CLINICAL PHARMACOLOGY BLA REVIEW

Division of Hematology
Office of Blood Review & Research

Supplement BLA 125350/316
Product: IgPro20, Immune Globulin Subcutaneous (Human), 20% liquid
Sponsor: CSL Behring
Indication: For the treatment of primary immunodeficiencies (PID)
Date Received: November 30, 2012
Reviewer: Carl-Michael Staschen, M.D., Ph.D.
RPM: Pratibha Rana
Through: Iftekhar Mahmood Ph.D. and Basil Golding, M.D.

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EXECUTIVE SUMMARY

Primary immunodeficiencies (PIDs) include a variety of disorders in which there is an intrinsic defect in the immune system that renders patients more susceptible to infections. These infections may be fatal if left untreated. The PID disorders constitute a spectrum of more than 100 defects in the body's immune system. Immune globulin (IG) replacement therapy is the standard treatment for patients with PID. Weekly subcutaneous (IGSC) replacement therapy in subjects with PID is an effective and convenient alternative to monthly intravenous (IGIV) treatment. Furthermore, as an alternative to weekly SC infusions, every two weeks (biweekly) SC treatment is a desirable option that would allow further flexibility for patients.

IgPro10 (Privigen®) is an immune globulin intravenous (human), 10% liquid indicated for treatment of PID (for patients 3 years and older) and chronic immune thrombocytopenic purpura. It was approved by the FDA on July 26, 2007.

IgPro20 (Hizentra®), immune globulin subcutaneous (human), 20% liquid, is a ready-to-use, sterile 20% (0.2 g/mL) protein liquid preparation of polyvalent human immunoglobulin G (IgG) and is indicated for patients diagnosed with PID. The drug was approved by FDA (2010) for weekly subcutaneous administration in adults and pediatric patients 2 years and older. Before receiving treatment with Hizentra, patients need to have received Immune Globulin Intravenous (Human) (IGIV) treatment at regular intervals for at least 3 months.

CSL Behring is using population PK based modeling and simulation techniques to seek approval for its human immune globulin product IgPro20 to

1. switch from weekly SC to biweekly SC dosing and
2. switch from IgPro10 IV to weekly or biweekly SC dosing with IgPro20 (with an IV:SC dose adjustment coefficients (DAC) of 1:1.53).

Report Title:

Pharmacometric analysis of human normal immune globulin intravenous (IgPro10, Privigen®) and subcutaneous (IgPro20, Hizentra®) infusions in subjects with primary immunodeficiency to model and simulate biweekly dosing of IgPro20 (Report No.: 2012-2)

Objectives

The goals of this pharmacometric analysis are to:

- Characterize population pharmacokinetic (PK) of human normal immune globulin, administered as IgPro10 intravenous (IV) and IgPro20 subcutaneous (SC) infusions in subjects with primary immunodeficiency (PID).
- Quantify relative bioavailability of IgPro20 SC infusions.

- Simulate and compare the steady-state concentration time profiles and exposure parameters following every two weeks (biweekly) and weekly SC infusions with Hizentra®.
- Simulate switching from weekly SC to biweekly SC dosing and switching from IV IgG (IgPro10) to biweekly IgPro20 SC dosing (dose adjustment coefficient for IV:SC = 1.53).

Methods

Modeling Human Immune Globulin serum concentration data consisting of > 3800 samples from 151 pediatric and adult subjects with PID (four Phase 3 studies: ZLB03_002, ZLB04_009, ZLB05_006, and ZLB06_001) were analyzed by nonlinear mixed effects modeling using the software package –(b)(4)---. The base model was a two-compartment PK model. Bodyweight effects on clearance of human immune globulin (CL) and volume of distribution of the central compartment (V2) were included. All study subjects in the analysis data set were on IgG treatment prior to and during all study periods.

Simulation Three hundred trials with 25 subjects each were simulated to compare steady state exposure parameters such AUC, C_{max} and C_{min} following IV, biweekly or weekly SC infusions.

Results

Modeling The base model described the IgG concentration data well. The PK model with the fixed endogenous IgG level IgG_{ENDO} = 4.0 g/L was considered to be the final population PK model. The allometric exponents on bodyweight for CL and V2 were estimated to be 0.80 and 0.48, respectively. The population PK parameters CL, V2, volume of distribution of the peripheral compartment (V3), and absorption rate constant (KA) were estimated to be 0.142 L/day, 3.94 L, 4.18 L, and 0.439 per day, respectively. Bioavailability after SC dosing was estimated to be on the order of 0.67.

External validation Model-predicted PK profiles (i.e. increases in IgG over predose/ trough IgG level) following biweekly SC dosing were consistent with those reported in the literature (Gustavson et al., Clin Exp Immunol. 2008).

Simulation Steady-state results for biweekly vs weekly SC infusions are shown in Table 1 and indicate that weekly and biweekly SC infusions produce similar AUC values, and C_{min} and C_{max} stay within ± 10%. Steady-state exposure parameters for IV-dosing compared to weekly and biweekly SC dosing are similar. IgG trough levels are ~ 25% to 35% higher with weekly SC dosing than with IV dosing. IgG trough levels are ~ 15% to 30% higher with biweekly SC dosing than with IV dosing. Based on the estimated bioavailability after IgPro20 SC-dosing, a DAC of 1.53 is appropriate to switch from Privigen IV to both weekly and biweekly Hizentra SC dosing.

Table 1: Predicted ratios* [Median (5th, 95th percentiles)] of AUC, Cmax and Cmin and changes in IgG trough levels upon switching between IgG dosing regimens

IgG Dosing Regimen Switch		AUC	C_{max}	C_{min}	Predicted Change in Trough†
From:	To:				
IGIV	Weekly Hizentra‡	1.04(0.96-1.12)	0.73 (0.65-0.81)	1.23 (1.13-1.33)	25% increase
IGIV	Biweekly Hizentra§	1.03 (0.96-1.11)	0.76 (0.69-0.85)	1.16 (1.07-1.25)	15% increase
Weekly Hizentra	Biweekly Hizentra§	1.00 (0.98-1.03)	1.06 (1.02-1.09)	0.95 (0.92-0.98)	5% decrease

* Ratios are based on comparison of second regimen vs. first regimen.
† Approximate change in trough based on predicted median C_{min} ratio.
‡ Weekly dose based on dose adjustment coefficient of 1.53 when switching from IGIV.
§ Biweekly dose = 2x weekly dose.
AUC, area under the curve, calculated as $AUC_{0\text{-}28days}$ for the IGIV to Hizentra switches and as $AUC_{0\text{-}14days}$ for the weekly to biweekly Hizentra switch; C_{max}, maximum IgG concentration; C_{min}, minimum IgG concentration during a 28-day period (for the IGIV to Hizentra switches) or a 14-day period (for the weekly to biweekly Hizentra switch).

Conclusions:

- For the same total 2-week dose, biweekly and weekly SC infusions yield equivalent exposure with overlapping steady-state concentration time profiles, similar IgG AUC values, and IgG peak and trough levels that stay within ± 10%.
- With a dose adjustment coefficient of 1.53, biweekly SC infusions yield similar or slightly higher IgG AUC values, 20% to 25% lower IgG peak levels, and 15% to 30% higher IgG trough levels than those with IV infusions.
- Modeling estimated individual clearance values as a function of age (3 to 72 years) does not substantiate special dose recommendations. The results support body weight-adjusted dosing.

OVERALL COMMENTS

- In general, the results of the population PK analysis, subsequent simulations and conclusions to support a change to a biweekly dosing regimen of IgPro20 (Hizentra®) are acceptable from a Clinical Pharmacology perspective.
- The demonstrated relationship between estimated individual drug clearances and age suggest that dosing per kg weight is appropriate for all age groups (3 years and older). It appears therefore, that no further dose adjustments for pediatric and geriatric patients are necessary.
- Noteworthy is the allometrically estimated bodyweight exponent on central volume of distribution (0.48). This estimate differs significantly from the theoretically derived exponent of 1 which is often fixed to 1 during a population PK analysis.

CLINICAL PHARMACOLOGY DOSE JUSTIFICATION

IgPro20 (Hizentra®) is an Immune Globulin Subcutaneous (Human) (IGSC), 20% liquid indicated for the treatment of primary immunodeficiency (PI) in adults and pediatric patients 2 years of age and older. Before receiving treatment with Hizentra, patients need to have received Immune Globulin Intravenous (Human) (IGIV) treatment at regular intervals for at least 3 months. The currently approved SC dosing regimen is once per week. The new proposed dosing regimen is twice per week (biweekly) and is based on a population pharmacokinetic analysis with subsequent simulations of steady-state concentrations and exposure parameters.

Population PK analysis:

Human Immune Globulin serum concentration data from four Phase 3 studies, including pediatric and adult subjects with PID, were analyzed by nonlinear mixed effects modeling. The population PK model described the IgG concentration data well. External model validation was consistent with those reported in the literature.

Simulations

Adjusted for dose, biweekly and weekly SC infusions yield equivalent exposure with overlapping steady-state concentration time profiles and similar IgG AUC values. IgG peak and trough levels stayed within ± 10%. With a dose adjustment coefficient of 1.53, biweekly SC infusions yielded similar or slightly higher IgG AUC values, 20% to 25% lower IgG peak levels, and 15% to 30% higher IgG trough levels than those with IV infusions.

In short, based on population PK analysis and simulations, it appears that (1) changing from a weekly to a biweekly SC-infusion and (2) changing from IV-infusions to biweekly SC-infusions using an IV:SC dose adjustment coefficient of 1.53 will be efficacious in pediatric and adult PID patients.

CLINICAL PHARMACOLOGY LABELING COMMENTS

Dosage and Administration:

- *Adjust the dose of Hizentra over time based on clinical response and serum IgG trough levels. Measure the serum IgG trough level during IGIV therapy prior to switching to Hizentra and again after 2 to 3 months of treatment with Hizentra. When switching from IGIV to weekly Hizentra, trough levels will be~25% higher than the last trough level during prior IGIV therapy. When switching from IGIV to biweekly Hizentra, trough levels will be ~15% higher. When switching from weekly to biweekly Hizentra, trough levels will be ~5% lower.*

Comment: the %-values of 25%, 15%, and 5% should be complemented with the absolute value.

xxx = to be calculated by sponsor.

Replace: 25% with xxx mg/dL (25%), 15% with xxx mg/dL (15%), and 5% with xxx mg/dL (5%)

Section 2.2 Dosage, Dose Adjustment,

Weekly dosing: When switching from IGIV to weekly Hizentra dosing, the target serum IgG trough level is projected to be approximately 25% higher than the last trough level during prior IGIV therapy (see Pharmacokinetics [12.3]).

Biweekly dosing: When switching from IGIV to biweekly Hizentra dosing, the target serum trough level is projected to be approximately 15% higher than the last IGIV trough level. When switching from weekly to biweekly Hizentra dosing, the target trough is projected to be approximately 5% lower than the last weekly trough level (see Pharmacokinetics [12.3]).

Comment: the %-values of 25%, 15%, and 5% should be complemented with the absolute value.

xxx = to be calculated by sponsor.

Replace: 25% with xxx mg/dL (25%), 15% with xxx mg/dL (15%), and 5% with xxx mg/dL (5%)

Section 12.3 Pharmacokinetics

To be added:

Pediatric Pharmacokinetics

The population PK base modeling and simulation results indicate that body weight-adjusted biweekly dosing accounted for age-related (> 3 yr) differences in clearance of Hizentra®, thereby maintaining systemic IgG exposure (AUC values) in the therapeutic range.

Comment to the applicant:

Please provide pediatric PK information for the weekly dosing of Hizentra®

CLINICAL PHARMACOLOGY RECOMMENDATION

The results of the population PK analysis, simulations, and conclusions are acceptable and the sponsor's proposed biweekly regimen for IgPro20 (Hizentra®) given to pediatric and adult patients older than 3 years appears to be adequate and sufficient to achieve and sustain therapeutic concentrations. The individual dose should be bodyweight adjusted on a per kg basis.

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INTRODUCTION / BACKGROUND

Primary Immunodeficiencies (PID) include a variety of disorders in which there is an intrinsic defect in the immune system that renders patients more susceptible to infections. These infections may be fatal if left untreated. The PID disorders constitute a spectrum of more than 100 defects in the body's immune system. Common PIDs include disorders of humoral immunity (affecting B-cell differentiation or antibody production), T-cell defects and combined B- and T-cell defects, phagocytic disorders, and complement deficiencies. Immunoglobulin replacement therapy is the standard treatment for patients with PID. Subcutaneous administered immune globulin products (IGSC) are an effective alternative to Immune Globulin Intravenous (Human) products (IGIV) for patients who prefer self-administration at home, who have poor venous access, or who cannot tolerate systemic adverse events associated with intravenous (IV) infusions of IgG.

Weekly IGSC replacement therapy in patients with PID is an effective and convenient alternative to monthly (i.e. every 3 or 4weeks) IGIV treatment; it has a low risk of systemic adverse reactions and leads to higher trough levels than equivalent IGIV therapy. Furthermore, as an alternative to weekly SC infusions, every two weeks (biweekly) SC treatment is a desirable option that would allow further flexibility for patients. A biweekly dosing SC regimen with a comparable drug product has been previously evaluated in a pharmacokinetic/safety study conducted in Europe by Gustafson et al. (Clin Exp Immunol., 2008), in which 12 adult subjects with PID were switched from weekly IGSC to biweekly IGSC for 24 weeks. This study has demonstrated that biweekly IGSC administration represents a safe, effective and convenient alternative therapy regimen for subjects with PID.

IgPro10 (Privigen®) is an immune globulin intravenous (human), 10% liquid indicated for treatment of PID (for adults and pediatric patients 3 years and older) and chronic immune thrombocytopenic purpura. It was approved by FDA in 2007. IgPro10 is administered as IV-infusion, every 3 or 4 weeks, using an individualized dose regimen of 200 - 800 mg IgG per kg of bodyweight.

IgPro20 (Hizentra®), a subcutaneous (SC) formulation of human immune globulin, received FDA approval on March 4th 2010 for the treatment of PID. This indication was approved based upon the pivotal clinical study (ZLB04_009CR). This study provided safety and efficacy data for weekly SC administration of IgPro20. This study also included a pharmacokinetic (PK) substudy that assessed the PK of IgPro20 in subjects with PID and determined the dose adjustment coefficient for subjects switching from previous therapy with Immune Globulin Intravenous (Human) (IGIV). The drug was approved for weekly subcutaneous administration in adults and pediatric patients 2 years and older. Before receiving treatment with Hizentra, patients need to be on IGIV treatment at regular intervals for at least 3 months. The current minimum weekly SC

dose of IgPro20 is 200 mg/kg and individually adjusted based on trough IgG levels and clinical response.

CSL Behring is using population PK based modeling and simulation techniques to seek regulatory approval for its human immune globulin product IgPro20 (Hizentra®) to

1. switch from IgPro20 weekly SC to IgPro20 biweekly SC dosing and
2. switch from IgPro10 IV-infusion to IgPro20 weekly or biweekly SC dosing (with an IV:SC dose adjustment coefficient (DAC) of 1:1.53).

Report Title:

Pharmacometric analysis of human normal immune globulin intravenous (IgPro10, Privigen®) and subcutaneous (IgPro20, Hizentra®) infusions in subjects with primary immunodeficiency to model and simulate biweekly dosing of IgPro20 (**Report No.**: 2012-2)

Objectives:

The objectives of this pharmacometric analysis were to:

- Characterize population PK of human normal immune globulin, administered as IgPro10 IV and IgPro20 SC infusions in subjects with PID.
- Quantify the bioavailability of IgPro20 SC infusions.
- Simulate and compare steady-state concentration time profile and exposure parameters such as AUC, maximum ("peak") IgG concentration (C_{max}), and minimum ("trough") IgG concentration (C_{min}) ratios following biweekly and weekly SC infusions with IgPro20.
- Simulate switching from weekly SC to biweekly SC dosing and switching from IgPro10 IV to weekly or biweekly SC dosing with IgPro20 (with an IV:SC DAC of 1:1.53).

Studies Included in the Analysis:

This population PK analysis includes IgG concentration data from four phase III studies (ZLB03_002, ZLB04_009, ZLB05_006, ZLB06_001) in PID subjects.

- ZLB03_002 was the pivotal US PID trial for IgPro10, an IV formulation, for which ZLB05_006 was the extension study.
- Study ZLB04_009 was the IgPro20 US pivotal SC study, in which ZLB03_002 and ZLB05_006 subjects with PK profiles as well as new subjects could participate.
- Study ZLB06_001 was the European IgPro20 pivotal SC study.

A summary of these four studies including trial design, patient's demographic, dosing regimens and PK blood sample times is provided in Table 1.

Table 1: Summary of studies included in the population PK analysis.

Study (Phase)	Design (Sites)	Population	Treatment Frequency and Duration	Serum Concentration Measurement Time points
ZLB03_002 (III)	Multicenter, open-label, single-arm, prospective (United States, France, UK, Germany, Belgium, Switzerland)	Male or female subjects > 3 - 70 years of age with primary humoral immunodeficiency (i.e. common variable immunodeficiency [CVID] or X-linked agammaglobulinemia [XLA]) who: a) previously received regular and stable intravenous immune globulin (IVIG) therapy for 3- or 4- week intervals for at least 6 months prior to infusion with IgPro10 and b): who had at least one documented IgG trough serum level of ≥ 4 g/L, during 6-month period.	IgPro10 (Privigen) was to be administered as intravenous (IV) infusion, every 3 or 4 weeks for a period of 12 months, using an individualized dose regimen of 200 - 800 mg IgG per kg of body weight.	*3-weekly dose regimen* All subjects: 30 - 10 min pre-infusion trough sample at week 0, 3, 6, 9, 12, 15, 21, 24, 27, 30, 33, 36, 39, 42, 45, and 48. Subjects with PK profile: trough samples and the following sampling at week 18: 3 - 20 min, 24 ± 2 hours, 3, 7, 10, 14 ± 1 and 21 ± 2 days post-infusion (prior to next infusion). *4-weekly dose regimen* All subjects: 30-10 min pre-infusion trough sample at week 0, 4, 8, 12, 20, 24, 28, 32, 36, 40, 44, and 48. Subjects with PK profile: trough samples and the following sampling at week 16: 3 - 20 min, 24 ± 2 hours, 3, 7, 10, 14 ± 1, 21 ± 1 and 28 ± 2 days post-infusion (prior to next infusion).
ZLB06_001 (III)	Multicenter, open-label, single arm, prospective study (Europe)	Male or female subjects > 2 - ≤ 65 years of age (UK: ≥ 16 years) with primary humoral immunodeficiency (i.e. common variable immunedeficiency [CVID], X-linked agammaglobulinaemia [XLA], or autosomal recessive agammaglobulinemia [ARAG]). Subjects had to have previously received Human Normal Immune globulin for Intravenous Administration (IGIV) at regular 3- or 4-week intervals or Human Normal Immune globulin for Subcutaneous Administration (IGSC) at regular weekly intervals for at least 6 months at a stable dose, and had to have at least 3 documented total IgG Ctrough values of ≥ 5 g/L during 3 months on IgG therapy immediately prior to receiving IgPro20 (2 Ctrough values could go back up to 6 months in case of stable dosing for at least 3 months prior to the assessment).	IgPro20 (Hizentra) was administered as SC infusion at weekly intervals by the subject/parent/guardian (after a training period at the study site) for a total of approximately 10 months. The initial weekly IgPro20 dose was 100% of the subjects' previous weekly equivalent IGIV or IGSC dose. The study consisted of a 12-week wash-in/wash-out period followed by a 28-week efficacy period. In a PK substudy, PK assessments were performed during 1 treatment interval at steady-state (Week 28± 1).	Screening samples that took place 1 - 4 weeks prior to the first IgPro20 infusion; trough samples at week 1, 2, 3, 4, 8, 12, 13, 14, 15, 16, 17, 20, 24, 28, 32, 36, and 40. Subjects with PK profile: trough samples and the following sampling at week 28 ± 1: pre-infusion sample (30 - 0 min), prior to end of infusion sample (10 min ± 5), post-infusion samples: 2 hours ± 1, 1 day ± 8 hours, 2 days ± 8 hours, 3 days ± 8 hours, 4 days ± 8 hours, 7 days ± 8 hours.

ZLB05_006 (III)	Multicenter, open-label, single-arm, prospective extension study (United States)	Male or female subjects with primary humoral immunodeficiency (i.e. common variable immune-deficiency [CVID] or X-linked agammaglobulinemia [XLA]) who: a) participated in the Phase III pivotal clinical study with intravenous (IV) IgPro10 (study ZLB03_002CR) at 3 or 4 week intervals for 12 months ('old' subjects), or b) were ≥ 6 years of age, on other stable intravenous immune globulin (IVIG) therapy (200 - 800 mg IgG per kg of body weight at 3 or 4 week intervals for at least 6 months, and were interested in participating in study ZLB04_009CR, the Phase III clinical study with subcutaneous (SC) IgPro20 ('new' subjects).	IgPro10 (Privigen) was to be administered as an IV infusion, every 3 or 4 weeks for the duration of the study (until the market launch of IgPro10 or, for those subjects who elected to do so, until they were switched to study ZLB04_009CR for SC administration), using an individualized dose regimen. For 'old' subjects, the amount of IgPro10 administered was to be consistent with previous IgPro10 treatment in study ZLB03_002CR. In these 'old' subjects, the dose of IgPro10 was to be taken from the last 3 infusions during study ZLB03_002CR and the dose regimen was to remain unchanged throughout the study period unless there was a medically justified need to change it. Infusions were to start at a low rate. If the infusion was well tolerated within 30 minutes, the rate could be increased at the discretion of the Investigator. For 'old' subjects, if the subject tolerated the maximum infusion rate during study ZLB03_002CR (8 mg/kg/min) well, the infusion rate in this extension study could be increased up to a maximum of 12 mg/kg/min at the discretion of the Investigator. For 'new' subjects, the dose regimen was to be consistent with previous IVIG therapy (200 - 800 mg/kg), and the dose of IgPro10 was to be the same as given during the last 3 infusions of previous IVIG treatment. Dose regimen and infusion rate adjustments were similar to what was done for 'old' subjects, except that the maximum infusion rate for 'new' subjects was 4.0 mg/kg/min.	*'Old subjects'* with PK profile: 60 min -1 min pre-infusion, and 3 min – 20 min, 24 ± 2 hours, 3, 7, 10, 14 ± 1 days, 21 ± 1 days post- infusion, and 28 ± 1 days [subject on 4-week dosage only] post infusion. *'New subjects – 3-weekly dose regimen* with PK profile: 60 min – 1 min pre-infusion, and 3 min – 20 min, 24 ± 2 hours, 3, 7, 10, 14 ± 1 and 21 ± 1 day post-infusion. *'New subjects' – 4-weekly dose regimen* with PK profile: 60 min – 1 min pre-infusion, and 3 min – 20 min, 24 ± 2 hours, 3, 7, 10, 14 ± 1, 21 ± 1, and 28 ± 1 day post-infusion.
ZLB04_009 (III)	Multicenter, open-label, single arm, prospective study (United States)	Male or female subjects from > 6 - 75 years of age with primary humoral immunodeficiency (i.e. common variable immune-deficiency or X-linked agammaglobulinemia). Subjects had to have previously received IGIV with Privigen therapy at regular 3- or 4-week intervals for at least 3 months prior to starting treatment with IgPro20 in the current study, and to have had at least 3 documented serum Ctrough measurements of ≥ 5 g/L during the previous 3 months on IGIV replacement therapy.	IgPro20 (Hizentra) was administered as an SC infusion at weekly intervals for approximately 15 months. During the initial 12-week wash-in/wash-out period, subjects received an individualized dose regimen of 1.30 times their weekly equivalent IGIV dose received in preceding studies with Privigen. In the 12-month efficacy period, the dose was adjusted on the basis of steady-state Ctrough values at Weeks 9 - 12, aiming to attain the individual C_{min} levels in serum that had been determined during previous IGIV treatment with Privigen. The (historical) reference therapy was IGIV treatment with Privigen in preceding studies. Data obtained during earlier treatment with Privigen were used for calculating the initial IgPro20 dose during the wash-in/wash-out period as well as the C_{min} for IgPro20, and for evaluating the non-inferiority of systemic IgG exposure during treatment with the adjusted dose of IgPro20 in Part II of the PK substudy. Privigen is a marketed liquid IGIV at a concentration of 10%. In the preceding studies, Privigen was administered IV every 3 or 4 weeks using an individualized dose regimen of 200 - 800 mg IgG/kg body weight.	Screening samples 1 - 4 week prior to 1st SC infusion with IgPro20. *PK substudy Part 1* Weekly SC infusion with 1.3 times IGIV dose: trough sample at week 1, 2, 3, 4, 8, 9, 10, 11, and 12, 16, 20, 24, and 28. *PK substudy Part 2* Subjects with PK profile: at week 28 pre-infusion sample (30 - 10 min), prior to end of infusion sample (10 min ± 5), Post-infusion samples: 2 hours ± 1, 1 day ± 8 hours, 2 days ± 8 hours, 3 days ± 8 hours, 4 days ± 8 hours, 7 days ± 8 hours.

Analytical Methods

All serum total IgG levels were measured by central laboratories for respective studies. In all cases, a validated immunoturbidimetric assay was utilized.

Pharmacometric Approach

The population PK methods were based on guidelines of population PK analyses [FDA Population PK Guidance for Industry]. The Final Analysis Data Set was analyzed with the

------(b)(4)---------- for non-linear mixed effects models running under ----------
---------(b)(4)---------- on a grid of ----(b)(4)------- servers.

Base Model

Structural Components

The base model was comprised of a standard two-compartment PK model. Absorption of exogenous IgG from the depot site of SC infusions into the central compartment was modeled as a 1st-order process with absorption rate constant (KA, 1/day). IV administration of IgG was modeled as IV infusion directly into the central compartment. The actual rates (g/L/day) at which SC and IV doses (g/kg) were administered into the depot and central compartments, respectively were both derived from recorded total dose amount and infusion duration data.

Bioavailability F1 (SC) was estimated, whereas relative bioavailability of IV (F2) was fixed to 1. CL (L/day) and V2 (L) V3 (L) and Q (L/day) were systemic drug clearance, volumes of distribution of the peripheral compartments and inter-compartment clearance, respectively.

A total of 57 (38%) and 66 (44%) of study subjects were below 16 and 18 years of age, respectively. Bodyweight was included as a covariate effect on the key PK parameters CL and V2 in all models.

Of the study subjects in the analysis data set, approximately 75% had common variable immunodeficiency (CVID). With the exception of one subject with autosomal recessive agammaglobulinemia (ARAG), the remainder had X-linked agammaglobulinemia (XLA). Mean IgG_{ENDO} levels in subjects with XLA (< 2 g/L) tend to be lower than those in subjects with CVID (4 g/L). All study subjects in the analysis data set were on IgG treatment prior and during all study periods and measured IgG concentrations were a combination of endogenous and exogenous IgG. For this reason the IgG_{ENDO} was fixed to 4.0 g/L in the base model. Total IgG concentration in serum was calculated as the sum of the fixed IgG_{ENDO} level and the predicted IgG concentration in the central compartment.

Statistical Components

A variety of functional forms for residual variability were evaluated including proportional, additive and combined error models. Inter-individual variability was modeled for all PK parameters as follows:

$$\theta_i = \theta_T \cdot e^{(\eta_i)}$$

Where θ_i is the PK parameter of interest value for the *ith* participant, θ_T is the population mean parameter estimate, and η_i (or ETA) is a random inter-individual effect with mean 0 and variance ω^2. The ω^2 values are the diagonal elements of the inter-individual variance-covariance matrix (Ω) of the η_is.

Covariate Models and Reference Models

Body weight effect on the key parameters CL and V2 was included in all models. In addition, information on the demographic factors age and gender was available in the analysis dataset and both factors were evaluated as covariates on the two key parameters CL and V2 (univariate covariate testing).

IgG_{ENDO} was set to 4.0 g/L in base and covariate models and the final population PK model with IgG_{ENDO} = 4.0 g/L was called reference model 4.0 **(**RM4.0). As average IgG_{ENDO} level in subjects of the Gustafson study [Clin Exp Immunol., 2008] was ~ 1.54 g/L, the final population PK model with IgG_{ENDO} = 1.5 g/L was used for predicting the Gustafson PK data (i.e. external validation). This model is referred to throughout the remainder of this report as reference model 1.5 (RM1.5), and was also used for sensitivity analyses and simulation purposes.

Data and Modeling Results

Initial Analysis Data Set

The numbers of subjects with PK profiles and IgG trough data for the four clinical studies included in this analysis were as follows:

1. ZLB04_009, IgPro20 US pivotal trial: a total of 49 subjects with IgG trough concentrations, of which 18 subjects additionally had a PK profile.
2. ZLB03_002, IgPro10 US pivotal trial: a total of 80 subjects with IgG trough concentrations, of which 25 subjects additionally had a PK profile.
3. ZLB05_006, IgPro10 US extension study: a total of 55 subjects with IgG trough concentrations, of which 13 subjects additionally had a PK profile.
4. ZLB06_001, European IgPro20 pivotal study: a total 46 subjects with IgG trough concentrations, of which 24 subjects additionally had a PK profile.

Because 53 subjects participated in more than one study (ZLB03_002, ZLB05_006, and/or ZLB04_009), the number of individuals in the data set (151) is less than the sum of the individual study sample sizes (230). Thus, the initial population PK data set consisted of 3871 serum IgG concentrations from 230 study subjects, for which demography is reported in Table 2.

Table 2: Baseline demographic variables of study subjects with IgG concentration data by clinical study in the population PK data set.

Study	N	Age, year Median (min-max)	Pediatric Subjects (< 16 years) N (%)	Pediatric Subjects (< 18 years) N (%)	Body Weight, kg Median (min-max)	Sex (% Males)	Diagnosis %CVID/%XLA/%ARAG
ZLB04_009	49	32.0 (5 - 72)	10 (20.4)	17 (34.7)	66.0 (21.0 104)	44.9	91.8/8.2/0.0
ZLB03_002	80	25.0 (3 - 69)	31 (38.8)	34 (42.5)	66.5 (14.0 - 130.0)	57.5	73.8/26.2/0.0
ZLB05_006	55	23.0 (4 - 81)	21 (38.2)	24 (43.6)	62.0 (18.0 135)	47.3	80.0/20.0/0.0
ZLB06_001	46	18.0 (3 - 60)	22 (47.8)	24 (52.2)	53.5 (13.0 - 96.0)	67.4	60.9/36.9/2.2

Note: There were 5 additional ZLB06_001 subjects in the data set with dose/kg and body weight data but no IgG concentration records (i.e. there were a total of 51 ZLB6_001 subjects in the data set). There were 8 unique geriatric subjects with age > 65 years. There were 57 and 66 unique pediatric subjects with age < 16 years and age < 18 years, respectively.

Final Analysis Data Set

The initial analysis data set consisted of 3871 serum IgG concentrations. A statistical criterion was applied to WRES from the fit of the initial base model and 16 IgG concentrations with |WRES| > 4 were flagged as "unreliable" IgG concentrations and excluded. Thus a total of 34 IgG concentrations (< 1%) were excluded in all subsequent models and the final analysis data set had 3837 IgG concentrations (> 99% of initial population PK data set) from all 151 study subjects (100% of initial population PK data set).

Base Model

A two-compartment PK model with 1st-order rate of absorption (KA, 1/day) of exogenous IgG into the central compartment following SC administration into a depot compartment and IV administration into the central compartment described the IgG concentration data well. Body weight effects on the key parameters CL and V2 were included in all covariate models, as removal of these effects resulted in an increase (worsening) in the objective function of 208 points.

Covariate Models and Reference Models

In addition to weight effects on CL and V2, age and gender were each evaluated as covariates on the key parameters CL and V2. None of the four tested univariate effects resulted in a likelihood ratio test that was significant at the pre-defined p = 0.005 level. Similarly, when an additional weight effect on V3 was tested, it also failed to achieve the required level of statistical significance. Thus the final population PK model (i.e. reference model RM4.0) had two covariate effects: body weight on CL and V2.

Final population parameter estimates for RM4.0 are presented in Table 3. To illustrate how model parameters calibrate to account for a lower IgG_{ENDO} than 4.0 g/L, parameter estimates for the reference population PK model with IgG = 1.5 g/L (RM1.5) are also provided in this table (e.g. CL, V2 and V3 are estimated to be lower with RM1.5 than with RM4.0). It should be noted that

the ETA on KA was set to a value of ~ 0.5 in RM4.0 and RM1.5, a value consistent with the estimated ETA on KA in models that utilize the reduced PK data set (i.e. data from subjects with at least one PK profile).

Table 3: Summary results of reference models RM4.0 and RM1.5 (full data set)

Model Description	Parameter Estimates from RM4.0	Parameter Estimates from RM1.5
• Two–compartment PK model • SC infusions with 1st–order input (KA) into central compartment (CMT = 2) from depot compartment (CMT=1) • IV infusion directly into CMT = 2 • 1st–order elimination from CMT = 2 • Relative bioavailability (F1) of SC dose in reference to IV dose (i.e. F2 set to 1) • Population endogenous (ENDO) set to 4.0 g/L or 1.5 g/L • Body-weight (BW) exponents on CL and V2 • ETA on KA set to ~ 0.5 a value consistent with estimated ETA on KA in models utilizing the reduced data set (i.e. data from subjects with at least one PK profile) • Minimization successful	CL (θ_2) = 0.142 L/day BW effect on CL (θ_7) = 0.799 CL (%CV) = 35.8 Shrinkage (CL) = 15.1%. V2 (θ_3) = 3.94 L BW effect on V2 (θ_8) = 0.477 V2 (%CV) = 84.0 Shrinkage (V2) = 24.1%. V3 (θ_4) = 4.18 L V3 (%CV) = 132 Shrinkage (V3) = 24.2%. Q (θ_5) = 0.252 L/day Q (%CV) = 56.6 Shrinkage (Q) = 51.6%. F1 (θ_1) = 0.660 F1 (%CV) = 32.5 Shrinkage (F1) = 37.9%. KA (θ_6) = 0.439 day^{-1} Proportional Error (PK profiles) = 10.3% Additive Error (PK troughs) = 0.41 g/L Proportional Error (PK troughs) = 7.9%	CL (θ2) = 0.100 L/day BW effect on CL (θ7) = 0.840 CL (%CV) = 31.2 Shrinkage (CL) = 13.8%. V2 (θ3) = 3.70 L BW effect on V2 (θ8) = 0.526 V2 (%CV) = 76.4 Shrinkage (V2) = 22.7%. V3 (θ4) = 2.92 L V3 (%CV) = 109 Shrinkage (V3) = 25.6%. Q (θ5) = 0.249 L/day Q (%CV) = 65.1 Shrinkage (Q) = 48.6%. F1 (θ1) = 0.672 F1 (%CV) = 29.9 Shrinkage (F1) = 36.5%. KA (θ6) = 0.418 day-1 Proportional Error (PK profiles) = 10.9% Additive Error (PK troughs) = 0.87 g/L

Note: Typical value of fixed effect parameter = θ; %CV of inter-subject variability in random effect parameter = (SQRT(ω)*100) %; shrinkage in the random effect parameter (%)

The final population PK model (RM4.0) was rerun with the entire data set (i.e. full data set with the 34 outliers re-included). Parameter estimates were consistent with the full data set with outliers excluded.

Sensitivity Analyses

Sensitivity analyses with various IgG_{ENDO} were performed to evaluate the impact of IgG_{ENDO} on key model parameters such as CL and F1 for SC infusions. Changes in bioavailability F1 were minimal whereas CL decreased with decreasing IgG_{ENDO}. For evaluated models with two occasions, estimated IOV in CL appears to be on the order of ~25%.

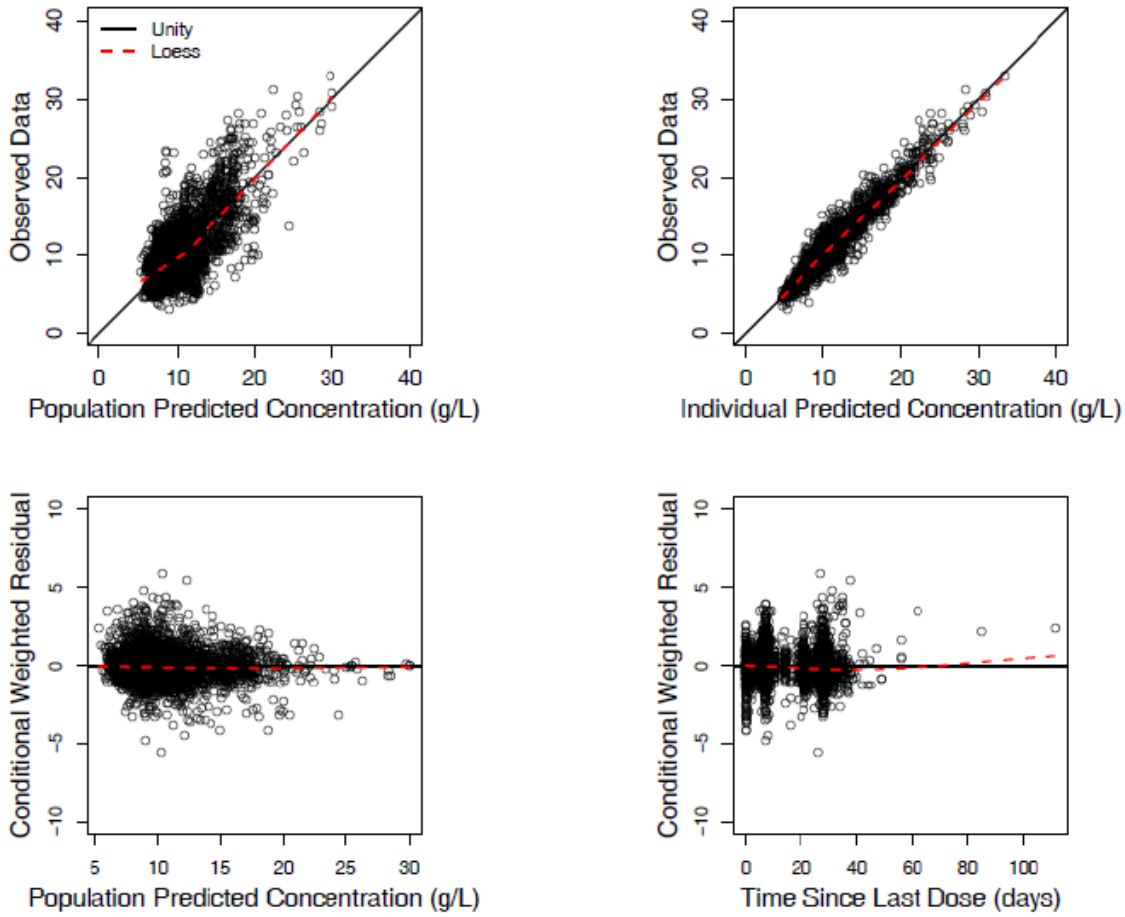
Evaluation of Reference Models

The median values of CL, V2, V3, Q, KA as well as F1 of SC from bootstrapping were consistent with the original population PK estimates. Visual predictive checks for the final population PK model RM4.0 do not indicate any substantive deficiency in the ability of the final reference model to characterize the trend and variability in the observed PK data.

Diagnostic Graphics

Standard diagnostic plots (Figure 1) indicate that the observed data are reasonably well described by the final population PK model **RM4.0**.

Figure 1: Diagnostic plots: observed concentrations dependant variable (DV) vs. population predicted concentrations (PRED); DV vs. individual predicted concentrations (IPRED); conditional weighted residual (CWRES) vs. (PRED); (CWRES) vs. time after last dose (final population PK model RM4.0)



Note: Solid line represents the line of unity (y = x) in upper panel plots and is at 0 (zero) in lower panel plots. Dashed lines represent the loess smooth in S-plus applied to the data points in the plots.

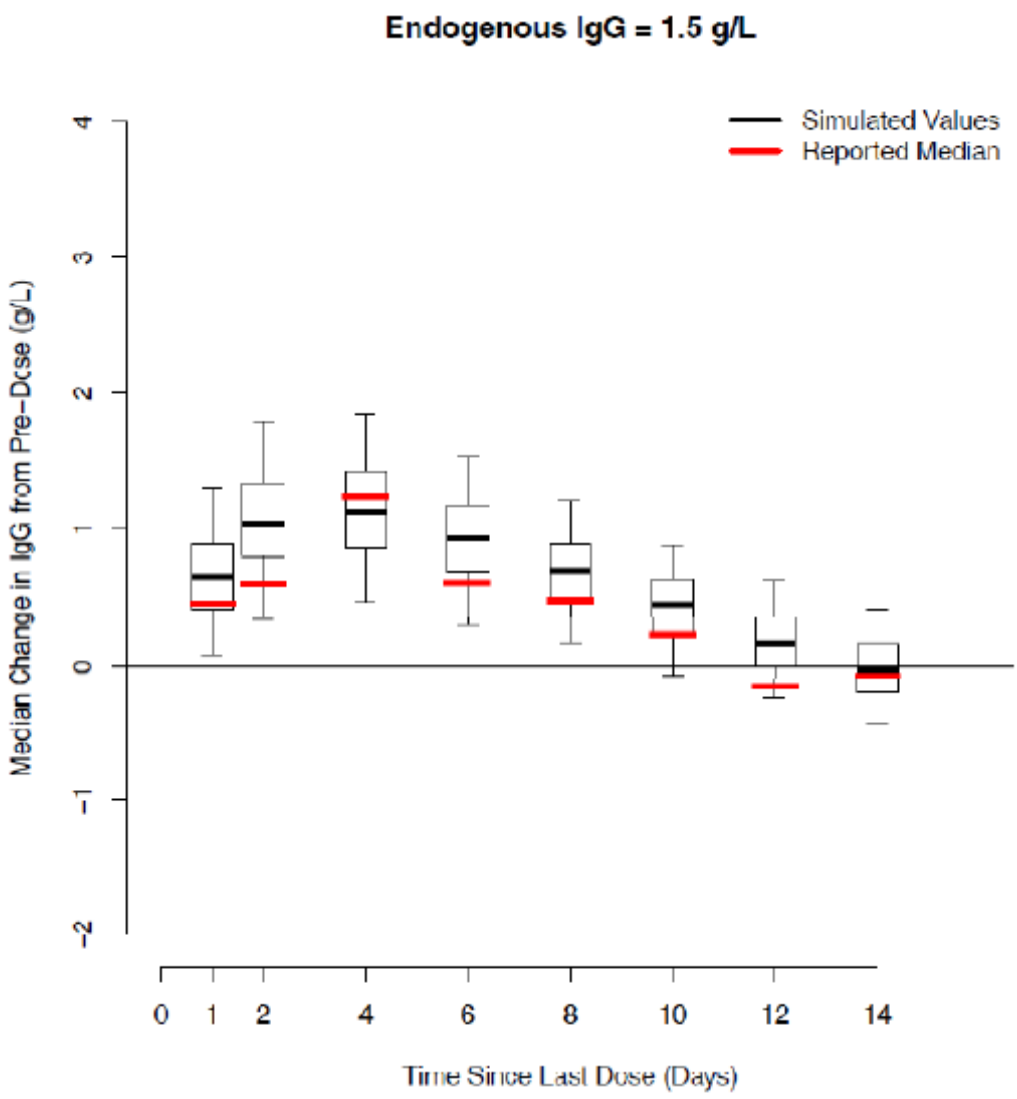
External Validation of Reference Model RM1.5

A biweekly dosing SC regimen has been previously evaluated in a PK/safety study conducted in Europe by Gustafson et al. [Clin Exp Immunol., 2008], in which 12 adult subjects with PID were switched from weekly SC dosing (using a 16% IGSC [Subcuvia®, Baxter AG, Vienna, Austria]) to biweekly SC dosing for 24 weeks. The biweekly SC dose administered was fixed to 200 mg/kg, which was twice the regular weekly dose. Figure 2 in the Gustafson article was digitized to obtain median, 25th and 75th percentiles of observed IgG increases on days 1, 2, 4, 6, 8, 10, 12, and 14 relative to IgG trough concentrations (i.e. IgG concentrations immediately prior to the third biweekly SC dose; day 0). These PK data were not available in the publication in tabularized form. As the reported average of IgG_{ENDO} concentrations in subjects of the Gustafson study was ~ 1.54 g/L, an external validation using the reference population PK model with IgG_{ENDO} = 1.5 g/L (RM1.5) was performed.

A total of a thousand trials with 12 subjects each with patient characteristics in the Gustafson study were simulated. Figures 2 indicates that reference model RM1.5 is able to predict observed PK profiles (i.e. changes in IgG from pre-dose/trough IgG level) in the Gustafson study. The 75th percentiles of observed increases in IgG tended to be in the lower range of 90% prediction intervals of the 75th percentiles of IgG concentrations. This is not surprising, as the small, homogenous study population in the short-term Gustafson study had fixed weekly dosing and provided PK data up to 6 months whereas subjects in the analysis data set had a wide range of weekly IV or SC dosing and a total observation period of up to 4 years.

Results further indicate that models with IgG_{ENDO} set to 1.5 g/L (including the reference model RM1.5) accurately predict not only PK profiles (i.e. increases in IgG from pre-dose IgG level) but also trough IgG levels. Median AUC predicted from the reference model RM1.5 matched the actual value in Table 2 of the Gustafson article. Predicted median AUC (90% prediction interval) from 300 simulated trials was 11437 (9478 - 14091) d·mg/dL, whereas the reported median AUC (confidence interval) was 11400 (10200 - 11800) d·mg/dL.

Figure 2: Predicted PK profiles based on population PK models with IgG_{ENDO} = 1.5 g/L (reference model RM1.5). Boxes show interquartile ranges and whiskers extend to their maximum of 1.5 times the inter-quartile ranges of simulated median changes in IgG concentrations, lines represent observed median changes in IgG concentrations.



Simulation Results

Both reference population PK models RM1.5 and RM4.0, utilizing IV and SC data from four clinical phase III studies with more than 3837 IgG samples. were applied to perform the following simulations:

1) simulation of steady-state IgG concentration time profiles (biweekly vs. weekly SC; biweekly SC vs. 4-weekly IV),
2) simulation of exposure metrics such as steady-state AUC, Cmax and Cmin ratios (biweekly SC vs. weekly SC; biweekly SC vs. 4-weekly IV; weekly SC vs. 4-weekly IV),
3) simulation of trough IgG concentration increases for various dose increments (weekly and biweekly SC infusions).

A bootstrap approach was applied to generate virtual subjects based on dosing information in available SC study subjects (n = 100; 49 ZLB04_009 and 51 ZLB06_001 subjects). Individual dose/kg and body weight combination were bootstrapped whereas PK parameters were simulated based on estimated parameter distributions obtained from reference models RM1.5 and RM4.0.

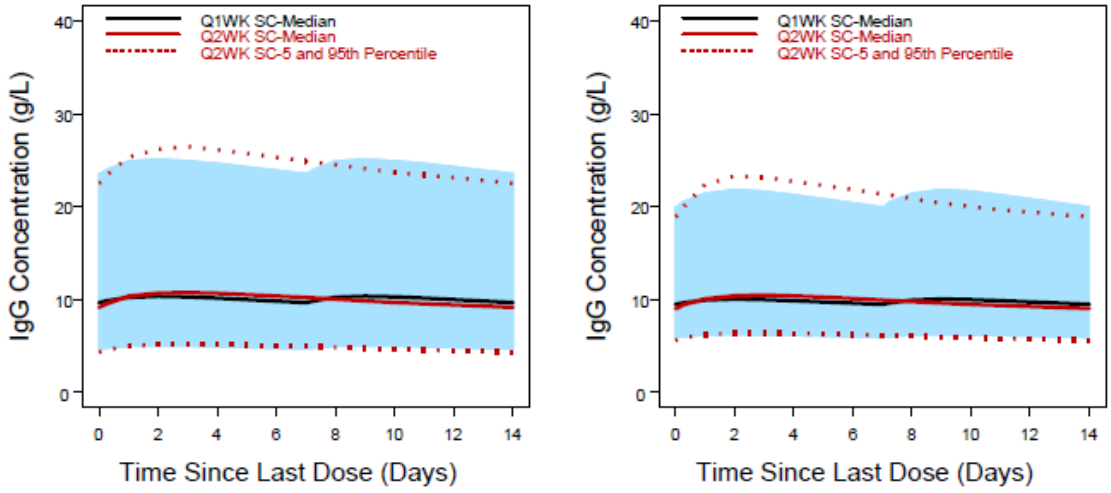
(1) Simulation of Steady-state IgG Concentration Time Profiles

One trial with 2500 subjects each were simulated to compare (i) steady-state IgG concentration time profiles up to 14 days following weekly or biweekly SC dosing, (ii) steady-state IgG concentration time profiles up to 28 days following biweekly SC and 4-weekly IV dosing.

<u>Simulation of Steady-state IgG Concentration Time Profiles (Biweekly vs. Weekly SC Dosing)</u>

One trial with 2500 subjects was simulated to compare steady-state IgG concentration time profiles up to 14 days following weekly or biweekly SC dosing. The biweekly SC dose was set to 2 times the weekly SC dose. Figure 3 indicates that biweekly and weekly SC dosing provide equivalent exposure coverage over 2 weeks (14 days) in subjects with PID. It appears that variability in IgG concentration time profiles is slightly larger with RM1.5 than with RM4.0. A possible explanation for this finding is that the contribution of exogenous IgG to total IgG, which is the sum of endogenous and exogenous IgG, is larger with models that use IgG_{ENDO} = 1.5 g/L than with models that use IgG_{ENDO} = 4.0 g/L.

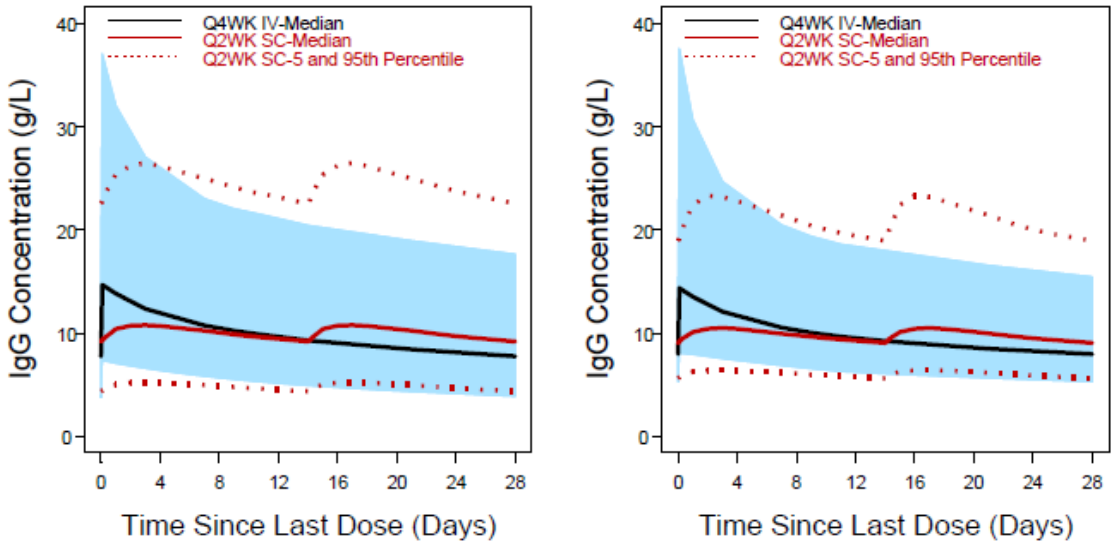
Figure 3: Simulated **s**teady-state IgG concentration time profiles for 2500 subjects (biweekly vs. weekly SC dosing). Shaded areas, 5th to 95th percentile of IgG concentrations with weekly SC dosing. Left panel, simulations with RM1.5; right panel, simulations with RM4.0.



Simulation of Steady-state IgG Concentration Time Profiles (Biweekly SC vs. IV Dosing)

One trial with 2500 subjects was simulated to compare steady-state IgG concentration time profiles up to 28 days following 4-weekly IV or biweekly SC dosing. The dose adjustment coefficient for switching from IV to SC was set to 1.53. Figure 4 shows steady-state IgG concentration time profiles with RM4.0 and RM1.5 for 4-weekly IV and biweekly SC dosing.

Figure 4: Simulated **s**teady-state IgG concentration time profiles for 2500 subjects (biweekly SC vs. 4-weekly IV dosing). Shaded areas, 5th to 95th percentile of IgG concentrations from 4-weekly IV dosing. Left panel, simulations with RM1.5; right panel, simulations with RM4.0



(2) Simulation of PK Exposure Parameters

Three hundred trials with 25 subjects each were simulated to compare

- exposure parameters (i.e. mean steady-state $AUC_{0\text{-}14days}$, C_{max}, C_{7days} and $C_{min14days}$ ratios) following weekly or biweekly SC dosing,
- exposure parameters (i.e. steady-state $AUC_{0\text{-}28days}$, C_{max}, C_{14days} and $C_{min28days}$ ratios) following 4-weekly IV dosing and biweekly SC dosing.

Intra-subject variability in observed of IgG trough levels was ~5% to 20% across study subjects and estimated IOV in CL was ~25%. Given these findings, simulations with RM4.0 and RM1.5 in which IOV in CL was set to 10% and 20% were considered to be the most likely (primary) scenarios. However, a conservative scenario was also considered in which IOV in CL was set to 30%, a value close to the estimated intersubject variability in CL, which is the theoretical upper limit of IOV. Finally, simulations from the reduced data set models were also presented for comparison purposes (secondary scenarios). A total of 50 simulation scenarios were evaluated.

Simulation of Exposure Parameters (Biweekly vs. Weekly SC Dosing)

Three hundred trials with 25 subjects each were simulated to compare exposure parameters (i.e. mean steady-state $AUC_{0\text{-}14days}$, C_{max}, C_{7days} and $C_{min14days}$ ratios) following weekly or biweekly SC dosing. The biweekly SC dose was set to 2 times the weekly SC dose.

Results (Table 4) from simulations of steady-state exposure parameters for weekly to biweekly SC switch show that

- at least 95% of mean AUC ratios are within the expected equivalence range (i.e. 0.8 to 1.25)
- mean AUC values with weekly and biweekly SC dosing are similar
- mean Cmax, C_{7days} and $C_{min14days}$ values are within ± ~ 10%

Table 4: Median, 5th and 95th percentile of mean steady-state AUC0-14days, Cmax, C7days and Cmin14days ratios (biweekly vs. weekly SC dosing). Three hundred trials with 25 subjects each based on RM4.0 and full data set.

Exposure Metrics (Ratios)	**Primary Scenarios**		Conservative Scenario	Alternative Scenarios	
	Inter-occasion Variability in CL Set to 10% (Model fd_e40)	**Inter-occasion Variability in CL Set to 20%** (Model fd_e40)	Inter-occasion Variability in CL Set to 30% (Model fd_e40)	Inter-occasion Variability in CL ~ 26% (Model fd_e40_cle8)	Inter-occasion Variability in CL ~ 23% (Model fd_e40_cle12)
$AUC_{0\text{-}14days}$ [g*day/L]	**1.00 (0.977 - 1.03)**	**1.01 (0.962 - 1.07)**	1.03 (0.952 - 1.12)	1.02 (0.956 - 1.10)	1.02 (0.959 - 1.08)
C_{max} [g/L]	**1.06 (1.02 - 1.09)**	**1.07 (1.01 - 1.13)**	1.08 (1.00 - 1.17)	1.07 (1.01 - 1.15)	1.07 (1.01 - 1.14)
C_{7days} [g/L]	**1.05 (1.03 - 1.09)**	**1.06 (1.01 - 1.13)**	1.08 (0.998 - 1.18)	1.07 (0.999 - 1.15)	1.06 (1.00 - 1.14)
$C_{min14days}$ [g/L]	**0.952 (0.923 - 0.983)**	**0.964 (0.910 - 1.02)**	0.980 (0.903 - 1.07)	0.976 (0.908 - 1.05)	0.971 (0.91 - 1.04)

These findings indicate that biweekly and weekly SC dosing provide equivalent exposure coverage over 14 days (2 weeks) in subjects with PID.

Simulation of Exposure Parameters (Weekly SC vs. 4-Weekly IV Dosing)

Three hundred trials with 25 subjects each were simulated to compare exposure parameters (i.e. mean steady-state $AUC_{0\text{-}28days}$, C_{max}, C_{14days} and $C_{min28days}$ ratios) following 4-weekly IV or weekly SC dosing. The dose adjustment factor for switching from IV to SC was set to 1.53 to reproduce the scenarios studies for the respective label in the US.

Results from simulations of steady-state exposure parameters for switching from 4-weekly IV to weekly SC with a dose adjustment coefficient of 1.53 show that

- mean AUC values with weekly SC dosing are similar (primary scenarios) or slightly higher (conservative scenario) than those with IV dosing,

- mean C_{max} values with weekly SC dosing are on the order of 25% to 30% lower than those with IV dosing,
- mean $C_{min28days}$ with weekly SC dosing are on the order of 15% to 35% higher than those with IV dosing.

These findings indicate that the DAC of 1.53 as provided in the US Hizentra label is appropriate for switching 4-weekly IV dosing to weekly SC dosing when the objective is to maintain similar total IgG AUC (i.e. achieve matching total serum IgG exposure), thus confirming the results of ZLB04_009 study.

Simulation of Exposure Parameters (Biweekly SC vs. IV Dosing)

Three hundred trials with 25 subjects each were simulated to compare exposure parameters (i.e. mean steady-state AUC0-28days, Cmax, C14days and Cmin28days ratios) following 4-weekly IV or biweekly SC dosing. The DAC for switching from IV to SC was set to 1.53.

Results from simulations of steady-state exposure parameters for switching from 4-weekly IV to biweekly SC with a DAC of 1.53 show that

1. mean AUC values with biweekly SC dosing are similar (base scenarios) or slightly higher (conservative scenario) than those with IV dosing,
2. mean C_{max} values with biweekly SC dosing are on the order of 20% to 25% lower than those with IV dosing,
3. mean $C_{min28days}$ with biweekly SC dosing are on the order of 15% to 30% higher than those with IV dosing.

These findings indicate that the DAC of 1.53 as provided in the US Hizentra label for weekly SC dosing is appropriate for switching IV dosing to weekly or biweekly SC dosing.

(3) Simulation of IgG Trough Level Increases for Dose Increments (IV Switch to Weekly SC or Biweekly SC Dosing)

Changes in steady-state IgG trough concentrations associated with dose increments of interest were simulated in available SC study subjects (n = 100; 49 in ZLB04_009 and 51 in ZLB06_001) to provide basis for IgPro20 package insert dosing recommendations. Simulations were performed with RM4.0 and RM1.5 for four different weight groups:

1. SC study subjects with body weight > 10 to 30 kg (n = 29)
2. SC study subjects with body weight > 30 to 50 kg (n = 38)
3. SC study subjects with body weight > 50 to 70 kg (n = 18)
4. SC study subjects with body weight > 70 kg (n = 15)

These four weight groups were selected based on sample size ($n \geq 15$) and clinical relevance.

Simulation results suggest that an increase in weekly dose results in slightly higher steady-state IgG trough levels with RM1.5 than with RM4.0. This finding is consistent with the observation that CL estimates were lower with models that use IgG_{ENDO} = 1.5 g/L than those with models with IgG_{ENDO} = 4.0 g/L. Since increases in steady-state IgG trough levels are greater with IgG_{ENDO} = 1.5 g/L than with IgG_{ENDO} = 4.0 g/L, dose increments with RM1.5 are lower than those with reference model RM4.0 for a given target IgG increase.

For target trough guidance, dose increments based on RM4.0 are more conservative than those of RM1.5, and may be preferred in order to ensure desired IgG increases in subjects exhibiting IgG trough levels below target levels. For example, a dose increment of 30 mg/kg/week could be considered for a subject of > 70 kg with a deficiency of 100 to 199 mg/dL relative to target IgG trough level.

Dosing in pediatric patients:

As shown in Tables 5a and 5b, based on modeling data, differences in absolute clearance values across the age groups are evident. However, when comparing bodyweight-adjusted clearance values using data for subjects <12 years from Table 5a (IgGendo = 1.5 g/L, substantiated since majority of pediatric patients constituted XLA patients with low internal/endogenous IgG production) and values for subjects >12 years from Table 5b (IgGendo = 4 g/L, more appropriate for this age group because almost all of the adults had CVID), then the clearance values in L/day/kg are essentially the same, irrespective of age. These results indicate that body weight-adjusted dosing accounted for age-related differences in clearance, thereby maintaining systemic IgG exposure (AUC values) in the therapeutic range.

Table 5a: Clearance (CL) by age range. Based on population PK model post-hoc values, assuming endogenous IgG concentrations of 1.5 g/L. Combined results for study ZLB04_009 and study ZLB06_001.

Age [year] Range	**N**	**Age [year]** Median [min, max]	**[1]BW [kg]** Median [min, max]	**[2]D [mg/kg]** Median [min, max]	**CL [mL/d]** Mean [min, max]	**CL [mL/d/kg]** Mean [min,max]
3 to < 6	8	5 [3, 5]	18 [12, 24]	115 [83.3, 283]	33.8 [20.7, 45]	1.86 [1.55, 2.93]
6 to < 12	12	9.5 [6, 11]	33 [20, 58]	124 [75.9, 347]	69 [33.3, 146]	1.97 [1.59, 3.25]
12 to < 16	8	14 [13, 15]	60 [38, 101]	141 [72.7, 346]	93.7 [75.1, 137]	1.51 [1.22, 1.98]
16 to < 65	54	34.5 [16, 60]	72.5 [40, 111]	140 [58.6, 386]	104 [59.3, 184]	1.48 [0.65, 2.48]
≥ 65	4	68 [67, 72]	67 [38, 73]	180 [126, 296]	89.7 [66.2, 130]	1.5 [0.96, 1.78]

[1]BW = bodyweight
[2]D = dose

Table 5b: Clearance (CL) by age range. Based on population PK model post-hoc values, assuming endogenous IgG concentrations of 4.0 g/L. Combined results for study ZLB04_009 and study ZLB06_001.

Age [year] Range	**N**	**Age [year]** Median [min, max]	**[1]BW [kg]** Median [min, max]	**[2]D [mg/kg]** Median [min, max]	**CL [mL/d]** Mean [min, max]	**CL [mL/d/kg]** Mean [min,max]
3 to < 6	8	5 [3, 5]	18 [12, 24]	115 [83.3, 283]	53.6 [29.7, 77.1]	2.93 [2.25, 5.02]
6 to < 12	12	9.5 [6, 11]	33 [20, 58]	124 [75.9, 347]	100 [46.9, 187]	2.84 [2.3, 4.16]
12 to < 16	8	14 [13, 15]	60 [38, 101]	141 [72.7, 346]	128 [104, 177]	2.08 [1.58, 2.73]
16 to < 65	54	34.5 [16, 60]	72.5 [40, 111]	140 [58.6, 386]	149 [77.3, 303]	2.12 [1.0, 3.81]
≥ 65	4	68 [67, 72]	67 [38, 73]	180 [126, 296]	123 [107, 160]	2.1 [1.5, 2.83]

[1]BW = bodyweight
[2]D = dose

Summary:

Results from this pharmacometric analysis indicate that:

(i) biweekly and weekly SC dosing provide equivalent exposure coverage over 14 days (2 weeks) in subjects with PID and that the biweekly SC dose can be set to 2 times weekly SC dose

(ii) the DAC of 1.53 as provided in the US Hizentra label for weekly SC dosing is appropriate for switching IV to weekly or biweekly SC dosing where the objective is to achieve matching total serum IgG exposure (AUC)

(iii) target IgG trough level for weekly SC dosing could be defined as 1.25 times IgG trough level observed with IV dosing and target IgG trough level for biweekly SC dosing could be set to 1.15 times IgG trough level observed with IV dosing when a DAC of 1.53 is used

Conclusions

Modeling

- A two-compartment PK model adequately characterized serum IgG concentrations in pediatric and adult subjects with PID.
- The population average value of CL and V2 were estimated to be 0.142 L/day and 3.94 L, respectively.
- Allometrically estimated body weight exponents on the parameters CL and V2 were estimated to be 0.80 and 0.48, respectively.
- Bioavailability F1 of the Hizentra SC formulation is estimated to be on the order of 0.66, which is consistent with previous reports for Hizentra and other SC IgG products.
- Modeling results of clearance values as a function of age do not substantiate special dose recommendations for any of the studied age groups.

Simulations

- For the same total 2-week dose, biweekly and weekly SC infusions yield equivalent exposure with overlapping steady-state concentration time profiles, similar IgG AUC values, and IgG peak and trough levels that stay within ± 10%.
- With a dose adjustment coefficient of 1.53, biweekly SC infusions yield similar or slightly higher IgG AUC values, 20% to 25% lower IgG peak levels, and 15% to 30% higher IgG trough levels than those with IV infusions.

Reviewer's Comment:

- Overall, the population PK analysis, sensitivity analysis, internal and external model validation steps, subsequent simulations of steady-state concentration-time profiles and simulations of exposure parameter to support a biweekly IgPro20 dosing regimen, and conclusions of this study are acceptable from a Clinical Pharmacology perspective.
- The demonstrated relationship between estimated individual drug clearances and age deserves special attention. The results suggest that dosing per kg weight is appropriate for all age groups (3 years and older). It appears therefore, that no further dose adjustments for pediatric and geriatric patients are necessary.
- Regarding simulations, fixing ω^2 to 0.5 for the first-order absorption rate constant KA is acceptable, because this would assume a population between-subject-variability (BSV) of 71% [SQRT(ω^2)]. A BSV of this magnitude for KAs is consistent with reports in the literature.