

CLINICAL PHARMACOLOGY BLA REVIEW

Division of Hematology
Office of Blood Review & Research

STN 125402

Sponsor: Baxter Healthcare Corporation

Product: Immune globulin infusion (Human) 10% with recombinant human hyaluronidase

Indication: Treatments of patients with primary immunodeficiency (PID) associated with defects in humoral immunity

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Study #2: Phase I/II determination of the dose of recombinant human hyaluronidase required enabling up to 600 mg/kg body weight of immune globulin intravenous (human), 10% to be administered subcutaneously in a single infusion site in subjects with primary immunodeficiency diseases (study report: 16062). 14

Study #3: Efficacy, tolerability and pharmacokinetic comparison of immune globulin intravenous (human), 10% (GAMMAGARD LIQUID/KIOVIG) administered intravenously or subcutaneously following administration of recombinant human hyaluronidase (rHuPH20) in subjects with primary immunodeficiency diseases (PIDD) (study report: 16063). 17

Introduction

Defective antibody formation is the most common abnormality in the majority of primary immunodeficiency (PID) diseases. It is most often reflected by a decrease in serum immunoglobulins, which in turn leads to increased susceptibility to bacterial infections. Individuals with these diseases require replacement therapy with immune globulins to prevent or reduce the severity of infections. For many years, immune globulin replacement therapy was

given intramuscularly and then by the intravenous (IV) route. Currently, the vast majority of immune globulins in the United States are licensed for IV administration. During the past few years, SC application of immune globulin preparations was introduced in many countries.

GAMMAGARD LIQUID/KIOVIG is a liquid unmodified IgG preparation developed by Baxter Healthcare Corporation. Data from two completed Baxter clinical studies (160601 and 160602) show that immune globulins including GAMMAGARD LIQUID/KIOVIG are also efficacious and well tolerated when administered subcutaneously. The primary disadvantage of SC therapy has been the limited volume that can be infused in a single SC site, necessitating the use of multiple needle sites on a weekly or biweekly basis rather than a single IV infusion once every 3 to 4 weeks. If larger amounts of IgG could be rapidly infused in a single site, it would be highly desirable and might enable more patients to attempt SC therapy. Therefore, a clinical study (Study 160602) was conducted by Baxter to investigate the ability of Recombinant Human Hyaluronidase (rHuPH20) to facilitate the SC administration of large quantities of GAMMAGARD LIQUID/KIOVIG.

Human hyaluronidase is produced by genetically engineered Chinese Hamster Ovary (CHO) cells containing a deoxyribonucleic acid (DNA) plasmid encoding for a soluble fragment of human hyaluronidase. HYLENEX, a preparation of rHuPH20 at a concentration of 150 U/mL, is approved by the Food and Drug Administration (FDA) as an adjuvant to increase the absorption and dispersion of other injected drugs, for SC fluid administration and as an adjunct in SC urography for improving resorption of radiopaque agents. Following hyaluronidase injection, the rHuPH20 enzyme rapidly depolymerizes hyaluronan, which provides a barrier to bulk fluid infusion, and locally and transiently increases the permeability of the active drug substance. In a study that assessed SC hydration with and without rHuPH20, it was shown that single administration of rHuPH20 enabled the infusion of large volumes of Lactated Ringer's (LR) solution that were well tolerated.

In a study (study 160602), it was shown that prior infusion of a minimum dose of rHuPH20 of 50 U/g IgG is required for tolerability of a full 4-week SC dose of IGIV, 10%. The mean duration of administration of a tolerated full 4-week dose was 2.9 h, which compares favorably with rapid administration of 4 weekly doses using SC 16% immunoglobulin in 1 or 2 infusion sites.

CLINICAL PHARMACOLOGY LABELING COMMENTS

USE IN SPECIFIC POPULATIONS

- Pediatric: ~~The pharmacokinetics, safety and efficacy data were similar to those in the adult population.~~ Deleted because no formal PK study was conducted in pediatric population. The assumption that if the trough levels are equal between adults and children then the AUC should be similar is not necessarily true. There is no evidence of this assumption.

1.1 Pediatric Use

Safety and efficacy of HyQvia was evaluated in 22 pediatric subjects aged 2 to <16 years old (13 were 4 to <12 years old and 9 were 12 to <16). ~~The pharmacokinetics, safety and efficacy data were similar to those in the adult population.~~ The safety and efficacy of HyQvia has not been evaluated in neonates or infants under the age of 2.

2 CLINICAL PHARMACOLOGY

2.1 Mechanism of Action

The Immune Globulin Infusion (Human), 10% provides the therapeutic effect of HyQvia. The Recombinant Human Hyaluronidase contributes to the dispersion and absorption of the Immune Globulin Infusion (Human), 10% thereby improving bioavailability, resulting in more of the infused IgG reaching the systemic circulation than when Immune Globulin Infusion (Human), 10% is administered alone. The Immune Globulin Infusion (Human), 10% of HyQvia supplies a broad spectrum of opsonizing and neutralizing IgG antibodies against a wide variety of bacterial and viral agents. The Immune Globulin Infusion (Human), 10% also contains a spectrum of antibodies capable of interacting with and altering the activity of cells of the immune system as well as antibodies capable of reacting with cells such as erythrocytes. The role of these antibodies and the mechanisms of action of IgG in the Immune Globulin Infusion (Human), 10% have not been fully elucidated.

(Deleted because the description is too lengthy and will not be helpful to a prescribing physician).

~~The Recombinant Human Hyaluronidase component of HyQvia facilitates increased bioavailability of Immune Globulin Infusion (Human), 10% component of HyQvia by temporarily increasing the permeability of the subcutaneous tissue⁸. Hyaluronan, a polysaccharide found in the intercellular ground substance of connective tissue, binds large quantities of water and forms large, random coil structures that create barriers to flow through the subcutaneous interstitial matrix. Hyaluronan is degraded by the naturally occurring enzyme hyaluronidase. Unlike the stable structural components of the interstitial matrix, hyaluronan has a very fast turnover with a half life of approximately 5 days. Recombinant Human Hyaluronidase takes advantage of this natural turnover process, accelerating the breakdown of hyaluronan, resulting in~~

~~a temporary increase in the permeability of the interstitial matrix that facilitates more rapid dispersion, increased absorption into the capillaries and lymphatics and improved bioavailability of the Immune Globulin (Human), 10%, resulting in more of the infused IgG reaching the vascular space. The naturally occurring rapid regeneration of hyaluronan results in complete recovery of the interstitial barrier to flow within 24 to 48 hours. In the doses administered, Recombinant Human Hyaluronidase acts only locally and does not result in detectable levels in the circulation.~~

2.3 Pharmacokinetics (Deleted because the description is too lengthy and will not be helpful to a prescribing physician).

~~The pharmacokinetics (PK) of HyQvia was evaluated during the clinical study of subjects with PI who were 12 years and older (see *CLINICAL STUDIES (14)*). The PK of HyQvia was compared to that of subjects on IgG treatment administered intravenously in this study and to that of subjects on IgG treatment administered intravenously and subcutaneously in a previous study. In the previous study, subjects were first treated every 3 or 4 weeks for 12 weeks with intravenously administered Immune Globulin Infusion (Human), 10% and then treated with subcutaneously administered Immune Globulin Infusion (Human), 10% weekly for an average of one year at 137% of the intravenous dose. Thirty one of these subjects transferred into the current study. Additional subjects who participated only in this study were treated every 3 to 4 weeks for 12 weeks with intravenously administered Immune Globulin Infusion (Human), 10%. Following intravenous treatment, these subjects, as well as the subjects from the previous study which evaluated subcutaneously administered Immune Globulin Infusion (Human), 10%, were treated with HyQvia for a minimum of 12 weeks at a dose that was 108% of the intravenous dose. Subsequently, all subjects were evaluated for dose individualization using the trough IgG levels, as described below. Close to the end of the study, the PK evaluation was repeated on 60 subjects 12 years of age or older. For subjects < 12 years of age the trough level was used to adjust the dose to avoid having to do a formal PK analysis, with the assumption that if the trough levels were equivalent the AUC should be similar. During the efficacy phase of the study, which started after the ramp up of the dose [see *CLINICAL STUDIES (14)*], the median weekly dose for subjects aged 12 years and older was 130 mg/kg (range 80 to 450 mg/kg) and for subjects aged 2 to < 12 years was 150 mg/kg/week (range 100 to 230 mg/kg). The means \pm SD were 154 ± 54 mg/kg/week for subjects 12 years of age or older and 164 ± 43 mg/kg/week for subjects 2 to < 12 years of age. Thus, there was not a significant difference in the dose requirement for children. The ratios of the intravenous dose were 108.98% and 107.52% respectively. At this dose adjustment, the geometric mean ratio of the AUC for intravenously administered Immune Globulin Infusion (Human), 10% vs. HyQvia was 93.3% (90% CI 91.4 to 95.2%). This is within the range (80 to 125%) considered to be pharmacokinetically equivalent to intravenous administration. Bioavailability determined by serum IgG levels was comparable for infusions of HyQvia in subjects aged 2 to < 12 and those aged \geq 12 years, which is consistent with the demonstration of PK equivalence in terms of AUC.~~

The bioavailability, calculated as the ratio of the AUC per dose/kg between HyQvia and subcutaneously administered Immune Globulin Infusion (Human), 10% ~~in the previous study~~, revealed a 20% (95% CI: 18 to 25%) improvement with the use of Recombinant Human Hyaluronidase. In other words, it required 20% less HyQvia than subcutaneously administered Immune Globulin Infusion (Human), 10% to reach the same AUC as intravenous treatment.

The pharmacokinetic parameters of HyQvia compared to intravenously administered Immune Globulin Infusion (Human), 10% are shown in Table 8. The mean IgG dose in weekly equivalents was 154 mg/kg \pm 54 (range 80 to 450 mg/kg). The serum IgG trough levels were comparable, the median serum IgG trough with HyQvia was 1040 mg/dL compared to 1010 mg/dL of intravenously administered Immune Globulin Infusion (Human), 10%. The peak serum IgG levels were lower with HyQvia (1550 mg/dL) than with intravenously administered Immune Globulin Infusion (Human), 10% (2190 mg/dL). Time to reach maximum concentration of IgG following SC administration was 5 days. ~~(consistent with slower absorption into the circulation, as shown by the later peak IgG concentration which occurred 5 days (3.3 to 5.1) after the HyQvia infusion. By contrast, in the previous study of subcutaneously administered Immune Globulin Infusion (Human), 10% administered weekly at 137% of the intravenous dose, the median trough IgG level was 1260 mg/dL (1060-1400) and the peak was 1410 mg/dL (1250-1630). Thus, the peak IgG levels with HyQvia are comparable to a higher dose of subcutaneously administered Immune Globulin Infusion (Human), 10% and lower than the peak level following intravenous administration. The trough is slightly lower than subcutaneously administered Immune Globulin Infusion (Human), 10% (1040 mg/dL versus 1260 mg/dL but with significant overlap of the ranges.~~

Please provide dose and dose range, clearance, and bioavailability values in Table 8.

Table 1.
Pharmacokinetic Parameters of HyQvia Compared to Intravenously Administered Immune Globulin Infusion (Human), 10%

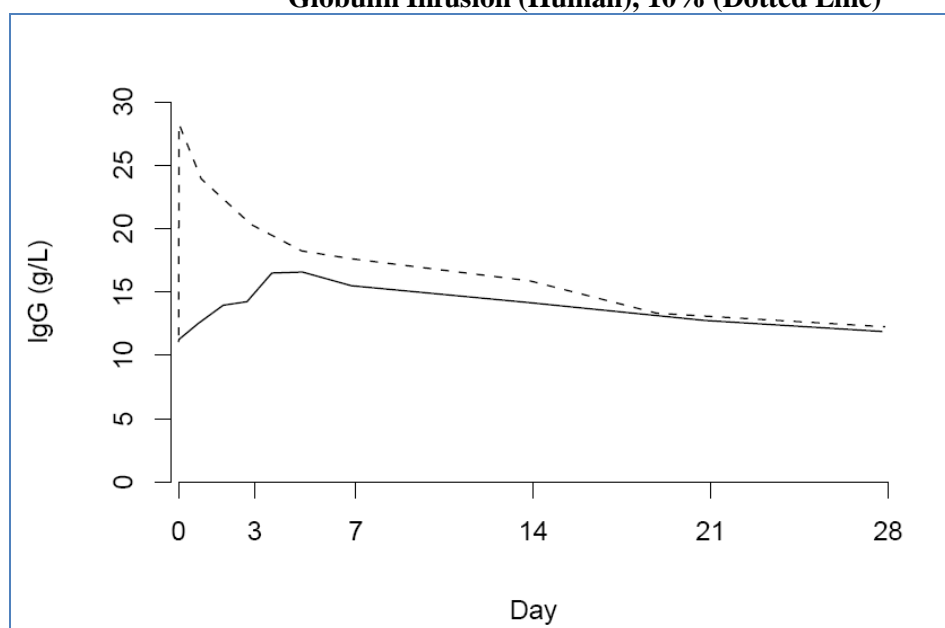
	HyQvia	Intravenously Administered Immune Globulin Infusion (Human), 10%
Number of Subjects	60	68
IgG Peak Levels		
Median	1550 mg/dL	2190 mg/dL
95% CI	1450 to 1710 mg/dL	2070 to 2390 mg/dL
IgG Trough Levels		
Median	1040 mg/dL	1010 mg/dL
95% CI	940 to 1120 mg/dL	950 to 1090 mg/dL
AUC ¹		

Median 95% CI	90.5 days * g /L 83.8 to 98.4 g/L	93.9 days * g/L 89.1to 102.1 g/L
T max [days] Median 95% CI	5.0 3.3 to 5.1	0.1 0.1 to 0.1

1. Standardized to a 7 day interval

As shown in Figure 1, the plot of concentration vs time is similar to that of intravenous administration but without the high peak. The peak to trough variation is more similar to subcutaneous administration, even with every 3 to 4 week administration. **Does the plot represent a single subject or mean of all subjects' data?**

Figure 1
HyQvia (Solid Line) vs. Intravenously Administered Immune Globulin Infusion (Human), 10% (Dotted Line)



Graphical representation of a typical infusion of HyQvia (solid line) compared to infusion of intravenously administered Immune Globulin Infusion (Human), 10% (dotted line). The dose of HyQvia was 100% of the intravenous dose and bioavailability determined by AUC was 86% (taken from Phase I study of HyQvia).

The trough levels of the IgG subclasses reflected the normal profile and there was no significant difference between the levels when administered intravenously or through facilitated subcutaneous administration with HyQvia.

Detailed and lengthy, Please provide this information in a Table with a brief description.

~~The trough levels of specific antibodies to *Clostridium tetani* toxoid, *Haemophilus influenzae* b, measles virus, or Hepatitis b surface antigen were determined throughout both the intravenously~~

~~administered Immune Globulin Infusion (Human), 10% and the HyQvia treatment periods. The titers were slightly higher during treatment with HyQvia but the differences were not significant and were significantly higher than the minimum protective levels. The titers against tetanus toxoid were 2.580 IU/mL (95% CI 0.990; 3.810) for subjects aged 2 to <12 and 2.525 IU/mL (90% CI 2.270; 2.850) for subjects 12 years and older. The trough titers against Haemophilus influenzae b at the end of the study were 1.97 mcg/mL (95% CI 1.69; 4.94 for subjects 2 to <12 and 2.58 mcg/mL (95% CI 2.30; 2.95) for subjects 12 years and older. At the end of the study, the median reciprocal anti-measles virus antibody titer in subjects aged 2 to <12 years was 768.0 (95% CI: 256.0; 2048.0) and the median in subjects aged \geq 12 years was 1024.0 (95% CI: 512.0; 1024.0). The median concentrations of HBsAg antibodies at the end of Epoch 2 were 242.2 mIU/mL (95% CI: 125.5; 871.9) in the 2 to <12 year age group and 249.2 mIU/mL (95% CI: 225.0; 289.3) in subjects aged 12 years and over.~~

RECOMMENDATION

The design, results, and conclusions of the pharmacokinetic studies presented in this submission are acceptable from clinical pharmacology perspective. The sponsor should modify the clinical pharmacology as well as pediatric sections of the labeling as suggested by the Agency.

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Study #1

Study Title: Tolerability and pharmacokinetic comparison of immune globulin intravenous (human), 10% (IGIV, 10%), administered intravenously or subcutaneously in subjects with primary immunodeficiency diseases (study report: 16061).

Objectives: The purpose of the study was to evaluate the pharmacokinetics and tolerability of IGIV, 10% given subcutaneously and compare the pharmacokinetics of IGSC with IGIV 10% in subjects with primary immunodeficiency (PID) disorders. A further aim was to evaluate efficacy in terms of acute serious bacterial infections.

Study Design: This was a prospective, open-label, uncontrolled, multi-center study in subjects with PID. The pharmacokinetics of IGIV, 10% administered subcutaneously was compared with the pharmacokinetics of IGIV, 10% administered intravenously. Approximately 23 subjects with PID aged 12 years and older (including a minimum of 4 subjects aged between 12 years and <16 years) who had previously been treated with intravenous (IV) immune globulin and approximately 12 subjects with PID aged 2 to <12 years who also had received previous treatment with IV immune globulin were enrolled and treated. The study consisted of 4 parts plus an optional study extension part: study part 1, which included IV treatment, and study parts 2, 3a, 3b, and the study extension part with SC treatment.

Study Part 1: All subjects received IV infusions of IGIV, 10% (every 3 or every 4 weeks, ± 2 days) for 12 weeks at the dose and schedule that they were on prior to the study (300 to 1000 mg/kg/4 weeks). Trough levels were evaluated before every infusion in all subjects. Blood for full pharmacokinetic (PK) analysis was taken from all subjects aged 12 years and older after the third or fourth IV infusion, depending on the treatment interval. One week (± 1 day) after regular IV treatment (fourth or fifth infusion) given at the end of the PK evaluation, subjects began SC treatment. Blood samples for PK studies were collected before infusion and at 30 minutes (± 3 minutes) after completion of the infusion, and on days 1, 4, 9 (± 1 day), 14 (± 2 days) and 21 (± 2 days) for 3-week treatment interval and day 28 (± 2 days) for 4-week treatment interval after infusion. IgG trough levels were determined on the day of each IV infusion.

Study Part 2: All subjects received weekly (± 1 day) SC IGIV, 10% infusions at a dose that was 130% of the weekly equivalent of the IV dose administered in Study Part 1 for a minimum of 12 weeks. Trough levels were evaluated monthly and blood for full PK analysis was taken from all subjects aged 12 years and older following the eighth infusion. Blood samples were collected on days 0, 1, 3, 5, and 7. IgG trough levels were determined in all subjects on the days of SC infusions number 1, 5, and 9.

All subjects participated in Study Part 2 for a minimum period of at least 12 weeks and until the first 15 subjects aged 12 years and older had completed the PK assessment and the results

were available. The PK analysis was used to determine the “Adjusted Dose” to be administered in Study Part 3a for all subjects, including subjects aged 2 to <12 years. This Adjusted Dose was expressed as a ratio of the weekly IV dose. In addition, the expected increase in IgG trough levels during Study Part 3a relative to the trough level during IV infusions (Study Part 1) was estimated and a nomogram was derived to individually adapt the dose in Study Part 3b, in case the expected IgG trough level increase was not attained in Study Part 3a.

Study Part 3: Study Part 3 consisted of Study Part 3a and Study Part 3b.

Study Part 3a: All subjects were treated subcutaneously for 6 weeks using the Adjusted Dose (as a ratio of the weekly IV dose). This Adjusted Dose was calculated based on the PK assessments from the first 15 subjects aged 12 years and older in Study Parts 1 and 2. Since a single Adjustment Factor was used for deriving the SC dose from the weekly IV dose, a further correction of the dose could be required for individual subjects. To determine whether each subject received an adequate dose, trough levels were determined at Week 5 (after four weekly infusions in Study Part 3a) and subject trough levels on SC (Study Part 3a) and IV treatment (Study Part 1) were compared within the next 2 weeks. During this period, the subject received another 2 infusions of the Adjusted Dose. If the increase in trough levels was not within 15% of the expected increase, the dose was individually adapted (“Individually Adapted Dose”) using an Individual Adaptation Factor read from the nomogram derived from the analysis of the first 15 PK subjects in Study Part 2. No PK study was conducted in this study (part 3a). IgG trough levels were determined in all subjects on the days of SC infusions number 1 and 5.

Study Part 3b: All subjects received weekly SC infusions for 12 weeks. The dose administered to a subject was determined as follows:

- If the increase in trough levels was within 15% of the expected increase over the trough level determined in Study Part 1, the subject received the same dose (Adjusted Dose) as during Study Part 3a
- If the increase in trough levels was not within 15% of the expected increase over the trough level in Study Part 1, the subject received the Individually Adapted Dose.

Following Infusion number 8, blood samples were collected on days 0, 1, 3, 5, and 7 in all subjects aged 12 years and older. IgG trough levels were determined in all subjects on the days of SC infusions number 1, 5, and 9 and at the end of the study.

Study Extension Part: In the optional Study Extension Part, all subjects received the same dose as in Study Part 3b.

Nine (9) study sites enrolled a total of 49 subjects who received treatment in the study. Of these, 14 were 2 to <12 years old and 35 were 12 years and older (of these, 4 were aged between

12 and <16 years and 4 were >65 years). A total of 38 subjects were naïve to SC immune globulin replacement therapy, 14 in the lower age group (2 to <12 years) and 24 in the higher age group (12 years and older). There were 6 females and 8 males in the age group 2 to <12 years (range: 3 to 11 years) and there were 22 females and 27 males in the age group of 12 years and older (range: 14 to 77 years). Disposition of subjects is shown in Figure 1 (page #12).

Pharmacokinetic Assessment:

In subjects aged 12 years and older, bioavailability of IgG was assessed after administration of IGIV, 10%, intravenously, subcutaneously, and subcutaneously at an Adjusted/Individually Adapted Dose, as measured by area under the IgG concentration (AUC) versus time curve per week. In subjects aged 2 to <12 years, bioavailability of IgG was assessed after administration of IGIV, 10%, intravenously, subcutaneously and subcutaneously at an Adjusted/Individually Adapted Dose, as measured by trough levels of IgG. In all subjects, trough levels of IgG, and levels of antibody to tetanus, Haemophilus, influenza (H. influenza), measles and hepatitis B for IV and SC treatment in Study Parts 1, 2, 3a and 3b were determined.

PK parameters determined in subjects aged 12 years and older include the area under the concentration versus time curve between subsequent infusions, AUC_{0-τ}, and clearance (CL) for Study Parts 1, 2 and 3b. Half-life was determined for IV administration (Study Part 1) only, as it was not a meaningful PK parameter for SC administration when given weekly.

For bioequivalence assessment, a 90% confidence interval was applied to AUC_(0-t)/week following IV administration of IGIV and SC administration of IGIV, 10% and Adapted Dose. For subjects aged 2 to <12 years, a formal demonstration of PK equivalence was not feasible due to the limited sample size.

Results: The pharmacokinetics parameters obtained from this study are summarized in Table 1. In Table 2, the IgG and IgG subclasses trough levels are presented. The bioavailability of IGIV following SC administration was 95.2% (n =29) with 90% confidence interval ranging from 92.3% to 98.2%. This was not surprising since subjects in SC group received 130% of the dose given to subjects in IV group. IgG, IgG1, and IgG2 levels were comparable between children aged 2 to <12 years and subjects ≥16 years of age. On the other hand, IgG3 and IgG4 levels were comparatively higher in children than the older subjects.

Conclusions: This study indicates that in order to achieve PK equivalence (measured by AUC) of IGIV, 10% administered intravenously and subcutaneously, the dose-level of SC administration should be between 130-140% of the IV dose.

Figure 1

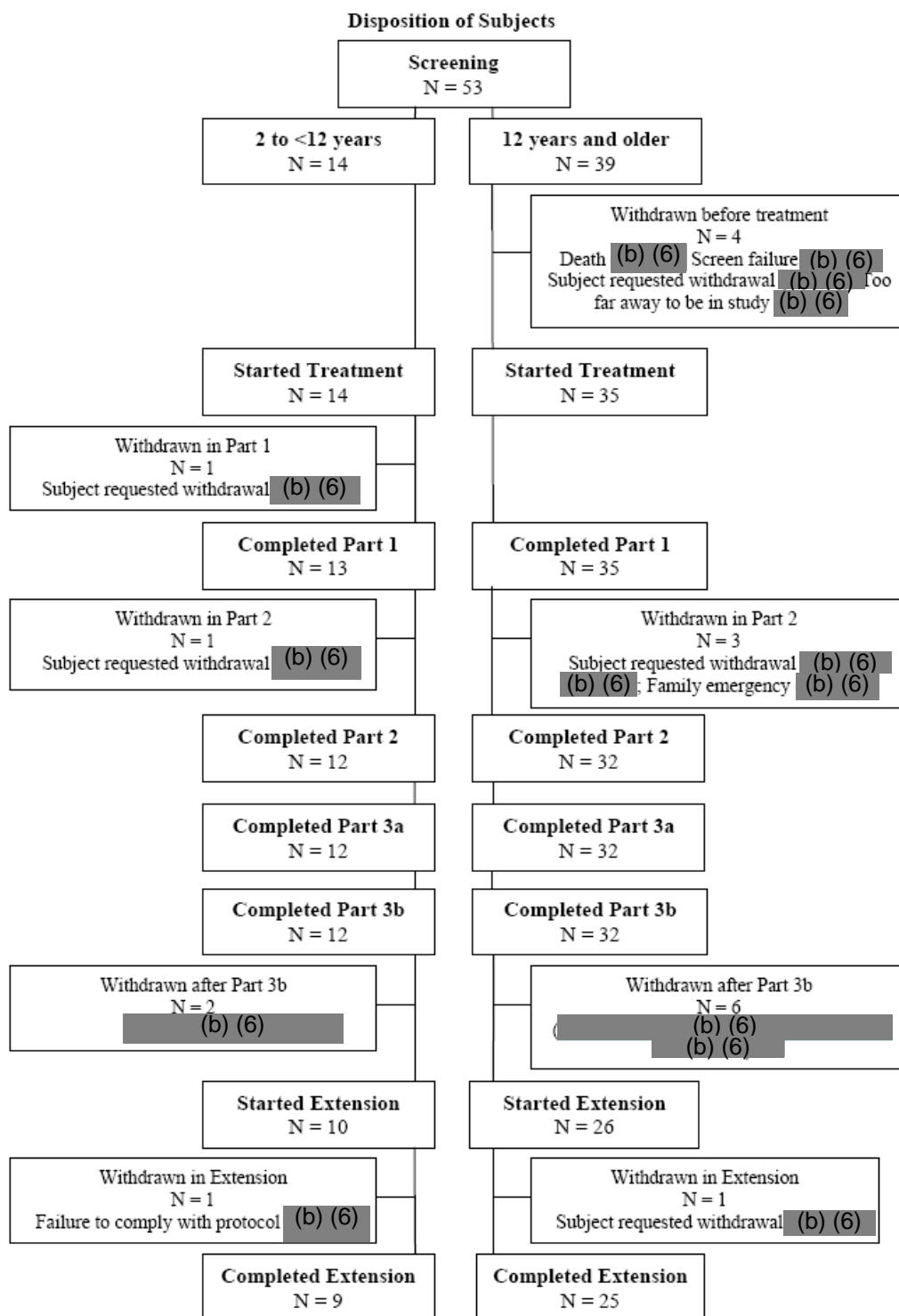


Table 1

**Table 14.2.2-1:
Summary of Pharmacokinetic Parameters for Subjects Aged 12 Years and Older
(PKIV,PKSC)**

Study Part	Parameter	N	Median	95% CI for Median
Study Part 1	C _{max} [g/L]	32	22.7	21.0 to 25.0
	C _{min} [g/L]	32	10.1	9.4 to 12.4
	AUC [g*days/L]	32	384	348 to 433
	AUC per week [g*days/L]	32	97.4	92.0 to 113.9
	Clearance [mL/kg/day]	32	1.36	1.23 to 1.42
	Initial Half-life [days]	32	9.6	5.5 to 25.8
	Terminal Half-life [days]	32	33.1	28.7 to 41.4
Study Part 2	C _{max} [g/L]	31	14.5	12.3 to 16.4
	T _{max} [days]	31	4.8	3.0 to 4.9
	C _{min} [g/L]	31	12.5	11.3 to 14.2
	AUC [g*days/L]	31	94.2	83.8 to 106.3
	Clearance [mL/kg/day]	31	1.86	1.61 to 2.04
Study Part 3B	C _{max} [g/L]	32	14.1	12.5 to 16.3
	T _{max} [days]	32	2.9	1.2 to 3.2
	C _{min} [g/L]	32	12.6	10.6 to 14.0
	AUC [g*days/L]	32	94.6	80.4 to 106.9
	Clearance [mL/kg/day]	32	2.00	1.84 to 2.12

Table 2: Mean ± SD trough levels of igG and IgG subclasses

Parameters	IgG (g/L)	IgG1 (mg/dL)	IgG2 (mg/dL)	IgG3 (mg/dL)	IgG4 (mg/dL)
Aged 2 to <12 years*					
End of treatment period IV	11 ± 3	625 ± 217	362 ± 99	45 ± 23	27 ± 24
End of treatment period SC	13 ± 3	678 ± 300	407 ± 140	44 ± 22	33 ± 26
Aged 12 to <16 years (n=4)					
End of treatment period IV	9 ± 2	729 ± 186	342 ± 65	56 ± 26	19 ± 16
End of treatment period SC	12 ± 2	682 ± 172	348 ± 96	53 ± 40	17 ± 7
Aged ≥16 years (n=31)					
End of treatment period IV	11 ± 3	588 ± 204	383 ± 138	35 ± 16	18 ± 11
End of treatment period SC	13 ± 3	701 ± 168	464 ± 141	39 ± 13	26 ± 10

*14 subjects in IV and 12 subjects in SC group

Study #2

Study Title: Phase I/II determination of the dose of recombinant human hyaluronidase required enabling up to 600 mg/kg body weight of immune globulin intravenous (human), 10% to be administered subcutaneously in a single infusion site in subjects with primary immunodeficiency diseases (study report: 16062).

Objectives: The objectives of the study were:

- To determine the feasibility of infusing a full 4-week dose of IGIV, 10% in a single SC site and the amount of rHuPH20 needed to infuse that dose (a dose of up to a maximum of 600 mg of IgG/kg BW) with no more than mild local adverse drug reactions (ADRs).
- To obtain preliminary data on the ability of rHuPH20 to improve the bioavailability of subcutaneously administered IGIV, 10% to approximate the bioavailability after intravenous (IV) administration.

Study Design: This was a prospective, open-label, uncontrolled, two-arm multicenter study with the aim of determining the dose of rHuPH20 necessary to infuse a full 4-week dose of IGIV 10%, in a single SC site (up to 600 mg/kg BW of IgG) with good tolerability, and to compare the pharmacokinetics (PK) of the rHuPH20-facilitated subcutaneously administered IgG with the pharmacokinetics of intravenously administered IgG. All infusions were administered at the treatment center. The first and the last PK samples were drawn at the center, while all intermediate samples could be drawn by a home care agency, as determined by the subject and physician. If a subject was to receive more than 600 mg/kg BW/4 weeks, a second infusion site was to be used for administration of IGIV, 10% with the appropriate amount of rHuPH20. This was not considered a treatment failure.

In order to prove tolerability in the study, a minimum of 90% of the subjects had to tolerate one half of a 4-week dose (at least 200 mg/kg BW) and a minimum of 50% had to tolerate a full 4-week dose (at least 400 mg/kg BW) of IgG in a single site with no more than mild local ADRs, such as minimal swelling, redness or pain that the investigator did not assess to be unacceptable for medical reasons.

Study Arm 1: In Study Arm 1, 4 adult/adolescent subjects were to receive only SC infusions of IGIV, 10% to determine tolerability. Infusions started with one quarter of a monthly dose of IGIV, 10% (approximately 10 g) and 150 U of rHuPH20/g IgG. The amount of IGIV, 10% to be infused and the ratio of rHuPH20 per gram IgG were adapted according to a predetermined schedule to achieve infusion of a full 4-week dose. The initial dose of rHuPH20 was calculated on the basis of 150 Units (U)/g IgG in IGIV, 10%, rounded up to the next higher gram of IgG. Thus, if the dose of IgG to be administered was between >7 g and ≤ 8 g, the dose of rHuPH20 was to be 8×150 U or 1,200 U. Subsequent doses of rHuPH20 were also calculated on a per-gram

basis, always rounded up to the next higher gram of IgG. Administration of rHuPH20 was to be completed 5 minutes prior to starting the infusion of the IGIV, 10%.

If one-quarter of the dose was tolerated, 1 week later a half SC dose was administered with a reduced ratio of rHuPH20 (100 U/g IgG) to determine if 150 U/g dose was excessive. If half of the 4-week dose preceded by a ratio of rHuPH20 to IgG of 100 U/g was tolerated, the ratio of rHuPH20 to IgG was progressively reduced, increasing the IGIV, 10% dose first to 3 quarters of the full dose and then to the full 4-week dose while decreasing the ratio of rHuPH20 to IgG to 66 U/g IgG and finally to 50 U/g IgG. After several subjects had tolerated a full 4-week SC dose preceded by the minimum of 50 U of rHuPH20/g IgG, the protocol was amended to attempt using 25 or 10 U/g IgG.

If half of the 4-week dose of IGIV, 10% was not tolerated with 100 U of rHuPH20/g IgG, this dose of IGIV, 10% was repeated 2 weeks later using a ratio of 150 U of rHuPH20/g IgG. If this dose was tolerated, 3 quarters of the 4-week dose were infused 2 weeks later using 150 U of rHuPH20/g IgG, and, provided the latter was tolerated, 3 weeks later a full 4-week dose of IGIV, 10% was administered at the same ratio.

Two males and two females were enrolled in the study arm 1. The age ranged from 26 to 74 years.

Study Arm 2: In this arm, 6 to 8 subjects were to be infused first intravenously with a 4-week dose of IGIV, 10% to determine the pharmacokinetics over the ensuing month. The dose of IGIV, 10% was equivalent to a 4-week dose, regardless of whether the subject had been on a 3- or 4-week schedule prior to the study. As soon as the PK study was complete, subjects received another IV infusion of a 4-week dose of IGIV, 10%. SC infusion of IGIV, 10% combined with rHuPH20 started 1 week later. Administration of rHuPH20 and IGIV, 10% in Study Arm 2 followed the same schedule as used for the tolerability subjects in Study Arm 1. If infusion of an entire 4-week dose of IGIV 10% in a single SC site was tolerated, another 4-week SC dose was administered at the ratio of IgG and rHuPH20 used in the previous treatment and a second PK study was performed over a 4- week period. The results were compared to the PK results obtained after IV infusion in terms of bioavailability as determined by AUC of the IgG concentrations.

If the AUC of the subcutaneously administered IGIV, 10% was below 90% of the IV AUC, the last dose of rHuPH20 used was increased 4-fold (but at a minimum to a dose of 200 U/g IgG or at a maximum to a total dose of 48,000 U), and another SC infusion followed by a PK study was performed.

Two males and five females were enrolled in the study arm 2. The age ranged from 20 to 76 years. Blood samples following IV administration for PK study were drawn at time 0, 30 minutes, days 1, 3, 5, 7, 14, 21, and 28 days. Blood samples following SC administration for PK study were drawn at time 0, 30 minutes, days 1, 2, 3, 4, 5, 7 (on 1 week schedule), 14 (on 2-week schedule), 21 (on 3-week schedule), and 28 days (on 2-week schedule).

To assess the pharmacokinetic equivalence of IV and SC routes of administration, the 90% confidence interval for the difference of the mean logarithms of $AUC_{0-\tau}/\text{dose}$ was calculated.

Results: Table 1 summarizes dose of rHuPH20 per gram IgG in subjects who tolerated dose in a single site with no more than mild ADRs. The primary endpoint criterion of tolerability of half of a 4-week dose by at least 90% was not achieved (82% was achieved). However, more than 50% of the subjects in the safety data set tolerated a full 4-week dose of IGIV 10% facilitated by rHuPH20.

Table 1: Dose of rHuPH20 per gram IgG in subjects who tolerated dose in a single site with no more than mild ADRs

			Dose of rHuPH20 per Gram IgG [U/g]			
Study Arm	Dose Category	N	Mean	SD	Min	Max
STUDY ARMS 1&2	SC (1/4 dose)	8	157	3.9	152	164
	SC (1/2 dose)	9	103	2.8	99	109
	SC (3/4 dose)	9	68	2.0	66	72
	SC (full dose)	9	51	0.9	49	51

The PK parameters of study in Arm 2 are summarized in Table 2. The absolute bioavailability (when compared with IGIV) of IgGSC was 92% (90% Confidence interval ranged from 85% to 100%).

Table 2: Pharmacokinetic parameters of IgG following IV and SC administration

Parameters	# of subjects	Mean \pm Sd
AUC/week (days*g/L) (IV)	7	99 \pm 11
AUC/week (days*g/L) (SC)	7	92 \pm 15
Clearance (mL/day/kg) (IV)	7	1.27 \pm 0.18
Clearance (mL/day/kg) (SC)	7	1.38 \pm 0.23

Conclusions: Due to small size it is not possible to make any definitive conclusion regarding bioavailability of IgGSC administered with rHuPH20. However, it appears that rHuPH20 does facilitate the absorption of IgGSC and improves the bioavailability of IgGSC (without rHuPH20 the bioavailability of IgGSC is 72%).

Study #3

Study Title: Efficacy, tolerability and pharmacokinetic comparison of immune globulin intravenous (human), 10% (GAMMAGARD LIQUID/KIOVIG) administered intravenously or subcutaneously following administration of recombinant human hyaluronidase (rHuPH20) in subjects with primary immunodeficiency diseases (PIDD) (study report: 16063).

Purpose and Objectives: The purpose of the study was to develop a subcutaneous (SC) treatment option for subjects with PID that allows an administration of GAMMAGARD LIQUID at the same frequency as intravenous (IV) administration. The primary objective of the study was to evaluate the efficacy of GAMMAGARD LIQUID administered via the SC route after an administration of rHuPH20 in preventing serious bacterial infections in subjects with PID. The secondary objectives of the study were to evaluate the tolerability and pharmacokinetics (PK) of GAMMAGARD LIQUID and rHuPH20 administered via the SC route.

Study Design: This was a prospective, open-label, non-controlled, multi-center study. Approximately 80 subjects with PID were enrolled in this study. The study consisted of two parts; intravenous (IV) infusion (part 1) and a subcutaneous (SC) administration (part 2).

The dose and interval of GAMMAGARD LIQUID infusions were based on treatment prior to the study, with a minimum dose of 300 mg/kg once every 3 or 4 weeks. Serum trough levels of IgG >4.5 g/L had to be maintained throughout the study; if levels fell to ≤ 4.5 g/L, the dose was to be adjusted and trough levels re-evaluated at the next infusion. An initial infusion rate of 0.5 mL/kg body weight/hour was to be used and increased as tolerated to a maximum rate of 5.0 mL/kg body weight/hour at the discretion of the investigator.

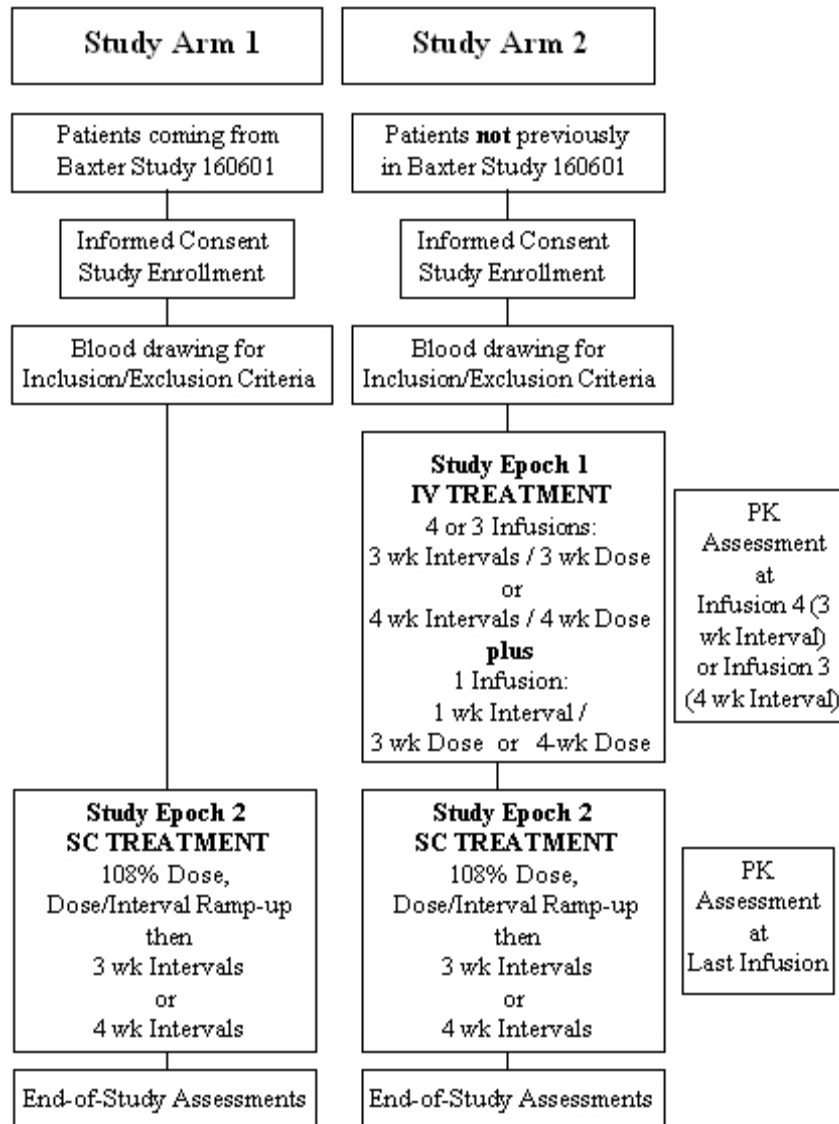
Treatment intervals and doses for the initial SC infusions were to be gradually increased during the first weeks of treatment. The aim was to treat subjects with SC administration at the same intervals (every 3 or 4 weeks) at which they had received IV treatment before the study. The dose was to be calculated and administered on the basis of weekly equivalents, 1 weekly equivalent being the dose calculated for a 4-week period, multiplied by 108% and divided by 4. The 3- or 4-week adjusted dose was 108% of the 3- or 4-week equivalent of the dose used during IV treatment.

When a subject reached steady-state at a SC interval equal to the IV interval (after 3 or 4 SC infusions at 4- or 3-weeks intervals, respectively), the IgG trough level (IgG_{SC}) were reviewed and compared with the trough level determined during IV treatment. If the trough level ratio was not within 15% of the expected value of 108%, the dose was corrected, using the formula for the next infusion:

$$\text{Dose}_{(\text{corrected})} = \text{Dose} * (1 + (1.08 - \text{IgG}_{\text{SC}} / \text{IgG}_{\text{IV}}) / 2)$$

Dose of rHuPH20: rHuPH20 was administered at a dose ratio of at least 75 U/g IgG before the SC infusion of GAMMAGARD LIQUID. Doses were rounded up to the nearest appropriate vial size. The maximum volume of rHuPH20 for the majority of subjects was approximately 20 mL (3,000 U). rHuPH20 was administered before each SC GAMMAGARD LIQUID infusion. rHuPH20 was injected at a rate of 1 to 2 mL/min.

Figure 1: Study design for study 160603



The study population consisted of approximately 80 subjects, at least 2 years of age at the time of screening, males and females of any ethnic group and race with PID including 16 to 20 subjects below the age of 18.

PK was assessed following IV infusion #4 (for 3-week treatment interval) or IV Infusion #3 (for 4-week treatment interval). PK was also assessed following the last SC infusion (for 3-week or 4-week treatment interval, depending on the subject's treatment schedule). Blood samples for subjects 12 years and older were collected at time 0, 30 minutes after infusion, days 1, 4, 9, 14, and 21 and 28 (for 4 week treatment). For subjects 2 to <12 years blood samples were taken at IgG trough levels at baseline and day of each infusion following IV administration and day of each infusion (except during the ramp-up and at the end of the study following SC administration). The concentrations of IgG, IgG subclasses, anti-H influenza antibody and anti-tetanus antibody were determined. The main objective of PK study was to determine bioavailability of GAMMAGARD LIQUID as follows:

- a. Bioavailability of IgG after administration of GAMMAGARD LIQUID given via IV or SC with rHuPH20 as measured by area under the IgG concentration versus time curve (AUC) for subjects aged 12 years and older
- b. Bioavailability of IgG after administration of GAMMAGARD LIQUID given IV or SC with rHuPH20 as measured by trough levels of IgG for subjects aged 2 to < 12 years. A formal demonstration of PK equivalence was not feasible for subjects aged 2 to <12 years due to the limited number of blood samples taken from this population as well as sample size. Nonetheless, the median and range of the ratios of the geometric mean of 2 IgG trough levels with IV and SC administration will be used to assess pharmacokinetic equivalence in subjects aged 2 to <12 years.
- c. Comparison of bioavailability of IgG after SC administration of GAMMAGARD LIQUID without rHuPH20 (data from clinical study 160601) and after SC administration of GAMMAGARD LIQUID with rHuPH20 (data from this study, Study Arm 2) as measured by AUC/trough levels.

Results: GAMMAGARD LIQUID was administered at a mean weekly equivalent dose of 0.137 g/kg BW (IV treatment) and 0.164 g/kg BW (SC treatment with rHuPH20) in subjects aged 2- <12 years. In subjects aged ≥ 12 years, the mean total dose per week was 0.144 g/kg BW for IV treatment and 0.154 g/kg BW for SC treatment. In SC-naïve subjects, the mean total dose per week was similar to that in the safety analysis data set (SADS) in subjects aged ≥ 12 years, but was lower in subjects aged 2- <12 years (0.105 g/kg BW in IV treatment and 0.117 g/kg BW in Sc treatment excluding the ramp-up).

The bioavailability (based on AUC) of SC administration with rHuPH20 in subjects ≥ 12 years was 93.3% (90% Confidence Interval (CI) = 91.4% to 95.2%). Bioavailability determined by serum IgG trough levels was 103.8% in subjects aged 2 to <12 years, and 98.5% in subjects aged ≥ 12 years. The PK parameters of the study are summarized in Table 1 and the levels of IgG and IgG subclasses are presented in Table 2.

Table 1: Pharmacokinetic parameters of IgGV following IV and SC administration

Parameters	# of subjects	Mean \pm Sd
AUC/week (days*g/L) (IV)	69	99 \pm 24
AUC/week (days*g/L) (SC)	60	91 \pm 21
Clearance (mL/day/kg (IV)	69	1.40 \pm 0.36
Clearance (mL/day/kg (SC)	60	1.63 \pm 0.48

Table 2: Mean \pm Sd trough levels of igG and IgG subclasses

Parameters	IgG (g/L)	IgG1*	IgG2*	IgG3*	IgG4*
Aged 2 to <12 years	19 subjects in IV and 11 subjects in SC group				
End of treatment period IV	10 \pm 2	545 \pm 166	348 \pm 108	38 \pm 19	26 \pm 21
End of treatment period SC	10 \pm 3	544 \pm 171	362 \pm 124	53 \pm 25	34 \pm 36
Aged 12 to <16 years	19 subjects in IV and 11 subjects in SC group				
End of treatment period IV	12 \pm 2	729 \pm 186	342 \pm 65	56 \pm 26	19 \pm 16
End of treatment period SC	12 \pm 2	698 \pm 169	346 \pm 61	66 \pm 30	22 \pm 16
Aged \geq 16 years (n=31)	73 subjects in IV and 61 subjects in SC group				
End of treatment period IV	11 \pm 3	588 \pm 204	383 \pm 138	35 \pm 16	18 \pm 11
End of treatment period SC	11 \pm 3	567 \pm 208	373 \pm 146	37 \pm 18	19 \pm 13

*Units of IgG subclasses are in mg/dL

IgG, IgG1, and IgG2 levels were comparable between children aged 2 to <12 years and subjects \geq 16 years of age. On the other hand, IgG3 and IgG4 levels were comparatively higher in children than the older subjects.

Conclusions: The results of the study indicate that administration of IgGSC along with rHuPH20 increases the bioavailability of IgG by 20% as compared to the bioavailability of IgG SC when given alone (without rHuPH20). Furthermore, the bioavailability of IgGSC determined based on trough levels in children is unreliable.