Clinical Review Memorandum

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

Date: September 28, 2009

To: To File (BLA STN 125350/0)

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

Through: Nisha Jain, Acting 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: Mid-Cycle Review

Recommendation

The following comments should be conveyed to the applicant:

Please address the following comments pertaining to Study ZLB04_009CR:

1. Itching and local pain are subjective evaluations. Please clarify why they fall under "assessment by the investigator", and how the scoring by Investigator at the study visit could accurately reflect what happens at home infusions.
2. Since the wash-in/wash-out period involved IGSC administration, efficacy analysis during this period should not be excluded. Please conduct additional analyses of the efficacy endpoints including the entire period of IgPro20 use.
3. Repeated filling of infusion pumps to deliver high doses of IGSC allows for more than 4 injection sites to be used consecutively at the same infusion. Please clarify whether this is considered protocol violation or not. The tolerability of such infusions should be compared with that of other infusions which followed the up-to-4-site rule.
4. It is not clear why there was a decrease from 3.9% to 0.2% for the use of ≥ 10 injection sites per infusion from the wash-in/wash-out period to the efficacy period. Please clarify whether the use of large infusion volumes and hence numerous injection sites predisposed to withdrew from study.
5. There were five infusions with infusion rate reduction or premature cessation. Please submit details of these infusions.
6. Please submit the CRFs for Subject -(b)(6)-.
7. The concept of TLR is theoretical, and dependent on an intermediary link between hypothetical IGIV and IGSC average daily levels that yield equivalent AUC. It is uncertain that there is a linear relationship between C_{trough} and "average daily level", and so the basis of the TLR concept has to be tested with actual data from the individualized dosing in the PK subjects. The basis of testing TLR applicability in non-PK subjects using an arbitrary range of $1.29\pm15\%$ derived from PK subjects' data appears to be unsound. In fact, you have noticed that TLR within the $1.29\pm15\%$ range could be associated with a wide distribution of trough levels in the non-PK subjects. Please conduct an analysis of this ratio in the PK subjects upon attainment of steady state in the efficacy period with individualized dosing.
8. Please conduct an analysis of ratio of the number of infusions with temporally associated adverse events (within 72 hours of the end of infusion) to the total number of infusions, including point estimate and 95% confidence intervals.

9. It appears contradictory that only one infusion was associated with an injection site reaction of severe intensity (subject -(b)(6)-), and yet three injection site reaction of severe intensity were reported as adverse events (subject -(b)(6)- with two infusions and subject -(b)(6)-). Please clarify.
10. Please submit a PREA deferral request for data submission on the children and adolescent age groups ($\geq$2 to 12, and $\geq$12 to 16 years of age respectively).

Executive Summary

CSL-Behring (CSLB) submits BLA STN 125350 in support of its new IGSC 20% product (IgPro20, proprietary name Hizentra®) for the indication of primary humoral immunodeficiency (PI). This product is a higher strength of the marketed IGIV product Privigen, which is of 10% strength. Hizentra is a 20% liquid formulation of human immunoglobulin containing 250 mmol/L L-proline and $\leq$30 mg/L polysorbate 80 at a pH of 4.8 for subcutaneous infusion using an infusion pump.

The applicant has presented the following clinical trials to support the application:
*   **ZLB06_003CR.** A single-center, randomized, single-blind, 2-way cross-over study to compare the safety of intravenous (IV) administration of 10% (IgPro10, Privigen®) and 20% (IgPro20) liquid human immunoglobulin
*   **ZLB04_008CR.** A single-center, randomized, 4-way cross-over, assessment-blinded trial to investigate the local tolerability of a newly developed subcutaneous immunoglobulin G with different concentrations in comparison to Vivaglobin®.
*   **ZLB04_009CR.** A phase III open-label, prospective, multicenter study of the efficacy, tolerability, safet, and pharmacokinetics of Immune Globulin Subcutaneous (Human), IgPro20 in subjects with primary immunodeficiency (PID).

ZLB06_003CR and ZLB04_008CR were conducted on healthy volunteers. The former was to compare IgPro20 to its parent product IgPro10 (Privigen) upon IV administration, and the latter is a local tolerability study comparing IgPro20 in three different doses with CSLB's marketed product, Vivaglobin, upon SC administration before embarking on studies in primary immunodeficiency patients. These studies provided preliminary safety data to move forward in product development but not for licensure for the proposed indication of treatment of primary immunodeficiency.

ZLB04_009CR was conducted as a Phase 3, prospective, open-label, multicenter, single-arm, study of IgPro20 in subjects with PI, with a 12-week wash-in/wash-out period followed by a 12-month efficacy period. The primary efficacy endpoint was the rate of serious bacterial infections per subject per year in the 12-month efficacy period, as defined in FDA's *Guidance for Industry: Safety, Efficacy, and Pharmacokinetic Studies to Support Marketing of Immune Globulin Intravenous (Human) as Replacement Therapy for Primary Humoral Immunodeficiency* of 2008.

ZLB04_009CR enrolled 49 subjects with common variable immunodeficiency or X-linked agammaglobulinemia to enter the 12-week wash-in/wash-out period, 38 of whom entered the 12-month efficacy period. The study met its primary endpoint, with zero incidence of serious bacterial infections during the efficacy period. The adverse events observed in this study included local injection site reactions which are anticipated for subcutaneous administration, as well as systemic reactions common to immune globulin products. Ten serious adverse events were reported in 7 subjects, none of which appear to be related to treatment. There were no consistent clinical laboratory abnormalities observed, including protocol-specified evidence of hemolysis.

Study ZLB04_009CR would support the effectiveness of IgPro20 as an IGSC replacement therapy in primary humoral immunodeficiency. There are insufficient

pediatric data from this study to establish use in the pediatric population, and deferral of pediatric data submission postapproval would be recommended upon licensure of the adult indication.

No show-stoppers have been identified at this time. Recommend sending FDA comments to be addressed by CSLB.

Background
This submission for a liquid IGSC 20% formulation from CSL-Behring, is electronic via the Gateway in Global Submit Review, and is in the ICH Common Technical Document (CTD) format.

The IGSC product with the proprietary name Hizentra in this submission is a higher strength of CSLB's marketed IGIV product, Privigen, which is of 10% strength. Hizentra is a 20% liquid formulation of human immunoglobulin containing 250 mmol/L L-proline and ≤30 mg/L polysorbate 80, at a pH of 4.8 for SC infusion using an infusion pump. The indication in the draft labeling is "the treatment of primary immunodeficiency (PI)."

PIs include a variety of disorders in which there is an intrinsic defect in the immune system that renders subjects more susceptible to infections. Such conditions are considered to be relatively uncommon. Immunoglobulin (IG) replacement therapy is the standard treatment for PI. This has evolved from IG administered intramuscularly (IM) to intravenous (IV) infusions, and more recently subcutaneous (SC) infusions. The systemic adverse event (AE) rate of SC infusions of IgGs may be lower than that of IV infusions. Efficacy of Immune Globulin Subcutaneous (Human) (IGSC) treatment in subjects with PI has been demonstrated in the case of a marketed product, Vivaglobin.

For this BLA submission:
- **Financial certification and disclosure information (Form 3454 on Study ZLB04_009CR) have been submitted in Module 1, Section 1.3.4. The applicant certifies that there has been no arrangements where the compensation could have been affected by the outcome of the study.**
- **In Module 1, Section 1.9, CSLB requests:**
    - **Waiver of pediatric studies for neonates and children up to 2 years of age – reasons cited: studies are impossible or highly impracticable.**
  Ten subjects in Study ZLB04_009CR were aged 16 or under (3 children and 7 adolescents). There were no apparent differences in the safety and efficacy profiles vs adults, and no pediatric-specific dosing requirements were observed to achieve the desired serum IgG levels.

Comment   It may be insufficient for 3 children and 7 adolescent subjects in the database to adequately establish pediatric use, especially in the children subpopulation. However, CSLB will have data from at least 23 patients (18 children and 5 adolescents) from their European study that can be used to support use in those subpopulations. Discussions have been held with CSLB and agreement has been reached to request for deferral of submission of PREA-required pediatric data.

BLA Clinical Module (Module 5)
The clinical module contains the clinical study reports for these trials:
- **ZLB06_003CR.** A single-center, randomized, single-blind, 2-way cross-over study to compare the safety of intravenous (IV) administration of 10% (IgPro10, Privigen®) and 20% (IgPro20) liquid human immunoglobulin
- **ZLB04_008CR.** A single-center, randomized, 4-way cross-over, assessment-blinded trial to investigate the local tolerability of a newly developed subcutaneous immunoglobulin G with different concentrations in comparison to Vivaglobin®.

- **ZLB04_009CR.** A phase III open-label, prospective, multicenter study of the efficacy, tolerability, safet, and pharmacokinetics of Immune Globulin Subcutaneous (Human), IgPro20 in subjects with primary immunodeficiency (PID).

Clinical Studies in Support of IgPro20 (Hizentra®)

ZLB06_003CR. A single-center, randomized, single-blind, 2-way cross-over study to compare the safety of intravenous (IV) administration of 10% (IgPro10, Privigen®) and 20% (IgPro20) liquid human immunoglobulin (STUDY PERIOD: 7/9/08 to 10/2/09)

INVESTIGATOR(S):
Principal Investigator: Dr. Alla Radicke
Co-Investigators: Drs. Anke Gauliard, Sara Armani-Sand
PAREXEL International GmbH, Clinical Pharmacology Research Unit, Spandauer Damm 130,
Haus 31, 14050 Berlin, Germany

OBJECTIVES:
To assess the safety and tolerability of IV administration of IgPro20 when given at the subcutaneous (SC) dose used for IgG replacement therapy, compared to IV administration of IgPro10.

DESIGN:
Single-center, randomized, single-blind, 2-way cross-over, single dose study of 20 healthy male subjects aged $\geqslant$18 and $\leqslant$45 years; BMI $\geqslant$21 and $\leqslant$29 kg/m^2, comparing IgPro20 10 g/50 mL IV infusion (Lot #43108-00010) and IgPro10 (Privigen®) 10 g/100 mL IV in fusion (Lot #05342-00020).

Comment   Only males were enrolled in this study.

Each subject received single dose of 50 mL of IgPro20 and single dose of 100 mL of IgPro10 were given as IV infusions of ~45 minutes. The period between treatments was 14 $\pm$ 7 days. The infusion rate for IgPro20 was half the infusion rate for IgPro10.

EVALUATIONS:
Safety:
- Adverse events (AEs): AEs considered as at least possibly related to IMP by the Investigator and which were temporally associated with the infusion (i.e. within 72 hours after end of infusion) were defined as the primary safety endpoint, designated related AEtemp;
- 12-lead electrocardiogram (ECG): P wave, PR interval, QRS complex, QT interval, QTc interval (QT interval corrected for heart rate using Bazett´s formula), heart rate;
- Vital signs: systolic and diastolic blood pressure (BP) and pulse in supine position; oral body temperature;
- Standard laboratory safety: Hematology, hemolysis parameters, blood coagulation parameters (D-Dimer [DD], thrombin-antithrombin fragments (TAT), and prothrombin fragments 1 and 2 [F1+2]); serum biochemistry; urinalysis; drug and alcohol screen in urine; virus safety (Human immunodeficiency virus (HIV)–1 and HIV–2, Hepatitis A virus (HAV), Hepatitis B virus (HBV), Hepatitis C virus (HCV), Parvovirus B19);
- Serum IgG concentrations;
- Exploratory laboratory parameter: Tumor necrosis factor-alpha (TNFα).

Comment   Temporally associated AEs (within 72 hours after end of infusion) should be analyzed regardless of potential relatedness to product infusion.

STATISTICAL METHODS:
- The analyses were performed separately for the 2 treatments. Continuous data were analyzed using descriptive statistics and categorical data summarized by frequency counts and percentages.
- Related AEstemp were analyzed separately in subjects completing the 72-hour observation period with modified Wilson score method to build a 1-sided 95% upper confidence limit for the difference between IgPro20 and IgPro10 in the proportions of subjects with the above outcomes. As supportive

analysis, 1-sided 97.5% upper confidence limit, was also calculated. The primary endpoint analysis assumed neither period effects nor carry-over effects.

RESULTS:

Demographics and Subject Disposition:
The 20 subjects enrolled were all male, and 19 were Caucasian (one "Oriental"). Age range was 20 – 45, with mean of 33.6. All subjects completed the two periods of study.

Safety Results:
Overall, 39 AEs were reported by 14 subjects for the treatment with IgPro10 and IgPro20. The following shows an analysis of the AEs by period.

Summary of all AEs by system organ class, preferred term and descending frequency

System organ class / Preferred term	IgPro10		IgPro20		Overall	
	Number (%) of subjects N=20	Number of AEs	Number (%) of subjects N=20	Number of AEs	Number (%) of subjects N=20	Number of AEs
Any adverse event						
Overall	10 (50)	17	12 (60)	22	14 (70)	39
General disorders and administration site conditions	**7 (35)**	**9**	**8 (40)**	**13**	**9 (45)**	**22**
Chills	2 (10)	2	4 (20)	4	4 (20)	6
Chest discomfort	2 (10)	2	3 (15)	3	3 (15)	5
Feeling cold	3 (15)	3	2 (10)	2	3 (15)	5
Feeling hot	1 (5)	1	2 (10)	2	2 (10)	3
Extravasation	—	—	1 (5)	1	1 (5)	1
Fatigue	—	—	1 (5)	1	1 (5)	1
Infusion site pain	1 (5)	1	—	—	1 (5)	1
Nervous system disorders	4 (20)	4	3 (15)	3	6 (30)	7
Headache	2 (10)	2	2 (10)	2	4 (20)	4
Paraesthesia	1 (5)	1	1 (5)	1	1 (5)	2
Somnolence	1 (5)	1	—	—	1 (5)	1
Vascular disorders	—	—	3 (15)	3	3 (15)	3
Haematoma	—	—	3 (15)	3	3 (15)	3
Blood and lymphatic system disorders	1 (5)	1	2 (10)	2	2 (10)	3
Neutropenia	1 (5)	1	2 (10)	2	2 (10)	3
Cardiac disorders	1 (5)	1	1 (5)	1	1 (5)	2
Palpitations	1 (5)	1	1 (5)	1	1 (5)	2
Psychiatric disorders	1 (5)	1	—	—	1 (5)	1
Insomnia	1 (5)	1	—	—	1 (5)	1
Reproductive system and breast disorders	1 (5)	1	—	—	1 (5)	1
Ejaculation disorder	1 (5)	1	—	—	1 (5)	1

N= Total number of subjects in population; AE= adverse event.

The incidence of related AEstemp (up to 72 hours post infusion) was similar between both treatments. The report's primary analysis (related AEstemp according to the modified Wilson score) revealed no significant differences between IgPro20 (11 of 20 subjects) and IgPro10 (10 of 20 subjects) in the proportions of subjects reporting related AEstemp. A consistent period effect indicating a potential sensitization of subjects during the first period was not evident for either treatment.

Most of the AEs were probably or possibly related to the treatments: 36 of the 39 AEs as assessed by the Investigator, and were of mild intensity (31 AEs). The three AEs considered not related to treatment were hematomas from venipucture with IgPro20 infusion. The majority of AEs started within 2 hours, mostly within about 30 to 40 min, after the start of the infusion.

There was no serious AE (SAE), no AE which led to a discontinuation of a subject from the study, or a series of AEs which resulted in premature termination of the study.

Lab Findings. There were no clinically relevant changes on the safety laboratory parameters, including significant changes over time in liver and renal function tests. There were no signs of hemolysis. Two

subjects had transient decreases in neutrophils reported as AEs (neutropenia). Coagulation markers indicated slight transient increase in mean prothrombin fragment 1+2 and mean TAT concentrations. A transient self-limiting increase in TNFα upon infusion of IgPro10 or IgPro20 was observed in both periods with unknown significance.

There was no clinically relevant impact of IgPro10 or IgPro20 on the vital signs or ECG variables. There were no abnormal findings in physical examination at the Follow-up visit.

Conclusions:
1. Although the primary analysis based on the modified Wilson score for related AEstemp is flawed because it does not include all AEs temporally associated with infusion, only three events were not included (all hematomas associated with venipuncture), and it revealed no significant differences between IgPro20 and IgPro10 in the proportions of subjects with related AEstemp when they were infused intravenously.

2. There may be little risk associated with IgPro 20 inadvertly infused intravenously, as IgPro20 was found tolerable for IV administration when given at the SC dose used for IgG replacement therapy. Local and systemic tolerability of IgPro20 was comparable to IgPro10.

3. The most frequent AEs (chills, chest discomfort, feeling cold, and headache) are adverse events commonly occurring with the use of immunoglobulin preparations.

4. This study has not included females, and the safety of igPro20 in females has to be demonstrated in other studies.

ZLB04_008CR A single-center, randomized, 4-way cross-over, assessment-blinded study to investigate the local tolerability of a newly developed subcutaneous Immunoglobulin G with different concentrations in comparison to Vivaglobin® (STUDY PERIOD: 1/9/06 to 3/17/06)

INVESTIGATORS:
Drs. Eugen Baumgaertner, Ingo Meyer, Kirsten Hauswald, Alexander Smiewski
QUINTILES GmbH PHASE I Unit, Obere Hardtstraße 8-16, D-79114 Freiburg, Germany

OBJECTIVES:
The primary objective of this study was the assessment of local tolerability of IgPro16 and IgPro20 in comparison to Vivaglobin® at pre-defined time points using the following parameters:
• Assessment of pain (performed by the subject)
• Assessment of erythema, edema/induration, local heat and itching (performed by the assessment-blinded investigator)

The secondary objective of this study was the determination of the safety of IgPro16 and IgPro20 in comparison to Vivaglobin®. This objective was achieved by assessment of the following parameters: adverse events, safety laboratory values, IgG serum concentrations, ECG evaluation and evaluation of vital signs.

DESIGN:
Single-center, randomized, 4-way cross-over, assessment-blinded study of 28 healthy, male Caucasian subjects between 18 and 45 years, with each subject receiving 4 different SC infusions in a randomized sequence between wash-out periods of exactly 7 days each:
• Treatment A: IgPro16, 15 mL
• Treatment B: IgPro20, 15 mL
• Treatment C: IgPro20, 12 mL
• Treatment D: Vivaglobin®, 15 mL
The SC infusions involved the use of an infusion pump, and were at a rate of 25 mL/hr
    The product batch numbers were:
      • IgPro16 #43106-00001 (Expiry date: 5/21/06)
      • IgPro20 #43108-00001 (Expiry date: 10/24/06)
      • Vivaglobin® #23140621F (Expiry date: 10/30/07), and #00140611G (Expiry date: 5/31/08)

Subjects were screened for eligibility on Day -21 to Day -3 before treatment. The screening included: written informed consent, check of inclusion and exclusion criteria, demographic data, physical examination, medical history, ECG 12 leads, blood pressure (BP), pulse rate (PR), body temperature (BT), clinical laboratory (hematology, serum biochemistry, urinalysis and serology (HBV, HCV, HIV-1/2 and Parvovirus B19)), urine drug screen, alcohol breath test, documentation of concomitant diseases and concomitant medication.

Study Procedures (Treatment A, B, C or D): The subjects came to the Unit in the evening prior to the infusion days. On infusion days (Days 1, 8, 15, and 22) measurements of vital signs and ECG, physical examination and blood sampling for safety laboratory (including IgG) were performed prior to the infusions; the infusions were administered; the end of infusion was defined as time point "0"; assessments of local tolerability were performed at -15 min (during the infusion), 0 hrs (end of infusion), 1hr, 8 hrs and 24 hrs; the subjects were discharged in the morning of the following day after measurement of vital signs, ECG, local tolerability and blood sampling for safety laboratory parameters (including IgG). They return for the assessment of local tolerability 48 hrs and 72 hrs after end of infusion. Additional ambulant visits were arranged, when local reactions were still persisting. Subjects were to attend the Unit for follow up examination at least 7 days after the last administration. During this examination, the following procedures were done: physical examination, vital signs (BP, PR, BT), body weight, ECG (12 leads), clinical laboratory profile (hematology, serum biochemistry, urinalysis and serology incl. HBV, HCV, HIV-1 and Parvovirus B19).

Eligibility Criteria:

Inclusion criteria
1. Male
2. Age between 18 - 45 years, inclusive
3. Body mass index between 21-27 kg/m2, inclusive
4. Subjects had signed an informed consent document indicating that they understood the purpose of the study and procedures required for the study and were willing to participate in the study
5. No clinically significant medical history according to the Investigator
6. Subjects were in good health as determined by a detailed medical history, complete physical examination (including blood pressure and pulse rate measurement), 12-lead ECG and clinical laboratory screening
7. All values for hematology, biochemistry and urinalysis were within clinically acceptable ranges, judged by the Investigator, prior to administration of study drug
Exclusion criteria
1. Evidence of clinically relevant pathology that could interfere with the study results or put the subject's safety at risk
2. Subjects with a resting supine blood pressure of < 90/50 mmHg or >140/95 mmHg or a resting pulse rate outside the range of 45 to 100 beats/min
3. History of relevant drug and/or food allergies
4. History of hypersensitivity (anaphylactic response) to the study medication and its ingredients or to drugs with similar chemical structures (e.g. IVIGs, intramuscular IgGs, specific immunoglobulins)
5. Active immunisation within the previous 3 months
6. Intake of medication, including OTC within 14 days prior to administration (except Paracetamol: may be used up to 3 days before first dose administration)
7. Cigarette consumption of more than 10 cigarettes per day or equivalent amounts of nicotine
8. History of alcohol abuse or drug addiction
9. Donation of blood within 90 days prior to drug administration
10. Positive screen for drugs of abuse (opiates, cocaine, amphetamines, cannabinoids, barbiturates, benzodiazepines, alcohol)
11. Positive screen for HBV, HCV, HIV
12. Acute illness within seven days prior to administration of study drug
13. Major illness (e.g. pneumonia) within two months prior to administration of study drug
14. Participated in a clinical study within 30 days prior to screening
15. Psychological and/or emotional problems, which would render the informed consent invalid, or limit the ability of the subject to comply with the study requirements
16. Any condition that, in the opinion of the investigator would complicate or compromise the study or the well-being of the subject
17. History of any known hyperprolinemia
18. Any known disposition to allergies including seasonal allergic rhinitis

EVALUATIONs:
Local tolerability assessment

The observation period covered the time up to 72 hrs after the end of infusion and was extended, if necessary, i.e. injection site reactions were not resolved. Assessments were performed by the "assessment-blinded" Investigator as well as by the subject. To ensure "assessment-blinding" conditions for the Investigator, the "end of infusion" was defined as time point "0" and additionally the blinding procedures were clearly defined.

Scores of local tolerability parameters:

- Pain: VAS scale from 0 mm (no pain) to 100 mm (unbearable pain).
- Erythema: none, very slight (barely perceptible), well-defined, moderate to severe, severe (beet redness) to slight eschar formations (injuries in depth).
- Edema/induration: none, very slight (barely perceptible), slight (edges of area well defined by definite raising), moderate (raised approximately 1 mm) and severe (raised more than 1 mm).
- Itching & local heat: none, mild (easy to tolerate), moderate (hard to tolerate), severe (intolerable).

STATISTICAL METHODS:

Safety data were analyzed based on the all dosed population by treatment. Demographic and background characteristics (medical history, physical examination) as well as study drug administration were analyzed descriptively. Descriptive statistics were also performed for all safety parameters.

All analyses of primary and secondary endpoints were done by treatment. The primary endpoint, pain intensity measured on VAS scale, was also analyzed by period (including over all periods).

The maximum pain and mean pain scores per subject were analyzed by a linear model, in each case including the factors *period, treatment and subject* (random). Two-sided 90% confidence intervals (CI) were calculated for the difference in maximum pain and the difference in mean pain between each of the treatment groups A, B and C and the Vivaglobin® treatment group. The time when maximum pain was measured was analyzed descriptively.

For the tolerability variables to be assessed by the investigator (i.e. edema/induration, erythema, itching and local heat) descriptive statistics of incidence of each reaction *by period and treatment* with reference to maximum intensity, including estimates over all periods were calculated.

RESULTS:

Demographics and Subject Disposition:

The subjects were all male and of Caucasian descent. The mean age was 33.7 and range was 22 to 45. All 28 subjects completed the study.

Local Tolerability

1. Pain: The results of the linear model show, that the factors period and treatment did not have an impact on the maximum pain. Similar results were seen for mean pain regarding period. The effect of the factor treatment on mean pain was only borderline, as shown in the following Table:

Maximum Pain and Time to Maximum Pain by Treatment – All Dosed

Variable/Treatment	N				
Maximum pain		**Mean [mm]**	**(SD) [mm]**	**Median [mm]**	**(min / max) [mm]**
IgPro16 (15 mL)	28	6.8	(12.52)	2.5	(0 / 60)
IgPro20 (15 mL)	28	7.6	(12.46)	4.0	(0 / 63)
IgPro20 (12 mL)	28	6.9	(12.13)	2.0	(0 / 58)
Vivaglobin®	28	9.3	(14.18)	4.0	(0 / 73)
Time to maximum pain		**Mean [h]**	**(SD) [h]**	**Median [h]**	**(min / max) [h]**
IgPro16 (15 mL)	28	2.40	(9.91)	-0.22	(-0.25 / 47.57)
IgPro20 (15 mL)	28	1.61	(6.25)	-0.22	(-0.25 / 24.05
IgPro20 (12 mL)	28	1.90	(6.33)	-0.22	(-0.23 / 24.08)
Vivaglobin®	28	3.27	(8.47)	-0.10	(-0.23 / 23.93)

In general, the 90% confidence intervals for the treatment differences were very narrow: widths < 4.6 mm for *maximum pain*, widths < 2.2 mm for *mean pain*. The sequence did not have an influence on either pain parameter. For both of these two parameters, IgPro20 (15 mL) was comparable with Vivaglobin®.

For the median and mean values of *mean pain*, no relevant differences between the treatments were observed. The overall median and mean values of *maximum pain* and *time to maximum pain* showed no relevant differences between the treatments. The median of the *time to maximum pain* was negative in most cases, i.e. the maximum pain was in general observed before the end of infusion (time point -15

minutes). In general pain was highest on Day 1 during infusion and then decreased. In many cases the pain was resolved at the end of Day 1.

2. Erythema: In 104 out of 112 observations (93%) erythema was reported.
- Severity. Most of the observed erythema was well-defined erythema", followed by "very slight erythema". A small number of "moderate to severe erythema" was observed and only one "severe erythema" was described under treatment of IgPro20 (15 mL).
- Time course. Comparison of the time courses of the mean scores shows no treatment specific differences. The maximal mean intensities were observed at the end of infusion for all 4 treatments, and their time courses show similar decreases: (a) at the end of the scheduled observation period on Day 4, in 94 (84%) out of 112 observations no erythema was observed, (b) at the end of the optional observation period on Day 7, in 108 (96%) out of 112 observations no erythema was observed, and at the follow-up examination (Day 8 of period 4), all erythema had resolved.

3. Edema / Induration: All subjects showed edema/induration during the treatments (112 cases of edema/induration in 112 observations; 100%).
- Severity. The majority (99%) of the observed edema/induration was scored as "severe".
- Time course. By comparison of the time courses of the mean scores of swelling, the maximum mean intensities of edema/induration were observed at the end of infusion in all treatments, and no differences were observed between the 4 treatments: (a) decrease of the mean severity started during Day 1, (b) decrease continued on Day 2 (24 hrs after end of infusion), with no edema/induration observed in 31 (28%) out of 112 observations, (c) at the end of the scheduled observation period on Day 4, in 79 (71%) out of 112 observations no edema/induration was observed, (d) at the end of the optional observation period on Day 7, in 104 (93%) out of 112 observations no edema/induration was observed, and (e) at the follow-up examination (Day 8 of period 4), all edema/induration were resolved, except in one case, which was scored as "very slight". Overall, the time courses of mean surface area of edema/induration showed no relevant differences between the treatment groups.

4. Itching. In 51 out of 112 observations (46%) subjects itching was reported.
- Severity. 92% of the cases of itching were scored as "mild", 8% "moderate". No differences were observed between the different treatments.
- Time course. In general, itching started during the infusion and was resolved in the majority of cases 8 hrs after the end of infusion, when only 1 subject reported "mild" itching. At the end of the scheduled observation period on Day 4, 1 subject reported "mild" itching. All itchings were resolved during the optional observation period on Day 6.

5. Local heat. In 15 out of 112 observations (13%) subjects reported local heat.
- Severity. The score for the cases of reported local heat was always "mild". No differences were observed between the different treatments.
- Time course. Local heat started to occur during the infusion and was resolved shortly after the end of infusion. Eight hours after end of infusion all reported cases of local heat were resolved (100%).

Systemic Safety:
All subjects who were enrolled completed the study according to protocol.

No serious AE occurred during this study. A total number of 16 AEs and one pre-treatment AE were reported by 12 subjects during this study. All AEs were of mild to moderate intensities and were resolved without sequelae at the end of the study.

Incidence of Subjects with AEs by Treatment				
	Treatment A IgPro16 (15 mL) (n = 28)	Treatment B IgPro20 (15 mL) (n = 28)	Treatment C IgPro20 (12 mL) (n = 28)	Treatment D Vivaglobin® (15 mL) (n = 28)
Number of all AEs	4	6	2	4
Number (%) of Subjects	2 (7.1)	6 (21.4)	2 (7.1)	4 (14.3)
System Organ Class				
Preferred Term				
Nervous System Disorders	**2 (7.1)**	**5 (17.9)**	**1 (3.6)**	**1 (3.6)**
Headache	2 (7.1)	4 (14.3)	1 (3.6)	1 (3.6)
Somnolence	--	1 (3.6)	--	--

Syncope vasovagal	1 (3.6)	--	--	--
Infections and Infestations	**--**	**--**	**--**	**3 (10.7)**
Nasopharyngitis	--	--	--	3 (10.7)
Gastrointestinal Disorders	**--**	**--**	**1 (3.6)**	**--**
Toothache	--	--	1 (3.6)	--
Respiratory, Thoracic and Mediastinal Disorders	**--**	**1 (3.6)**	**--**	**--**
Pharyngolaryngeal pain	--	1 (3.6)	--	--

Comment   The AEs in this study are subsequent to the infusion of a very small amount of IG as opposed to administration of a therapeutic dose. Thus, the small number of such AEs would in no way support product safety for the proposed indication.

Seven of the AEs were considered study drug-related. The most frequently observed possibly study drug-related TEAE was headache, reported 6 times by 6 subjects during the study. Another study drug-related AE was somnolence, reported once by 1 subject.

There were no clinically significant abnormal laboratory values. Due to the low doses administered IgG serum levels under the treatment with subcutaneous IgG were unchanged during the course of the study. No changes on the physical examination were reported at the post study examination as compared to the findings evaluated at screening. Vital signs and body weight did not reveal any clinically significant findings from baseline. Findings in the ECG recordings observed during screening and during the study were also not clinically significant.

Conclusions:

1. This study involves administration of very small quantities of IG, and thus the systemic safety profile is not representative of therapeutic doses administered in the treatment of primary immunodeficiency. However, the observation of local reactions provides useful information, because the volumes administered may be similar to that infused at a single site in the therapeutic scenario (see below under ZLB04_009CR).

2. The observed local reactions in this study fit in the known pattern of local reactions after SC infusions with IGs, and are common between the IGSCs, Hizentra and Vivaglobin. Most of the local reactions were resolved by Day 4, i.e. 3 days after the end of infusions, suggesting that they may be safe and well tolerated while administered in healthy, adult subjects.

3. The most frequent systemic AE (headache) is consistent with what is commonly observed with the use of immunoglobulin preparations.

4. This study has not included females, and the safety of igPro20 in females has to be demonstrated in other studies.

ZLB04_009CR. A Phase III Open-Label, Prospective, Multicenter Study of the Efficacy, Tolerability, Safety, and Pharmacokinetics of Immune Globulin Subcutaneous (Human), IgPro20 in Subjects with Primary Immunodeficiency (PID)

The report states that this study was performed in compliance with Good Clinical Practice and the Declaration of Helsinki (1996), and the study protocol, informed consent, and other appropriate study-related documents were reviewed and approved by an Institutional Review Board (IRB)..

INVESTIGATORS:
The study was performed as a multicenter study at 12 study sites in the USA (see below).

OBJECTIVES:
The overall objective of this study was to investigate the efficacy, safety, and tolerability of IgPro20 in subjects with PID. A further objective was to investigate the PK of IgPro20 in a PK substudy, the results of which are reported in a separate PK study report (reviewed by Dr. I. Mahmood).

Primary objective: to evaluate whether the annual rate of SBIs per subject was less than one. SBIs were defined as:
• Bacterial pneumonia.

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- Bacteremia / septicemia.
- Osteomyelitis / septic arthritis.
- Bacterial meningitis.
- Visceral abscess.

<u>Secondary objectives:</u>
- Rate of SBIs in the per-protocol efficacy (PPE) and intention-to-treat (ITT) populations.
- Number of infection episodes (serious and non-serious).
- Number of days out of work/school/kindergarten/day care or unable to perform normal daily activities due to infections.
- Number of days of hospitalization due to infections.
- Use of antibiotics for infection prophylaxis and treatment.
- Total serum IgG C_{trough} values.
- Rate, intensity, and relatedness of any AEs per subject and infusion.
- Assessment of local tolerability in terms of injection site reactions.
- Changes in clinical laboratory parameters (blood chemistry, hematology, and urinalysis) as compared to baseline assessments.
- Changes in physical examination results as compared to screening assessments.
- Vital sign changes.
- Changes in concomitant medications.
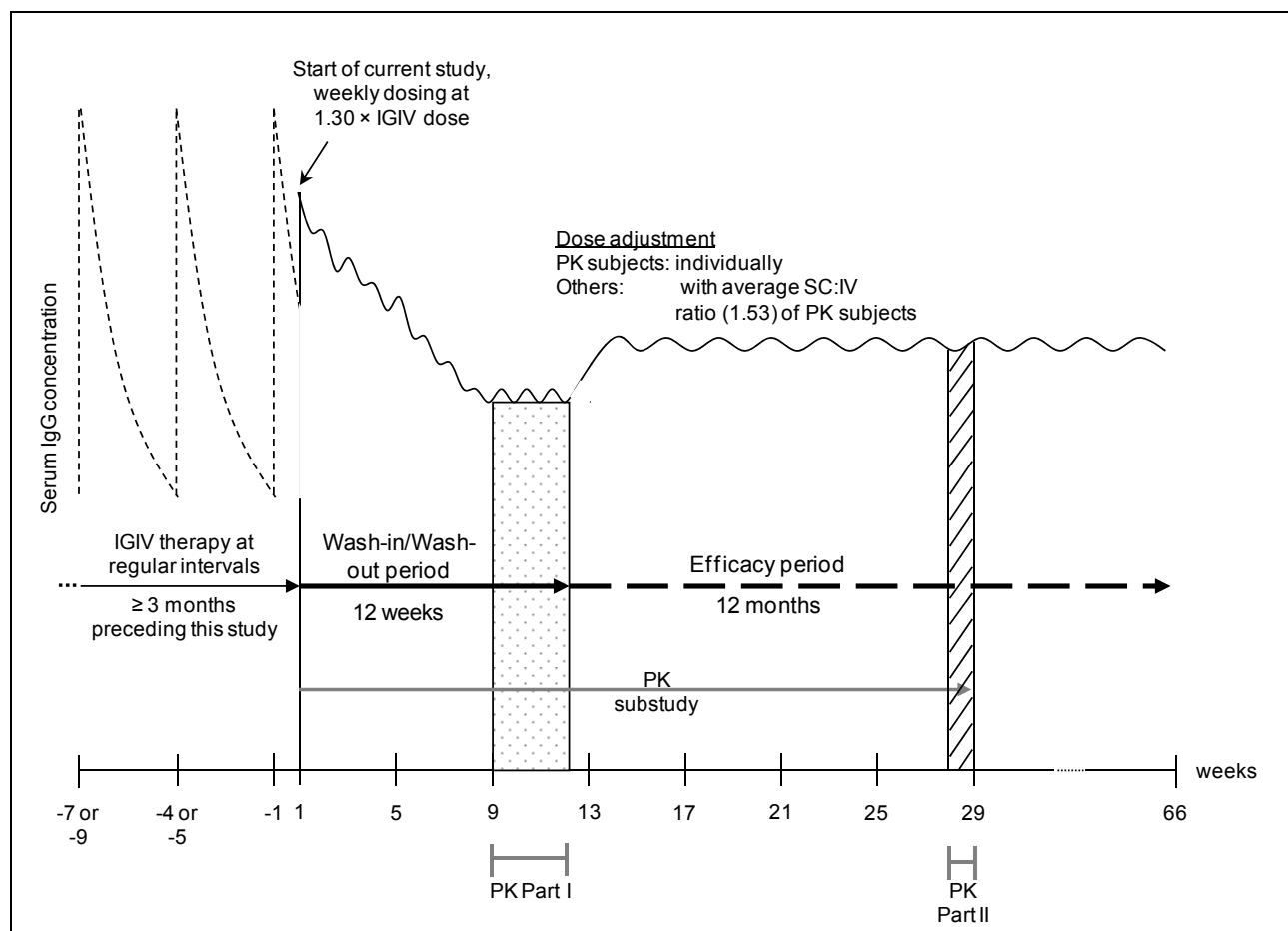- Changes in viral safety markers as compared to baseline assessments.

DESIGN:
Prospective, open-label, multicenter, single-arm, Phase 3 study of IgPro20 in subjects with PI, with a 12-week wash-in/wash-out period followed by a 12-month efficacy period, during which the efficacy, safety, and tolerability of IgPro20 were evaluated.

Within this framework, a 2-part PK substudy was conducted in a subset of subjects.
- Part I determined an appropriate dose adjustment for IGSC treatment with IgPro20 (as compared to the preceding dose during IGIV treatment with Privigen) to be used to attain individual target IgG trough levels during the efficacy period. This dose adjustment was based on IgG C_{trough} values during IgPro20 treatment at the end of the wash-in/wash-out period (Weeks 9 to 12) (the mean dose adjustment coefficient was 1.53).
- Part II evaluated whether the adjusted dose of IgPro20 used during the efficacy period provided a non-inferior AUC for serum IgG compared to the AUC measured in a preceding study during IGIV treatment with Privigen.

Figure 1 - Schematic overview of the overall study design

IGIV = Immune Globulin Intravenous (Human); IV = Intravenous; PK = Pharmacokinetic; SC = Subcutaneous.

The initial weekly dose of IgPro20 administered during the wash-in/wash-out period was one fourth (previous 4-week schedule) or one third (previous 3-week schedule) of the average dose of the previous 3 IGIV infusions received before the start of this study, multiplied by 1.30. After the 12-week wash-in/wash-out period, the weekly SC dose of IgPro20 was adjusted to achieve the target IgG level for the subsequent 12-month efficacy period. Subjects who had participated in the PK substudy had their IgPro20 doses adjusted by applying individual dose adjustment coefficients, calculated on the basis of their individual IgG C_{trough} values measured during Part I of the PK substudy. Subjects who did not participate in the PK substudy (non-PK subjects) had IgPro20 doses adjusted by applying the mean dose adjustment coefficient from the PK substudy population with evaluable data for Part I (1.53 times the subjects' preceding IGIV doses). The applicant refers to the PK study report that after adjusting with a coefficient of 1.53 times the previous Privigen dose to the dose of IgPro20, the geometric mean AUC ratio for IGSC vs. IGIV was 1.002 and the lower limit of the 90% confidence interval of this ratio was 0.951.

During the 12-month efficacy period, subjects visited the study site at 4-week intervals for the efficacy and safety evaluations and recorded into a diary details of the dose of IgPro20 administered and certain aspects of the efficacy and safety of IgPro20. The diaries were collected and reviewed by study personnel at each study visit. The 12-month efficacy period covered all seasons. Some subjects entered the efficacy period prior to their dose adjustment for IgPro20, i.e., they remained on their initial dose (1.30 times the weekly equivalent of the average dose of the preceding 3 IGIV infusions) until all PK subjects had completed Part I of the PK substudy. An influence on efficacy parameters was not apparent because IgG C_{trough} values during the previous IGIV treatment had been relatively high, and no critical decrease of IgG C_{trough} values occurred with IGSC doses 1.30 times higher as compared to previous IGIV treatment.

ELIGIBILITY CRITERIA:
Inclusion criteria
- Male or female subjects 2 to 75 years of age.
- Subjects with one of the following primary humoral immunodeficiencies:
  o CVID as defined by Pan-American Group for Immunodeficiency and European Society for Immunodeficiencies.
  o XLA.

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• Subjects who had received: (a) Privigen IV therapy at regular 3- or 4-weekly intervals, or (b) IGIV therapy at regular 3- or 4-weekly intervals for at least 3 months prior to receiving IgPro20.
• For subjects who switched from the Privigen extension study (ZLB05_006CR): at least 3 documented serum IgG C_{trough} values of ≥5 g/L during the previous 3 months on IGIV replacement therapy. For other subjects: at least one documented serum IgG C_{trough} value of ≥ 5 g/L during the previous 6 months of IGIV replacement therapy (could be obtained during screening).
• Women of childbearing potential had to use medically approved contraception and had to have a negative pregnancy test.
• Written informed consent.

Exclusion criteria
• Newly diagnosed PI and not having received previous IGIV treatment.
• Evidence of an active serious infection at the time of screening (e.g., but not limited to: bacteremia / septicemia, pneumonia, and fungal osteomyelitis).
• Malignancies of lymphoid cells such as lymphocytic leukemia, Non-Hodgkin's lymphoma, and immunodeficiency with thymoma.
• Known hyperprolinemia.
• Hypoalbuminemia, protein-losing enteropathies, and any proteinuria.
• Allergic reactions to immunoglobulins or other blood products.
• Known antibodies to immunoglobulin A (IgA).
• Treatment with steroids (oral or parenteral, ≥0.15 mg of prednisone equivalent/kg/day) or other systemic immunosuppressants.
• Pregnancy, breast feeding, or planning a pregnancy during the course of the study.
• Participation in a study with an investigational product other than IGIV within one month prior to enrollment.
• 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.
• Any condition likely to interfere with evaluation of the study drug or satisfactory conduct of the study.

TREATMENTS:
IgPro20 was administered SC using ----------(b)(4)---------- infusion pumps (------------(b)(4)-------------). The number of injection sites depended on the volume of the total dose. After selection of appropriate injection sites, e.g., on the abdomen, thighs, upper arms, and/or lateral hip, 2 or more injection sites could have been used simultaneously (up to a total of 4 sites using 2 pumps, each with bifurcated catheters). The actual points of injection were to be changed with each weekly administration. In total, each subject was to receive 66 infusions.

Treatment was predominantly home-based and performed by the subject (or parent or guardian) after a training period at the study site. After this initial training period, every 4th weekly SC infusion was at the study site, when the subject's (or parent's or guardian's) infusion technique was observed by the physician or nurse for proper methodology. Overnight infusions were not allowed.

At the beginning of the study, subjects performed at least 3 supervised infusions at the study site. The number of supervised infusions was not to exceed 8. An exception was made for subjects living in remote areas, so that only the first training was required to take place at the study site. After consultation with the sponsor, certain training infusions (Infusions 2 and 3 were obligatory; Infusions 5, 6, and 7 were optional) could have taken place at the subject's home under the supervision of a trained home health nurse.

The product lot numbers of IgPro20 used in this study were: 43109-00001, 43109-00002, 43109-00003, 43109-00004, 43109-00005, 43109-00006

Selection of doses in the study: see above, under DESIG for calculation from past IGIV dose. The initial volume per injection site was 15 mL and could be increased to 20 mL after the fourth infusion and to a maximum of 25 mL per site, depending on tolerability. The total infusion flow rate was not to exceed 15 mL/h for the first infusion and could then be increased up to 50 mL/h using a maximum of 2 pumps simultaneously. The number of injection sites for each subject depended on the total volume to be infused, but was not supposed to exceed 4 (using 2 pumps, each equipped with a bifurcated catheter). In practice, by filling the pumps several times to administer high doses of IGSC, more than 4 injection sites could be used consecutively during the same infusion.

Comment Repeated filling of infusion pumps to deliver high doses of IGSC allows for more than 4 injection sites to be used consecutively at the same infusion. It is unclear whether this is considered

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protocol violation or not. The tolerability of such infusions should be compared with that of other infusions which followed the up-to-4-site rule.

Prior and concomitant therapy
- Premedication taken on the same day prior to infusion, to prevent or alleviate AEs for IGSC infusion was not allowed, with the exception of local anesthetics, which could be applied before infusion, if a subject experienced the pricking with the needle as uncomfortable, and was recorded as concomitant medication.
- Other immunoglobulins (i.e., IGSCs or IGIVs) or systemic immunosuppressive drugs (except steroids) were prohibited during the study.
- Oral and parenteral steroids were allowed if the average daily dose was <0.15 mg of prednisone equivalent/kg/ day. While daily doses could exceed this limit, the long-term average dose was to be kept below this limit.
- Any medication not intended for the primary purpose of masking signs of adverse reactions to the infusions, and which was taken by the subject on a regular basis, could be continued.

STUDY FLOWCHART:

	Screening[2]	Wash-in / Wash-out period — Weekly SC infusion with 1.30 times IGIV							Efficacy period[3] — Weekly SC infusion with adjusted dose							Completion visit
Infusion number[4]		1[5]	2	3[6]	4	5, 6, 7[7]	8[8]	12	16, 20, 24	28	32, 36	40	44, 48, 52, 56, 60	64	66	1 week after last infusion[9]
Informed consent	X															
Physical exam	X															X
Demographics & medical history	X															
CXR or CT Scan	X[10]															
Virology	X[11]	X			X											X[12]
Hematology	X[13]	X			X					X		X		X[14]		X
Serology																
IgA, IgM, albumin	X															
Direct Coombs' test[15,16]		X			X					X[17]				X[18,19]		X
IgG C_trough & backup	X	X	X	X	X		X	X	X	X	X	X	X	X		X
Blood chemistry	X	X			X					X		X		X[20]		X
Urinalysis	X	X			X					X		X				X
Pregnancy test	X															X
Vital signs[21]	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Injection site evaluations[22]		X	X	X	X	X	X	X	X	X	X	X	X	X		
Weight		X			X		X	X	X	X	X	X	X	X		
Subject diary[23]	X[24]	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Concomitant meds	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Last IGIV infusion	X[25]															
Last IGSC infusion															X	

1 Dose adjustment in non-PK subjects took place when all PK subjects had completed the wash-in/wash-out period.
2 Screening took place 1-4 weeks prior to 1st SC infusion.
3 The efficacy period of all subjects started with Infusion 13.
4 Only infusions with examinations or blood sampling are listed in the flow chart. Infusion 66 is the last infusion.
5 Infusion 1 took place one week after the last infusion of the previous IGIV.
6 Minimum number of infusions for subject training on subcutaneous (SC) technique.
7 Optional visits for subject training on SC technique.
8 Maximum number of infusions for subject training on SC technique.
9 7 ± 2 days after last infusion (Infusion 66).
10 Only if X-ray / computed tomography (CT) scan obtained within the previous 6 months was not available.
11 Including testing for parvovirus B19.
12 Including testing for parvovirus B19 (only for subjects who were negative at screening) and hepatitis A virus (HAV).
13 Including blood typing (blood groups ABO and Rhesus factor).
14 Blood samples for hemoglobin only test collected 4 times (part of end of study hemolysis testing): pre-Infusion 64, post-Infusion 64, 2-3 days and 6-7 days after Infusion 64 (prior to Infusion 65).
15 Blood sampling for Direct Coombs' test was performed 10-30 minutes before and 10-30 minutes after the infusions.
16 Any positive Direct Coombs' test was followed by antibody elution and identification.
17 Only for PK subjects on Day 3 of PK substudy Part II.
18 Taken 3 times (part of end of study hemolysis testing): pre-Infusion 64, post-Infusion 64, and 2-3 days after Infusion 64. Repeated 6-7 days after Infusion 64 (prior to Infusion 65) if any of the previous 3 tests was positive.
19 If a positive Direct Coombs' test pre- or post-Infusion 64, 2-3 days or 6-7 days after Infusion 64 was accompanied by a decrease of $\geq$ 2 g/dL of hemoglobin compared to the pre-Infusion 64 blood test results testing for biochemical indicators of hemolysis (lactate dehydrogenase [LDH], serum haptoglobin, plasma-free hemoglobin, urine hemosiderin, and complete blood count [CBC]) was performed (part of end of study hemolysis testing).
20 Blood samples for LDH only test collected pre-Infusion 64 (part of end of study hemolysis testing).
21 Vital sign measurements were performed 10 min   5 min pre-infusion, 30 min ± 5 min and 60 min ± 5 min after the start of infusion, and 10 min   5 min post-infusion.
22 Injection site evaluations were performed 15-45 min post-infusion by the investigator.
23 Was to be checked prior to infusions at study site and on an ongoing basis if necessary.
24 Handover only.
25 Took place one week before the first infusion with IgPro20.

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EVALUATIONS:

Efficacy measurements

The underline efficacy endpoint was the annual rate of SBIs. Information on occurrences of SBIs was obtained from the record of AEs on the CRF. In case of a suspected SBI, the methods for evaluating infections were as proposed in the FDA Guidance for Industry of 2008, in accordance to its criteria for bacterial pneumonia, bacteremia/septicemia, osteomyelitis/arthritis, bacterial meningitis, and visceral abscess.

Secondary efficacy endpoints. At the screening visit, the subjects were issued a diary for recording information used for the evaluation of secondary efficacy endpoints. Daily entries were not required, but the subjects could record information about side-effects at any time. The only mandatory entry was an assessment on the overall perception of local reactions at 24 ± 3 h after the end of infusion. Appropriate completion of the diary was checked at every visit to the study site. Blood samples for serum were collected 30 to 10 min prior to infusion of IgPro20 at each visit for C_{trough} values of total IgG. The samples were analyzed by a central laboratory. The secondary efficacy variables were:
• Rate of SBIs in the ITT and PPE populations.
• Number of infection episodes (serious and non-serious).
• Number of days out of work/school/kindergarten/day care or unable to perform normal daily activities due to infections.
• Number of days of hospitalization due to infections.
• Use of antibiotics for infection prophylaxis and treatment.
• Total serum IgG C_{trough} values.

Safety measurements

Evaluation of safety included the analysis of AEs and local tolerability (injection site reactions). The rate, intensity, and relatedness of AEs to the study drug were documented. Clinical laboratory parameters (hematology, clinical chemistry, and urinalysis at central lab), physical examination, concomitant medication, and viral safety markers were also assessed, as well as vital signs pre- and post-infusion, at selected time-points.
- If the start date of an AE was incomplete or missing, it was assumed to have occurred after the first infusion of study drug unless an incomplete date indicated that the AE had started prior to treatment.
- If the intensity of an AE was missing, the AE was included in the frequency tables using a missing category for the intensity.
- If the relationship to study drug was missing, the AE was assessed as unrelated if it started before the first infusion of study drug, and as possibly related if started after the first infusion of study drug.

Assessment of local tolerability - injection site reactions
- Assessment by the subject. Local tolerability at the infusion site was assessed by the subject throughout the study. Subjects recorded a general judgment on the overall perception of the local reactions at 24 ± 3 h after the end of the infusion in the subject diary on a scale of none (0), very slight (1), slight (2), moderate (3), and severe (4). In addition, subjects had the possibility to record information about side-effects at any time during the study, including during the infusions. Diaries were returned to the investigator during scheduled visits. Information about side-effects was extracted from the diary, reviewed by the investigator, and, if necessary, reconciled with the subject during the visits to the study site. The information was then transcribed onto the appropriate CRF pages.
- Assessment by the investigator. The investigators performed their assessment of local tolerability at the subjects' obligatory visits to the study site at 15 to 45 min post-infusion for the first 4 infusions at the study site and at every visit to the study site thereafter, including any optional visits that became necessary for training of subjects on the SC infusion technique (Infusions 5, 6, and 7). If several injection sites were used, every site was judged, but only the site with the strongest reaction was recorded, according to the following scales:
  • Erythema. 0 = None, 1 =Very slight (barely perceptible), 2 = Well-defined   , 3 = Moderate to severe, and 4 = Severe (beet redness) to slight eschar formations (injuries in depth)
  • Edema/induration. The size of the edema/induration was determined by measuring the smallest and the largest diameter in millimeters.
  • Itching, local pain, and local heat. The intensity of the local reactions of itching, local pain, and local heat was assessed by questioning the subject based on the categories of none (0), very slight (1), slight (2), moderate (3), and severe (4).

STATISTICAL METHODS:

The statistical analyses performed in this study were initially specified in the study protocol dated 27 September 2006. Additional details of the planned statistical analyses were provided in the statistical analysis plan (version 2.0 dated 08 May 2008).

Analysis populations

Efficacy analyses were carried out on the MITT and PPE populations.

- The MITT population comprised all subjects treated with the study drug during the efficacy period (starting with Week 13) who had the disease under study.
- The PPE population consisted of all subjects who completed the 12-month efficacy period. Protocol compliance with regard to the disease under study and efficacy measurements (i.e., documentation of SBIs) was required. Major deviations from the treatment schedule also led to an exclusion from the per protocol data set.
- All safety analyses were carried out on the safety data set, which was identical to the ITT data set. The ITT safety data set comprised all subjects treated with the study drug during any study period (also used for some efficacy analyses).

Data from all centers were pooled to provide an adequate number of subjects available for analysis. Descriptive statistics for continuous variables included number of subjects, mean, standard deviation (SD), and the 0% (minimum), 25%, 50% (median), 75%, and 100% (maximum) quantiles. Frequency distributions were given for categorical data.

Subgroup analyses were regarded as exploratory and were conducted for subpopulations according to the following criteria: Gender, age class (≥ 2 to < 12 years, children; ≥ 12 to < 16 years, adolescents; ≥ 16 to < 65 years, adults; ≥ 65 years, geriatrics), disease type (CVID, XLA), race, median dose of IgPro20, and PK vs. non-PK subjects (to be performed only for incidence of subjects with SBIs). AEs and local tolerability (injection site reactions) were also analyzed by subgroups of IgPro20 infusion rate and dose.

Efficacy analyses

Efficacy analyses were generally restricted to the efficacy period, starting with Week 13 (Day 85), and extending to the completion visit (usually 7 ± 2 days after the last infusion).

The following null and alternative hypotheses were tested with regard to efficacy:

$$H0: \lambda_I \geq 1.0 \text{ versus } Ha: \lambda_I < 1.0$$

where λ_I represents the rate of SBIs in the IgPro20 group per subject through the 12-month efficacy period. The 12-month rate (λ_I) of SBIs was estimated along with its upper 1-sided 99% (λ_I upper) confidence limit:

$$\lambda_I = 365\,\frac{y}{t}\,, \quad \lambda_I \text{ upper} = \frac{365}{t} \times 0.5\ \chi^2_{0.99, 2y+2}$$

with $\chi^2_{1-\alpha, v}$ representing the upper 1-α percentile of the Chi-Square distribution with v degrees of freedom, y the total number of SBIs within the study duration, and t the sum of all study days over all subjects. No imputation was made in the primary analysis for subjects discontinued before regular completion of the study.

- <u>Handling of periods not under claimed dose.</u> The primary analysis was repeated with a restricted efficacy period, which consisted only of the observed time periods after the switch to the individual or average adjusted dose. Only SBIs falling within the restricted efficacy period were to be considered in this robustness analysis. No adjustment of the significance level was intended as a consequence of the exploratory nature of this analysis.
- <u>Imputation methods (robustness analyses).</u> Although every effort was made during the conduct of the study to ensure that most of the subjects included in the study completed the 12 month-efficacy phase, a number of subjects were discontinued from the study. The analyses described in this section were only exploratory

A common feature of all imputation methods used was that in a first step, the number of SBIs per year (Y) was determined for each subject. For subjects who completed the study (approximately 12 months) the documented number of SBIs was used in the analysis. For subjects who discontinued (say, after x months in the study) the number of SBIs per year was estimated according to the following formula:

$$Y = D[0\text{-}x] + E(x\text{–}12)$$

where D[0-x] was the documented number of SBIs during the x months in the study and E(x–12) was the estimated number of SBIs for the remaining 12–x months.

In a second step, upper one-sided 99% confidence limits for the number of SBIs (i.e., the parameter of the Poisson distribution) were calculated for all the analyses in this section. The confidence interval was based on the Chi-square distribution (see above). Non-integer values for the imputed number of SBIs were allowed and no rounding was necessary. The following have been attempted by the applicant:

1. A worst case approach for all discontinued subjects
2. A worst case approach only for subjects discontinued due to insufficient efficacy
3. An extrapolation approach
4. A mean number approach
5. A best case approach

Analyses of secondary efficacy endpoints were based on the MITT data set, except for the rate of SBIs, which was analyzed in the ITT and PPE populations. The following analysis were conducted by the applicant:

- Rate of SBIs in the ITT and PPE populations
- Days out of work/school/kindergarten/day care or unable to perform normal activities due to infections
- Days of hospitalization due to infections
- Use of antibiotics
- Serum IgG trough levels

Safety analyses

Safety analyses were generally extended to the full study period, starting on Day 1, and ending at the completion visit (7 $\pm$ 2 days after the last infusion). AEs were analyzed based on the safety data set (ITT). AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 11.0. Analyses were performed by primary system organ class (SOC) and preferred term. Only AEs occurring after onset of treatment and up to the completion visit were included in the summarizing analyses. AEs occurring before the onset of treatment or after the completion visit were only listed.

Analyses of AEs were conducted at the subject level and at the infusion level. For the latter, rates were given as a ratio: No. of AEs / No. of infusions. AEs were considered temporally associated with infusion of the study drug if they occurred in the period from the start of the infusion until 72 h after the end of the infusion. Analyses were split according to whether they occurred within 24 h, 48 h, or 72 h after the end of infusion. AEs were also analyzed for infusions with an infusion rate <15 mL/h, 15 to 25 mL/h, and >25 mL/h.

Local tolerability - injection site reactions

- Subject assessment. Local tolerability assessed by subjects in the diary was displayed graphically by study week. The intensity of local reactions (none, very slight, slight, moderate, severe) was tabulated as the rate of occurrences per 100 infusions.
- Investigator assessment. Local tolerability as assessed by investigators during visits was analyzed by the scheduled week of assessment. Number and percentage of subjects showing erythema (none, very slight, slight, moderate, severe), itching/local pain/local heat (none, very slight, slight, moderate, severe), and edema/induration were tabulated. The surface area S of edema/induration was summarized by descriptive statistics, using the following formula:

$$S = \tfrac{1}{4}\,\pi\,a\,b$$

where a and b represent the smallest and greatest diameter.

Pharmacokinetic analyses

The PK analyses conducted in the context of the PK substudy, including the proposal to use the TLR (trough level ratio)[1] based on the relationship between a calculated "average daily level" and the C_{trough}

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[1] The TLR is the factor by which the steady-state IGSC C_{trough} should exceed the previous steady-state IGIV C_{trough} to ensure matching systemic IgG exposure, i.e., matching AUC values, during IGSC and IGIV treatment.

- The average daily IgG concentration (derived from the AUC) of PK subjects (who had matching AUCs as indicated by non-inferiority of sAUC values) during IGIV treatment was 1.33 times higher than the IgG C_{trough} value at steady-state IGIV treatment.
- During IGSC treatment, the average daily IgG concentration was 1.03 times the IgG C_{trough} value at steady-state.

when the subject is on IGSC and on IGIV to guide dosing adjustments, are described in a separate PK study report (see Dr. I. Mahmood's review).

PROTOCOL AMENDMENTS:
There were 4 amendments (Amendments 1, 2, 3, and 4) to the original study protocol (27 September 2006).

- Amendment 1 (29 November 2006). A health-related quality of life assessment was incorporated, references to the subject diary as an electronic tool were removed, and minor changes to the schedule of assessments were incorporated. It was implemented before any subject had received the first infusion of study drug.
- Amendment 2 (17 January 2007). The design of the health-related quality of life assessment was changed from comparative to single group longitudinal, and the assessment of local tolerability was clarified. Itwas implemented after 2 subjects had received their first infusion of study drug.
- Amendment 3 (23 April 2007). Changes associated with the switch from the electronic to the paper diary used for collecting subject information were described, references to the health-related quality of life substudy were removed, and entry criteria for new subjects regarding the number of required serum IgG Ctrough values measured prior to study entry were clarified to match the current USA standard of care. It was implemented after 23 subjects had received their first infusion of study drug.
- Amendment 4 (30 April 2008). The maximum number of injection sites to be infused simultaneously and maximum total body flow rate of IgPro20 were described, additional timepoints for vital signs evaluation during visits to the study site were added, several statistical concepts were clarified, completion visit procedures were updated, and the lower limit of polysorbate 80 concentration in IgPro20 was specified. In addition, a set of tests to follow a newly positive Direct Coombs' test result was specified. It was implemented after 25 subjects had received their first infusion of study drug.

FDA recommended the following changes to the planned analyses described in the original SAP (version 1.0, dated 5 Dec 2006), and these were implemented:
- The subgroup analyses on SBIs were to be enhanced to cover PK vs. non-PK ("efficacy only") subjects.
- Subgroup analyses were to be conducted with primary and secondary efficacy endpoints if at least 3 events (e.g., SBIs) were found in the respective category (instead of originally at least 5 events).
- Subjects who did not fulfill the inclusion criterion for age were not to be excluded from per protocol analyses under any circumstances.
- An additional analysis was to be performed for the proportion of subjects or infusions for which the infusion rate was reduced or stopped (1) for any reason or (2) due to an AE, including local reactions.
- In addition to the line listing of subjects with SBIs, a similar listing for severe AEs or SAEs was to be provided.
- Unscheduled dose adjustments (not PK guided, not weight related) were to be listed.
- Using the IGIV (Privigen) profiles for IgG at steady-state for the PK population in the current study and from all PK subjects in the 2 predecessor studies with Privigen, the relationship between the AUC-derived target IgG concentration (C_{target}) and trough level at steady-state (C_{last}) was to be explored.
- Using the above ratio, target IgG concentrations for the non-PK population were to be calculated; these were to be compared with steady-state IgG C_{trough} values in the same subjects after 12 to 16 weeks of treatment with the appropriate adjusted dose in the efficacy period of the current study.
- Subjects with a conversion of the Direct Coombs' test (as compared to baseline) and a decrease in hemoglobin of ≥ 2 g/dL (as compared to the last hemoglobin test) were to be listed.
- In addition to SOCs, the category of local reactions (i.e., AEs of injection site reaction, injection site bruising, infusion site scab, injection site cyst, injection site eczema, injection site irritation, injection site nodule, and injection site pain) was created to provide the possibility for a combined analysis of local reactions.

RESULTS

1. SUBJECT DISPOSITION and DEMOGRAPHICS:
This multicenter study was conducted at 12 sites in the USA and screened 52 subjects, with 49 subjects enrolled and treated with IgPro20. Of the 3 subjects who were screened but not treated, 2 subjects (-------(b)(6)---------) withdrew consent, and one (-(b)(6)-) was judged to be non-compliant. The following is information on site enrollment:

SITE	INVESTIGATOR	No. of Subjects

Dividing these geometric mean ratios (average daily IgG concentration vs. C_{trough}) for IGIV (1.33) and IGSC treatment (1.03) resulted in the TLR of 1.29. CSLB hypothesizes that this ratio can be used to evaluate whether non-PK subjects were adequately dosed during IGSC treatment: for matching AUCs, a target IgG trough level for IGSC treatment can be calculated as 1.29 times the IgG C_{trough} value at steady-state IGIV. Adequate dosing with IGSC was assumed if the TLR (individual IGSC C_{trough} vs. IGIV C_{trough}) was within ± 15% of the TLR that predicts matching AUCs (i.e., 1.29 ± 0.19), with in a lower threshold of 1.10 and upper of 1.48. The criterion whether individual TLRs were within the range of 1.10 to 1.48 was used to evaluate if non-PK subjects in this study were adequately dosed in the efficacy period. In addition, target IgG concentrations were imputed for non-PK subjects by multiplying their last IGIV C_{trough} by 1.29 and were compared to actual IgG concentrations attained during the efficacy period.

1	Robert Nelson, MD Section of Hematology/Oncology Indiana University Cancer Center 535 Barnhill Drive, RT473 Indianapolis, IN 46202-5289	9
2	Elena Perez, MD, Ph.D. The Children's Hospital of Philadelphia Abramson Research Center Room 1216G 3615 Civic Center Boulevard Philadelphia, PA 19104-4318	1
3	Alan P. Knutsen, MD SSM Cardinal Glennon Children's Medical Center Pediatric Allergy/Immunology 1465 South Grand Boulevard Saint Louis, Missouri 63104	3
4	Lisa Kobrynski, MD, MPH 2015 Uppergate Drive Atlanta, GA 30322	2
5	Mary Beth Fasano, MD, MSPH University of Iowa Hospitals and Clinics 200 Hawkins Drive Iowa City, Iowa 52242	2
6	John Hagan, MD Mayo Clinic, W15 200 First Street SW Rochester, MN 55905	1
8	Mark R. Stein, MD Allergy Associates of the Palm Beaches, P.A. 840 US Highway #1, Suite 230-250 North Palm Beach, FL 33408	5
13	Richard L. Wasserman, MD, PhD Allergy/Immunology Research Center of North Texas 7777 Forest Lane, Suite B-332 Dallas, TX 75230	6
14	Joseph A. Church, MD Children's Hospital Los Angeles Division of Clinical Immunology & Allergy 4650 Sunset Boulevard, MS#75 Los Angeles, CA 90027	3
15	Isaac R. Melamed, MD 1st Allergy and Clinical Research Center 7286 South Yosemite Street, Suite 180 Centennial, CO 80112	15
16	Hassan N. Taki, MD Fort Wayne Medical Institute 4424 East State Boulevard Fort Wayne, IN 46815	3
17	Sheldon Spector, MD California Allergy & Asthma Medical Group 11645 Wilshire Boulevard, #1155 Los Angeles, CA 90025	2

Accounting of Subjects

Subject Accounting in ZLB04_009CR

Screened 52				
Withdrew consent 2; Judged to be non-compliant 1	Enrolled and treated 49 (ITT)			
	Discontinued at wash-in/wash-out period 11	Completed wash-in/wash-out period 38 (MITT)		
		Discontinued at efficacy period 10	Completed study (wk 66) 28	
			Major violations 3	Completed per protocol (PPE) 25

The reasons for discontinuation during the wash-in/wash-out period for the 11 subjects were: withdrawal of consent (8 subjects: -----------------------------------(b)(6)--), AE (2 subjects: --------(b)(6)-------), and disqualifying laboratory results (one subject: -(b)(6)-). For subject -(b)(6)-, although the reason for discontinuation was violation of the exclusion criterion "ASAT or ALAT concentration > 2.5 times the ULN", the subject also had an AE classified as leading to discontinuation: chronic hepatitis. However, the condition of chronic hepatitis already existed long before the start of the study.

The reasons for discontinuation during the efficacy period for the 10 subjects were: withdrawal of consent (6 subjects: --------------------------(b)(6)------------------------------), multiple violations of the protocol (one subject: -(b)(6)-), lost to follow-up (one subject: -(b)(6)-), non-compliance (one subject: -(b)(6)-), and termination of the study site (one subject: -(b)(6)-).

A total of 21 of the 49 enrolled subjects (--(b)(6)-------------------------------------- ---) were included in the PK substudy, and 18 of them completed the PK substudy. Two of the 3 subjects who did not complete the PK substudy had the wrong planned starting dose (-----(b)(6)------) and in one subject the AUC of IgG was not measured at Week 28 ± 1 (reported as "PK was not done") (-(b)(6)-). All PK subjects were represented in the ITT and MITT populations.

- The 19 subjects who were treated with IgPro20 and completed Part I of the PK substudy are referred to as "PK subjects". The remaining 30 subjects treated with IgPro20, who were not included in the PK substudy and were evaluated only for efficacy and safety, are referred to as "non-PK subjects".

Comment   There is a dropout rate of ~20% over the wash-in/wash-out period and another ~20% over the efficacy period. Since the efficacy period is longer than the wash-in/wash-out period (12 months vs 12 weeks), the dropout rate has probably stabilized, but the number of withdrawals suggests there could be problems of tolerability. Many of the discontinuations are due to "withdrawal of consent", which eludes clear definition of the actual reason. Thus, the study population might have been enriched for subjects that tolerate the IGSC therapy, and interpretation of the safety data must be made with caution.

Protocol Deviations
Major protocol deviations leading to exclusion of subjects from analysis populations were defined in the SAP. Other protocol deviations included noteworthy departures from the study protocol that did not affect the analysis of the data.

- Major protocol deviations. A total of 11 subjects (22.4%) in the ITT population were excluded from the MITT population because they were not treated during the efficacy period (---------------------(b)(6)--------------------- --).

A total of 13 subjects (34.2%) in the MITT population had major protocol deviations and were therefore excluded from the PPE population (--(b)(6)---). The deviations were "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), and "subject did not obtain IgPro20 infusions on 3 consecutive weeks during efficacy period" (2 subjects).

- o There were 10 subjects (26.3%) excluded from the PPE population because they did not complete the 12-month efficacy period; this usually coincides with an insufficient number of infusions in the efficacy period.
- o Two subjects in the ITT population who were not included in the MITT population also had major protocol deviations (subject -(b)(6)-: violation of inclusion criterion 3 [subjects who have received IgPro10 IV therapy at regular 3- or 4-weekly intervals or IGIV therapy at regular 3- or 4-weekly intervals for at least 3 months prior to receiving IgPro20] and violation of inclusion criterion 4 [at least 3 documented serum IgG C_{trough} values of $\geqslant 5$ g/L during the previous 3 months on IGIV replacement therapy]; subject -(b)(6)-: violation of exclusion criterion 12 [ASAT or ALAT concentration > 2.5 times the ULN]).

- Other protocol deviations. Other noteworthy deviations which did not affect the analysis of the data, included:
  - o Two subjects (-----(b)(6)-----) had 3 consecutive IgPro20 infusions with unknown doses during the wash-in/wash-out period (Appendix 16.2.1.2.1).
  - o Subject -(b)(6)- had one period, and subject -(b)(6)- had 2 periods of 3 consecutive IgPro20 infusions with unknown doses during the efficacy period (Appendix 16.2.1.2.1). Subject 17001 claimed to have administered these infusions at home and did not remember the doses (private communication).

Subject Demographics

Demographic characteristics

Parameter	ITT population (N=49)	MITT population (N=38)
Sex, n (%)		
Female	27 (55.1)	21 (55.3)
Male	22 (44.9)	17 (44.7)
Age (years)		
Mean (SD)	34.4 (20.09)	36.3 (19.52)
Median (Range)	32.0 (5-72)	36.5 (5-72)
Age group, n (%)		
2 - < 12 years	3 (6.1)	3 (7.9)
12 - < 16 years	7 (14.3)	3 (7.9)
16 - < 65 years	33 (67.3)	28 (73.7)
≥ 65 years	6 (12.2)	4 (10.5)
Race, n (%)		
White	46 (93.9)	37 (97.4)
Black or African American	3 (6.1)	1 (2.6)
Ethnic group, n (%)		
Hispanic or Latino	6 (12.2)	2 (5.3)
Weight (kg)		
Mean (SD)	67.3 (21.24)	70.0 (21.34)
Median (Range)	65.7 (21-104)	70.0 (21-104)
N = Total number of subjects in the population; n = Number of subjects; SD = Standard deviation.		

Viral markers were not detected in any subject at screening.

CVID was the primary disease in 36 of the 38 subjects in the MITT population, with 32 of these subjects having had the disease for >2 years at enrollment into the study. The remaining 2 subjects had XLA, and had had the disease for > 2 years at enrollment into the study. The distribution of type and duration of the primary disease in the ITT and PPE populations were similar to those of the MITT population. In the MITT population, the majority (28/38, [73.7%]) had been treated with Privigen. During this time, the mean of the weekly equivalent median doses (with a 3- or 4-week dosing schedule) of IGIV was 144.4 mg/kg bw.

The mean of the individual median serum IgG C_{trough} values during the last 3 months of treatment with IGIV, before participating in the current study, was 10.09 g/L in the MITT population. The mean serum IgG "C_{trough}" with IGIV treatment immediately before the start of IGSC treatment with IgPro20 in the current study was 16.1 g/L in subjects with a 3-weekly dosing schedule and 13.6 g/L in subjects with a 4-weekly dosing schedule. However, these were measured only one week after infusion of the full 3- or 4-weekly IGIV dose. In the ITT and PPE populations, the corresponding statistics were similar to those in the MITT population.

2. STUDY DRUG ADMINISTRATION:
All 38 MITT subjects (100%) received the intended 12 infusions during the wash-in/wash-out period. During the efficacy period, 23 subjects (60.5%) received the intended 54 infusions, and 15 subjects (39.5%) received between 11 and 53 infusions. The number of subjects treated and the number of exposure days with IgPro20 in the efficacy period was equally distributed over all seasons.

The number of injection sites per infusion was 4 or more for 75.9% of infusions during the wash-in/wash-out period and for 80.7% of infusions during the efficacy period. More than 4 injection sites for one infusion indicate that they were used consecutively during one infusion. Ten or more injection sites per infusion were used for 3.9% of infusions during the wash-in/wash-out period and for 0.2% of infusions during the efficacy period.

Comment It is not clear why there was a decrease from 3.9% to 2% for >10 injection sites per infusion from the wash-in/wash-out period to the efficacy period. The concern is that the subjects who needed large volumes and thus numerous injection sites withdrew from study. This should be explained by the applicant.

- The mean IgPro20 dose per week during the wash-in/wash-out period ranged from 176.8 to 182.9 mg/kg body weight (bw). In the efficacy period, starting at Week 13, the mean IgPro20 dose ranged from 179.6 to 224.3 mg/kg bw.
- The mean of the individual median IgPro20 doses during the wash-in/wash-out period was 181.4 mg/kg bw, corresponding to 1.27 times the previous IGIV dose. During the efficacy period, the mean of individual median IgPro20 doses was 213.2 mg/kg bw, corresponding to 1.49 times the IGIV dose. While most subjects in the MITT population had their IgPro20 dose adjusted by Week 16 (29 subjects [76.3%]), the remaining subjects were switched between Week 24 and 44. Thus, the mean adjusted IgPro20 dose during the efficacy period was lower than the intended dose of 1.53 times the IGIV dose.

The first infusion during the wash-in/wash-out period had the longest median duration (3.3 h) because the infusion rate for the first infusion should not exceed 15 mL/h. Increased total body infusion rates during subsequent infusions (up to 50 mL/h using 2 pumps) resulted in shorter median durations of infusion. Thus, the median duration of infusion per week ranged between 1.9 and 3.3 h during the wash-in/wash-out period and between 1.6 and 2.0 h during the efficacy period, and the mean of the individual median overall (total body) infusion rates was 30.9 mL/h during the wash-in/wash-out period and 39.1 mL/h during the efficacy period.

For a total of 5 infusions in 5 subjects (ITT population) the infusion rate was either reduced or the infusions stopped prematurely. The reason for one of the 3 cases in which the infusion was stopped was an AE (injection site reaction of moderate intensity in subject -(b)(6)-), while 2 infusions were stopped due to mechanical problems. A total of 3 subjects had unscheduled dose adjustments exceeding 3 mL that were not PK guided or weight related (subjects -(b)(6)- [infusion 21 - error in the original dose calculation], -(b)(6)- [infusion 43 - subject administered only a lower dose], and -(b)(6)- [infusion 13 - subject administered only half of the dose and used only one pump]).

Comment There were five infusions with infusion rate reduction or premature cessation. Details of these infusions should be submitted.

3. EFFICACY RESULTS:
Definitions of the analysis populations in this study have been defined above (Sections on Statistical Methods and on Subject Disposition). The main efficacy analysis population was the MITT population, and the results are described below for this population.

Primary efficacy endpoint
1. Serious bacterial infections. There were no subjects with an SBI (as defined in the FDA Guidance for Industry and summarized in protocol) in the MITT population. Therefore, the annual rate of SBIs per subject was zero (upper 99% confidence limit: 0.132) and the primary objective of the study was achieved because this rate was less than one.

2. Potential serious bacterial infections. Five AEs in 3 subjects were identified as suspected SBIs and were adjudicated by the review committee according to the criteria pre-specified in the protocol.
- In subject -(b)(6)-, pneumonia was suspected twice, during hospitalization for cellulitis and urinary tract infection, and an AE of bacteremia during hospitalization for cellulitis was evaluated for consistency with the SBI criteria.
- In subject -(b)(6)-, a staphylococcal infection during hospitalization for gastroenteritis was a suspected SBI of bacteremia.
- In subject -(b)(6)-, an AE of "pneumonia" was evaluated for consistency with the SBI criteria. None of the evaluated events was consistent with the pre-specified criteria for an SBI.

Comment The adjudication reports have been presented by the applicant, as well as the CRFs of Subject -------(b)(6)-------. The CRFs for Subject -(b)(6)- should be submitted.

1. Rate of serious bacterial infections in the ITT and PPE populations
There were no subjects in the ITT or the PPE populations who had an SBI. The annual rate of SBIs per subject in these populations was therefore less than one, i.e., zero, with upper 99% confidence limits of 0.104 for the ITT population and 0.176 for the PPE population.

2. Other secondary efficacy endpoints

Summary of results for other secondary efficacy endpoints (MITT population)

Secondary efficacy endpoint	Number (%) of subjects	Number (annual rate) of events/days
Infection episodes (serious [a] and non-serious)	(N=38) 31 (81.6)	(N=12697) 96 (2.76)
Days out of work/school/kindergarten/day care or unable to perform normal activities due to infections	(N=38) 12 (31.6)	(N=12605) 71 (2.06)
Days hospitalized due to infections	(N=38) 1 (2.6)	(N=12605) 7 (0.2)
Days with antibiotics for infection prophylaxis or treatment	(N=38) 27 (71.1)	(N=12697) 1688 (48.5)

N = Total number of subjects in the population or total number of days. [a] There were no serious infections during the study.

a) Number of infection episodes
A total of 31 subjects (81.6%) in the MITT population had a non-serious infection (there were no serious infections) in the efficacy period (12697 subject days) (see above Table). The total rate of infection was 2.76 infections/subject year (95% confidence limits: 2.235; 3.370). The most frequent infection was sinusitis (15 subjects [39.5%] had acute, chronic, or unspecified sinusitis), followed by nasopharyngitis (6 subjects [15.8%]), bronchitis, viral infection, and upper respiratory tract infection (4 subjects [10.5%] each), urinary tract infection and otitis media (3 subjects [7.9%] each), and cystitis, otitis externa, conjunctivitis, gastroenteritis, influenza, and staphylococcal infection (2 subjects [5.3%] each). All other reported infections were each recorded in only one subject. The annual rates of specific infections ranged between 0.03 and 0.40 infections/subject year.

Although one subject (-(b)(6)-) experienced pneumonia, this event was not considered to be consistent with the pre-specified criteria for an SBI (see above).
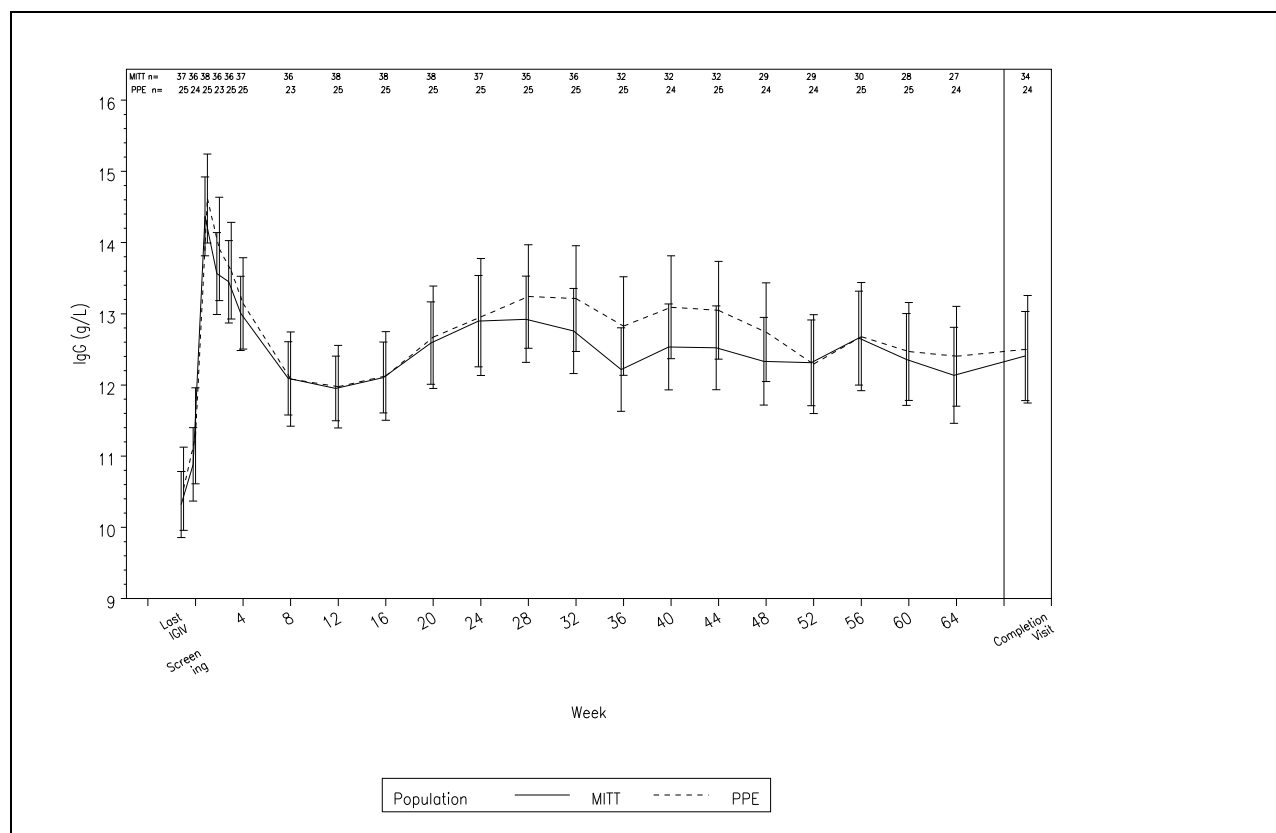
b). Number of days out of work/school/kindergarten/day care or unable to perform normal activities due to infections, Number of days hospitalized due to infections and Number of days with antibiotics for infection prophylaxis or treatment
- In the MITT population, 12 subjects (31.6%) missed work/school/kindergarten/day care or were unable to perform normal activities due to infections on 71 days during the efficacy period, which amounted to an annual rate of 2.06 days/subject year. Because of the low numbers, there was no clear trend over time in the rate of days out of work/school/kindergarten/day care or unable to perform normal activities due to infections. The mean number of days for each subject during the efficacy period was 1.87 (SD: 5.07 days, range: 0-29 days).

- In the MITT population, one subject was hospitalized during the efficacy period over 7 days due to infections (in the time period between Weeks 44 and 47), which amounted to an annual rate of 0.20 days/subject year. The mean number of days each subject was hospitalized due to infections in the efficacy period was 0.18 (SD: 1.14 days, range: 0-7 days).
- Overall, 27 subjects (71.1%) were treated with antibiotics on 1688 days during the efficacy period, amounting to an annual rate of 48.5 days/subject year. Antibiotics were used mainly for treatment of an AE (25 subjects [65.8%]), followed by treatment of a medical/surgical/current condition (9 subjects [23.7%]), and prophylaxis (2 subjects [5.3%]). Subjects used antibiotics for a median duration of 32.0 days (range: 4-370 days).

Trough levels of total IgG serum concentrations
Mean IgG C_{trough} values were generally stable at Weeks 9 to 12 of the wash-in/wash-out period, and after dose adjustment during the efficacy period (see Figure below). For the MITT population, the mean of the individual median IgG C_{trough} values was 12.56 g/L (SD: 2.92 g/L) during the wash-in/wash-out period and 12.53 g/L (SD: 3.21 g/L) during the efficacy period. When compared to the last 3 months of IGIV use. before start of IgPro20 use in the current study, the mean IgG C_{trough} increased by 2.44 g/L (24.2%) during the efficacy period. No subject had an IgG C_{trough} value <5 g/L during IgPro20 treatment in this study.

Mean serum IgG trough levels over time

IgG = Immunoglobulin G; IGIV = Immune Globulin Intravenous (Human); MITT = Modified intention-to-treat; n = Number of subjects with available data; PPE = Per-protocol efficacy. Mean and standard error data are shown. Only the first reported value per visit was taken into account.

<u>Examination of subgroups</u>
Based on the PPE population, subgroup analyses were to be conducted for the primary and secondary efficacy analyses if 3 or more events or days (as applicable) were detected in the overall population. Because no SBIs occurred in this study, subgroup analyses were conducted only for the secondary efficacy analyses.

The subgroups to be analyzed were gender, age, disease type (CVID, XLA), race (Black or African American, White), and median dose of IgPro20 (< 100 mg/kg, 100 to 150 mg/kg, > 150 mg/kg).
Due to all subjects in the PPE population having CVID and a race classification of White, analyses by disease type and race were not possible. Most subjects in the PPE population were in the ⩾ 16 to < 65 years age class. There were only 2 subjects ⩾ 2 to < 12 years of age, 2 subjects ⩾ 12 to < 16, and 3 subjects ⩾ 65 years of age. For median IgPro20 dose, most subjects in the PPE population were in the >150 mg/kg dose group. There was only 1 subject in the <100 mg/kg group, and 2 in the 100-150 mg/kg group. Thus, no age- or dose-related trends could be identified in the efficacy parameters.

Effect of gender
- The incidence of subjects with any infections was higher in males (88.9%) than in females (75.0%), but there were no specific gender-related trends in the incidences of individual types of infection.
- The incidence of subjects with any days missing work/school/kindergarten/day care or unable to perform normal activities due to infections was higher in males (44.4%) than in females (25.0%), but for both genders the total number of days affected was low, with an annual rate of 3.75 and 1.26 days/subject year, respectively. Because of low numbers, there was no clear trend over time in the rate of days out of work/school/kindergarten/day care or unable to perform normal activities due to infections for either gender.
- None of the males, and only one female, was hospitalized due to infection (for 7 days between Weeks 44 and 47, representing a total annual rate of 0.42 days/subject year for females). Thus, no gender-related trend could be discerned for days hospitalized due to infections.
- The incidence of subjects with any days taking antibiotics for infection prophylaxis or treatment was comparable in males (77.8%) and females (75.0%), as was the annual rate of days taking antibiotics (54.5 and 54.6 days/subject year, respectively). For both genders, the most frequent indications for use of an antibiotic were AE and treatment of medical, surgical, and current conditions.
- During the efficacy period, the mean of individual median serum IgG Ctrough values was comparable in males (13.06 g/L) and females (12.53 g/L).

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Trough level ratio in non-PK subjects
- Based on data from the PK subjects, CSLB suggests that the target trough IgG concentration for non-PK subjects on steady-state IGSC can be calculated as 1.29 times their IGIV C_{trough} (see above). The geometric mean calculated target IgG concentration for non-PK subjects was 11.42 g/L. Geometric mean actual IgG concentrations in non-PK subjects (N=19 in the efficacy period) measured in the efficacy period ranged between 10.62 g/L in Week 16 and 12.01 g/L in Week 56. The geometric mean of IgG concentrations obtained at least 4 weeks after dose adjustment in non-PK subjects was 11.85 g/L, and thus attained the geometric mean calculated target IgG concentration of 11.42 g/L.
- Individual TLRs for non-PK subjects were determined for IgG C_{trough} values measured before infusions in the efficacy period and compared to the TLR of 1.29 ± 15%, presumably associated with matching AUCs. The geometric mean of individual TLRs of non-PK subjects in the efficacy period was 1.33.
- Individual TLRs for non-PK subjects were calculated for 163 of 166 infusions at steady-state while being treated with the adjusted IgPro20 dose (to 1.53 times the previous IGIV dose) during the efficacy period.
  - Of these 166 infusions, individual TLRs for 106 infusions (63.9%) were within the desired range of 1.10 to 1.48 (1.29 ± 15%).
  - A further 40 infusions (24.1%) in 7 subjects resulted in TLRs that were higher than the upper threshold of 1.48 (range: 1.49 to 2.01). Thus, IGSC C_{trough} values in 88.0% of weekly IgPro20 infusions were associated with TLR values above the safe lower threshold of 1.10.
  - There were 17 infusions (10.2%) in a total of 5 subjects with TLRs less than the lower threshold of 1.10 (range: 0.89 to 1.09). Yet, these subjects had IgG C_{trough} values >8 g/L, with only 2 exceptions. Even these 2 IgG C_{trough} values <8 g/L were in the "normal" range (5.04 to 14.64 g/L for the 5 year-old subject -(b)(6)- with XLA with an IgG C_{trough} of 5.89 g/L, and 7.00 to 16.00 g/L for the 68 year-old subject -(b)(6)- with an IgG C_{trough} of 7.10 g/L).

  Overall, TLRs in the range of 1.10 to 1.48 were associated with a wide distribution of IgG C_{trough} values (between ~7 and 20 g/L), suggesting that the TLR should not be the only indicator for adequate dosing.
- The 10 non-PK subjects who had previously received IGIV preparations other than Privigen (Section 11.2.3) attained a range of individual TLRs (1.05 to 1.92) similar to the range for non-PK subjects previously treated with Privigen (0.92 to 2.01). This observation suggests that the TLR of 1.29 ± 15% is applicable to the evaluation of the use of other IGIV preparations.

Comment   The concept of TLR is theoretical, and dependent on an intermediary link between hypothetical IGIV and IGSC average daily levels that yield equivalent AUC. It is uncertain that there is a linear relationship between C_{trough} and "average daily level", and so the basis of the TLR concept has to be tested with actual data from the individualized dosing in the PK subjects. The testing in non-PK subjects using an arbitrary range of 1.29+15% derived from PK subjects' data appears to be unfounded. In fact, CSLB has noticed that TLR within the 1.29+15% range could be associated with a wide distribution of trough levels in the non-PK subjects. CSLB should conduct an analysis of this ratio in the PK subjects upon attainment of steady state in the efficacy period with individualized dosing.

Efficacy conclusions
1. Study ZLB04_009CR has met its primary efficacy endpoint by achieving a SBI rate of <1 per subject per year (upper bound of 99% confidence interval).
2. A total of 31 subjects (81.6%) in the MITT population had a non-serious infection during the efficacy period of the study (annual rate of 2.76 infections/subject). The infections observed represented the types of infections that subjects with PI usually acquire as part of their underlying disease, even while undergoing IgG replacement therapy, including sinusitis, nasopharyngitis, bronchitis, viral infection, and upper respiratory tract infection.
3. During the efficacy period, 12 subjects (31.6%) missed work/school/kindergarten/day care or were unable to perform normal activities due to infections on a total of 71 days, which amounted to an annual rate of 2.06 days/subject year. One subject was hospitalized for 7 days due to infections during the efficacy period (annual rate of 0.20 days/subject year). A total of 27 subjects (71.1%) used antibiotics on 1688 days (annual rate of 48.5 days/subject year).
4. No IgG C_{trough} value < 5 g/L was observed during IgPro20 treatment.

4. SAFETY RESULTS:
All safety summaries and analyses are based on the ITT population that included all 49 subjects who had received IgPro20 during any study period (See above).

Extent of Exposure
A total of 2264 weekly infusions of IgPro20 were administered to 49 subjects (ITT population) in this study. A total of 38 subjects (77.6%) received the maximum of 12 infusions during the wash-in/wash-out period, and 23 subjects (46.9%) received the maximum of 54 infusions during the efficacy period. The median treatment interval was 7 days throughout the study. The mean of individual weekly doses was 181.5

mg/kg bw during the wash-in/wash-out period (range of median: 66 to 331 mg/kg bw) and 213.2 mg/kg bw during the efficacy period (range of median: 72 to 379 mg/kg bw).

Number of IgPro20 infusions by treatment phase (ITT population)

	Number of infusions	Number (%) of subjects(N=49)
	Total number of infusions	2264
Wash-in/wash-out period	1	3 (6.1)
	2	2 (4.1)
	3	2 (4.1)
	4	1 (2.0)
	5	1 (2.0)
	7	1 (2.0)
	10	1 (2.0)
	12	38 (77.6)
Efficacy period	11	2 (4.1)
	20	1 (2.0)
	22	1 (2.0)
	23	1 (2.0)
	28	2 (4.1)
	32	1 (2.0)
	44	1 (2.0)
	48	1 (2.0)
	50	1 (2.0)
	51	1 (2.0)
	53	3 (6.1)
.	54	23 (46.9)

N = Total number of subjects in the population.

Adverse Event Summary

Summary of subjects with adverse events (ITT population)

	Number (%) of subjects (N=49)	
AE category	All	Events excluding local reactions
Subjects with AEs	49 (100)	45 (91.8)
Subjects with at least possibly related AEs	49 (100)	25 (51.0)
Subjects with temporally associated AEs (24 h)	48 (98.0)	38 (77.6)
Subjects with temporally associated AEs (48 h)	49 (100)	41 (83.7)
Subjects with temporally associated AEs (72 h)	49 (100)	41 (83.7)
Subjects with at least possibly related, temporally associated AEs (72 h)	49 (100)	23 (46.9)
Subjects with serious AEs	7 (14.3)	7 (14.3)
Subjects with at least possibly related serious AEs	0	0
Subjects who died due to AEs	0	0
Subjects discontinued due to AEs	2 (4.1)	1 (2.0)
Subjects discontinued due to at least possibly related AEs	1 (2.0)	0

AE = Adverse event; N = Total number of subjects in the population.

Summary of adverse event rates (ITT population)

	Number (rate) of AEs (N=2264)	
AE category	All events	Events excluding local reactions
AEs	1749 (0.773)	409 (0.181)
At least possibly related AEs	1436 (0.634)	98 (0.043)
Temporally associated AEs (24 h)	1291 (0.570)	141 (0.062)
Temporally associated AEs (48 h)	1496 (0.661)	177 (0.078)
Temporally associated AEs (72 h)	1566 (0.692)	244 (0.108)
At least possibly related, temporally associated AEs (72 h)	1397 (0.617)	77 (0.034)
Serious AEs	10 (0.004)	10 (0.004)
At least possibly related serious AEs	0	0
AEs, where infusion had to be stopped	1 (< 0.001)	0
At least possibly related AEs, where infusion had to be stopped	1 (< 0.001)	0
AEs leading to discontinuation of the subject	2 (< 0.001)	1 (< 0.001)
At least possibly related AEs leading to subject discontinuation	1 (< 0.001)	0

AE = Adverse event; N = Total number of infusions given in the study.

Analysis of Adverse Events
1. Adverse events by system organ class

Incidence of subjects with all and temporally associated adverse events (experienced by ⩾2 subjects per system organ class) by system organ class and rate per infusion, irrespective of causality (ITT population)

System organ class	All events		Temporally associated (72 h)	
	Number (%) of subjects (N=49)	Number (rate) of events (N=2264)	Number (%) of subjects (N=49)	Number (rate) of events (N=2264)
Local reactions [a]	49 (100)	1340 (0.592)	49 (100)	1322 (0.584)
Any system organ class	**49 (100)**	**1749 (0.773)**	**49 (100)**	**1566 (0.692)**
General disorders and administration site conditions	49 (100)	1367 (0.604)	49 (100)	1335 (0.590)
Infections and infestations	35 (71.4)	121 (0.053)	27 (55.1)	70 (0.031)
Gastrointestinal disorders	22 (44.9)	38 (0.017)	17 (34.7)	24 (0.011)
Nervous system disorders	17 (34.7)	48 (0.021)	15 (30.6)	37 (0.016)
Respiratory, thoracic and mediastinal disorders	15 (30.6)	38 (0.017)	11 (22.4)	21 (0.009)
Musculoskeletal and connective tissue disorders	14 (28.6)	41 (0.018)	12 (24.5)	23 (0.010)
Skin and subcutaneous tissue disorders	12 (24.5)	24 (0.011)	9 (18.4)	16 (0.007)
Injury, poisoning and procedural complications	10 (20.4)	16 (0.007)	7 (14.3)	9 (0.004)
Investigations	9 (18.4)	9 (0.004)	3 (6.1)	3 (0.001)
Psychiatric disorders	7 (14.3)	7 (0.003)	6 (12.2)	6 (0.003)
Eye disorders	6 (12.2)	8 (0.004)	3 (6.1)	5 (0.002)
Ear and labyrinth disorders	4 (8.2)	5 (0.002)	2 (4.1)	2 (< 0.001)
Blood and lymphatic system disorders	3 (6.1)	5 (0.002)	2 (4.1)	3 (0.001)
Surgical and medical procedures	3 (6.1)	3 (0.001)	2 (4.1)	2 (< 0.001)
Vascular disorders	3 (6.1)	3 (0.001)	2 (4.1)	2 (< 0.001)
Metabolism and nutrition disorders	2 (4.1)	3 (0.001)	1 (2.0)	2 (< 0.001)
Renal and urinary disorders	2 (4.1)	3 (0.001)	1 (2.0)	1 (< 0.001)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	2 (4.1)	2 (< 0.001)	1 (2.0)	1 (< 0.001)
Endocrine disorders	2 (4.1)	2 (< 0.001)	0	0

AE = Adverse event; MedDRA = Medical Dictionary for Regulatory Activities; N = Total number of subjects in population or total number of infusions given in the study.

a This category is not a MedDRA system organ class, it groups the AEs injection site reaction, injection site bruising, infusion site scab, injection site cyst, injection site eczema, injection site irritation, injection site nodule, and injection site pain, which are also included in their MedDRA system organ class (general disorders and administration site conditions).

2. Adverse events by preferred term

Incidence of subjects with common adverse events (experienced by ⩾ 4 subjects) by preferred term and rate per infusion, irrespective of causality (ITT population)

Preferred term	All events		Temporally associated (72 h)	
	Number (%) of subjects (N=49)	Number (rate) of events (N=2264)	Number (%) of subjects (N=49)	Number (rate) of events (N=2264)
Any preferred term	**49 (100)**	**1749 (0.773)**	**49 (100)**	**1566 (0.692)**
Injection site reaction	49 (100)	1314 (0.580)	49 (100)	1298 (0.573)
Sinusitis	14 (28.6)	20 (0.009)	7 (14.3)	10 (0.004)
Headache	13 (26.5)	40 (0.018)	12 (24.5)	32 (0.014)
Nasopharyngitis	11 (22.4)	15 (0.007)	8 (16.3)	8 (0.004)
Cough	8 (16.3)	9 (0.004)	5 (10.2)	6 (0.003)
Diarrhoea	7 (14.3)	8 (0.004)	5 (10.2)	6 (0.003)
Bronchitis	6 (12.2)	9 (0.004)	5 (10.2)	6 (0.003)
Fatigue	6 (12.2)	6 (0.003)	4 (8.2)	4 (0.002)
Injection site bruising	5 (10.2)	19 (0.008)	5 (10.2)	18 (0.008)
Back pain	5 (10.2)	11 (0.005)	4 (8.2)	5 (0.002)
Acute sinusitis	5 (10.2)	7 (0.003)	4 (8.2)	5 (0.002)
Nausea	5 (10.2)	5 (0.002)	4 (8.2)	4 (0.002)
Abdominal pain upper	5 (10.2)	5 (0.002)	3 (6.1)	3 (0.001)
Upper respiratory tract infection	5 (10.2)	6 (0.003)	3 (6.1)	3 (0.001)
Rash	5 (10.2)	7 (0.003)	2 (4.1)	3 (0.001)
Pain in extremity	4 (8.2)	7 (0.003)	4 (8.2)	6 (0.003)
Viral infection	4 (8.2)	7 (0.003)	3 (6.1)	3 (0.001)
Migraine	4 (8.2)	5 (0.002)	3 (6.1)	4 (0.002)
Pain	4 (8.2)	5 (0.002)	3 (6.1)	4 (0.002)
Epistaxis	4 (8.2)	6 (0.003)	2 (4.1)	3 (0.001)
Pharyngolaryngeal pain	4 (8.2)	6 (0.003)	2 (4.1)	2 (< 0.001)
Arthralgia	4 (8.2)	5 (0.002)	2 (4.1)	3 (0.001)
Urinary tract infection	4 (8.2)	4 (0.002)	1 (2.0)	1 (< 0.001)

N = Total number of subjects in population or total number of infusions given in the study.

Almost all AEs (99%) were mild or moderate in intensity. Injection site reactions were mostly mild (93.4%) in intensity, 6.3% were moderate and only 0.3% were severe. The only AEs of severe intensity were headache (4 subjects [8.2%], rate of 0.002), injection site reaction (3 subjects [6.1%], rate of 0.002), and chest pain (2 subjects [4.1%], rate of < 0.001), and small intestinal obstruction, toothache, chronic hepatitis, gastroenteritis, post procedural infection, musculoskeletal stiffness, papillary thyroid cancer, migraine, and asthma (one subject [2.0%] each).

3. Causally related, and causally related and temporally associated adverse events
Since this is an uncontrolled study, it is difficult to exclude bias when adverse event reporting is considered in terms of causality. Causality as provided in the study report cannot be easily verified, and so no reliance can be placed on its accuracy. The analysis by preferred terms in the study report is given here:

Incidence of subjects with common causally related adverse events (experienced by ≥ 2 subjects) by preferred term and rate per infusion (ITT population)

Preferred term	Causally related		Causally and temporally associated (72 h)	
	Number (%) of subjects (N=49)	Number (rate) of events (N=2264)	Number (%) of subjects (N=49)	Number (rate) of events (N=2264)
Any preferred term	**49 (100)**	**1436 (0.634)**	**49 (100)**	**1397 (0.617)**
Injection site reaction	49 (100)	1313 (0.580)	49 (100)	1297 (0.573)
Headache	12 (24.5)	36 (0.016)	11 (22.4)	31 (0.014)
Injection site bruising	5 (10.2)	19 (0.008)	5 (10.2)	18 (0.008)
Vomiting	3 (6.1)	3 (0.001)	3 (6.1)	3 (0.001)
Pain	3 (6.1)	4 (0.002)	2 (4.1)	3 (0.001)
Fatigue	3 (6.1)	3 (0.001)	2 (4.1)	2 (< 0.001)
Contusion	2 (4.1)	3 (0.001)	2 (4.1)	3 (0.001)
Back pain	2 (4.1)	3 (0.001)	2 (4.1)	2 (< 0.001)
Diarrhoea	2 (4.1)	2 (< 0.001)	2 (4.1)	2 (< 0.001)
Abdominal pain upper	2 (4.1)	2 (< 0.001)	2 (4.1)	2 (< 0.001)
Nausea	2 (4.1)	2 (< 0.001)	2 (4.1)	2 (< 0.001)
Migraine	2 (4.1)	3 (0.001)	1 (2.0)	2 (< 0.001)
Rash	2 (4.1)	2 (< 0.001)	1 (2.0)	1 (< 0.001)
Arthralgia	2 (4.1)	2 (< 0.001)	1 (2.0)	1 (< 0.001)

N = Total number of subjects in population or total number of infusions given in the study.

4. Subgroup analyses of adverse events
Subgroup analyses of AEs by gender, age class, IgPro20 dose, and IgPro20 infusion rate are summarized in the following sections. Subgroup analyses of AEs by disease type and race are not summarized in the following sections because low numbers of subjects in some individual subgroups (e.g., only 3 out of 49 subjects had XLA and only 3 subjects were Black or African American) meant that meaningful conclusions could not be drawn.

- a) Adverse events by gender

Subgroup analysis by gender for incidence of subjects with common adverse events (experienced by ≥ 5 subjects) by preferred term and rate per infusion (ITT population)

Preferred term	Number (%) of subjects		Number (rate) of events	
	Male (N=22)	Female (N=27)	Male (N=995)	Female (N=1269)
Any preferred term	**22 (100)**	**27 (100)**	**742 (0.746)**	**1007 (0.794)**
Any preferred term (excluding local reactions)	**18 (81.8)**	**27 (100)**	**187 (0.188)**	**222 (0.175)**
Injection site reaction	22 (100)	27 (100)	550 (0.553)	764 (0.602)
Sinusitis	7 (31.8)	7 (25.9)	12 (0.012)	8 (0.006)
Headache	4 (18.2)	9 (33.3)	27 (0.027)	13 (0.010)
Nasopharyngitis	3 (13.6)	8 (29.6)	4 (0.004)	11 (0.009)
Cough	6 (27.3)	2 (7.4)	7 (0.007)	2 (0.002)
Diarrhoea	1 (4.5)	6 (22.2)	1 (0.001)	7 (0.006)
Bronchitis	4 (18.2)	2 (7.4)	4 (0.004)	5 (0.004)
Fatigue	3 (13.6)	3 (11.1)	3 (0.003)	3 (0.002)
Injection site bruising	1 (4.5)	4 (14.8)	2 (0.002)	17 (0.013)
Back pain	2 (9.1)	3 (11.1)	3 (0.003)	8 (0.006)
Acute sinusitis	3 (13.6)	2 (7.4)	4 (0.004)	3 (0.002)
Nausea	1 (4.5)	4 (14.8)	1 (0.001)	4 (0.003)
Abdominal pain upper	2 (9.1)	3 (11.1)	2 (0.002)	3 (0.002)
Upper respiratory tract infection	4 (18.2)	1 (3.7)	5 (0.005)	1 (< 0.001)
Rash	2 (9.1)	3 (11.1)	3 (0.003)	4 (0.003)

ITT = Intention-to-treat; N = Total number of subjects or events in population. Preferred terms are ordered by decreasing frequency in the entire ITT population.

Most AEs were mild or moderate in intensity, with no specific pattern among males and females for the few severe AEs. In men, 5 AEs were severe in intensity (one each of injection site reaction, chronic hepatitis, musculoskeletal stiffness, headache, and migraine). In females, 14 AEs were severe (3 AEs each of headache and injection site reaction, 2 AEs of chest pain, and 1 AE each of small intestinal obstruction, toothache, gastroenteritis, post procedural infection, papillary thyroid cancer, and asthma).

- b) Adverse events by age

Most subjects (33 out of 49) were in the age class of 16 to < 65 years, with only low numbers of subjects in the other age classes that were too small to allow firm conclusions.

Subgroup analysis by age class for incidence of subjects with common adverse events (experienced by ≥ 5 subjects) by preferred term (ITT population)

	Number (%) of subjects			
Preferred term	2 to < 12 years (N=3)	12 to < 16 years (N=7)	16 to < 65 years (N=33)	≥ 65 years (N=6)
Any preferred term	**3 (100)**	**7 (100)**	**33 (100)**	**6 (100)**
Any preferred term (excluding local reactions)	**3 (100)**	**6 (85.7)**	**30 (90.9)**	**6 (100)**
Injection site reaction	3 (100)	7 (100)	33 (100)	6 (100)
Sinusitis	0	2 (28.6)	11 (33.3)	1 (16.7)
Headache	0	2 (28.6)	8 (24.2)	3 (50.0)
Nasopharyngitis	1 (33.3)	1 (14.3)	8 (24.2)	1 (16.7)
Cough	1 (33.3)	1 (14.3)	5 (15.2)	1 (16.7)
Diarrhoea	1 (33.3)	1 (14.3)	4 (12.1)	1 (16.7)
Bronchitis	1 (33.3)	0	4 (12.1)	1 (16.7)
Fatigue	0	1 (14.3)	5 (15.2)	0
Injection site bruising	0	1 (14.3)	3 (9.1)	1 (16.7)
Back pain	0	1 (14.3)	4 (12.1)	0
Acute sinusitis	1 (33.3)	0	3 (9.1)	1 (16.7)
Nausea	0	1 (14.3)	3 (9.1)	1 (16.7)
Abdominal pain upper	0	1 (14.3)	3 (9.1)	1 (16.7)
Upper respiratory tract infection	1 (33.3)	1 (14.3)	3 (9.1)	0
Rash	0	1 (14.3)	4 (12.1)	0

ITT = Intention-to-treat; N = Total number of subjects in population.
Preferred terms are ordered by decreasing frequency in the entire ITT population.

Most AEs were mild or moderate in intensity; none of the 3 subjects 2 to < 12 years of age experienced an AE of severe intensity, the few AEs of severe intensity occurred with no specific trend among the other age groups. In subjects 12 to < 16 years of age, 2 AEs were severe in intensity (injection site reaction and chronic hepatitis). In subjects 16 to < 65 years of age, 13 AEs were severe in intensity (3 AEs of injection site reaction, 2 AEs of chest pain, and one AE each of small intestinal obstruction, toothache, gastroenteritis, musculoskeletal stiffness, papillary thyroid cancer, headache, migraine, and asthma). In subjects ≥ 65 years of age, 4 AEs were severe in intensity (3 AEs of headache, and one AE of post procedural infection).

Subgroup analysis by age class for incidence of common adverse events (experienced by ≥ 5 subjects) by preferred term and rate per infusion (ITT population)

	Number (rate) of events			
Preferred term	2 to < 12 years (N=194)	12 to < 16 years (N=188)	16 to < 65 years (N=1637)	≥ 65 years (N=245)
Any preferred term	**173 (0.892)**	**168 (0.894)**	**1229 (0.751)**	**179 (0.731)**
Any preferred term (excluding local reactions)	**22 (0.113)**	**74 (0.394)**	**260 (0.159)**	**53 (0.216)**
Injection site reaction	150 (0.773)	90 (0.479)	955 (0.583)	119 (0.486)
Sinusitis	0	2 (0.011)	17 (0.010)	1 (0.004)
Headache	0	6 (0.032)	29 (0.018)	5 (0.020)
Nasopharyngitis	2 (0.010)	1 (0.005)	11 (0.007)	1 (0.004)
Cough	1 (0.005)	1 (0.005)	6 (0.004)	1 (0.004)
Diarrhoea	1 (0.005)	1 (0.005)	5 (0.003)	1 (0.004)
Bronchitis	1 (0.005)	0	7 (0.004)	1 (0.004)
Fatigue	0	1 (0.005)	5 (0.003)	0
Injection site bruising	0	2 (0.011)	10 (0.006)	7 (0.029)
Back pain	0	2 (0.011)	9 (0.005)	0
Acute sinusitis	2 (0.010)	0	4 (0.002)	1 (0.004)
Nausea	0	1 (0.005)	3 (0.002)	1 (0.004)
Abdominal pain upper	0	1 (0.005)	3 (0.002)	1 (0.004)
Upper respiratory tract infection	1 (0.005)	2 (0.011)	3 (0.002)	0
Rash	0	2 (0.011)	5 (0.003)	0

ITT = Intention-to-treat; N = Total number of subjects in population.
Preferred terms are ordered by decreasing frequency of number of subjects with this event in the entire ITT population.

- c) Adverse events by IgPro20 dose

Subgroup analysis by median IgPro20 dose for incidence of subjects with common adverse events (experienced by ≥ 5 subjects) by preferred term (ITT population)

Preferred term	Number (%) of subjects		
	< 100 mg/kg (N=2)	100 - 150 mg/kg (N=10)	> 150 mg/kg (N=37)
Any preferred term	**2 (100)**	**10 (100)**	**37 (100)**
Any preferred term (excluding local reactions)	**2 (100)**	**10 (100)**	**33 (89.2)**
Injection site reaction	2 (100)	10 (100)	37 (100)
Sinusitis	0	2 (20.0)	12 (32.4)
Headache	0	3 (30.0)	10 (27.0)
Nasopharyngitis	1 (50.0)	1 (10.0)	9 (24.3)
Cough	0	3 (30.0)	5 (13.5)
Diarrhoea	0	2 (20.0)	5 (13.5)
Bronchitis	1 (50.0)	2 (20.0)	3 (8.1)
Fatigue	0	1 (10.0)	5 (13.5)
Injection site bruising	0	1 (10.0)	4 (10.8)
Back pain	0	1 (10.0)	4 (10.8)
Acute sinusitis	0	1 (10.0)	4 (10.8)
Nausea	0	1 (10.0)	4 (10.8)
Abdominal pain upper	0	2 (20.0)	3 (8.1)
Upper respiratory tract infection	0	2 (20.0)	3 (8.1)
Rash	0	0	5 (13.5)

ITT = Intention-to-treat; N = Total number of subjects in population.
Preferred terms are ordered by decreasing frequency in the entire ITT population.

Of the 7 subjects who experienced SAEs, 6 subjects had a median IgPro20 dose > 150 mg/kg and one subject had a median dose between 100 and 150 mg/kg. Most AEs were mild or moderate in intensity; the few AEs of severe intensity occurred without a specific pattern between the dose groups. In the 100 to 150 mg/kg group, 7 AEs were severe in intensity (3 AEs of headache, 2 AEs of injection site reaction, and one AE each of chest pain and musculoskeletal stiffness). In the > 150 mg/kg group, 11 AEs were severe in intensity (2 AEs of injection site reaction, and one AE each of small intestinal obstruction, toothache, chest pain, chronic hepatitis, gastroenteritis, post procedural infection, papillary thyroid cancer, headache, and asthma). One severe AE of migraine occurred after an unknown dose of IgPro20.

Subgroup analysis by IgPro20 dose for incidence of common adverse events (experienced by ⩾ 5 subjects) by preferred term and rate per infusion (ITT population)

Preferred term	Number (rate) of events		
	< 100 mg/kg (N=118)	100 - 150 mg/kg (N=423)	> 150 mg/kg (N=1703)
Any preferred term	**79 (0.669)**	**341 (0.806)**	**1302 (0.765)**
Any preferred term (excluding local reactions)	**8 (0.068)**	**100 (0.236)**	**281 (0.165)**
Injection site reaction	70 (0.593)	235 (0.556)	1003 (0.589)
Sinusitis	0	4 (0.009)	16 (0.009)
Headache	1 (0.008)	12 (0.028)	27 (0.016)
Nasopharyngitis	1 (0.008)	2 (0.005)	12 (0.007)
Cough	0	3 (0.007)	4 (0.002)
Diarrhoea	0	2 (0.005)	6 (0.004)
Bronchitis	1 (0.008)	2 (0.005)	5 (0.003)
Fatigue	0	2 (0.005)	4 (0.002)
Injection site bruising	0	6 (0.014)	12 (0.007)
Back pain	0	4 (0.009)	6 (0.004)
Acute sinusitis	0	2 (0.005)	4 (0.002)
Nausea	0	1 (0.002)	4 (0.002)
Abdominal pain upper	0	3 (0.007)	2 (0.001)
Upper respiratory tract infection	0	2 (0.005)	4 (0.002)
Rash	0	1 (0.002)	6 (0.004)

ITT = Intention-to-treat; N = Total number of subjects in population.
Preferred terms are ordered by decreasing frequency of number of subjects with this event in the entire ITT population.

- d) Adverse events by infusion rate

Subgroup analysis by infusion rate for incidence of subjects with common adverse events (experienced by ⩾ 5 subjects) by preferred term and rate per infusion (ITT population)

Preferred term	Number (%) of subjects		Number (rate) of events		
	15-25 mL/h [a] (N=21)	> 25 mL/h [a] (N=28)	< 15 mL/h (N=1)	15-25 mL/h (N=913)	> 25 mL/h (N=1331)
Any preferred term	**21 (100)**	**28 (100)**	**1 (1.000)**	**810 (0.887)**	**913 (0.686)**
Any preferred term (excluding local reactions)	**19 (90.5)**	**26 (92.9)**	**0**	**222 (0.243)**	**168 (0.126)**
Injection site reaction	21 (100)	28 (100)	1 (1.000)	572 (0.627)	736 (0.553)
Sinusitis	4 (19.0)	10 (35.7)	0	6 (0.007)	14 (0.011)
Headache	7 (33.3)	6 (21.4)	0	26 (0.028)	14 (0.011)
Nasopharyngitis	5 (23.8)	6 (21.4)	0	6 (0.007)	9 (0.007)
Cough	4 (19.0)	4 (14.3)	0	4 (0.004)	3 (0.002)
Diarrhoea	3 (14.3)	4 (14.3)	0	3 (0.003)	5 (0.004)
Bronchitis	5 (23.8)	1 (3.6)	0	9 (0.010)	0
Fatigue	3 (14.3)	3 (10.7)	0	3 (0.003)	3 (0.002)
Injection site bruising	3 (14.3)	2 (7.1)	0	11 (0.012)	7 (0.005)
Back pain	4 (19.0)	1 (3.6)	0	9 (0.010)	1 (< 0.001)
Acute sinusitis	2 (9.5)	3 (10.7)	0	2 (0.002)	4 (0.003)
Nausea	2 (9.5)	3 (10.7)	0	2 (0.002)	3 (0.002)
Abdominal pain upper	2 (9.5)	3 (10.7)	0	2 (0.002)	3 (0.002)
Upper respiratory tract infection	3 (14.3)	2 (7.1)	0	3 (0.003)	3 (0.002)
Rash	2 (9.5)	3 (10.7)	0	3 (0.003)	4 (0.003)

ITT = Intention-to-treat; N = Total number of subjects in population. [a] Median infusion rate.
Preferred terms are ordered by decreasing frequency in the entire ITT population.

- Of all 7 subjects who experienced SAEs, 5 subjects had median infusion rates of > 25 mL/h and 2 subjects had median infusion rates between 15 and 25 mL/h.
- The median duration of headaches was comparable for the 26 headaches in the 15 to 25 mL/h group (0.6 days) and the 13 headaches in the > 25 mL/h group with available duration (1.0 days). The median time from start of infusion to onset of headache was 15.1 h in the 15 to 25 mL/h group and 19.9 h in the > 25 mL/h group.
- The duration of injection site reactions (median of 1.4 days in the 15 to 25 mL/h group, and 1.5 days in the > 25 mL/h group) and the time from start of infusion to onset of the injection site reaction (median of 3.7 h for infusion rates between 15 and 25 mL/h and 3.8 h for infusion rates > 25 mL/h) were also unaffected by the infusion rate.
- There was no specific pattern between the different infusion rate groups for the few AEs of severe intensity. In the 15 to 25 mL/h group, 9 AEs were severe in intensity (4 AEs of injection site reaction and one AE each of small intestinal obstruction, toothache, chronic hepatitis, papillary thyroid cancer, and headache) (Table 14.3.2.30 and Table 14.3.2.30a). In the > 25 mL/h group, 9 AEs were severe in intensity (3 AEs of headache, 2 AEs of chest pain, and one AE each of gastroenteritis, post procedural infection, musculoskeletal stiffness, and asthma). One severe AE of migraine occurred after an infusion with unknown infusion rate.

- e) Conclusions on subgroup analyses of adverse events
Taken together, the subgroup analyses of AEs excluding local reactions revealed no clinically relevant trends according to gender, age class, IgPro20 dose group, or infusion rate in the overall incidences of subjects with AEs, or specific types of AEs. There were no trends in the overall AE rates per infusion apart from a higher AE rate at lower infusion rates of 15 to 25 mL/h, which was not accounted for by a difference in the rate of injection site reactions.

5. Deaths, Other Serious Adverse Events, and Other Significant Adverse Events
- Deaths. There were no deaths in this study.
- Other serious adverse events. Seven subjects experienced a total of 10 treatment-emergent SAEs (subject -(b)(6)-: gastroenteritis; subject -(b)(6)-: small intestinal obstruction, and chest pain; subject -(b)(6)-: tooth abscess, cellulitis, and urinary tract infection; subject -(b)(6)-: hemoglobin decreased (history of iron deficiency anemia); subject -(b)(6)-: chest pain; subject -(b)(6)-: musculoskeletal stiffness; and subject -(b)(6)-: papillary thyroid cancer), none of which were considered by the investigator to be related to study drug. Narratives of these events are described in the study report, Section 12.3.2.2.
- Other significant adverse events. Other significant AEs defined for this study included AEs leading to study discontinuation, AEs related to hemolysis, and SBIs. In addition, an AE of chronic hepatitis in subject -(b)(6)-, who had several pre-defined changes in blood chemistry parameters, was considered a significant AE leading to discontinuation, but actually was a violation for exclusion criteria. A narrative is provided in study report Section 12.3.2.3.

Two other subjects discontinued from the study due to AEs (subject -(b)(6)-: injection site reaction; subject -(b)(6)-: myositis [post-treatment AE]). Including the post-treatment AE of myositis, 2 of the 3

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AEs classified as leading to discontinuation were considered related to the study drug (injection site reaction and myositis). Two of the AEs were ongoing at final assessment (myositis and chronic hepatitis). Brief narratives for the significant AEs that were reasons for discontinuation are provided Section 12.3.2.3.1 of the study report.

There were no SBIs in this study.

There were no AEs of hemolysis. Five subjects (-----------------------(b)(6)-------------------------) had a decrease in hemoglobin of ⩾2 g/dL during the study. One subject (-(b)(6)-) had 3 non-serious AEs of anemia and was hospitalized due to decreased hemoglobin attributed to the subject's underlying disease of iron-deficient anemia. The 5 subjects with a decrease in hemoglobin ⩾2 g/dL did not have positive Direct Coombs' test during the study, and subject -(b)(6)- had 2 positive Direct Coombs' tests before and after Infusion 1, but subsequent Direct Coombs' tests were negative. No case fit the protocol's definition of hemolytic anemia that required positive Coombs' test and decrease in hemoglobin of >2 g/dL.

6. Local tolerability - injection site reactions

All subjects experienced an AE of injection site reaction during the study. The rate of injection site reaction per infusion was not specifically affected by the IgPro20 infusion rate, with a rate of 0.627 in the 15 to 25 mL/h group and 0.553 in the > 25 mL/h group. The time from start of infusion to onset of injection site reaction (median of 3.7 h in the 15 to 25 mL/h group and 3.8 h in the > 25 mL/h group) and the duration of injection site reactions (median of 1.4 days in the 15 to 25 mL/h group and 1.5 days in the > 25 mL/h group) were also not specifically affected by the infusion rate.

> Erythema. The proportion of subjects with erythema after infusion varied between 32.4% (12 subjects) and 60.7% (17 subjects), with no clear trend over time. Most of the erythema was assessed by the investigator to be "very slight" in intensity, with "well-defined" erythema being reported in 3.4% to 21.4% of all subjects (one to 6 subjects) (Table 14.3.3.3). None of the erythema was categorized as "moderate to severe" or "severe to slight eschar formations".
>
> Edema/induration. The proportion of subjects with induration after infusion varied over time between 57.6% and 82.1% (19 and 23 subjects). Despite some variability, there was no clear trend over time. The median surface area of edemas/indurations assessed by the investigator at scheduled visits ranged from 1080 to 2513 mm2. In the first 3 weeks of the study the median surface area of edemas/induration was approximately 1100 mm2, after which the median surface area increased along with the increasing maximum volume per injection site from 15 to 25 mL and remained relatively consistent at ~2000 mm2.
>
> Local heat, itching, and local pain. According to the investigators' assessments at each visit, 4.8% to 27.3% of all subjects (2 to 12 subjects) experienced local heat after infusion, 0% to 21.2% (0 to 7 subjects) had itching, and 2.6% to 26.7% (one to 8 subjects) had local pain.

The subjects assessed the intensity of these injection site reactions; most were assessed as "very slight" or "slight" in intensity; none was "severe".

> Incidence of subjects with injection site reactions per week. According to the investigators' assessments at each visit (15 to 45 min after the end of the infusion), the proportion of subjects with injection site reactions was approximately 75% after each infusion, ranging between 64.9% and 87.0%. However, according to assessments by the subjects themselves (24 h after the end of each infusion), the proportion of subjects with injection site reactions was ~ 40% every week, ranging between 26.7% and 54.3%. No clear trend over time could be discerned for the proportion of subjects who experienced an injection site reaction.

Comment The study report actually discusses differences between Investigator and subject evaluations. The difference between the investigators' and subjects' assessments of the proportions of subjects with injection site reactions was approximately 35%. As the investigators assessed the injection site reactions at 15 to 45 min after the end of infusion, and the subjects made their assessment at 24 h after the end of infusion, this difference suggests that approximately 50% of the injection site reactions observed by the investigators were resolved within 24 h. However, the difference also reflects that different endpoints were analyzed: while the investigator evaluated specific symptoms (i.e., erythema, edema/induration, itching, local pain, and local heat) shortly after the end of infusion, the subjects judged their overall perception after 24 h.

> Most of the injection site reactions (94.8%) were reported by the subjects to have been "very slight" or "slight" in intensity. In Week 1, after the first infusion, 5 subjects (10.2%) had injection site reactions that were "very slight" in intensity, 18 subjects (36.7%) had injection site reactions that were "slight" in intensity, and 2 subjects (4.1%) had injection site reactions that were "moderate" in intensity. The proportion of "very slight" and "slight" injection site reactions was equal in Week 2 (11 subjects [23.9%] each) and starting from Week 3, there were more "very slight" than "slight" injection site reactions, with only a few exceptions. The number of "moderate" injection site reactions varied only slightly over time.

Among the 2264 <u>infusions</u> administered in this study, only one was associated with an injection site reaction that was "severe" in intensity (subject -(b)(6)-; according to the subjects' assessments 24 h after infusion). However, 3 injection site reactions of severe intensity were <u>reported as AEs</u>. One severe injection site reaction in subject -(b)(6)- led to discontinuation of the study. The AE was reported one day after Infusion 3, there had been no signs of an injection site reaction 15 to 45 min after this infusion according to the investigator's assessment, and no subject assessment was available. This subject also had a severe AE injection site reaction after Infusion 2. For subject -(b)(6)-, a severe injection site reaction was reported on the day of Infusion 4; the investigator's assessment shortly after the end of infusion was "well-defined" erythema and an edema with a surface area of 5027 mm2, the subject's assessment of local reactions on the next day was "none".

Comment   It appears contradictory that only one infusion was associated with an injection site reaction of severe intensity (subject -(b)(6)-), and yet three injection site reaction of severe intensity were reported as adverse events (subject -(b)(6)- with two infusions and subject -(b)(6)-).

<u>Clinical Laboratory Evaluation</u>
There were no safety issues regarding clinical laboratory parameters (hematology, clinical chemistry and urinalysis) over the course of the study. Abnormal clinically significant values were observed in a small number of subjects, and all such values either returned to normal or to not clinically significant levels, except for 3 subjects, of whom 2 discontinued from the study due to an AE (myositis) and violation of exclusion criterion (ASAT or ALAT concentration > 2.5 times the ULN).

There was no indication that administration of IgPro20 was associated with hemolysis, and no subject had a positive Direct Coombs' test in combination with a decrease in hemoglobin of > 2g/dL. A total of 3 subjects had positive Direct Coombs' tests at screening, and 7 subjects converted to positive Direct Coombs' tests during the study, none of which was accompanied by a decrease > 2g/dL in hemoglobin.

No abnormal values for HAV, HBV, HCV, HIV-1, HIV-2, or parvovirus B19 were observed at any time during the study.

<u>Other Observations related to Safety</u>
Vital signs, physical findings, and concomitant medication use did not reveal any additional safety issues in this study.

The most frequent reasons for administration of concomitant medication were treatment of medical, surgical, or current condition, followed by treatment of AEs and prophylaxis. The most common drug used as concomitant medication was ibuprofen (25 subjects [51.0%]), followed by salbutamol (22 subjects [44.9%]), and paracetamol (21 subjects [42.9%]). Subject 17001 had been using salbutamol and seretide as treatment for PI since 2003.

A total of 11 subjects in the ITT population used the prohibited medications methylprednisolone, prednisone, prednisolone, or immunoglobulin G human. The reasons for administration of methylprednisolone, prednisone, and prednisolone were treatment of AEs in 6 subjects and treatment of medical, surgical, or current condition in 4 subjects. Two subjects (4.1%) used human immunoglobulin G: one subject (-(b)(6)-) received IGIV 7 days before start of IgPro20 treatment, and this was recorded erroneously as concomitant medication; another subject (-(b)(6)-) received 2 IGIV infusions when the subject was technically still in the study but had already decided to discontinue from the study.

Summary of most frequent concomitant medication (used by ≥ 5 subjects) by decreasing frequency (ITT population)

ATC (level 2)	Number (%) of subjects (N=49)
Analgesics	36 (73.5)
Nasal preparations	34 (69.4)
Antibacterials for systemic use	32 (65.3)
Antiinflammatory and antirheumatic products	32 (65.3)
Drugs for obstructive airway diseases	32 (65.3)
Antihistamines for systemic use	31 (63.3)
Drugs for acid related disorders	20 (40.8)
Cough and cold preparations	19 (38.8)
Corticosteroids for systemic use	15 (30.6)
Psychoanaleptics	14 (28.6)
Ophthalmologicals	13 (26.5)
Sex hormones and modulators of the genital system	13 (26.5)
Antithrombotic agents	11 (22.4)
Mineral supplements	11 (22.4)
Antipruritics, including antihistamines, anesthetics, etc.	9 (18.4)
Psycholeptics	9 (18.4)
Antianemic preparations	8 (16.3)
Antibiotics and chemotherapeutics for dermatological use	8 (16.3)
Antidiarrheals, intestinal antiinflammatory / antiinfective agents	8 (16.3)
Thyroid therapy	8 (16.3)
Antimycotics for systemic use	7 (14.3)
Lipid modifying agents	7 (14.3)
Muscle relaxants	7 (14.3)
Antiepileptics	6 (12.2)
Corticosteroids, dermatological preparations	6 (12.2)
Vitamins	6 (12.2)
Anti-acne preparations	5 (10.2)
Antivirals for systemic use	5 (10.2)
Blood substitutes and perfusion solutions	5 (10.2)
Vaccines	5 (10.2)

ATC = Anatomical therapeutic classification; N = Total number of subjects in the population.

Safety Conclusions

- The safety of IgPro20 was evaluated in all 49 subjects enrolled and treated in this study with weekly SC infusions with IgPro20. A total of 2264 IgPro20 infusions were administered.
- Overall, there were no safety concerns with the use of IgPro20 in subjects with PI. 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 was temporally associated with an infusion (i.e., occurred during or within 72 h of infusion). Excluding local reactions, 45 subjects (91.8%) had AEs, of which 25 subjects (51.0%) had at least possibly related AEs, 41 subjects (83.7%) had AEs that were temporally associated with an infusion, and 23 subjects (46.9%) had at least possibly related AEs that were also temporally associated with an infusion.
- Based on the 2264 infusions administered in this study, the overall AE rate per infusion was 0.773 (0.181 excluding local reactions), the rate of AEs that were temporally associated with study drug (within 72 h of infusion) was 0.692 (0.108 excluding local reactions), and the rate of AEs that were at least possibly related to study drug was 0.634 (0.043 excluding local reactions). The most common AE was injection site reaction, experienced at least once by all subjects and occurred at a rate of 0.580 per infusion.
- There were no trends in the overall AE rates per infusion apart from a higher AE rate at lower infusion rates of 15 to 25 mL/h, which was not accounted for by a difference in the rate of injection site reactions.
- No deaths occurred in this study. Ten SAEs (gastroenteritis, small intestinal obstruction, tooth abscess, cellulitis, urinary tract infection, chest pain [2 events], hemoglobin decreased, musculoskeletal stiffness, and papillary thyroid cancer) and one pre-treatment SAE (abdominal pain) occurred in 7 subjects (14.3%). None of the SAEs were assessed by the investigator to be related to the study drug.
- An AE was the reason for discontinuation in 2 subjects, and one subject who was discontinued due to violation of the exclusion criterion "ALAT or ASAT > 2.5 times the ULN" also had an AE that was classified as leading to discontinuation. Two of the 3 AEs classified as leading to discontinuation were related to study drug (injection site reaction and myositis [post-treatment AE]).
- There were no special safety issues on clinical laboratory parameters over the course of the study, and administration of IgPro20 did not meet pre-specified criteria for hemolysis(positive Direct

Coombs' test in combination with a decrease in hemoglobin of > 2g/dL). Regarding virus safety, no cases of infections due to HIV 1, HIV 2, HCV, HBV, HAV, or parvovirus B19 were observed.

Conclusions

1. In a prospective, open-label, multicenter, single-arm, Phase 3 study (ZLB04_009CR) to evaluate the efficacy, tolerability, safety, and PK of IgPro20 in subjects with PI, CSLB has provided substantial evidence of effectiveness of weekly SC administration of IgPro20 with the absence of serious bacterial infections during the study's efficacy period.
2. Because of the small number of pediatric subjects enrolled in ZLB04_009CR, CSLB should provide data from other studies on pediatric patients aged ≥ 2 to 16 using IgPro20 to fulfill PREA requirements.
3. The subcutaneous use of IgPro20 is associated with local injection site reactions, and it is possible that this has accounted for the larger than usual rate of dropouts in ZLB04_009CR, but systemic safety appears to be acceptable. However, there is a high withdrawal rate in this study. Many of the discontinuations are due to "withdrawal of consent", which eludes clear definition of the actual reason. Thus, the study population might have been enriched for subjects that tolerate the IGSC therapy, and interpretation of the safety data must be made with caution.
4. The use trough level ratio (TLR) for monitoring IGSC treatment by studying non-PK subjects in ZLB04_009CR has not been established from the data presented.
5. Overall, no "show-stoppers" are identified at this point, but information requests for clarification of issues in this BLA submission should be conveyed to CSLB.

Recommendation

Convey comments to CSLB on this BLA submission as follows:

Please address the following comments pertaining to Study ZLB04_009CR:
1. Itching and local pain are subjective evaluations. Please clarify why they fall under "assessment by the investigator", and how the scoring by Investigator at the study visit could accurately reflect what happens at home infusions.
2. Since the wash-in/wash-out period involved IGSC administration, efficacy analysis during this period should not be excluded. Please conduct additional analyses of the efficacy endpoints including the entire period of IgPro20 use.
3. Repeated filling of infusion pumps to deliver high doses of IGSC allows for more than 4 injection sites to be used consecutively at the same infusion. Please clarify whether this is considered protocol violation or not. The tolerability of such infusions should be compared with that of other infusions which followed the up-to-4-site rule.
4. It is not clear why there was a decrease from 3.9% to 0.2% for the use of ≥ 10 injection sites per infusion from the wash-in/wash-out period to the efficacy period. Please clarify whether the use of large infusion volumes and hence numerous injection sites predisposed to withdrew from study.
5. There were five infusions with infusion rate reduction or premature cessation. Please submit details of these infusions.
6. Please submit the CRFs for Subject -(b)(6)-.
7. The concept of TLR is theoretical, and dependent on an intermediary link between hypothetical IGIV and IGSC average daily levels that yield equivalent AUC. It is uncertain that there is a linear relationship between C_{trough} and "average daily level", and so the basis of the TLR concept has to be tested with actual data from the individualized dosing in the PK subjects. The basis of testing TLR applicability in non-PK subjects using an arbitrary range of $1.29 \pm 15\%$ derived from PK subjects' data appears to be unsound. In fact, you have noticed that TLR within the $1.29 \pm 15\%$ range could be associated with a wide distribution of trough levels in the non-PK subjects. Please conduct an analysis of this ratio in the PK subjects upon attainment of steady state in the efficacy period with individualized dosing.

8. Please conduct an analysis of ratio of the number of infusions with temporally associated adverse events (within 72 hours of the end of infusion) to the total number of infusions, including point estimate and 95% confidence intervals.
9. It appears contradictory that only one infusion was associated with an injection site reaction of severe intensity (subject -(b)(6)-), and yet three injection site reaction of severe intensity were reported as adverse events (subject -(b)(6)- with two infusions and subject -(b)(6)-). Please clarify.
10. Please submit a PREA deferral request for data submission on the children and adolescent age groups ($\geq$2 to 12, and $\geq$12 to 16 years of age respectively).