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Food and Drug Administration  
Center for Biologics Evaluation and Research  
Office of Biostatistics and Epidemiology  
Division of Biostatistics

## Mid-Cycle Statistical Review and Evaluation - BLA

**BLA/Supplement Number:** 125402/0

**Product Name:** Immune Globulin Infusion (Human), 10% (IGI, 10%) with Recombinant Human Hyaluronidase (rHuPH20)

**Indication(s):** Primary Immunodeficiency Diseases

**Applicant:** Baxter Healthcare Corporation, Baxter BioScience

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**Review Priority:** Standard

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## 1. EXECUTIVE SUMMARY

This statistical review memo serves as the mid-cycle review commitment for BLA 125402/0.

### 1.1 Conclusions and Recommendations

1. The major analysis results are reproducible.
2. The pivotal study 161003 met the efficacy success criterion that the rate of validated acute serious bacterial infections per year is significantly lower than 1.0, for subjects with PIDD using IGSC, 10% + rHuPH20.
3. Both study 161001 and study 170901 part 4 were not able to show that the pre-administered rHuPH20 enhanced SC administration of IGSC, 10%.
4. In study 160602, a volume of one half of a 4-week SC dose and the full 4-week SC dose of IGIV, 10% facilitated by rHuPH20 was tolerated by 9 out of 11 subjects each at the first infusion of the respective dose. Thus, the primary endpoint criterion of tolerability of half of a 4-week dose by at least 90% was not achieved.
5. As for product approval, although the pivotal study 161003 met the efficacy success criterion, the other three major factors should be taken into consideration: 1) safety, 2) tolerability, and 3) the benefit of pre-administered rHuPH20.

### 1.2 Major Statistical Issues and Findings

The two major statistical issues were all related to the pivotal study 161003.

1. Among the subjects received IGIV, 10% SC + rHuPH20 treatment in Epoch 2, 40 subjects had not previously been exposed to the SC route and they were included in the Subcutaneous Immunoglobulin Naive Subjects Data Set (SNDS). Presumably, compared to the other 41 subjects who had previously been exposed to the SC route (non-SNDS), these subjects were expected to have worse tolerance and more AEs. This reviewer's analyses (Table 13) seem to confirm such assumption. Therefore, the safety analyses based on the full population could be biased. This issue also relates to which results to be reported in the labeling.
2. In Epoch 1, 2 of the 109 (1.8%) related AEs were local, while 146 of the 196 (74.5%) related AEs were local in Epoch 2 (Table 11).

## 2. INTRODUCTION

### 2.1 Overview

#### 2.1.1 Product Information

Immune Globulin Infusion (Human) 10% (IGSC, 10%) is identical to Baxter's licensed product Immune Globulin Intravenous (Human), 10% Solution (IGIV, 10%), a liquid human immunoglobulin G (IgG) preparation for intravenous (IV) administration. When IGIV, 10% is infused subcutaneously, it is referred to as IGSC, 10%.

Baxter's combination product, IGSC, 10%, with Recombinant Human Hyaluronidase (rHuPH20) has been developed to enable administration of IgG subcutaneous (SC) every 3 or 4 weeks as an alternative to IV administration or more frequent SC administration in patients

with primary immunodeficiency diseases (PIDD). The function of rHuPH20 in the new product combination is to promote the dispersion and absorption of IGSC, 10% by temporarily increasing the permeability of the subcutaneous tissue. HYLENEX, a preparation of rHuPH20, was approved by the 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. The proposed indication for IGSC, 10% with rHuPH20 is the treatment of patients with PIDD associated with defects in humoral immunity.

### 2.1.2 Clinical Studies

Five clinical studies were conducted to support Baxter’s application for the licensing of IGSC, 10% with rHuPH20 for IgG replacement therapy in PIDD.

**Table 1.** Overview of Clinical Studies

Study	Study Phase and Design	Objectives of Study	n
160601	Phase 2/3 Prospective, open-label, nonrandomized, multi-center study (Oct 2007 to Jul 2009)	To evaluate tolerability and PK of IGIV, 10% given SC in subjects with PIDD. To evaluate efficacy in acute serious bacterial infections	49
160602	Phase 1/2 prospective, open-label, nonrandomized, 2-arm multicenter study (Dec 2006 to Nov 2007)	Determination of the dose of rHuPH20 enabling up to 600 mg/kg BW of IGIV, 10% to be administered SC in a single infusion site in subjects with PIDD	11
<b>160603 pivotal</b>	Phase 3, prospective, open-label, nonrandomized, multi-center study (Dec 2008 to Nov 2011)	To evaluate efficacy, safety, tolerability and PK comparison of IGIV, 10% administered IV or SC following administration of rHuPH20 in subjects with PIDD	87
161001	Phase 1, prospective, randomized, within-subject/ between-subjects, placebo controlled, single-center study (Sep 2010 to Dec 2010)	Evaluation of the effectiveness of rHuPH20 in enhancing SC administration of IGSC, 10% in healthy volunteers	53
170901 Part4	Phase 1 randomized, double blind, controlled study (Aug 2009 to Dec 2010)	IGSC, 10% administered either alone or in combination with rHuPH20 for the evaluation of safety, tolerability, and optimal dose ratio in healthy volunteers	12

### 2.2 Data Source

This is an eCTD submission. Data sources are located in the FDA’s Electronic Document Room (EDR) at the following link:

----- (b) (4) -----

## 3. STATISTICAL EVALUATION

### 3.1 Study 160601 (under IND (b)(4))

#### 3.1.1 Study Design and Endpoints

This is a Phase 2/3, prospective, open-label, non-controlled, multi-center study in subjects with PIDD with the aim of determining the tolerability and pharmacokinetics of IGIV, 10%

given subcutaneously. The pharmacokinetics of IGIV, 10% administered subcutaneously was compared to the pharmacokinetics of IGIV, 10% administered intravenously.

Subjects received IV infusions of IGIV, 10% (study part 1) for 12 weeks, and then received weekly SC IGIV, 10% infusions for 30 weeks (part 2, part 3a, part 3b).

**Pharmacokinetics primary endpoint:**

- Area under the IgG concentration versus time curve (AUC) per week in subjects aged 12 years and older
- Trough levels of IgG in subjects aged 2 to <12 years

**Efficacy:** infections

**Safety:** ability to tolerate IGIV, 10% administered intravenously or subcutaneously

**3.1.2 Patient Disposition, Demographic and Baseline Characteristics**

The full safety dataset (FSDS) comprises 49 subjects who received any amount of investigational product. Among them, one subject did not complete study part 1, and four additional subjects did not finish parts 2 and 3.

22 of the 49 subjects were female and 46 of them were Caucasian. Among the subjects aged 2 to <12 years, the median age at enrollment was 7.5 (range 3 to 11) years; among the subjects aged 12 years and older, it was 36 (range 14 to 77) years.

**3.1.3 Results**

**Pharmacokinetics:**

Analysis results of the primary endpoint, PK equivalence in terms of  $AUC_{0-\tau}$ /week following IV administration and SC administration of IGIV, 10% at an Adjusted/Individually Adapted Dose in Study Part 3b in subjects aged 12 years and older, are listed in Table 2.

**Table 2.** Pharmacokinetic Equivalence by AUC/Week for Subjects  $\geq 12$  yrs (Table 14.2.1-1\*)

Dataset	Parameter	N	Ratio AUC_SC/AUC_IV	90% CI for Ratio
PKEQUI	AUC per week	29	95.2%	92.3% to 98.2%

\*: This table is copied from sponsor’s Table 14.2.1-1.

PK equivalence was demonstrated within the predetermined margins of equivalence of 80% to 125% at an Adjusted/Individually Adapted SC Dose of 137.3% in subjects aged 12 years and older with PIDD.

**Infections:**

A total of 3 subjects had acute serious bacterial infections while on SC treatment with IGIV, 10%, which resulted in an annual rate of 0.067 with 99% upper confidence limit of 0.134. All 3 infections were bacterial pneumonias. No acute serious bacterial infections were reported during the 12-week period of IV replacement.

For the FSDS including subjects of all ages (N=49), an estimated annual infection rate of 5.1 (95% CI 3.7 to 6.9) was calculated for the IV treatment period (Study Part 1). For all SC

treatment periods (Study Parts 2, 3a, 3b, and Extension), the cumulative, estimated annual infection rate was 4.1 (95% CI 3.2 to 5.1).

### **Safety:**

A total of 226 AEs were reported during the IV treatment period (Study Part 1), and 634 AEs were reported during the SC treatment periods (Study Parts 2, 3, and Extension). Among these, 85 AEs were considered related to the use of IGIV, 10% during IV treatment, and 150 AEs were considered related during SC treatment.

None of the 4 SAEs reported during the IV and SC treatment periods were considered related to the use of IGIV, 10% by the investigator.

The proportion of infusions associated with related AEs was higher after IV infusion (22.2%; 46/207) than after SC infusion of IGIV, 10% (5.5%; 127/2294).

The proportion of infusions associated with systemic AEs (excluding infections) that began during infusion or within 72 h of completion of infusion was higher during IV treatment (28.0%, 58/207) than during SC treatment (6.8%, 155/2294). The proportion of infusions associated with local AEs was 1.0% in Study Part 1 during IV replacement, 4.9% in Study Part 2, 2.2% in Study Part 3a, 1.5% in Study Part 3b, and 1.1% in the Study Extension Part.

The major symptom/AE reported during SC administration was injection-site reactions. The most frequently reported related systemic AE was headache.

Among all subjects in FSDS, reduction of the infusion rate and/or interruption or discontinuation of the infusion occurred

- in Study Part 1 in 18.4% (9/49) for any reason, in 16.3% (8/49) for tolerability reasons
- in Study Part 2 in 29.8% (14/47) for any reason, in 4.3% (2/47) for tolerability reasons
- in Study Part 3a in 15.9% (7/44) for any reason, in 2.3% (1/44) for tolerability reasons
- in Study Part 3b in 13.6% (6/44) for any reason, in 2.3% (1/44) for tolerability reasons

### **3.1.4 Reviewer's Comments**

1. A total of 3 subjects had acute serious bacterial infections during the 30-week SC treatment with IGIV, 10%, while no acute serious bacterial infections were reported during the 12-week period of IV replacement. Although the treatment duration was longer for the SC infusion, it may be necessary for the clinical reviewer to investigate the 3 subjects with acute serious bacterial infections in details.
2. It seems that Study Part 2 involved with more frequent infusion associated with local AEs. For example, the proportion of infusions associated with local AEs was 1.0% in Study Part 1 during IV replacement, 4.9% in Study Part 2. In addition, among all subjects in FSDS, reduction of the infusion rate and/or interruption or discontinuation of the infusion occurred was 18.4% in Study Part 1 and 29.8% in Study Part 2 respectively. The clinical reviewer may need to evaluate whether it was acceptable.

### **3.2 Study 160602 (under IND (b)(4))**

#### **3.2.1 Study Summary**

Study 160602 was a phase 1-2 pilot study conducted in 11 adults with PIDD.

The first 4 subjects were included in Study Arm 1 investigating the tolerability of a full 4-week SC dose of IGIV, 10% facilitated by pretreatment with rHuPH20 using a predefined schedule. After initial assessment of tolerability in Study Arm 1, 7 subjects were enrolled in Study Arm 2 for determination of tolerability of SC infusions as described for Study Arm 1 and comparison of PK parameters obtained after IV and SC administration of IGIV, 10%.

A volume of one half of a 4-week SC dose and the full 4-week SC dose of IGIV, 10% facilitated by rHuPH20 was tolerated by 9/11 subjects each at the first infusion of the respective dose. Thus, the primary endpoint criterion of tolerability of half of a 4-week dose by at least 90% was not achieved.

Two (2) SC infusions, 1 in each study arm, had to be interrupted due to mild infusion site pain and mild chest pain, respectively.

In all of the 10 subjects who completed the study, administration of a full 4-week SC dose of IGIV, 10% was accomplished. Only 1 subject had a moderate injection site pruritus, which rendered the full 4-week SC dose not tolerated according to the study protocol.

Bioavailability of IGIV, 10% administered subcutaneously, as measured by AUC, was calculated to be 92% (90% confidence interval [CI]: 85% to 100%) of the bioavailability after IV infusion.

#### **3.2.2 Reviewer's Comments**

1. In this study, a volume of one half of a 4-week SC dose and the full 4-week SC dose of IGIV, 10% facilitated by rHuPH20 was tolerated by 9/11 subjects each at the first infusion of the respective dose. Thus, the primary endpoint criterion of tolerability of half of a 4-week dose by at least 90% was not achieved. Will this concern CBER?
2. Among the 11 subjects enrolled, 1 subject (9%) had a moderate injection site pruritus, which rendered the full 4-week SC dose not tolerated according to the study protocol. Will this concern CBER?

### **3.3 Study 161003 (under IND 13840)**

#### **3.3.1 Study Design and Endpoints**

Study 161003 was a prospective, open-label, non-controlled, multi-center study to evaluate the efficacy of GAMMAGARD LIQUID/KIOVIG administered via the SC route after an administration of rHuPH20 in preventing serious bacterial infections in subjects with PIDD.

87 subjects were enrolled at 14 study sites in the USA and Canada.

The study consisted of 2 study epochs:

- Study Epoch 1: once every 3 or 4 weeks, for 13 weeks, IV treatment with GAMMAGARD LIQUID/KIOVIG

- Study Epoch 2: starting with a ramp-up with treatment intervals of 1 week, then 2 weeks, then 3 weeks, (then 4 weeks if applicable); then once every 3 or 4 weeks for 14 months, SC treatment with GAMMAGARD LIQUID/KIOVIG after administration of rHuPH20.

Subjects were to be enrolled into one of 2 study arms:

- Study Arm 1 comprised of subjects who previously participated in the Clinical Study 160601 and wished to also participate in this follow-up study. These subjects only completed Study Epoch 2 (as bioavailability/exposure for IV treatment had already been obtained in the previous study, Study 160601).
- Study Arm 2 comprised all other subjects. These subjects completed Study Epoch 1 and Study Epoch 2.

The primary endpoint was the validated acute serious bacterial infection rate, defined as the mean number of validated acute serious bacterial infections per subject per year in the intent-to-treat population.

The secondary efficacy endpoints include pharmacokinetics, infections, IgG trough levels and specific antibody titers, days off school/work, on antibiotics, acute physician visits and in hospital.

### 3.3.2 Patient Disposition, Demographic and Baseline Characteristics

The following data sets were analyzed.

**Full Analysis Data Set (FADS; n=81):** All subjects who had been exposed to either or both study drugs and who provided data for the primary endpoint for any period of time.

**Per-Protocol Data Set (PPADS; n=74):** A subset of the FADS including only subjects who completed at least 6 months of SC treatment after the ramp-up.

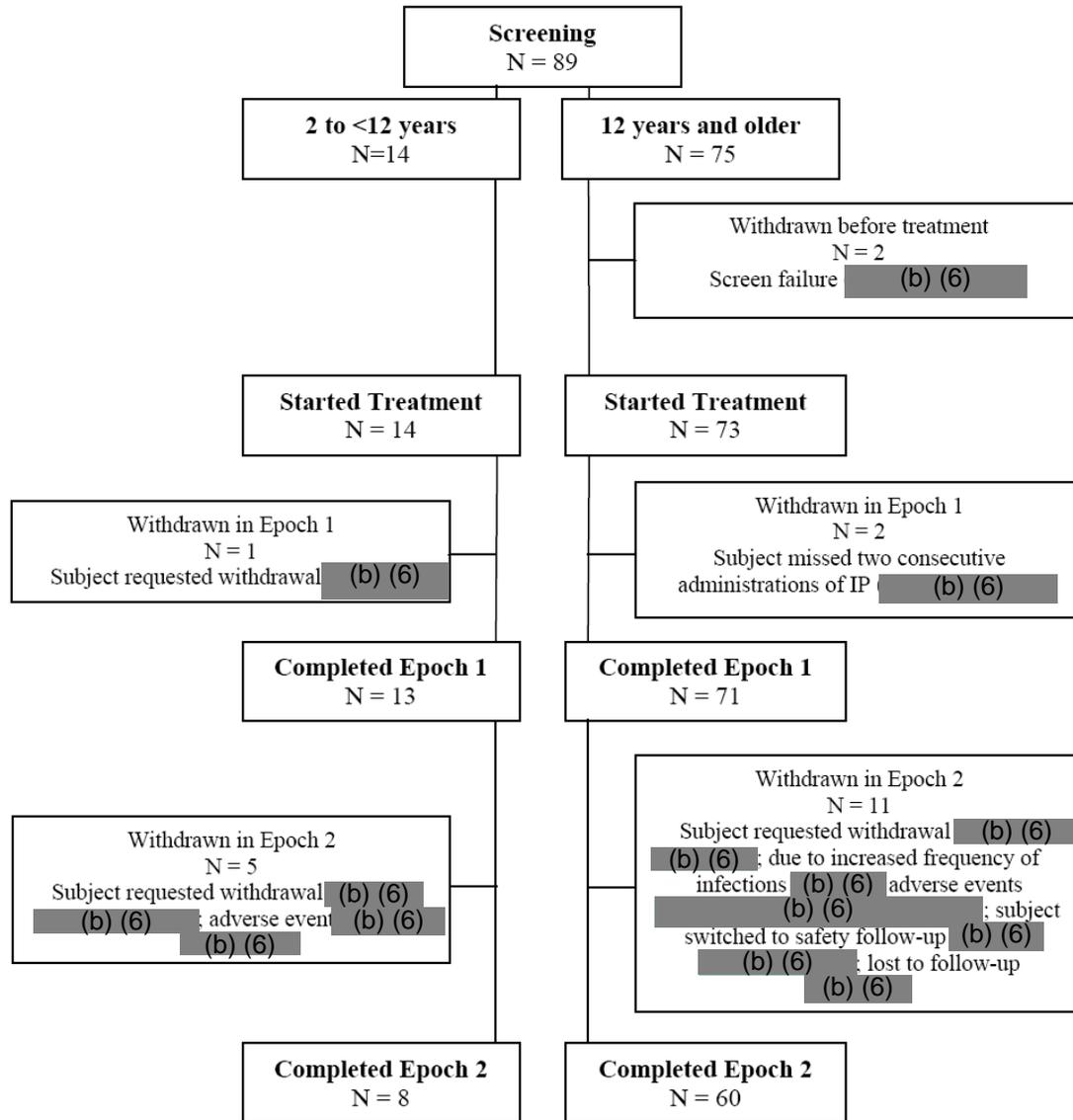
**Safety Analysis Data Set (SADS, n=87):** All subjects exposed to either or both study drugs.

**Subcutaneous Immunoglobulin Naive Subjects Data Set (SNDS; n=44):** Subjects who had not previously been exposed to immunoglobulins by the SC route.

Among the 87 subjects in SADS, 73 (84%) of them were aged 12 years and older and 14 (16%) of them were aged 2 to <12 years. The median age was 35.0 years (range: 4-78 years). 57% of them were male. The majority of subjects (79/87; 90.8%) were white.

Common variable immune deficiency (CVID) was the most commonly diagnosed PIDD (49/87 subjects), followed by hypogammaglobulemia (17/87 subjects) and X-linked agammaglobulinemia (6/87).

**Figure 1.** Disposition of Subjects (Figure10.1-1)



### 3.3.3 Statistical Methodologies

The primary endpoint, validated acute serious bacterial infections/subject/year, was to be analyzed using a Poisson model. A point estimate of the rate and its 99% upper confidence limit was to be provided.

The null hypothesis of one or more validated acute serious bacterial infections/subject/year was to be tested against the alternate hypothesis of less than 1 validated acute serious bacterial infection/subject/year at the 1% level of statistical significance.

In subjects of age 12 years or older, pharmacokinetic equivalence of IV GAMMAGARD LIQUID/KIOVIG and SC GAMMAGARD LIQUID/KIOVIG treatment with rHuPH20 was to be assessed by a 90% confidence interval for the ratio of AUC<sub>0-t</sub>.

Other secondary endpoints and safety variables were to be analyzed descriptively.

### 3.3.4 Results and Conclusions

#### Primary Endpoint

The results of the rate of validated acute serious bacterial infections per year during SC administration of GAMMAGARD LIQUID/KIOVIG with rHuPH20 were shown in Table 3.

**Table 3.** Analysis of Validated Acute Serious Bacterial Infections (Table 14.2-2)

Analysis Set	Point Estimate	Rate of VASBIs/Year
		Upper Limit of 99% CI
Full Analysis Set	0.025	0.046
Per-Protocol Analysis Set	0.025	0.048
SCIG Naive Subjects Analysis Set	0.000	0.130

In above three data sets, the rate of validated acute serious bacterial infections per year was significantly lower than 1.0 ( $p < 0.0001$ ).

Two validated acute serious bacterial infections (one each in Subjects -----(b)(6)-----) were reported during the prospectively planned observation period, which began with the day of the first SC infusion at the final infusion interval after the ramp-up. In addition, 1 validated acute serious bacterial infection occurred during the ramp-up (in Subject -(b)(6)--, which was not included in the observation period.

#### Bioavailability as Determined by $AUC_{0-\tau}$ of IgG

PK equivalence of IgG with respect to  $AUC_{0-\tau}$  for GAMMAGARD LIQUID/KIOVIG administered SC with rHuPH20 at an adapted dose vs. IV was demonstrated according to the prospective definition: a 2-sided 90% CI for the ratio of the geometric means contained completely in the margins of 80% to 125%. The results were shown in Table 4.

**Table 4.** PK Equivalence of IgG by AUC/Week for Subjects  $\geq 12$  Years (Table 14.2-6)

Analysis Set	N	AUC/Week	
		Ratio AUC Epoch 2/ AUC Epoch 1	90% CI for Ratio
Full Analysis Set	58	93.3%	91.4% to 95.2%
Per-Protocol Analysis Set	58	93.3%	91.4% to 95.2%
SCIG Naive Subjects Analysis Set	30	93.9%	91.1% to 96.8%

#### Bioavailability as Determined by IgG Trough levels

The median ratio of serum IgG trough levels at the end of Epoch 2 (SC infusions with rHuPH20) to at the end of Epoch 1 (IV infusions) were shown in Table 5 below.

**Table 5. Ratio of IgG Trough Levels (Table 14.2-11)**

Analysis Set	Age Group	N	Ratio IgG Trough Level at End of Epoch 2/ IgG Trough Level at End of Epoch 1	
			Median	95% CI for Median
Full Analysis Set	Subjects aged 2 to <12 years	11	103.8%	97.5% to 115.4%
	Subjects aged 12 years and older	70	98.5%	94.4% to 102.5%
Per-Protocol Analysis Set	Subjects aged 2 to <12 years	9	101.8%	94.9% to 105.5%
	Subjects aged 12 years and older	65	97.4%	94.2% to 102.2%
SCIG Naive Subjects Analysis Set	Subjects aged 2 to <12 years	3	99.6%	NA
	Subjects aged 12 years and older	37	101.4%	94.4% to 104.1%

**Bioavailability of SC Infusions With and Without rHuPH20, as Determined by AUC**

The bioavailability of GAMMAGARD LIQUID/KIOVIG with respect to AUC per dose/kg was approximately 20% higher when administered SC with rHuPH20 (in Study 160603) than SC without rHuPH20 (in Study 160601) shown in Table 6 below.

**Table 6. Analysis of Bioavailability of IgG Subcutaneously With and Without rHuPH20 (Study 160603 + 160601)**

Stratum	N	Ratio of AUC/ (dose per kg)	90% CI for Ratio
Stratum A	19	118.7 %	113.6 % to 124.1 %
Stratum B	54	133.6 %	118.3 % to 150.8 %
Overall	73	120.4 %	115.5 % to 125.5 %

**Stratum A:** Subjects who provided data both on SC with and without rHuPH20 (subjects in Study Arm 1 of study 160603, i.e. subjects who participated in studies, 160601 and 160603).

**Stratum B:** Subjects who provided data on SC with or without rHuPH20, but not on both (subjects who participated in one of the studies, 160601 and 160603, but not the other).

**Rate of All Infections**

The point estimate of the annualized rate of all infections during SC administration with rHuPH20 was 2.97 [95% CI: 2.51; 3.47] compared to IV infusions 4.51 [95% CI: 3.50; 5.69].

An exploratory analysis accounting potential seasonal effects showed that the infection rate was 4.3/year for IV and 2.3/year for SC+rHuPH20 (p=0.0021).

**Sensitivity Analysis for Rate of All Infections**

Two sensitivity analyses for the rate of infections were performed to address the potential effects of subjects not completing the full year of SC treatment with rHuPH20. The first analysis employed Rubin's multiple imputation methods using the following rules:

- In subjects who terminated the study for increased frequency/severity of infections, twice the highest infection rate observed in subjects who completed more than 2 months in the same season was to be used.
- In subjects who did not leave the study for increased frequency/severity of infections, the subject's rate in that season was to be used, if more than 2 months were observed, and the rate observed in subjects who completed 2 months or more in the same season.

The point estimate of the annualized rate of all infections was 3.24 (95% CI: 2.65; 3.96) by multiple imputations.

The second analysis restricted to the 41 subjects in the FADS who had completed a full year of treatment to subjects. The point estimate of the rate of all infections per year was 2.75 (95% CI: 2.09; 3.54).

### Pharmacokinetics of IgG for IV Infusions and SC Infusions with rHuPH20

**Table 7.** PK Parameters of IgG for Subjects Aged  $\geq 12$  Years in FADS (Table 14.2-8)

Parameter	Treatment	N	Median	95% CI for Median
C <sub>min</sub> [g/L]	IV	68	10.1	9.5 to 10.9
	SC with rHuPH20	60	10.4	9.4 to 11.2
AUC/week [g*days/L]	IV	68	93.9	89.1 to 102.1
	SC with rHuPH20	60	90.5	83.8 to 98.4
Clearance [mL/kg/day]	IV	68	1.4	1.2 to 1.4
Apparent Clearance [mL/kg/day]	SC with rHuPH20	60	1.6	1.4 to 1.7
Terminal Half-life [days]	IV	68	35.7	32.4 to 40.4
	SC with rHuPH20	60	45.3	41.0 to 60.2
C <sub>max</sub> [g/L]	IV	68	21.9	20.7 to 23.9
	SC with rHuPH20	60	15.5	14.5 to 17.1
T <sub>max</sub> [days]	IV	68	0.1	0.1 to 0.1
	SC with rHuPH20	60	5.0	3.3 to 5.1

The difference between SC infusions with rHuPH20 and IV infusions was evident with respect to the median values for C<sub>max</sub> and T<sub>max</sub> in all efficacy data sets.

### Days off School or Work

The point estimates for SC with rHuPH20 and IV respectively for the number of days off school/work per month were 0.23 (95% CI: 0.15; 0.34) and 0.28 (95% CI: 0.20; 0.37), and the point estimates for acute physician visits were 0.33 (95% CI: 0.23; 0.45) and 0.40 (95% CI: 0.32; 0.49).

### Safety

All safety analyses were conducted on the Safety Analysis Data Set (n=87), which included all subjects exposed to the study drug(s). A total of 87 subjects began treatment by the IV route in Epoch 1, and 83 subjects began treatment with GAMMAGARD LIQUID/KIOVIG SC with rHuPH20 in Epoch 2 of the study.

Analyses of the safety endpoints were conducted for IV administration and for SC administration with rHuPH20 at the dose used in Study Epoch 2 after the ramp-up phase; therefore, the ramp-up phase was excluded from these analyses. The tolerability of SC infusions with rHuPH20 during the ramp-up phase was summarized separately.

### Extent of Exposure

A total of 365 infusions were administered IV and 1359 were administered SC with rHuPH20 (1129 in Epoch 2 and 230 in the ramp-up phase). Among the 1359 infusions given SC with rHuPH20, 90.1% were administered in the abdomen and 8.6% in the thighs.

The median duration of IV treatment in Epoch 1 was same for subjects aged 2-<12 years and those aged  $\geq 12$  years: 91.0 days. The durations in Epoch 2 (excluding the ramp-up) for SC infusions with rHuPH20 were compared among different analysis sets in Table 8 below.

**Table 8.** Summary of Duration of Treatment among Different Analysis Set [days] Epoch 2 (Table 14.3-2, Table 14.3-4, Table 14.3-5)

Dataset	Age Group	N	Mean	SD	Min	Median	Max
Safety Analysis Set	Subjects aged 2 to <12 years	11	360.3	120.5	156	366.0	505
	Subjects aged $\geq 12$ years	70	368.8	102.0	42	365.5	507
Per-Protocol Analysis Set	Subjects aged 2 to <12 years	9	404.2	78.6	274	423.0	505
	Subjects aged $\geq 12$ years	65	389.9	69.1	184	378.0	507
Naive Subjects Analysis Set	Subjects aged 2 to <12 years	3	284.3	133.8	156	274.0	423
	Subjects aged $\geq 12$ years	37	326.6	104.7	42	337.0	449

In the ramp-up period, GAMMAGARD LIQUID/KIOVIG was administered SC with rHuPH20 for a median of 42 days in both age groups and in all data sets.

**Table 9.** Summary of Duration of Infusion among Different Analysis Set [hrs] Epoch 2

Dataset	Age Group	N	Min	Median	Max
Safety Analysis Set	Subjects aged 2 to <12 years	11	1.15	1.73	3.28
	Subjects aged $\geq 12$ years	70	0.83	2.13	4.68
Per-Protocol Analysis Set	Subjects aged 2 to <12 years	9	1.33	1.73	3.28
	Subjects aged $\geq 12$ years	65	0.83	2.13	4.68
Naive Subjects Analysis Set	Subjects aged 2 to <12 years	3	1.15	1.65	1.98
	Subjects aged $\geq 12$ years	37	1.05	2.13	4.68

### Adverse Events

In both study Epoch 1 and Epoch 2 excluding the ramp-up, 100% of the infusions administered were tolerated. The proportion of infusions temporally associated with AEs including infections (ie one or more AEs began during the infusion or within 72 hours of completion of the infusion) were summarized in Table 10.

**Table 10.** Proportion of Infusions With  $\geq 1$  Temporally Associated AEs (Table 14.3-39)

Treatment	Total Number of Infusions	Infusions With One or More Temporally Associated AEs	
		Including Infections n (%)	Excluding Infections n (%)
IV	365	110 (30.1%)	105 (28.8%)
SC with rHuPH20	1129	277 (24.5%)	257 (22.8%)

**Table 11.** Summary of AEs (Table 14.3-58, Table 14.3-59)

		n	Related AEs	Local AEs	Systemic AEs
Epoch 1	SAEs	4	0	0	0
	Non-serious AEs	383	109	2 (1.8%)	107 (98.2%)
Epoch 2	SAE	11	0	0	0
	Non-serious AEs	1074	134 (IGIV)	37 (27.6%)	97 (72.4%)
			54 (rHuPH20)	46 (85.2%)	8 (14.8%)
			196 (both)	146 (74.5%)	50 (25.5%)
total		384	<b>229 (59.6%)</b>	<b>155 (40.4%)</b>	

AEs occurring during the ramp-up period were analyzed separately. All but 3 of the 230 SC infusions with rHuPH20 during the ramp-up were tolerated.

During SC administration with rHuPH20 and IV infusions respectively, 9.9% and 6.9% of subjects had infusion requiring flow rate reduction, 4.9% and 4.6% had infusions that were interrupted, and 1.2% and 0.0 had to be stopped due to tolerability concerns or adverse events.

No flow rate reduction, interruption or stopping was required for 97.7% of infusions administered SC with rHuPH20, and 95.9% of IV infusions.

A higher median rate of infusions associated with one or more moderate or severe temporally associated AEs was reported for SC administration with rHuPH20 than for IV administration when infections were included as AEs (5.9% [95% CI: 0.0; 7.1] versus 0.0 [95% CI: 0.0; 0;0]). However, the median rates were 0.0 for both IV infusions and SC administration with rHuPH20 when infections were excluded (95% CI for SC with rHuPH20: 0.0; 6.3; 95% CI for IV: 0.0; 0.0).

**Table 12.** Infusions With  $\geq 1$  Moderate or Severe AEs That Begin during Infusion or Within 72 Hours of Completion of Infusion

Treatment	Including Infections		Excluding Infections	
	Median Rate	95% CI for Median Rate	Median Rate	95% CI for Median Rate
IV	0.0%	0.0% to 0.0%	0.0%	0.0% to 0.0%
SC with rHuPH20	5.9%	0.0% to 7.1%	0.0%	0.0% to 6.3%

The median rate of infusions temporally associated with one or more local AEs was 5.9% (95% CI: 0.0; 8.3) for SC infusions with rHuPH20 and 0.0 (95% CI: 0; 0) for IV infusions, regardless of whether infections were included as AEs or not.

The rate of subjects who had any infusions associated with one or more local AEs was higher for SC administration with rHuPH20 (51.9%) than for IV administration (4.6%).

No deaths occurred in this study.

### 3.3.4 Reviewer's comments

1. This study met the efficacy success criterion that the rate of validated acute serious bacterial infections per year is significantly lower than 1.0. The two validated acute

serious bacterial infections occurred to two subjects below 12 years old (Subjects (b)(6): 11 years old and Subject (b)(6): 6 years old).

2. One validated acute serious bacterial infection occurred during the ramp-up (Subject (b)(6), which was not included in the analysis. Even this event were counted in, according to this reviewer’s analysis, the success criterion was still met.
3. For the PK Parameters of IgG for Subjects Aged  $\geq 12$  Years in FADS, the difference between SC infusions with rHuPH20 and IV infusions was evident with respect to the median values for Cmax and Tmax in all efficacy data sets (Table 7).
4. In Epoch 1, 2 of the 109 (1.8%) related AEs were local, while 146 of the 196 (74.5%) related AEs were local in Epoch 2 (Table 11). Is this acceptable to have such a large proportion of local AEs?
5. The median rate of infusions temporally associated with one or more local AEs was 5.9% (95% CI: 0.0; 8.3) for SC infusions with rHuPH20 and 0.0 (95% CI: 0; 0) for IV infusions, regardless of whether infections were included as AEs or not.
6. AEs occurring during the ramp-up period were analyzed separately by the sponsor. For example, 3 of the 230 SC infusions with rHuPH20 during the ramp-up were not tolerated. Is this an acceptable approach?
7. Among the subjects received IGIV, 10% SC + rHuPH20 treatment in Epoch 2, 40 subjects had not previously been exposed to the SC route and they were included in the Subcutaneous Immunoglobulin Naive Subjects Data Set (SNDS). Presumably, compared to the other 41 subjects who had previously been exposed to the SC route (non-SNDS), these subjects were expected to have worse tolerance and more AEs. This reviewer’s analyses seem to confirm this assumption. Therefore, the safety analyses based on the full population could be biased. This issue also relates to which results to be reported in the labeling. Tables 13 compares the two sets of population regarding duration of treatment, number of infusions, and AEs.

**Table 13.** Comparison of non-SNDS and SNDS Epoch 2

Dataset	Age Group	N	Mean	SD	Min	Median	Max
<b>Duration of treatment [days]</b>							
Non-SNDS	Subjects aged 2 to <12 years	8	388.8	110.5	169	411	505
	Subjects aged $\geq 12$ years	33	416.2	75.6	169	449	507
SNDS	Subjects aged 2 to <12 years	3	284.3	133.8	156	274.0	423
	Subjects aged $\geq 12$ years	37	326.6	104.7	42	337.0	449
<b>Number of infusions</b>							
Non-SNDS	Subjects aged 2 to <12 years	8	15.8	5.7	6	16	24
	Subjects aged $\geq 12$ years	33	15.8	3.7	6	16	24
SNDS	Subjects aged 2 to <12 years	3	9.7	5.5	4	10	15
	Subjects aged $\geq 12$ years	37	12.2	4.1	3	12	20
<b>Number of temporally associated AEs including infections</b>							
Non-SNDS	Subjects aged 2 to <12 years	8	3.5	3.9	0	2.5	12

	Subjects aged $\geq 12$ years	33	4.5	4.9	0	3	18
SNDS	Subjects aged 2 to $<12$ years	3	3.7	4.6	1	1	9
	Subjects aged $\geq 12$ years	37	7.1	8.5	0	4	29
<b>Rate of temporally associated AEs including infections</b>							
Non-SNDS	Subjects aged 2 to $<12$ years	8	0.31	0.41	0	0.1	1.0
	Subjects aged $\geq 12$ years	33	0.29	0.30	0	0.2	1.1
SNDS	Subjects aged 2 to $<12$ years	3	0.41	0.44	0.1	0.3	0.9
	Subjects aged $\geq 12$ years	37	0.68	0.97	0	0.3	5
<b>Number of temporally associated AEs excluding infections</b>							
Non-SNDS	Subjects aged 2 to $<12$ years	8	2.9	3.3	0	1.5	10
	Subjects aged $\geq 12$ years	33	4.3	4.9	0	2	18
SNDS	Subjects aged 2 to $<12$ years	3	3.3	4.0	1	1	8
	Subjects aged $\geq 12$ years	37	6.6	8.3	0	3	28
<b>Rate of temporally associated AEs excluding infections</b>							
Non-SNDS	Subjects aged 2 to $<12$ years	8	0.3	0.3	0	0.1	0.8
	Subjects aged $\geq 12$ years	33	0.3	0.3	0	0.2	1.0
SNDS	Subjects aged 2 to $<12$ years	3	0.4	0.4	0.1	0.3	0.8
	Subjects aged $\geq 12$ years	37	0.6	1.0	0	0.2	5

Comparison of non-SNDS and SNDS Epoch 2 (Table 13. -continued)

Dataset	Age Group	N	Mean	SD	Min	Median	Max
<b>Number of related AEs including infections</b>							
Non-SNDS	Subjects aged 2 to $<12$ years	8	2.6	3.5	0	1.5	10
	Subjects aged $\geq 12$ years	33	3.4	4.4	0	1	15
SNDS	Subjects aged 2 to $<12$ years	3	3.3	4.0	1	1	8
	Subjects aged $\geq 12$ years	37	6.5	8.7	0	3	28
<b>Rate of related AEs including infections</b>							
Non-SNDS	Subjects aged 2 to $<12$ years	8	0.3	0.6	0	0.1	1.7
	Subjects aged $\geq 12$ years	33	0.2	0.3	0	0.1	1
SNDS	Subjects aged 2 to $<12$ years	3	0.4	0.4	0.1	0.3	0.8
	Subjects aged $\geq 12$ years	37	0.6	1.1	0	0.2	5.5
<b>Number of related AEs excluding infections</b>							
Non-SNDS	Subjects aged 2 to $<12$ years	8	2.6	3.5	0	1.5	10
	Subjects aged $\geq 12$ years	33	3.4	4.4	0	1	15
SNDS	Subjects aged 2 to $<12$ years	3	3.3	4.0	1	1	8
	Subjects aged $\geq 12$ years	37	6.4	8.6	0	3	27
<b>Rate of related AEs excluding infections</b>							

Non-SNDS	Subjects aged 2 to <12 years	8	0.3	0.6	0	0.1	1.7
	Subjects aged ≥12 years	33	0.2	0.3	0	0.1	1
SNDS	Subjects aged 2 to <12 years	3	0.4	0.4	0.1	0.3	0.8
	Subjects aged ≥12 years	37	0.6	1.0	0	0.2	5.5
<b>Rate of infusions with local AEs excluding infections</b>							
Non-SNDS	Subjects aged 2 to <12 years	8	0.1	0.1	0	0	0.2
	Subjects aged ≥12 years	33	0.1	0.1	0	0.1	0.5
SNDS	Subjects aged 2 to <12 years	3	0	0	0	0	0
	Subjects aged ≥12 years	37	0.3	0.3	0	0.1	1

8. Seven subjects discontinued the study due to adverse events during Epoch 2, while there were no such discontinuations during Epoch 1. Although this could be partly explained by the longer study duration in Epoch 2, will this concern CBER?

### 3.4 Study 161001 (under IND 13840)

#### 3.4.1 Study Design and Endpoints

This was a Phase 1, prospective, randomized, within-subject/between-subjects placebo-controlled, single-center study to assess the effectiveness of rHuPH20 in facilitating subcutaneous (SC) infusion of IGSC, 10%. This study comprised two sequential epochs.

**Epoch 1:** A total of 8 subjects were enrolled in Epoch 1. Each subject was to receive 2 simultaneous infusions of IGSC, 10% solution immediately proceeded by rHuPH20 or LR control solution in the thighs (one treatment per thigh). Dosing in Epoch 2 was to begin if no unacceptable toxicity had been identified in Epoch 1.

**Epoch 2:** A total of 45 subjects were enrolled into Epoch 2 and randomly assigned to one of the four study arms below.

**Table 14.** Treatment Assignment – Epoch 2 (Table 9.1-1)

Study Arm	No. of Subjects	Left Thigh	Right Thigh
1A	16	IGSC, 10% + rHuPH20	IGSC, 10% + LR control
1B	17	IGSC, 10% + LR control	IGSC, 10% + rHuPH20
2A	6	Human albumin 0.25% in LR + rHuPH20	Human albumin 0.25% in LR + LR control
2B	6	Human albumin 0.25% in LR + LR control	Human albumin 0.25% in LR + rHuPH20

#### 3.4.2 Patient Disposition, Demographic and Baseline Characteristics

53 subjects were randomized (8 subjects in Epoch 1 and 45 subjects in Epoch 2). Of the 53 randomized subjects, 51 subjects completed the study (8 subjects in Epoch 1 and 43 subjects in Epoch 2). Of the 2 randomized subjects from Epoch 2 who did not complete the study, 1 subject discontinued due to an AE (Subject (b)(6) was withdrawn from treatment due to a

moderate event of hypotension at the end of rHuPH20/LR control injections but before IGSC, 10% infusions), and the other (Subject (b)(6) was lost to follow-up on Day 8.

The numbers of subjects in each of the 4 different datasets were as follows:

- Full Analysis Dataset (FADS): 52 subjects, 8 in Epoch 1 and 44 in Epoch 2 (32 in Arms 1A+1B [IGSC, 10%-treated] and 12 in Arms 2A+2B [0.25% human albumin-treated])
- Per-Protocol Analysis Dataset (PPADS): 51 subjects, 7 in Epoch 1 and 44 in Epoch 2 (32 in IGSC, 10%-treated and 12 in 0.25% human albumin-treated arms)
- Sub-Per-Protocol Analysis Dataset (SPPADS): 42 subjects, 5 in Epoch 1 and 37 in Epoch 2 (27 in IGSC, 10%-treated and 10 in 0.25% human albumin-treated arms)
- Safety Analysis Dataset (SADS): 53 subjects, 8 in Epoch 1 and 45 in Epoch 2 (33 in IGSC, 10%-treated and 12 in 0.25% human albumin-treated arms)

The median age in arms 1A + 1B was 10 years older than the median age in arms 2A + 2B (34 years old vs. 23) in Epoch 2. Thirty four subjects (64.2%) enrolled in this study were male, and 19 subjects (35.8%) were female.

### 3.4.3 Statistical Methodologies

The analysis of the primary endpoint was to compare the total time to complete IGSC, 10% infusions with and without rHuPH20 in Study Arms 1A and 1B. For incomplete infusions with slow flow (infusions that were stopped at 4 h from start of infusion), the total time to complete infusion was to be the sum of 4 h plus imputed time needed to deliver the remaining planned infusion volume. For infusions with no flow, the time to complete infusion was to be imputed as a large value (eg, 24 h). Two-sample Wilcoxon test, applied to the arithmetic difference in the total time to complete infusions given to the left and right thighs of the same subject, was used to compare Study Arms 1A and 1B.

### 3.4.4 Results and Conclusions

#### Primary Efficacy Endpoint:

- **Total Time to Complete IGSC, 10% Infusion**

The median time (hours: minutes) to complete IGSC, 10% infusions was similar with rHuPH20 and LR control pre-administrations: 0:52 (range: 0:30 to 104:20) and 0:54 (range: 0:30 to 3:35) in Epoch 2 (FADS, n=32), respectively. The median within-subject difference was 0:1 (range: -103:23 to 2:36). A sensitivity analysis using 2 imputation methods for subjects with incomplete and no flow infusions showed similar results as above.

- **Reduction in Time to Complete IGSC, 10% Infusion**

The median percent reduction in time to complete IGSC, 10% infusion with rHuPH20 pre-administration compared with and relative to LR control pre-administration was 1.1% (95% CI: -16.1 to 24.0%) for 32 subjects in FADS Epoch 2.

#### Secondary Efficacy Endpoint(s):

- **Interrupted or Incomplete Infusions**

Of these 32 subjects in the FADS with rHuPH20 pre-administration, 5 subjects -----  
------(b)(6)----- had interrupted or incomplete infusions due to  
significant tissue back pressure preventing flow of infusion solution, while none of them had  
an interrupted or incomplete IGSC, 10% infusion with LR control pre-administration.

### **Safety**

There were no deaths or other SAEs.

One subject (b)(6) was discontinued due to an AE (moderate event of hypotension) that  
occurred at the end rHuPH20 and LR control pre-administrations but before IGSC, 10%  
infusion.

Anemia in Subject (b)(6): A mild event that started on Sep 30, 2010, and was resolved on  
19Oct2010. This AE was deemed possibly related to both IGSC, 10% and rHuPH20 pre-  
administration, and was resolved completely.

### **3.4.4 Reviewer's comments**

1. This study showed very similar results for the two primary efficacy endpoints: total time to complete IGSC, 10% infusion and reduction in time to complete IGSC, 10% infusion between two study arms.
2. Of these 32 subjects in the FADS with rHuPH20 pre-administration, 5 subjects had interrupted or incomplete infusions due to significant tissue back pressure preventing flow of infusion solution, while none of them had an interrupted or incomplete IGSC, 10% infusion with LR control pre-administration. Will this concern CBER?

### **3.5 Study 170901 part 4 (under IND (b)(4))**

#### **3.5.1 Study Design and Endpoints**

It was a Phase 1, randomized, double-blind, controlled study designed to compare the safety, tolerability, and maximal flow rate of IGSC, 10% when administered sequentially following administration of rHuPH20 or its formulation buffer control. 12 eligible healthy volunteers were enrolled.

Each subject was to initially receive IGSC, 10% infusions at 0.3 g/kg BW/infusion with control or with rHuPH20 (Treatment 4A and Treatment 4B) in a blinded, crossover sequence. For each individual, the treatment(s) that was/were tolerated and successfully completed within 8 hours was to be repeated in a blinded fashion at the higher IGSC, 10% dose level of 0.6 g/kg BW/infusion (ie, Treatment 4C [control], Treatment 4D [with rHuPH20]).

4A: IGSC, 10% at 0.3 g/kg BW/infusion + Formulation Buffer Control

4B: IGSC, 10% at 0.3 g/kg BW/infusion + rHuPH20

4C: IGSC, 10% at 0.6 g/kg BW/infusion + Formulation Buffer Control

4D: IGSC, 10% at 0.6 g/kg BW/infusion + rHuPH20

There were 10 efficacy endpoints and 10 safety endpoints in this study.

### 3.5.2 Patient Disposition, Demographic and Baseline Characteristics

Study Part 4 was conducted first, but dosing was halted prematurely on October 30, 2009 due to the occurrence of SAEs and unexpected laboratory findings.

Eight of the 12 subjects completed the study. The four of them discontinued the studies were listed in Table 15 below.

**Table 15.** Subject Disposition (Table 10.1-1)

<b>Subject ID</b>	<b>Treatments Completed</b>	<b>Disposition</b>
(b)(6)	4B-4A-4C	Discontinued due to SAE of hemolytic anemia
(b)(6)	4B-4A-4D	Discontinued due to sponsor's decision to discontinue all Study Part 4 dosing
(b)(6)	4B-4A-4D	Discontinued due to sponsor's decision to discontinue all Study Part 4 dosing
(b)(6)	4A-4B-4C	Discontinued due to AE of influenza-like illness

Of the 12 treated subjects in this study:

- 8 were male and 4 female
- 7 were Black/African American and 5 White
- Mean ( $\pm$ SD) age was 38 ( $\pm$ 11) years, range: 26-64 years
- Mean ( $\pm$ SD) BMI was 28.9 ( $\pm$ 2.7) kg/m<sup>2</sup>, range: 23.0 - 31.9 kg/m<sup>2</sup>

There were no subjects with any ongoing, relevant medical conditions that could impact their participation in the study.

### 3.5.3 Results and Conclusions

#### **Efficacy Endpoint:**

- In general, increases in in-line pressure were observed as flow rate increased for all subjects. These increases did not appear to correlate with the volume of IGSC, 10% infused, nor were there any consistent differences in the magnitude or pattern of the pressure curves between infusions that were pre-administered with rHuPH20 as compared to the formulation buffer control.
- No differences in the mean maximum volume of IGSC, 10% infused was observed within the same IGSC, 10% dose between infusions that were pre-administered with rHuPH20 or formulation buffer control.
- No differences in the maximum tolerated flow rate of IGSC, 10% infused was observed between infusions that were pre-administered with rHuPH20 or formulation buffer control.
- The mean time to complete an infusion was the same or similar with and without rHuPH20 pre-administration at different IGSC, 10% dose level.
- No infusions were interrupted due to AEs or intolerability.

- There was a trend toward fewer instances (13/22 infusions with rHuPH20 as compared to 19/22 with formulation buffer control), shorter duration, and smaller areas of induration in IGSC, 10% infusions that were pre-administered rHuPH20.

### **Safety**

- Treatment-emergent AEs (TEAEs; AEs reported after first dose) were reported for all subjects across all treatments except for 1 subject in Treatment 4A.
- The most notable TEAEs include infusion site discoloration, infusion site induration, and infusion site pain in all subjects; infusion site pruritis (9/12 subjects ); injection site pain (6/12 subjects).
- Two subjects experienced SAEs of hemolytic anemia: Subjects -(b)(6)-- (moderate; unlikely related to rHuPH20 and possibly related to IGSC, 10%) and -(b)(6) (moderate; possibly related to rHuPH20 and possibly related to IGSC, 10%).
- Two subjects were discontinued from the study due to (S)AEs: Subject -(b)(6)- (SAE of hemolytic anemia), and Subject -(b)(6)- (AE of flu-like illness).
- As part of the investigation into the SAEs that occurred during the study, additional serological testing was performed. Ten of the 12 subjects, including the 2 subjects with flu-like illness and hemolytic anemia and the other 3 with a flu-like illness, seroconverted to H1N1 Influenza A during the study period.
- There were no deaths reported during the study.

### **3.5.4 Reviewer’s comments**

- This study did not show that the pre-administered rHuPH20 could facilitate the infusion of IGSC, 10%.
- This reviewer defer to the medical reviewer for the safety evaluation of this study.

## **4. SUMMARY AND CONCLUSIONS**

### **4.1 Statistical Issues and Collective Evidence**

Please refer to reviewer’s comments under each individual study.

### **4.2 Conclusions and Recommendations**

Please refer to section 1.1.

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