AND ANALYSED):

Planned enrolment: 51 subjects (18 children aged < 12 years, 5 adolescents aged 12 to <16)

Planned enrolment for PK substudy: Approximately 25 subjects

Actual enrolment / all treated (AT) population: 51 subjects

- Intention-to-treat (ITT) population (treated in the efficacy period): 46 subjects
- Per-protocol efficacy (PPE) population: 34 subjects
- Per-protocol PK (PPK) population: 23 subjects
- Full HRQL population (baseline and ≥ 1 follow-up assessment): 48 subjects
- Discontinued: 8 subjects

DIAGNOSIS AND ENROLLMENT CRITERIA:

Inclusion criteria

- Male or female subjects > 2 to ≤ 65 years of age (for sites in the UK: 16 to 65 years of age).
- Subjects with one of the following primary humoral immunodeficiencies:
 - CVID as defined by Pan-American Group for Immunodeficiency (PAGID) and European Society for Immunodeficiencies (ESID).
 - XLA as defined by PAGID and ESID.
 - ARAG (autosomal recessive agammaglobulinemia).
- Subjects who had received:
 - IGIV therapy at regular 3- or 4-week intervals, or
 - IGSC therapy at regular weekly intervals at a stable dose (variations of ± 10% were allowed) for at least 6 months prior to receiving IgPro20 (maintenance dose to reach a cumulative monthly dose of the order of 0.2 to 0.8 g/kg).
- Subjects who had at least 3 documented IgG C_{trough} values ≥ 5 g/L during 3 months on IGIV or IGSC replacement therapy immediately prior to receiving IgPro20; 2 of the 3 IgG C_{trough} values could go back up to 6 months prior to receiving IgPro20, in case of stable dosing for at least 3 months prior to this assessment.
- A chest X-ray or computed tomography (CT) scan had to be obtained within 1 year prior to enrolment.
- Women who were of childbearing potential had to use medically approved contraception and had to have a negative pregnancy test.
- Written informed consent.

The following additional inclusion criteria applied to subjects participating in the PK assessments:

- Male or female subjects ≥ 6 years of age (for sites in the UK: ≥ 16 years).
- Specific written informed consent to participate in PK assessments.

Exclusion criteria

- Newly diagnosed PI, i.e., not having received previous immunoglobulin replacement therapy.
- Ongoing SBI at the time of screening.
- Malignancies of lymphoid cells such as lymphocytic leukaemia, Non-Hodgkin's lymphoma and immunodeficiency with thymoma.
- Known hyperproliferative disease.
- Hypoalbuminaemia, protein-losing enteropathies, and any proteinuria (defined by total urine protein concentration > 0.2 g/L).
- Allergic or other severe reactions to immunoglobulins or other blood products associated with high anti-immunoglobulin A (IgA).

- Treatment with steroids (oral and parenteral, ≥ 0.15 mg of prednisone equivalent/kg/day) or other systemic immunosuppressants.
- Women who were pregnant, breast feeding, or planning a pregnancy during the course of the study.
- A positive result at screening for any of the following viral markers: human immunodeficiency virus (HIV), hepatitis C virus (HCV), or hepatitis B virus (HBV).
- Aspartate aminotransferase (ASAT) or alanine aminotransferase (ALAT) concentration > 2.5 times the upper limit of the normal range (ULN).
- Creatinine concentration > 1.5 times ULN.
- Participation in a study with an investigational product other than immunoglobulin within 3 months prior to enrolment.
- Evidence of uncooperative attitude.
- Condition likely to interfere with evaluation of study drug or satisfactory conduct of the study.
- Employees at the investigational site, relatives or spouse of the investigator.

DOSE AND MODE OF ADMINISTRATION, BATCH NO.:

IgPro20 was administered as SC infusion at weekly intervals by the subject/parent/guardian (after a training period at the study site) for a total of approximately 10 months. The initial weekly IgPro20 dose was 100% of the subjects' previous weekly equivalent IGIV or IGSC dose. Dose adjustments could be performed during the wash-in/wash-out period at the discretion of the investigator.

Lot numbers: 43108-00002, 43108-00003, 43108-00004, 43108-00005, 43108-00006, 43108-00008, 43108-00012, 43108-00013, 43108-00014, 43108-00015, 43108-00021

DURATION OF TREATMENT: Wash-in/wash-out period of 12 weeks and efficacy period of 28 weeks

CRITERIA FOR EVALUATION:

Primary efficacy variable: Total serum IgG Ctrough values. Ctrough values before Infusions 12 to 17 were descriptively compared to 3 Ctrough values obtained during the previous IGIV or IGSC treatment.

Secondary efficacy variables: Rate of clinically documented serious bacterial infections (SBIs; defined as bacterial pneumonia, bacteraemia/septicaemia, osteomyelitis/septic arthritis, bacterial meningitis, or visceral abscess), 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 of hospitalization due to infections, and use of antibiotics for infection prophylaxis and treatment.

PK: Area under the concentration-time curve (AUC), maximum concentration (C_{max}), and timepoint of C_{max} of total IgG; serum concentrations of IgG subclasses, specific IgGs, and L-proline.

HRQL: The influence of SC treatment on HRQL was assessed using validated HRQL questionnaires. Baseline and follow-up questionnaires completed by the subject (or parent/guardian) assessed the generic and treatment-specific subject status.

Safety and tolerability: Rate, intensity, and relatedness of any adverse events (AEs) per infusion and subject; local tolerability of SC infusions; changes in routine laboratory parameters (haematology, serum chemistry, urinalysis), as compared to baseline assessments; vital sign changes before and after infusions at the study site, and physical examination at baseline and completion.

STATISTICAL METHODS:

The primary analysis was a descriptive comparison of 6 consecutive IgPro20 IgG Ctrough values per subject (before Infusions 12 to 17) with IgG Ctrough values obtained prior to the first IgPro20 infusion, in the ITT population. Further efficacy and safety data were analyzed descriptively. PK parameters were derived by non-compartmental analysis and summarised descriptively. Changes in HRQL scores compared to baseline were analyzed descriptively, including median changes and confidence intervals.

RESULTS:

A. Study subjects:

All 51 subjects enrolled in the study were treated with IgPro20 and included in the AT (all treated) population. The ITT (intent-to-treat) population included all 46 subjects treated during the efficacy period after wash-in/wash-out. The PPE population included 34 subjects who completed the study per protocol. There were 23 subjects who completed PK evaluation (PPK population).

Within the pediatric population, there were 23 subjects enrolled into the wash-in/wash-out period (AT population), and 22 entering into the efficacy period (ITT population).

The following Table shows demographic characteristics:

Parameter	ITT population (N=46)	PPK population (N=23)	Difference ^a
Sex, n (%)			p = 0.8240
Female	15 (32.6)	8 (34.8)	
Male	31 (67.4)	15 (65.2)	
Age (years)			
Mean (SD)	21.5 (15.60)	20.6 (14.10)	p = 0.7646
Median (range)	16.5 (3-60)	15.0 (6-49)	ND
Age group, n (%)			p = 0.8991
2 - < 12	17 (37.0)	9 (39.1)	
12 - < 16	5 (10.9)	3 (13.0)	
16 - < 65	24 (52.2)	11 (47.8)	
Race, n (%)			NA
White	46 (100)	23 (100)	
Body weight (kg) by age group, mean (SD); median (range)			
Total	52.1 (24.75); 55.0 (13-96)	51.4 (20.92); 56.0 (20-77)	p = 0.8685
2 - < 12 years	25.4 (11.20); 22.0 (13-56)	30.8 (12.26); 27.0 (20-56)	ND
12 - < 16 years	57.1 (15.84); 53.3 (36-77)	60.3 (21.47); 68.2 (36-77)	ND
16 - < 65 years	69.9 (14.28); 72.8 (41-96)	65.8 (10.86); 70.4 (41-74)	ND
BMI (kg/m²) by age group, mean (SD); median (range)			
Total	20.6 (4.90); 20.1 (12-32)	20.3 (3.84); 20.7 (14-27)	p = 0.7185
2 - < 12 years	16.3 (2.89); 15.3 (12-24)	17.4 (3.27); 16.5 (14-24)	ND
12 - < 16 years	20.6 (2.29); 20.1 (18-23)	21.3 (2.96); 22.9 (18-23)	ND
16 - < 65 years	23.6 (4.16); 23.5 (16-32)	22.4 (3.10); 22.7 (16-27)	ND

^aDifferences between the observed values in the PPK population and the mean values in the ITT population (i.e., the assumed known values for the target population) were analysed by Chi-Square Goodness of Fit test for the categorical variables sex and age group, and by 1-sample t-test for the continuous variables age, body weight, and BMI.

All pediatric subjects were Caucasian. Age/sex distribution of the 23 subjects is as follows:

	Female	Male	Total
Age 2-<12	5	13	18
Age 12-<16	0	5	5

Twenty-eight subjects (60.9%) had CVID, 17 subjects (37.0%) had XLA, and 1 subject had ARAG. Among pediatric subjects, the diagnoses are as follows:

	CVID	XLA	ARAG	Total
Age 2-<12	7	10	1	18
Age 12-<16	0	5	0	5

B. Efficacy results (ITT population):

1. **Primary Efficacy** – the primary efficacy parameter in this study is the IgG trough level, to be compared before study and after the wash-in/wash-out period.

- The mean of individual median IgG Ctrough values increased by 8.1% with IgPro20 treatment (from 7.49 g/L with the previous IgG therapy to 8.10 g/L during Infusions 12 to 17). The report claims that the primary objective to achieve sustained IgG Ctrough values compared to the previous treatment was met.
- The following is an analysis of the data on IgG trough levels with respect to age:

		Median IgG trough level (g/L)		
		≥ 2 to < 12 years (N=17)	≥ 12 to < 16 years (N=5)	≥ 16 to < 65 years (N=24)
Pre-study	Mean (SD)	6.94 (1.223)	7.99 (1.946)	7.81 (1.666)
	Median (range)	6.77 (5.3-10.1)	7.88 (5.4-10.3)	7.49 (5.3-11.7)
Infusions 12 to 17	Mean (SD)	7.86 (1.720)	7.91 (1.432)	8.31 (1.250)
	Median (range)	7.66 (5.1-12.4)	7.54 (6.2-9.5)	8.15 (6.3-10.9)
Infusions 12 to 41	Mean (SD)	7.78 (1.510)	8.14 (1.390)	8.32 (1.211)
	Median (range)	7.67 (5.2-11.2)	7.71 (6.7-9.9)	8.25 (6.4-10.8)

2. Secondary Efficacy Results

a) Serious bacterial infection (SBI). Although the report states that none of the subjects had an SBI during the efficacy period of the study, i.e., the annual rate per subject was 0 (upper 99% confidence limit: 0.192), it acknowledges that one subject developed an SBI (pneumonia) during the wash-in/wash-out period (annual rate: 0.03 SBIs/subject/year for the full evaluation period; upper 99% confidence limit: 0.192) so that her subsequent pneumonia in the efficacy period was not counted as a separate episode.

- Subject -(b)(6)-, a 5-year-old female with CVID, experienced pneumonia that was reported as an SAE of moderate intensity (seriousness criterion: hospitalization) 3 days after Infusion 8. This SAE was classified as an SBI. Four days after Infusion 14, the subject experienced pyrexia that was reported as an SAE of moderate intensity (seriousness criterion: hospitalization). Four days after Infusion 22, the subject experienced another acute episode of pneumonia that was reported as an SAE of severe intensity (seriousness criterion: life threatening, hospitalization). Because of the subject's underlying disease of pneumonia, the second acute exacerbation of pneumonia during this study was not classified as a separate SBI. The first SAE of pneumonia resolved without sequelae after 34.0 days, the SAE of pyrexia resolved without sequelae after 1.9 days, and the second SAE of pneumonia was ongoing at final assessment.

Comment This patient actually had two pneumonia episodes. Since the first episode (3 days after infusion 8) resolved without sequelae after 34 days and the second (4 days after infusion 22) occurred over 9 weeks later, it is hard to count the second as continuation of the first. However, it is also recognized that the patient had a history of recurrent pneumonia requiring hospitalization prior to enrollment, and bronchoalveolar lavage had revealed atypical Mycobacterium (by PCR). She completed this study and was enrolled into the extension study ZLB07_002CR. She was reported to have another episode of "acute exacerbation of chronic pneumonia" requiring hospitalization from which she succumbed.

b) Infections. A total of 36 subjects (78.3%) had an infection during the efficacy period of the study (annual rate: 5.18 infections/subject/year; 95% confidence limits: 4.305; 6.171). The most common infection manifestations were cough (0.67 infections/subject/year), upper respiratory tract infection and bronchitis (0.63 infections/subject/year each), nasopharyngitis (0.54 infections/subject/year), and sinusitis and productive cough (0.29 infections/subject/year each). The age breakdown of the infection rate information is shown below:

Incidence of subjects with any infections (with an overall annual rate > 0.1) by age class (ITT population)

	Number of infections (annual rate)		
	<u>≥ 2 to < 12 years</u> (N=3290)	<u>≥ 12 to < 16 years</u> (N=986)	<u>≥ 16 to < 65 years</u> (N=4469)
Any infection	43 (4.77)	14 (5.18)	67 (5.47)
Cough	7 (0.78)	6 (2.22)	3 (0.25)
Bronchitis	4 (0.44)	0	11 (0.90)
Upper respiratory tract infection	8 (0.89)	2 (0.74)	5 (0.41)
Nasopharyngitis	2 (0.22)	1 (0.37)	10 (0.82)
Productive cough	0	0	7 (0.57)
Sinusitis	1 (0.11)	0	6 (0.49)
Rhinitis	1 (0.11)	1 (0.37)	2 (0.16)
Acute sinusitis	0	0	3 (0.25)
Enteritis	3 (0.33)	0	0
Giardiasis	0	0	3 (0.25)
Otitis media	2 (0.22)	0	1 (0.08)
Pyrexia	1 (0.11)	1 (0.37)	1 (0.08)
Respiratory tract infection	0	0	3 (0.25)

Comment These infection data are again discussed below in the section on safety. It would appear that the 2-<12 age group has higher incidence of cough and upper respiratory tract infections, but lower incidence of nasopharyngitis and sinusitis when compared to the 16-<65 age group. However, because of the small sample size in the age groups, it is difficult to draw specific conclusions from the observed differences. Essentially the analysis has not revealed consistent trends according to age in the overall incidence of infections.

c) Days of missed activities. During the efficacy period, 20 subjects (43.5%) missed work/school/kindergarten/day care, or were unable to perform normal activities due to infections on a total of 198 days (annual rate: 8.00 days/subject/year). A breakdown of the data by age is shown as follows:

Days missed work/school/kindergarten/day care or unable to perform normal activities due to infections by age class (ITT population)

Parameter	≥ 2 to < 12 years	≥ 12 to < 16 years	≥ 16 to < 65 years
Number (%) of subjects	(N=17)	(N=5)	(N=24)
	8 (47.1)	4 (80.0)	8 (33.3)
Number (annual rate) of days	(N=3406)	(N=1020)	(N=4607)
	139 (14.90)	5 (1.79)	54 (4.28)

The incidence of subjects with any days missing work/school/kindergarten/day care or unable to perform normal activities due to infections, as well as the annual rate for such days, was higher in subjects 2 to <12 years of age. This relatively high annual rate in children 2 to <12 years of age was mainly due to one subject who missed a total of 71 days during the efficacy period (subject -(b)(6)-, see above for details of the subject). Excluding this subject, the number of days missed work/school/kindergarten/day care or unable to perform normal activities due to infections ranged between 5 and 22 days in subjects 2 to <12 years of age, whereas for subjects 16 to < 65 years of age, this was between 1 and 16 days.

d) Hospitalizations and antibiotic use. Four subjects (8.7%) were hospitalized for a total of 86 days due to infections (annual rate: 3.48 days/subject/year): 3 of them in the 2-<12 age group (Subjects ----(b)(6)---- and -(b)(6)-) and the fourth subject being 18 years of age.

According to the study report, during the efficacy period (Infusions 13-41), there were 32 subjects (69.6%) who used antibiotics over a total of 1743 days (annual rate: 72.75 days/subject/year). Antibiotics were used mainly for treatment purposes (29 subjects) and medical/surgical/current conditions (7 subjects). Only 4 subjects used antibiotics for prophylaxis. Data for the entire evaluation period (Infusions 1 to 41) gave similar findings. These data are shown as follows:

Number of days with antibiotics - annualized rate and incidence (ITT)*

		Subjects affected (Total ITT N=46)		Days with antibiotics	
		N	%	N	Annualized rate
Main efficacy period (Infusion 13 to 41: total 8745 days)	Prophylaxis	4	8.70	297	12.40
	Adverse event	29	63.04	873	36.44
	Treatment of medical/ surgical/ current condition	7	15.22	691	28.84
	Total	32	69.57	1743	72.75
Full evaluation period (Infusion 1 to 41: total 12606 days)	Prophylaxis	7	15.22	447	12.94
	Adverse event	34	73.91	1122	32.49
	Treatment of medical/ surgical/ current condition	11	23.91	1013	29.33
	Total	37	80.43	2464	71.34

*Data derived from clinical study report Table 14.2.6.2

Comment The numbers in the report concerning use of antibiotics are not consistent with data listing information (Appendix 16.2.6.6). For antibiotic use, the data listing provides 35 subjects in the entire evaluation period (37 in the report) and 30 subjects in the efficacy period (32 in the report). The differences would need to be resolved. Based on the data listing information, the age breakdown for subjects using antibiotics shows similar distribution within the age subgroups. Thus, the proportion of subjects with antibiotic use can be shown as follows (ITT population):

	Number (%) of Subjects with Use of Antibiotics		
	≥ 2 to < 12 years (N=17)	≥ 12 to < 16 years (N=5*)	≥ 16 to < 65 years (N=24)
Efficacy period	11 (64.7%)	3 (60.0%)	21 (87.5%)
Full evaluation period	11 (64.7%)	1 (20.0%)	18 (75.0%)

*This sample size may be too small to draw inferences.

From the above data, there would appear to be no consistent trends to suggest that age had an effect on the efficacy of IgPro20.

3. PK results (other than primary endpoint (IgG trough level)) (PPK population).

With the overall PPK population, the mean total serum IgG concentrations during 1 dosing interval at steady-state were stable (7.44 to 7.98 g/L). The mean C_{max} was 8.26 g/L and was reached after a median time of 2.06 days. The changes in serum concentrations of specific IgGs over time were generally

low and comparable to those of total serum IgG and IgG subclasses. L-proline was rapidly eliminated from the circulation, with no signs of accumulation. PK results were comparable across different age classes as shown below:

Steady-state pharmacokinetics of serum IgG after treatment with IgPro20 (PPK population)

Parameter	Total (N=23)	Mean (SD); Tmax: median (range)		
		2 to < 12 years (N=9)	12 to < 16 years (N=3)	16 to < 65 years (N=11)
Cmax (g/L)	8.26 (1.255)	8.09 (1.492)	8.60 (1.443)	8.31 (1.096)
Tmax (day)	2.06 (0.94-6.92)	2.06 (0.94-6.92)	1.98 (1.93-2.94)	2.07 (0.95-3.98)
AUClast (day × g/L)	53.70 (9.161)	52.30 (9.987)	54.91 (11.548)	54.52 (8.672)
AUC _τ (day × g/L)	53.61 (9.984)	48.18 (10.044)	55.59 (12.335)	56.26 (9.040)

AUClast = Area under the concentration-time curve until last measured concentration; AUC_τ = Area under the concentration-time curve during regular dosing interval; Cmax = Maximum concentration; N = Total number of subjects in population or subgroup; SD = Standard deviation; Tmax = Timepoint of maximum concentration.

Comment Although there have been 12 pediatric subjects undergoing PK assessment, there were 3 adolescents (ages: 13, 15, 15) and 9 children, with all the children aged 6 or above (ages: 6, 7, 9, 9, 9, 10, 10, 10, 11). This may be due to difficulty in enrolling subjects under 6 for a full PK evaluation.

4. HRQL results (Full HRQL population):

This study has included quality of life assessments. Since the clinical trial was conducted overseas without input from FDA, the validation of the instrument(s) used has not been reviewed by the Agency. FDA has previously expressed concern in the use of HRQL measures for the U.S. clinical trial of IgPro20, and the finalized protocol of that study did not include quality-of-life evaluations.

Since the validation of the HRQL instruments for use in studies involving PI patients has not been reviewed by FDA and is not currently submitted, the HRQL data in this study are not reviewed.

C. Safety results (AT population):

1. Exposure

The safety of IgPro20 was evaluated in all 51 subjects enrolled and treated in this study with weekly SC infusions with IgPro20. A total of 1831 IgPro20 infusions were administered. The distribution of the exposure by age (ITT population) is as follows:

	Total (N=51)	2 to < 12 years (N=18)	12 to < 16 years (N=5)	16 to < 65 years (N=28)
Number of Infusions	1831	678	199	954

2. Deaths, serious adverse events (SAEs) and other significant adverse events (AEs)

No deaths occurred in this study. Seven SAEs occurred in 5 subjects (9.8%). All SAEs were assessed by the investigator as unrelated to the study drug. The SAEs were:

- Subject -(b)(6)- age 7: diarrhoea
- Subject -(b)(6)- age 5: pneumonia [2 events], pyrexia
- Subject -(b)(6)- age 18: bronchiolitis
- Subject -(b)(6)- age 10: appendicitis
- Subject -(b)(6)- age 51: sciatica

Two of the SAEs were temporally associated, i.e., occurred during or within 72 h after the end of an infusion (appendicitis and sciatica). Two SAEs were severe in intensity (pneumonia and appendicitis), 4 SAEs were moderate in intensity (pneumonia, pyrexia, bronchiolitis, and sciatica), and one SAE was mild in intensity (diarrhoea).

Six subjects discontinued from the study due to AEs:

- Subject -(b)(6)- age 8: myalgia, pyrexia, nausea, chest pain, and C-reactive protein increased
- Subject -(b)(6)- age 29: injection site pain and injection site pruritus
- Subject -(b)(6)- age 60: pulmonary tuberculosis
- Subject -(b)(6)- age 59: injection site reaction, fatigue, and feeling cold
- Subject -(b)(6)- age 20: injection site reaction and hypersensitivity
- Subject -(b)(6)- age 5: anaemia

The AEs of injection site pain, injection site pruritus, injection site reaction [2 events], fatigue, feeling cold, and hypersensitivity were considered at least possibly related to study drug, and all AEs except

hypersensitivity were temporally associated. Except for the AEs of pulmonary tuberculosis and anaemia that were ongoing at final assessment, all of the AEs resolved without sequelae.

3. AE frequencies

Almost all subjects had AEs and temporally associated AEs, irrespective of age, and the incidence of subjects with at least possibly related AEs was lower in subjects 2 to <12 years of age compared to subjects 16 to <65 years (38.9% vs. 78.6%), as was the incidence of subjects with at least possibly related and temporally associated AEs (38.9% vs. 71.4%). Similarly, the rate of AEs (number of AEs per infusion) was lower in subjects 2 to <12 years of age compared to subjects aged 16 to <65 (0.198 vs. 0.362), as were the rates of at least possibly related AEs (0.069 vs. 0.143), temporally associated AEs (0.128 vs. 0.223), and AEs that were at least possibly related and temporally associated to study drug (0.063 vs. 0.116) (See Tables below).

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

Category	Number of Subjects (%)			
	Total (N=51)	2 to < 12 years (N=18)	12 to < 16 years (N=5)	16 to < 65 years (N=28)
Subjects with AEs	50 (98.0)	18 (100)	5 (100)	27 (96.4)
Subjects with at least possibly related AEs	31 (60.8)	7 (38.9)	2 (40.0)	22 (78.6)
Subjects with temporally associated AEs*	48 (94.1)	17 (94.4)	5 (100)	26 (92.9)
Subjects with at least possibly related temporally associated AEs	29 (56.9)	7 (38.9)	2 (40.0)	20 (71.4)
Subjects with serious AEs	5 (9.8)	3 (16.7)	0	2 (7.1)
Subjects discontinued due to AEs	6 (11.8)	2 (11.1)	0	4 (14.3)
Subjects discontinued due to at least possibly related AE	3 (5.9)	0	0	3 (10.7)

*Temporally-associated refers to events occurring during or within 72 hrs of ending an infusion.

Subgroup analysis by age for adverse event rates (AT population)

Category	Number of AEs (rate - event per infusion)			
	Total (N=1831)	2 to < 12 years (N=678)	12 to < 16 years (N=199)	16 to < 65 years (N=954)
AEs	527 (0.288)	134 (0.198)	48 (0.241)	345 (0.362)
At least possibly related AEs	194 (0.106)	47 (0.069)	11 (0.055)	136 (0.143)
Temporally associated AEs*	324 (0.177)	87 (0.128)	24 (0.121)	213 (0.223)
At least possibly related temporally associated AEs	165 (0.090)	43 (0.063)	11 (0.055)	111 (0.116)
SAEs	7 (0.004)	5 (0.007)	0	2 (0.002)
Discontinuations due to AEs	14 (0.008)	6 (0.009)	0	8 (0.008)
Discontinuations due to at least possibly related AE	7 (0.004)	0	0	7 (0.007)

*Temporally-associated refers to events occurring during or within 72 hrs of ending an infusion.

Local reactions (defined as a group of 25 preferred terms related to the site of injection) were the most common AEs (total 110 events experienced by 25 subjects (49.0%)) and occurred at a rate per infusion of 0.060. Other common AEs (in > 5 subjects [$> 9.8\%$]) were bronchitis, pyrexia, headache, cough, upper respiratory tract infection, nasopharyngitis, diarrhea, and sinusitis (See Table below). Almost all AEs (98.7%) were mild or moderate in intensity.

	All Subjects		Age 2 to <12		Age 12 to <16		Age 16 to <65	
	No. of Subjects (%)	No. of AEs (AE/infusion)	No. of Subjects (%)	No. of AEs (AE/infusion)	No. of Subjects (%)	No. of AEs (AE/infusion)	No. of Subjects (%)	No. of AEs (AE/infusion)
Total	51	1831 infusions	18	678 infusions	5	199 infusions	28	954 infusions
Any AE	50 (98.0)	527 (0.288)	18 (100.0)	134 (0.198)	5 (100.0)	48 (0.241)	27 (96.4)	395 (0.414)
Local reaction	25 (49.0)	110 (0.060)	6 (33.3)	27 (0.040)	2 (40.0)	7 (0.035)	17 (60.7)	76 (0.080)
Bronchitis	16 (31.4)	26 (0.014)	5 (27.8)	6 (0.009)	1 (20.0)	1 (0.005)	10 (35.7)	19 (0.020)
Pyrexia	14 (27.5)	14 (0.008)	5 (27.8)	5 (0.007)	3 (60.0)	3 (0.015)	6 (21.4)	6 (0.006)
Headache	13 (25.5)	54 (0.029)	1 (5.5)	3 (0.004)	3 (60.0)	3 (0.015)	9 (32.1)	48 (0.050)
Cough	13 (25.5)	26 (0.014)	6 (33.3)	12 (0.018)	3 (60.0)	8 (0.040)	4 (14.3)	5 (0.006)
Upper respiratory tract infection	12 (23.5)	17 (0.009)	6 (33.3)	10 (0.015)	2 (40.0)	2 (0.010)	4 (14.3)	5 (0.005)
Nasopharyngitis	12 (23.5)	20 (0.011)	3 (16.7)	4 (0.006)	1 (20.0)	1 (0.005)	8 (28.6)	15 (0.016)

Diarrhea	10 (19.6)	16 (0.009)	3 (16.7)	4 (0.006)	1 (20.0)	1 (0.005)	6 (21.4)	11 (0.012)
Sinusitis	7 (13.7)	11 (0.006)	2 (11.1)	2 (0.003)	0 (0)	0 (0)	5 (17.9)	9 (0.009)

Comment There are some notable differences between age groups. Specifically, the younger age group (2-<12) has lower incidence of local reactions and headache when compared to the 16-<65 age group. Interestingly, the 2-<12 age group has higher incidence of cough and upper respiratory tract infections, but lower incidence of nasopharyngitis and sinusitis when compared to the 16-<65 age group. However, because of the small sample size in the age groups, it is difficult to draw any specific conclusions from the observed differences. Essentially these subgroup analyses of AEs have revealed no clinically relevant or consistent trends according to age in the overall incidences of subjects with AEs and rates per infusion.

4. Laboratory Findings, vital signs and physical examination

There were no particular safety issues regarding clinical laboratory parameters over the course of the study. There were also no clinically relevant changes in vital signs, and most physical examination findings were normal at baseline and at the completion visit.

CONCLUSIONS:

- ZLB06_001CR is a study on IgPro20 administered subcutaneously in the replacement therapy PI patients, and has included 23 pediatric subjects (18 aged 2-<12, and 5 aged 12-<16), 22 of whom participated with IgPro20 administration.
- This study has demonstrated clinical effectiveness of IgPro20 in preventing serious bacterial infections (as defined in FDA's Guidance), with a 99% upper confidence limit of 0.192 per subject per year. Except for one pediatric CVID subject (5-year-old female) with underlying "chronic pneumonia" and possible atypical Mycobacterium infection, the efficacy data have not demonstrated clinically relevant trends according to age with respect to the effectiveness of igPro20 in the treatment of PI.
- The primary PK evaluation in this study is based on comparable IgG trough levels at steady state between IgPro20 subcutaneous treatment and previous IG therapy (IGIV or IGSC). This is not a primary comparison recognized by FDA, as the Agency requires matching AUC for the investigational IGSC upon reaching steady state with the AUC obtained with previous IGIV treatment. Nevertheless, the trough levels and other PK parameters from this study have revealed that the pharmacokinetics in the pediatric subjects studied is similar to that in adults. The limitation to this conclusion is that within the 2-<12 age group, there were no subjects below 6 years of age studied for pharmacokinetics.
- There are no trends identified for differences between pediatric subjects and adults with respect to the data on adverse events, laboratory findings, vital signs and physical examination.

Revised Draft Package Insert

The revised labeling includes changes to -

- Pediatric Use subsection to address the PREA deferral data,
- Dosage and Administration section to incorporate FDA's request to change the calculation method for dose adjustment upon achieving steady state, and
- Warnings and Precautions section to distinguish aseptic meningitis syndrome from other IGIV adverse reactions as having been reported in IGSC therapy.

1. Specific labeling changes

a) Pediatric Use subsection to address the PREA deferral data.

Based on the data submitted in the clinical study report for ZLB06_001CR, the Applicant has proposed the following changes to the Pediatric Use subsection (Section 8.4) of the package insert of Hizentra® (IgPro20).

In the US study (see Clinical Studies [14]), Hizentra was evaluated in 10 pediatric subjects (3 children and 7 adolescents) with PI. In a study in subjects with PI conducted in Europe, the safety and efficacy of Hizentra was evaluated in 23 pediatric subjects (18 children and 5 adolescents). There were no differences in the safety and efficacy profiles as compared with adult subjects. No pediatric-specific dose requirements were necessary to achieve the desired serum IgG levels.

Hizentra was not evaluated in neonates or infants.

Comment The Pediatric Use subsection should use language consistent with 21 CFR 201.57(c)(9)(iv)(D)(1):

The safety and effectiveness of Hizentra have been established in the age groups 2 to 16. Use of Hizentra in these age groups is supported by evidence from adequate and well-controlled studies of Hizentra including pediatric subjects. Hizentra was evaluated in 10 pediatric subjects with PI (3 children and 7 adolescents) in a study conducted in the U.S. (see *Clinical Studies [14]*), and in 23 pediatric subjects with PI (18 children and 5 adolescents) in a study conducted in Europe. There were no differences in the safety and efficacy profiles as compared with adult subjects. No pediatric-specific dose requirements were necessary to achieve the desired serum IgG levels.

and 21 CFR 201.57(c)(9)(iv)(E):

Safety and effectiveness of Hizentra in pediatric patients below the age of 2 have not been established.

- b) Dosage and Administration section to incorporate FDA’s request to change the calculation method for dose adjustment upon achieving steady state, and
Concerning revisions on dosage adjustment at steady state, this is at FDA’s request to maintain consistency between the package inserts for Vivaglobin® and Hizentra®, both IGSC products from CSLB. No new data have been submitted for review.
- c) Warnings and Precautions section to distinguish aseptic meningitis syndrome from other IGIV adverse reactions as having been reported in IGSC therapy.
Concerning revisions on aseptic meningitis syndrome, it is at FDA’s request to maintain consistency between the package inserts for Vivaglobin® and Hizentra®, both IGSC products from CSLB. No new data have been submitted for review.

2. Review of other parts of the revised draft package insert

In addition to specific changes discussed above, the Applicant has revised the package insert with minor changes, such as editing information on administration technique to have consistency between the Dosage and Administration section and the “Information for Patients” attachment.

Comment The changes in other parts of the package insert are mostly editorial in nature and generally acceptable. This Reviewer has added further editing for clarification and correction to errors.

Comments Conveyed to CSLB on December 10, 2010 and CSLB Response

Based on the above review of the original supplement submission, FDA conveyed to CSLB on 12/10/10 labeling comments and information request to which CSLB submitted the following responses:

- a) revisions to draft package insert (on 12/16/10; Amendment 103.1), and
b) information addressing FDA’s questions (on 1/5/11; Amendment 103.2).
- With the draft package insert, CSLB has followed FDA’s comments in their revisions. The changes suggested by FDA have been reviewed by the Pediatric Review Committee (PeRC) at their 12/15/10 meeting and found to be acceptable. The revised label as submitted by CSLB is attached to this document.
 - For the submission on 1/5/11, CSLB addressed the following questions:

FDA QUESTION 2. A. Please submit the case report form (CRF) of Subject -(b)(6)-in Study ZLB06_001CR. (This was later clarified in an FDA email of

16 December 2010 to mean the subject's CRF from Extension Study ZLB07_002CR, as the CRF for ZLB06_001 CR for this subject was previously submitted on 19 August 2010.), and B. It is not clear from the CRF how the second pneumonia episode could be counted as a continuation of the first, as the first episode had resolved after 34 days without sequelae while the second occurred many weeks later. Please provide an explanation of the pneumonia episodes for Subject -(b)(6)-.

CSLB Response to Question 2

The requested CRF for Subject -(b)(6)- in Study ZLB07_002CR is found in Attachment 1 of the response. Although detailed information regarding Subject -(b)(6)- can be found in Clinical Study Report ZLB06_001CR, Section 14.3.3.1.2 Subject -(b)(6)-, an overall case narrative that includes studies ZLB06_001CR and ZLB07_002CR is also provided in Attachment 2 of the response.

Comment The information submitted does not change the previous conclusion that there actually have been two episodes of pneumonia because the end of the first episode and the beginning of the second were separated by about 9 weeks (2/3/09 to 4/6/09). While it is possible that the patient had chronic lung infection which was ongoing when she exited ZLB06_001CR and entered ZLB07_002CR, and ultimately died from an acute exacerbation of the chronic disease in ZLB07_002CR, it is unclear whether her pneumonia episodes were actually acute bacterial infections. The first episode showed *C. albicans* in the bronchoalveolar lavage (BAL) material and PCR positive for atypical mycobacteria not confirmed with culture. There is no bacteriology information in the second episode. The CRF only states that the laboratory findings were leukocytosis with left shift in the WBC count. It is fair to conclude that the patient had chronic lung infection with acute exacerbations but the nature of the underlying lung process has not been established.

FDA QUESTION 3. The numbers in the clinical study report for ZLB06_001CR concerning use of antibiotics are not consistent with data listing information (Appendix 16.2.6.6). For antibiotic use, the data listing provides 35 subjects in the entire evaluation period (37 in the report) and 30 subjects in the efficacy period (32 in the report). Please resolve these differences.

CSLB Response to Question 3

CSLB provided clarification, via emails of 13, 16 and 17 December 2010, regarding the apparent discrepancy between Appendix 16.2.6.6 (and the dataset ADCONMED) and Table 14.2.6.2 in the clinical study report with regards to the number of subjects with antibiotic use. Subsequently, FDA agreed there was no discrepancy and considered this resolved. There were 37 subjects in the entire evaluation period and 32 in the efficacy period.

Review by Pediatric Review Committee (PeRC)

The pediatric assessment in this submission and the labeling changes arising from the submitted data were presented to the PeRC on 12/15/10. The Committee also reviewed the Approval Letter of 3/4/10, and unanimously agreed that the PMR for PREA deferral has been fulfilled by the current supplement with labeling changes.

Conclusions

- The Applicant has fulfilled the PMR for PREA deferral with submission of the clinical study report of ZLB06_001CR, which includes pediatric assessment in 23 pediatric subjects (18 children and 5 adolescents).
- The Applicant has already received a PREA waiver for submission of pediatric assessment in neonates and infants.
- The Applicant has updated the package insert for Hizentra® to incorporate the pediatric findings from ZLB06_01CR, and revised it as recommended by FDA.

Recommendation

- It is recommended that this supplement be approved.