

BLA Clinical Review Memo

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| Application Type | Original BLA |
| Application Number(s) | 125402 |
| Received Date(s) | 30-June-2011 |
| PDUFA Goal Date | 29-JUL-2012 (reflects 3 month extension) |
| Division / Office | DH/OBRR |
| Priority Review | No |
| Reviewer Name(s) | Laurence Landow |
| Review Completion Date / Stamped Date | |
| Applicant | Baxter |
| Established Name | IMMUNE GLOBULIN INFUSION (HUMAN), 10% WITH RECOMBINANT HUMAN HYALURONIDASE |
| (Proposed) Trade Name | HYQVIA |
| Pharmacologic Class | Immune globulin |
| Formulation(s), including Adjuvants, etc | Dual vial unit containing 10% IgG (100 mg/mL) and 160 U/mL Recombinant Human Hyaluronidase |
| Dosage Form(s) and Route(s) of Administration | Subcutaneous |
| Dosing Regimen | <p><i>For Patients on Intravenous Treatment:</i> Same dose as intravenous treatment, starting with a 1 week dose and increasing to 3 or 4 week dose Adjust dose based on trough level compared to intravenous trough</p> <p><i>For Patients Naïve to IgG treatment or Receiving Subcutaneous Treatment:</i> 300 to 600 mg/kg every 3 to 4 weeks, based on clinical response</p> |
| Indication(s) and Intended Population(s) | Treatment of patients with Primary Immunodeficiency (PI) |

GLOSSARY

ASBI: acute, serious, bacterial infections

AR: adverse reaction

rHuPR20: Recombinant Human Hyaluronidase

Hyqvia: IGI 10% with rHuPH20 (administered subcutaneously)

IgG: immunoglobulin G

IGIV 10%: Immune Globulin Infusion 10% (Human)

IV: intravenous

PI: primary immunodeficiency

SAR: serious adverse reaction

SC: subcutaneous

SYNOPSIS

1. Material reviewed: final study reports for confirmatory Study #160603 and 4 exploratory studies (Studies #161001, 170901 part 4, 160602, and 160601) were reviewed. Except for Study #170901, no study was blinded, randomized, or concurrently controlled. Two studies enrolled healthy volunteers (170901 Part 4; 161001); PI subjects were enrolled in phase 1/2 study 160601 and phase 2/3 study 160602, as well as phase 3 study 160603.
2. Efficacy: Hyqvia was as effective in reducing acute serious bacterial infections in the phase 3 trial (primary endpoint). Compared to SC administration of Immune Globulin Infusion 10% alone at bioequivalent doses, the contribution of rHuPR20 in Hyqvia appeared to exert a clinical benefit of reduction of the median rate of infusion by 10 min (2.13 vs. 2.33 h) in the >12 year old cohort (N=73) and by 45 min (1.73 vs. 2.49 h) in the 2-12 year old cohort (N=14).
3. Safety: It appears that chronic rHuPR20 exposure could elicit anti-rHuPH20 antibodies and anti-rHuPH20 antibody-complexes could bind complement, resulting in immunological organ toxicity additive to that of IG, e.g., infertility; joint defects similar to that seen in a rare genetic deficiency of hyaluronidase (MPS-IX).
4. Recommendation
 - a. BIMO inspections of study sites in Study 160603 found that 7/19 subject diaries were missing from Study site 1 and Study site 11 was so poorly monitored (safety underreporting and failure to capture concomitant medications that the information is untrustworthy).
 - b. Based on concerns over potential safety issues with respect to anti-rHuPR20 and minimal clinical benefit exerted by co-administration of rHuPR20, I recommend that the sponsor submit data which address whether anti-rHuPR20 antibodies affect fertility or are associated with joint defects.
 - c. Deferral for a study in the 0 to 2 year population should be granted due to

the difficulty in recruiting subjects.

Clinical CR comment/question

Based on deficiencies identified by FDA inspectors, please recalculate a safety and efficacy analysis for Study 160603 that excludes data obtained from Study Site #1 (Dallas Allergy Immunology Research) and Study Site #11 (Children's Hospital Los Angeles).

1. EXECUTIVE SUMMARY

Background

Baxter's BLA for Hyqvia [IGI 10% with rHuPR20, Immune Globulin Infusion 10% (Human) with Recombinant Human Hyaluronidase] was submitted on 30-JUN-2011.

Hyqvia is a combination product indicated for the treatment of primary immunodeficiency (PI). It contains one vial each of IGI 10% and rHuPH20 and is for subcutaneous (SC) administration sequentially beginning with rHuPH20 and followed by IGI 10%. The sponsor's rationale for developing this combination product is the expectation that SC preadministration of rHuPH20, which improves drug dispersion in other medical settings, would permit larger volumes of IGI 10% to be infused SC than would be possible with IGI 10% alone, necessitating less frequent administration (q 3-4 weeks as opposed to q weekly SC administration without rHuPR20); a second rationale is that subcutaneous administration will improve patient comfort by obviating the need for intravenous administration.

The IGI 10% component is a 10% liquid formulation of Immunoglobulin G (IgG), identical to Baxter's GAMMAGARD LIQUID 10% (IGIV, 10%), which was licensed on 27-APR-2005 (STN 125105). The rHuPH20 component is similar to Hylenex (Hyaluronidase Human Injection product; Halozyme Therapeutics, Inc.), a recombinant human hyaluronidase that was licensed on 2-DEC-2005 (NDA 21-859). Also known as sperm adhesion molecule 1, Hylenex is a 65 kD monomer -----(b)(4)----- of CHO cells.

BLA Clinical Study Roster

Final study reports for confirmatory Study #160603 and 4 exploratory studies (Studies #161001, 170901 part 4, 160602, and 160601) were reviewed. Except for Study #170901, no study was blinded, randomized, or concurrently controlled. Two studies enrolled healthy volunteers (170901 Part 4; 161001); PI subjects were enrolled in phase 1/2 study 160601 and phase 2/3 study 160602, as well as phase 3 study 160603. See table, next page.

Table 1: Study Roster

| Study ID | Study Phase and Design | No. of Subjects Age Range Duration/Subject | Study Objectives | IPs |
|---------------|---|--|---|---|
| 161001 | A Phase 1, prospective, randomized, within subject/ between subjects, placebo controlled, single-center study | 57 adult healthy volunteers 19-65 years 6 weeks | To Evaluate the effectiveness of rHuPH20 in enhancing SC administration of IGSC 10% | IGIV, 10% IGSC 10% with rHuPH20 rHuPH20 alone |
| 170901 Part 4 | A Phase 1, prospective, randomized, double-blind, controlled study | 12 adult healthy volunteers 26-64 years 8 weeks | To assess the safety, tolerability, infusion pressure, and maximal flow rate of human IgG SC infusion administered with and without rHuPH20 | IGIV, 10% IGSC 10% with rHuPH20 |
| 160602 | A Phase 1/2, prospective, open-label, non-randomized, two-arm multicenter Phase 1/2 study in adult or adolescent PI subjects aged ≥ 16 years | 11 subjects 20-76 years 8-65 days (Arm1) or 133-165 days (Arm 2) | To determine the dose of rHuPH20 enabling up to 600 mg/kg of IGIV, 10% to be administered SC in a single infusion site in PI subjects. | IGIV, 10% IGSC 10% with rHuPH20 |
| 160601 | A Phase 2/3, prospective, open-label, non-randomized, multi-center study | 49 subjects 3-77 years ≥ 10 months each | To evaluate tolerability and PK of IGIV, 10% SC in PI subjects and to evaluate efficacy in ASBIs | IGIV, 10% IGSC 10%. |
| 160603 | A Phase 3, prospective, open-label, non-randomized, multi-center study | 87 subjects 4-78 years 14 months (Arm1) or 17 months (Arm 2) | To evaluate efficacy, tolerability and PK comparison of IGIV, 10% administered IV or SC following rHuPH20 in PI subjects | IGIV, 10% IGSC 10% with rHuPH20 |

Pediatric studies: 26 subjects aged 2 to <12 years were exposed to product: 14 subjects in Study 160603 and 12 subjects in Study 160601. Baxter requested a deferral for studies in the 0 to 2 year old population, arguing that it is difficult to study neonates with immune deficiency in a prospective, clinical trial because (a) diagnosis in this age group is rare and (b) a number of hospital visits and blood drawings would be required. See table, below.

EFFICACY

Synopsis: Hyqvia was as effective as IGIV 10% in reducing acute serious bacterial infections.

Phase 3 Study #160603 was conducted under IND 13840. It evaluated efficacy, tolerability and pharmacokinetics (PK) of the combination product in PI subjects > 2 years of age (N=87). Outcome measures included rate of acute serious bacterial infections (ASBI), all infections, adverse reactions, tolerability of the infusions, number of infusion sites per month, and infusion rate.

Study #160603 consisted of 2 Epochs. Epoch 1 consisted of subjects who received intravenous (IV) infusions with IGI 10% either in Epoch 1 or in an antecedent study (Study #160601). The Epoch 2 database consisted of subjects who received SC IGI 10% at 108% of the IV dose preceded by up to 75 U/g IgG rHuPH20. Treatment intervals and doses in Epoch 2 were gradually ramped-up with the aim of treating subjects SC at the same intervals (every 3 or 4 weeks) as they had been treated via the IV route of administration. Eighty-seven subjects began treatment and 81 were included in the efficacy analysis. At total of 44 subjects were naïve to SC IgG prior to the study.

Hyqvia was effective in reducing acute serious bacterial infections. The rate of validated acute serious bacterial infections per subject-year was 0.025 (upper limit of the 99% CI: 0.046); this is lower than the rate (0.067; upper limit of the 99% CI: 0.134) observed in phase 1 study 160601 using SC administration of IGI 10% without rHuPH20 and significantly lower ($p < 0.0001$) than the 1.0 rate threshold considered to provide substantial evidence of efficacy. No serious bacterial infections occurred when this product was administered SC. Compared to IV administration alone, SC administration with rHuPH20 was able to be administered at the same dosing interval and resulted in similar IgG trough levels. SC administration with rHuPH20 demonstrated higher bioavailability as determined by AUC per dose/kg than when infused SC without rHuPH20.

Secondary endpoints: (a) annualized number of hospital days due to infection was slightly lower for IGSC + rHuPR20 subjects (0.04; 99% confidence interval: 0.02, 0.06) than for IGIV 10% subjects (0.49; 0.27, 0.79); (b) number of days on antibiotic treatment was similar in subjects >12 years of age but lower in the 2-12 year subgroup; (c) number of days off work or school per subject per year was similar (range: 3.31 to 3.95).

Contribution of rHuPR20 to efficacy

Subcutaneous rHuPR20 administration exerted minimal clinical benefit on the rate and total volume of IG 10% infused into subjects.

1. **Study 170901, part 4** (N=12 volunteers; IGIV 10% vs. Hyqvia; phase 1): rHuPR20 preadministration had no effect on (a) in-line pressure vs. flow rate, (b) in-line pressure vs. cumulative volume infused curves, (c) total volume of IGSC 10% infused with and without rHuPH20 preadministration for both IGSC doses

(0.3 g/kg and 0.6 g/kg), (d) maximum tolerated flow rate (300 mL/h), and (e) median time needed to complete an infusion.

2. **Study 161001** (N=57 volunteers; IGIV 10% vs. Hyqvia; phase 1/2):
Effects of rHuPR20 preadministration were similar to Study 17091, part 4 in terms of effect, i.e., ***no effect***.
3. **Study 160603** (N=87 PI subjects; IGIV 10% vs. Hyqvia; phase 3):
Compared to IVIG (Epoch 1) at bioequivalent doses, Hyqvia administered SC (Epoch 2) ***reduced the median duration of infusion) by 10 min (2.13 vs. 2.33 h) in the >12 year old cohort (N=73 and by 45 min (1.73 vs. 2.49 h) in the 2-12 year cohort (N=14).*** Tolerability was virtually identical, i.e., 86% of subjects in Epoch 1 and 84% of subjects in Epoch 2 did not require a reduction in flow rate, interruption, or termination due to intolerance or ARs.

SAFETY

Synopsis: the safety profile of Hyqvia vs. IGIV is acceptable.

The rate of temporally associated ARs per infusion overall in Study #160603 was similar across the two treatment cohorts: 0.25 in the IGIV cohort (Epoch 1) vs. 0.21 in the Hyqvia (Epoch 2) cohort, including subjects who required a reduction in flow rate, interruption, or termination due to intolerance or ARs (86% in Epoch 1 and 84% in Epoch 2).

Serious safety events (all studies)

1. **Study #170901** (N=12 volunteers; prematurely terminated for safety by the sponsor)
 - a. Six cases of **anemia** Grade 2 or higher were reported (Grade 2: one case; Grade 3: five cases; Grade 4: one case; Final Study Report, Listing 16.2.8).¹ In addition, there were five cases of Grade 3 **lymphopenia** and six cases of **abnormally elevated enzyme levels** from muscle (CPK), liver (ALT, AST), and pancreas (amylase, lipase) attributed to a “flu-like” illness by the sponsor.

The frequency of abnormally elevated chemistry and hematology values Grade 2 or higher in the Hyqvia treatment cohort was one-third that of the IG + buffer (without rHuPR20) treatment cohort.

2. **Study #160602** (N=11)
 - a. One PI subject in phase 1 Study #160602 experienced **anaphylaxis** 24 h post-exposure to Hyqvia.

¹The sponsor indicates in the text (“Serious Adverse Events”) of their Final Study Report that only two anemia SAEs were observed.

Background: hyaluronidase is added to local anesthetics in ocular, dental, and plastic surgery procedures to enhance dispersal into tissues, and hypersensitivity reactions following its use have been reported for over half a century. A Medline search using the terms “hyaluronidase” and “anaphylaxis” reported 30 publications in the scientific literature. Although isolated reports of acute (immediate) anaphylaxis subsequent to hyaluronidase administration have been published (*Korean J Pain* 2011;24:221-225; *Allergy* 2005;10:1333-1334), delayed reactions also have been observed from 1 week to 4 months post subcutaneous injection (*Orbit* 2011;30:54-7). Thus, one or both components of the test article could have played a causal role, whereas the sponsor attributes the event to antibiotic administration one day post-treatment.

3. **Study #160603** (N=87)²
 - a. Two cases of **thrombosis**, one assessed as *unrelated* and the other as *unlikely to be related* to Hyqvia, were reported.
 - i. A 66 y/o male experienced a fatal MI 4 months after Hyqvia was discontinued.
 - ii. A 19 y/o male with PMH of diabetes and a positive family history of thrombosis experienced an upper extremity thrombosis confirmed by ultrasound 14 days after receiving his 7th dose of Hyqvia via the abdominal route. Forty days earlier he had undergone replacement of a non-functioning IV access device in the ipsilateral extremity.

Non-serious safety events

Local ARs

- *Clinical studies enrolling volunteers vs. PI subjects*

The incidence of Local ARs was more frequent in volunteers (Studies #161001 and #170904 Part 4) than in PI subjects (Studies #160601 and #160603).
- *Clinical studies using Hyqvia vs. IGSC 10% alone in PI subjects and volunteers*

PI subjects: except for more frequent local ARs of mild (0.235 vs. 0.054) and moderate (0.101 vs. 0.010) severity, PI subjects receiving Hyqvia every 3-4 weeks (Study #160603) exhibited a safety profile similar to that of weekly IGSC 10% (Study #160601; N=49). The most commonly reported reactions included infusion site pain, headache, infusion site erythema, and induration. The median time required for induration ARs to resolve in PI subjects (Study #160601) was 1:01 h (95% CI: 0:20; 1:39) for Hyqvia vs. 4:39 h (95% CI: 4:09; 5:01) for IGSC 10% with control. None of the induration ARs associated with Hyqvia was moderate or severe, whereas 54.5% were moderate or severe in the IGSC 10% + control group.

² While assessed by the investigator as “unrelated”, these two cases of thrombosis are presented here for informational purposes because the risk of thrombosis is listed in the PI of other IG products.

Volunteers: 7/12 volunteers in Study 170901 Part 4 had measurable induration using Hyqvia (dose: 0.3 g/kg BW) compared to 9/12 using IGSC 10% with buffer control. At the 0.6 g/kg BW dose of IgG, 6/10 Hyqvia subjects had measurable induration at the end of infusion compared to 10/10 who received IGSC 10% with control. Similar results were obtained in Study 161001 (N=57): for Epoch 1 and 2 combined (n=40), Hyqvia volunteers experienced 4 induration ARs compared to 44 induration ARs using IGSC 10% with lactated Ringer's control.

Systemic ARs

- *Hyqvia vs. IVIG infusion in PI subjects*
In Study #160603 (N=87), the frequency of systemic safety events temporally associated with product administration was higher in Epoch 1 (IVIG: headache, chills, nausea, fatigue, pyrexia, vomiting), whereas the frequency of local events was higher in Epoch 2 (Hyqvia: infusion site pain, infusion site erythema, infusion site discomfort, headache, infusion site pruritus, infusion site edema, and infusion site swelling). Similar trends were evident in the smaller trials as well.

Potential risks of anti-rHuPR20 antibodies

Concerns have been raised that chronic rHuPR20 exposure could elicit anti-rHuPH20 antibodies and that anti-rHuPH20 antibody-complexes could bind complement, resulting in immunological organ toxicity additive to that of IG, e.g., infertility; joint defects similar to that seen in a rare genetic deficiency of hyaluronidase (MPS-IX). The hypothesis underlying these concerns arises from two studies (one *in vivo* and the other *in vitro*) using a protein related to rHuPR20, PH-20.³

In Study #160603, 9 of 87 subjects (1:10) developed a persistently positive, *de novo* anti-rHuPH20 non-neutralizing antibodies as measured by a highly sensitive (b)(4) bridging electrochemiluminescent immunoassay. Even though this is markedly higher than the 1:160 cutoff attributable to passive transfer noted by the sponsor, the clinical implications of this finding are unknown.

At FDA request, the sponsor currently is conducting two *in vitro* studies to address this issue. The first evaluates binding of anti-rHuPH20 antibodies in a normal human tissue panel; the second evaluates whether rHuPH20-antibody complexes are capable of fixing complement. An interim report is expected shortly before the BLA Action Due Date (ADD).

AERS

An AERS database search using the term "human hyaluronidase" reported 3 systemic safety events associated with Hylenex, a licensed hyaluronidase. The first was a seizure in a 61 y/o male receiving lidocaine by continuous infusion for pain control. The second

3 Primakoff et al. Fully effective contraception in male and female guinea pigs immunized with the sperm protein PH-20. *Nature* 1988;543-6; Chan et al. Identification of linear surface epitopes on the guinea pig sperm membrane PH-20. *Life Sciences* 1999;64:1989-2000

involved a fatal mixed drug toxicity ---(b)(6)----- in a 58 y/o subject (ID --(b)(6)--; initials (b)(6) who had been previously enrolled in the completed phase 3 trial. The third was an 8 y/o male with moderate-severe dehydration who experienced subcutaneous infiltration at an IV site. Continuing vomiting and diarrhea led to hyponatremia.

RECOMMENDATION

Based on concerns over the potential effect of anti-rHuPR20, I recommend that the CR letter request the sponsor to submit data which address whether anti-rHuPR20 antibodies affect fertility or are associated with joint defects.

Deferral for a study in the 0 to 2 year population should be granted due to the difficulty in recruiting subjects.

2. CLINICAL AND REGULATORY BACKGROUND

Defective antibody formation is the most common abnormality in the majority of primary immunodeficiency (PI) 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.

Individuals with PI require IV replacement therapy with immunoglobulin products in the range of 0.3 to 0.6 g/kg body weight (BW) every 3 to 4 weeks. However, adverse drug reactions and the need for experienced medical personnel to administer the infusions have been problematic for many patients.

During the past few years, SC application of immune globulin preparations has been introduced in many countries. The primary disadvantage of SC therapy has been the limited volume that can be infused in a single SC site, necessitating use of multiple needle sites on a weekly or biweekly basis. The use of Recombinant Human Hyaluronidase (rHuPH20) is one approach to resolving this limitation.

rHuPH20 is a highly purified, neutral pH-(b)(4), human hyaluronidase produced by genetically engineered Chinese Hamster Ovary (CHO) cells containing a deoxyribonucleic acid (DNA) plasmid encoding for a soluble fragment of human hyaluronidase (PH20). rHuPH20 at a concentration of 150 U/mL is approved as an adjuvant to increase the absorption and dispersion of other injected drugs, for SC fluid administration (hypodermoclysis), and as an adjunct in SC urography for improving resorption of radiopaque agents.

2.1 Disease or Health-Related Condition(s) Studied

See Package Insert.

2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s) for the Proposed Indication(s)

Current treatment of PI is replacement therapy with human immune globulin (IG) products, usually administered intravenously (IV) every 3-4 weeks. There are four marketed products in the U.S. that allow for subcutaneous (SC) route of administration: Vivaglobin (CSL-Behring), Hizentra (CSL-Behring), Gamunex-C (Talecris) and Gammagard Liquid (Baxter).

2.3 Safety and Efficacy of Pharmacologically Related Products

The safety profile and effectiveness of human IG products for replacement therapy of PI have been well documented for the IV preparations. IG products for SC use have similar efficacy as the IV preparations with adequate dosing. SC IG differs from IV IG in the safety profile, as there is greater tendency for local infusion site reactions, but lower likelihood of severe systemic reactions.

2.4 Previous Human Experience with the Product (Including Foreign Experience)

GAMMAGARD LIQUID 10%:

GAMMAGARD LIQUID was licensed on 27 April 2005 (STN 125105) for the treatment of PI by IV route of administration. The SC route of administration (STN 125105/708) was licensed in July 2011.

rHuPH20-HYLENEX

HYLENEX Hyaluronidase was licensed on 2 December 2005 (NDA 21-859) as an adjuvant in SC fluid administration for achieving hydration to increase the dispersion and absorption of other injected drugs in SC urography for improving resorption of radiopaque agents. rHuPH20 in the combination product is formulated ----(b)(4)-----
----- at different fill volumes to accommodate different fill sizes of the IGI 10% product.

2.5 Summary of Pre-submission Regulatory Activity Related to Submission

- IND (b)(4): Phase 1-2 study
- 4/27/2005: GAMMAGARD LIQUID was approved by FDA (STN 125105) for the treatment of PI by IV route of administration.
- 12/2/2005: HYLENEX Hyaluronidase was approved by FDA (NDA 21-859) as an adjuvant in SC fluid administration for achieving hydration to increase the dispersion and absorption of other injected drugs in SC urography for improving resorption of radiopaque agents.
- 7/2011: GAMMAGARD LIQUID was approved (STN 125105/708) for the treatment of PI by SC route of administration.
- 8/20/2008: End of Phase 2 meeting discussed the design of the Phase 3 study and the development program to support the licensure of the combination product.

- 9/30/2008: IND 13840, a Phase 3 study to evaluate the combination product in the treatment of PI, was submitted.
- 6/30/2009: IND (b)(4)-, a Phase 1 study to evaluate the safety, tolerability, and optimal rHuPH20-to-IGI dose ratio in healthy volunteers, was submitted. Part 4 of the IND was to evaluate the safety, tolerability and the maximal tolerated flow rate of IGI 10% infusion given alone or sequentially following SC injection of rHuPH20.
- 10/6/2009: Pre-BLA Type B meeting discussed the data requirement to support the license of the combination product.
- 7/20/2010: IND 13840-19, protocol 161001 to replace protocol 170901 (part 4 of IND (b)(4)-, which was terminated earlier due to hemolysis adverse events occurred in 2 healthy volunteer subjects, was submitted.
- 8/31/2010: Type A meeting discussed the data requirements to support the independent contribution of rHuPH20 in the combination product.
- 10/6/2010: Type C CMC meeting discussed the related CMC issues.
- 12/16/2010: IND 13840/27, the Integrated Summary of Safety and Effectiveness (ISS & ISE) proposal for the combination product was submitted in response to FDA's responses on 3/14/2011.
- 6/25/2011: Pre-BLA Type B meeting discussed the results of clinical studies performed to support the BLA.

2.6 Other Relevant Background Information

Emphasis of data reviewed for this memo was placed on the safety assessment.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 SUBMISSION QUALITY AND INTEGRITY

The clinical portion of the submission included final study reports from 5 clinical trials. The submission was adequately organized and integrated to accommodate the conduct of a complete clinical review, despite the complex design of individual trials. Additional clarifications from the sponsor, especially with respect to disposition of subjects, were requested during the review.

3.2 Compliance with Good Clinical Practices

The sponsor claims the 5 studies were conducted in compliance with good clinical practices, and principles set forth in Title 21 CFR parts 50, 54, 56, 312 and 314, International Conference on Harmonization Guidelines for Good Clinical Practice, and local and national regulatory requirements. This was not entirely supported by a BIMO inspection that found major deficiencies at some sites, e.g., supervision of study personnel and oversight of study conduct. See the BIMO review memo.

3.3 Financial Disclosures

Financial certification and disclosure information (Form 3454) have been submitted. The applicant certifies that there have been no arrangements where the value of the compensation could have been affected by the outcome of the study. A list of Investigators for Study 160603 is included in the “Financial Disclosure” folder of the original supplement submission.

4. SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES

The major safety concerns are (a) **thromboembolic events** associated with all immune globulin products to date and (b) potential adverse effects of **antibodies to rHuPR20** administration.

4.1 Chemistry, Manufacturing, and Controls

- The combination product consists of one vial of IG, 10% and one vial of rHuPH20 160 U/mL connected together in a dual vial unit.
- There is no new CMC information submitted for IG, 10%. CMC information is cross-referenced to the original BLA STN 125105/0.
- rHuPH20 is similar to HYLENEX recombinant, which was previously approved on 2 December 2005 (NDA 21-859). The bulk enzyme of the rHuPH20 drug product is the same as that used in HYLENEX, but -----(b)(4)----- and presented in different volumes, with new final product specifications.
- Please see CMC reviewer Dr. Jennifer Reed’s memo for details.

4.2 Assay Validation

Please see Clinical Pharmacology reviewer Dr. Evi Struble’s review memo on assay validation for IgG in clinical samples and CMC reviewer Dr. Jennifer Reed’s memo on assay validation for rHuPH20.

4.3 Nonclinical Pharmacology/Toxicology

- The preclinical pharmacology/toxicology studies on IG, 10% cross-referenced to the original BLA STN 125105/0.
- The preclinical pharmacology/toxicology studies on rHuPH20 cross-referenced to NDA 21-859.
- Please see Clinical Pharmacology reviewer Dr. Evi Struble’s review memo on preclinical pharmacology/toxicology studies on the combination product of IG10% with rHuPH20.

4.4 Clinical Pharmacology

The IG provides the therapeutic effect of Hyqvia. rHuPR20 1 is intended improve dispersion and absorption of the IG. The IG of Hyqvia supplies a broad spectrum of opsonizing and neutralizing IgG antibodies against a wide variety of bacterial and viral agents. IG 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.

4.4.1 Mechanism of Action

- IG, 10% provides the therapeutic effect and rHuPH20 is intended to improve dispersion and absorption of IG, 10% and to improve bioavailability of IG, 10%.
- IG, 10% supplies a broad spectrum of opsonizing and neutralizing IgG antibodies against a wide variety of bacterial and viral agents. It 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 have not been fully elucidated.
- rHuPH20 is intended to facilitate increased bioavailability of IG,10% by temporarily increasing the permeability of the subcutaneous tissue. 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 and has a half-life of approximately 5 days. rHuPH20 accelerates the breakdown of hyaluronan, resulting in a temporary increase in the permeability of the interstitial matrix that facilitates dispersion, increased absorption into the capillaries and lymphatics and improved bioavailability of IG, 10%, theoretically resulting in more of the infused IgG reaching the vascular space. In the doses administered, rHuPH20 acts only locally and does not result in detectable levels in the circulation.

4.4.2 Human Pharmacodynamics (PD)

Please see Dr. Ifthekar Mahmood's review memo.

4.4.3 Human Pharmacokinetics (PK)

Please see Dr. Ifthekar Mahmood's review memo.

4.5 Statistical

The statistical reviewer verified that the primary study endpoint analyses cited by the applicant were supported by the submitted data.

5. SOURCES OF CLINICAL DATA AND OTHER INFORMATION CONSIDERED IN THE REVIEW

The clinical safety and efficacy data in the application are based on trials in PI adult and pediatric patients.

The following summaries were submitted to support the application.

- Clinical Study Report of 160601: ““Tolerability and Pharmacokinetic Comparison of Immune Globulin Intravenous (Human), 10% (IGIV, 10%) Administered Intravenously or Subcutaneously in Subjects with Primary Immunodeficiency Diseases”. This was the pivotal trial for approval of the SC route of administration (STN 125105/708). The study showed that in order to achieve PK equivalence (measured by AUC) of IGIV, 10% administered IV and SC, a dose-level of SC administration of 137% of the IV dose was required.
- Clinical Study Report of 161001: “A Phase 1 Study for the Evaluation of the Effectiveness of Recombinant Human Hyaluronidase (rHuPH20) in Enhancing the Subcutaneous Administration of Immune Globulin Subcutaneous (Human), 10% Solution (IGSC 10%) in Healthy Volunteers”.
- Clinical Study Report of 170901 (Part 4): “A Phase 1 Study of Immune Globulin Subcutaneous (Human) (IGSC) Administered Either Alone or in Combination with Recombinant Human Hyaluronidase (rHuPH20) Permeation Enhancer for the Evaluation of Safety, Tolerability, and Optimal rHuPH20-to-IGSC Dose Ratio in Healthy Volunteers”
- Clinical Study Report of 160602: “Phase 1/2 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”. The study showed 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. Bioavailability of IGI 10% administered SC with rHuPH20, as measured by AUC, was calculated to be 92% of that after IV infusion.
- Clinical Study Report of 160603: “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”. This was the pivotal phase 3 trial.

5.2 BLA/IND Documents That Serve as the Basis for the Clinical Review

The review of this BLA is based on the material submitted, including labeling claims in the package insert, as well as research on similar submissions on human immune globulin products, and the following Guidances’ for Industry: (a) *Providing Regulatory Submissions to the Center for Biologics Evaluation and Research (CBER) in Electronic Format — Biologics Marketing Applications*, and (b) *Safety, Efficacy, and Pharmacokinetic Studies to Support Marketing of Immune Globulin Intravenous (Human) as Replacement Therapy for Primary Humoral Immunodeficiency*.

Below are the design, objectives, sample size, and treatment arms of the 5 individual trials.

Table 1: Study Roster

| Study ID | Study Phase and Design | No. of Subjects Age Range Duration/Subject | Study Objectives | IPs |
|----------------------|---|--|---|---|
| 161001 | A Phase 1, prospective, randomized, within subject/ between subjects, placebo controlled, single-center study | 57 adult healthy volunteers 19-65 years 6 weeks | To Evaluate the effectiveness of rHuPH20 in enhancing SC administration of IGSC 10% | IGIV, 10% IGSC 10% with rHuPH20 rHuPH20 alone |
| 170901 Part 4 | A Phase 1, prospective, randomized, double-blind, controlled study | 12 adult healthy volunteers 26-64 years 8 weeks | To assess the safety, tolerability, infusion pressure, and maximal flow rate of human IgG SC infusion administered with and without rHuPH20 | IGIV, 10% IGSC 10% with rHuPH20 |
| 160602 | A Phase 1/2, prospective, open-label, non-randomized, two-arm multicenter Phase 1/2 study in adult or adolescent PI subjects aged ≥ 16 years | 11 subjects 20-76 years 8-65 days (Arm1) or 133-165 days (Arm 2) | To determine the dose of rHuPH20 enabling up to 600 mg/kg of IGIV, 10% to be administered SC in a single infusion site in PI subjects. | IGIV, 10% IGSC 10% with rHuPH20 |
| 160601 | A Phase 2/3, prospective, open-label, non-randomized, multi-center study | 49 subjects 3-77 years ≥ 10 months each | To evaluate tolerability and PK of IGIV, 10% SC in PI subjects and to evaluate efficacy in ASBIs | IGIV, 10% IGSC 10%. |
| 160603 | A Phase 3, prospective, open-label, non-randomized, multi-center study | 87 subjects 4-78 years 14 months (Arm1) or 17 months (Arm 2) | To evaluate efficacy, tolerability and PK comparison of IGIV, 10% administered IV or SC following rHuPH20 in PI subjects | IGIV, 10% IGSC 10% with rHuPH20 |

5.4 Consultations

Dr. Wiley Chamber (CDER) is the reviewer for rHuPH20. Dr. Ronald Wassel (CDER) conducted an AERS database search at his request.

5.4.1 Advisory Committee Meeting (if applicable)

6. Discussion of Individual Studies/Clinical Trials

6.1 Study #1: 161001 (phase 1)

Title: “A Phase 1 Study for the Evaluation of the Effectiveness of Recombinant Human Hyaluronidase (rHuPH20) in Enhancing the Subcutaneous Administration of Immune Globulin Subcutaneous (Human), 10% Solution (IGSC 10%) in Healthy Volunteers”

6.1.1 Objectives

To evaluate the effectiveness of rHuPH20 in enhancing SC administration of IGSC 10% solution.

6.1.2 Design Overview

Phase 1, prospective, randomized, within-subject/between-subjects placebo-controlled, single-center study.

The study evaluated the ability of rHuPH20 to increase the flow rate of gravity driven SC administration of IGSC 10%. Local tolerability of IGSC 10% administration with and without rHuPH20 also was evaluated. Systemic ARs were compared between subjects receiving IGSC 10% with rHuPH20 or its control vs. subjects receiving human albumin 0.25% in LR solution with rHuPH20 or its control.

The study comprised two sequential epochs and lasted 6 weeks. Subjects were enrolled sequentially into Epoch 1 followed by Epoch 2. Upon completion of infusions in Epoch 1, a blinded review of safety data was to be performed by the sponsor to decide whether to proceed into Epoch 2 or not. Dosing in Epoch 2 was to begin if no unacceptable toxicity had been identified in Epoch 1.

Epoch 1 was designed to assess the feasibility of gravimetric delivery of IGSC 10% solution with and without rHuPH20. Each subject received 2 simultaneous treatments in either thigh as indicated below (Table 1-1): Study arm 1 used IGSC 10% with rHuPH20 (1A, 0.25 g/kg per thigh for a total of 0.5 g/kg per subject) or LR (1B); Study arm 2 used human albumin 0.25% with rHuPH20 (2A, 75 U/g IgG) or LR (2B).

Table 1-1: Treatment Assignments (sponsor)

| Study Arm | No. of Subjects | Left Thigh | Right Thigh |
|------------------|------------------------|--|--|
| 1A | 16 | IGSC, 10% + rHuPH20 | IGSC, 10% + LR control |
| 1B | 16 | 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 |

6.1.3 Population

Inclusion Criteria

- Subject has signed and dated written informed consent.
- Male or female, 18 to 65 years of age inclusive, at the time of screening.
- BMI 19-29 kg/m² (inclusive) and body weight ≥ 60 kg at the time of screening.
- Healthy subject with no clinical evidence of acute and/or chronic disease and no clinically significant abnormalities on hematology panel, clinical chemistry panel, urinalysis, or ECG at the time of screening.
- Negative drug screen test at screening. Subject must agree to refrain from heavy alcohol consumption (more than 2 drinks per day on a regular basis) and use of narcotic drugs or illegal substances, for at least 2 weeks prior to screening and throughout the course of the study. Subject must also agree to drug screen testing at the discretion of the investigator at any time during the course of the study.
- Nonsmoker or ex-smoker with smoking cessation for a minimum of 6 months prior to screening. Subject must agree to refrain from smoking throughout the course of the study.
- For women of childbearing potential, the subject must have a negative pregnancy test at screening and must agree to employ adequate contraceptive measures (intrauterine device, diaphragm or condom with spermicidal jelly or foam, or birth control pills) throughout the course of the study and for at least 30 days after the last administration of investigational product.
- For males, the subject must agree to use an acceptable form of birth control throughout the study and for at least 90 days after dosing. Additionally, the subject must agree to abstain from sperm donation for 90 days after the last administration of investigational product.
- Subject is willing and able to comply with the requirements of the protocol.

Exclusion Criteria

- Known history of OR positive serological evidence for HBV, HCV, or HIV Type 1/2 infection.
- Known history of thrombophilia and/or thromboembolic episode (DVT, MI, CVA, PE, and sickle cell anemia with history of painful vaso-occlusive crisis).
- Known history of hypersensitivity or adverse reactions (urticaria, breathing difficulty, severe hypotension, or anaphylaxis) following administration of blood or blood components.
- IgA deficiency (<7 mg/dL at screening).
- Subject has known allergy to hyaluronidase of human or animal origin including bee or vesPI venom.
- Subject has severe dermatitis or anatomical abnormality on one or both of the thighs that would interfere with IP administration or endpoint assessments.
- If subject is taking antihistamines or medications with antihistamine properties, sedatives, anxiolytics, systemic steroids, or is applying topical steroids or antibiotics on any area below the chest, the subject is unable or unwilling to discontinue these medications for a minimum of 48 hours prior to the infusion visit and through 72 hours post-infusion.
- Subject is nursing or intends to begin nursing during the course of the study.
- Subject has participated in another clinical study involving immunoglobulin products within 12 months of screening.
- Subject has participated in another clinical study involving an investigational product or device within 30 days prior to screening, or intends to participate in another clinical study involving an investigational product or device during the course of this study.

6.1.4 Agents Mandated by the Protocol**IGSC (Human), 10%:**

- Two simultaneous administrations in a single infusion visit
- 0.25 g/kg BW per thigh for a total of 0.5 g/kg BW per subject

rHuPH20:

- Single administration immediately preceding SC infusion of IGSC 10% or albumin control (75 U/g IgG or 7.5 U/mL of albumin control solution)

Human albumin 0.25% in LR solution

- Single administration immediately preceding SC infusion of IGSC 10% or albumin control (75 U/g IgG or 7.5 U/mL of albumin control solution)

LR solution (placebo control for rHuPH20)

- Single administration immediately preceding SC infusion of IGSC 10% or albumin control (at matching volume to that of rHuPH20 (0.046875 mL/mL of infusion solution))

Lot number:

IGSC 10%: 5g (Lot # LE12K195 AB) and 10g (Lot # LE12K175AC)

rHuPH20: 2.5 mL (Lot # 913295) and 5 mL (Lot # 913296)

LR solution: Lot # 84-045-JT manufactured by (b)(4)

FLEXBUMIN 25%: Lot # LB009241

6.1.5 Study Procedures and Laboratory Assessments

Assessments performed at each infusion site included time to complete infusion, average flow rate over the course of an infusion, total subject-perceived pain/discomfort level, local infusion site reactions, and subject-rated treatment preference. In addition, safety laboratory assessments including a hemolytic panel and anti-rHuPH20 antibody testing were performed. See Table 2, below.

Table 2: Study Procedure and Assessment (Submission; Table 9.5-1 on page 39):

| Visit Name | Screening Visit | Infusion Visit ^a | 72-Hr Telephone Follow-Up | 1-Week Post-Infusion Visit | End-Of-Study/Early Termination Visit ^b |
|---|-----------------|-----------------------------|---------------------------|----------------------------|---|
| Informed consent ^c | X | | | | |
| Inclusion/Exclusion | X | | | | |
| Demographics | X | | | | |
| Medical, Medication, and Non-Drug Therapy History | X | | | | |
| Body Height | X | | | | |
| Body Weight | X | X ^d | | | |
| Vital Signs | X | X | | X | X |
| Physical Exam | X | | | X | X |
| 12-lead ECG | X | | | | |
| Laboratory Assessments ^e | X | X | | X | X |
| Investigational Product Infusion | | X | | | |
| Weight Measurements of Infusion Unit | | X | | | |
| Subject-rated pain/discomfort assessment | | X | X | X | |
| Subject-rated treatment preference | | X | | | |
| Infusion Site Observations | | X | X | X | |
| Photographic images | | X ^f | | (X) ^f | (X) ^f |
| Adverse Events | X | X | X | X | X |
| Concomitant Medications and Non-Drug Therapies | X | X | X | X | X |

- Infusion visit includes subject check-in at the study site on Day -1 through 48 (± 6) hours after both infusions are completed/terminated.
- End-of-study visit is to occur at 21 days after the day of infusion. Subjects who intend to withdraw or will be discontinued early from the study after having been exposed to any IP(s) will be asked to undergo the early termination visit (same procedures as the end-of-study visit) within 10 days after the infusion visit or as soon as AR has resolved, whichever occurs first.
- Written informed consent must be obtained prior to any study procedures including screening.
- Body weight measured at check-in (Day -1) will be used for the calculation of doses to be administered.
- For laboratory assessments, see table below.
- Photographs of local site reactions are to be taken at each infusion site after SC needle/angiocatheter placement but prior to any IP administration, and at the end of after the SC needle/angiocatheter has been removed. Additional photographs of infusion site reactions may be taken at any time during infusion should a local AR of at least moderate severity occur, and at 24 and 48 hours post-infusion or during subsequent on-site assessment visits (1-week follow-up visit or end-of-study/early termination visit) if a local site reaction of at least moderate severity at onset remains unresolved.

6.1.6 Endpoints and Criteria for Study Success

Primary Endpoint

Time to complete IGSC 10% infusion

Secondary Endpoints

Efficacy Endpoints:

- Average flow rate of IGSC 10% infusion over the course
- Proportion of subjects per treatment with infusion interruptions or incomplete infusion due to significant tissue resistance or impedance to flow preventing flow of infusion solution

Safety Endpoints:

Local ARs:

- Number (proportion) of local infusion site reactions by treatment (with vs. without rHuPH20)
- Number (proportion) of infusions associated with one or more moderate or severe local AEs begin during or within 72 hours of completion of an infusion
- Number (proportion) of infusions interrupted or stopped due to local intolerability and/or local ARs

Systemic ARs:

- Number (proportion) of subjects experiencing any ARs or SARs
- Number (proportion) of subjects experiencing any moderate or severe systemic ARs begin during infusion or within 72 hours of completion of an infusion
- Number (proportion) of subjects with any infusion(s) was interrupted or stopped due to systemic intolerability and/or systemic ARs
- Incidence of hemolysis based on laboratory evidence
- Number (proportion) of subjects experienced clinically significant abnormal laboratory values
- Number (proportion) of subjects who develop antibodies (total binding and neutralizing) to rHuPH20

6.1.7 Statistical Considerations

Sample size: based on the blinded Study Epoch 1 data, the probability of the thigh treated with rHuPH20 having the shorter infusion time ($P(X < Y)$) was estimated to be $14/16=0.875$ as follows: In 6 of the 8 subjects, there was a $> 20\%$ difference in the infusion times between the two thighs. Assuming the shorter infusion time in all these 6 subjects was observed in the thigh assigned to the “IGSC 10% + rHuPH20” treatment, this contributes to $P(X < Y)$: $6/8*1=0.75$. In the remaining 2 subjects, the differences in the total infusion times were within 20%. By random variation, either thigh could have been the one treated with rHuPH20. As the data is blinded, the probability that the thigh treated with rHuPH20 having the shorter infusion time is considered to be 50% as by randomization (contribution to $P(X < Y)$: $1/8=0.125$).

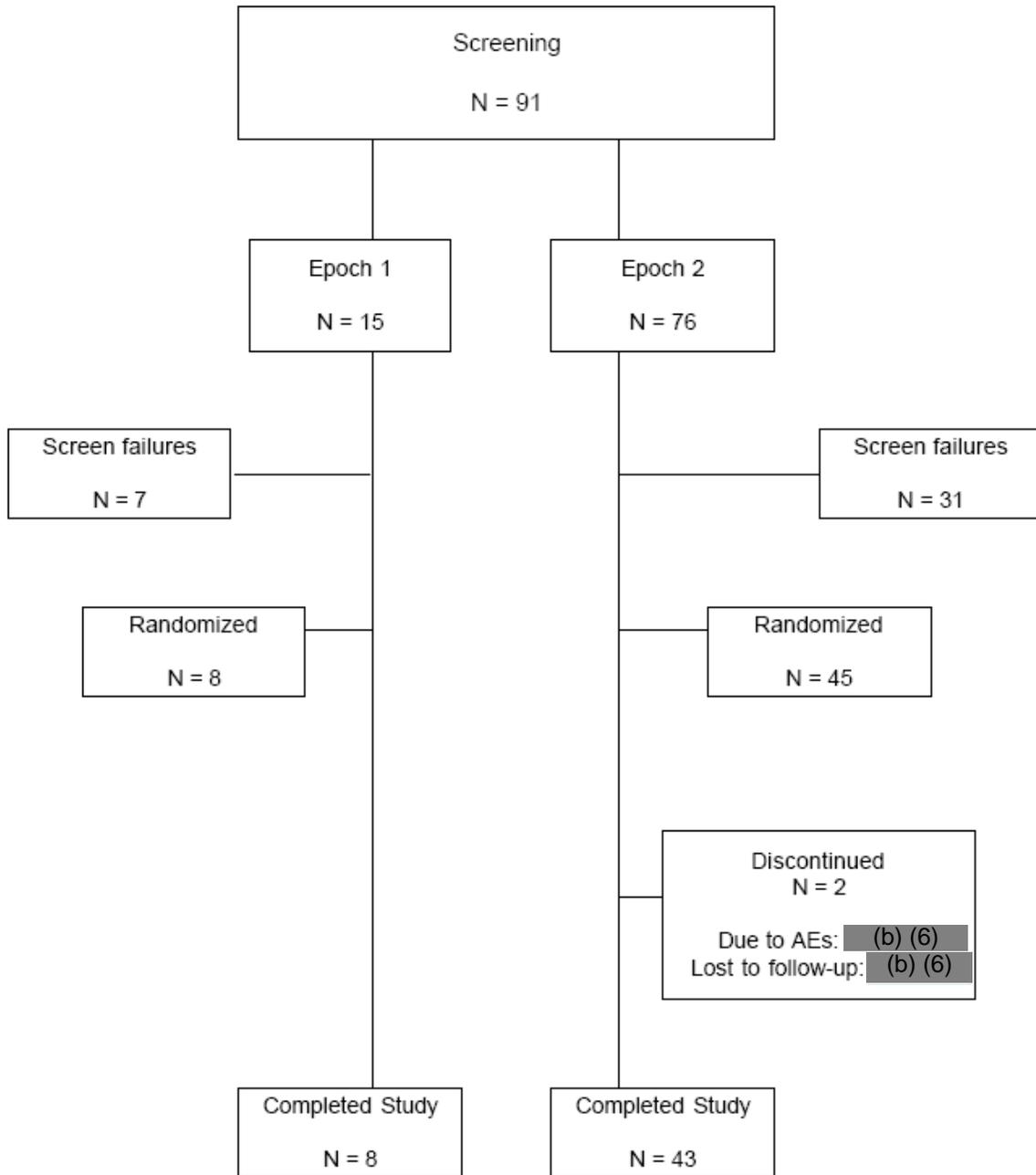
This estimate may be biased towards favorable outcome as the shorter infusion time was assumed to be associated with “+ rHuPH20” treatment. For sample size estimation, more conservative estimates in the range of 0.80 to 0.83 were considered. A sample size of 16+16=32 in Study Arms 1A and 1B would provide adequate power for the total time to complete IGSC 10% infusion endpoint, based on the blinded Epoch 1 data.

Primary Efficacy Endpoints

- The total time to complete IGSC 10% infusions with and without rHuPH20 in Study Arms 1A and 1B. For complete infusions, the total time to complete infusion included the time from the start of infusion to the end of infusion, including any and all infusion interruptions due to AR/intolerability/catheter leakage at infusion site. Mechanical interruptions and unintentional dislodging of the catheter were excluded from the calculation of the total time of infusion.
- For incomplete infusions with slow flow (infusions that were stopped at 4 hours from start of infusion), the total time to complete infusion was the sum of 4 hours plus imputed time needed to deliver the remaining planned infusion volume. For infusions with no flow, the time to complete infusion was imputed as a large value (e.g., 24 hours).
- Two-sample Wilcoxon test was used for the arithmetic difference in the total time to complete IGSC 10% infusions given to the left and right thigh of the same subject, to compare Study Arms 1A and 1B.
- Descriptive statistics for the difference in the time to complete infusion, as well as the percent reduction in time to complete infusion, were provided.

6.1.8 Disposition of Subjects

Additional Figure
Flow Chart – Subject Disposition
(Study 161001)



6.1.9 SAFETY

A total of 363 ARs were reported in 52 (98.1%) subjects. The majority of the related events were mild (211; 58.1%) or moderate (107; 29.5%) in severity. No cases of hemolysis were observed and no subject developed neutralizing antiHuPH20 antibodies.

SARs

There were no deaths or other SARs in the study.

Clinically Significant Systemic ARs

Hemolysis: Subject #(b)(6) (IGSC + rHuPH20) experienced mild anemia (Hg 14.2 mg/dL, normal: 14.0-18.0 mg/dL) on 30 September 2010 that was 13.6 mg/dL by 19 October 2010.

Leukopenia: Subject #(b)(6) (IGSC + rHuPH20) had a normal leukocyte level (4.7 x 10⁹/L; normal: 4.0-11.0/L) at screening which subsequently declined to 2.7 1 week post infusion and then returned to 3.9 at end of study.

Neutropenia: Subject #(b)(6) (IGSC + rHuPH20) also experienced relative neutropenia from 2.8 at screening (normal: 1.4-8.2) to 1.6 during an unscheduled assessment.

Increased ALT, AST, and pancreatic enzymes: Subject # (b)(6) (IP not described) showed progressively elevated ALT and AST levels that had not resolved by the last follow-up assessment. Amylase and lipase were both abnormally elevated (amylase peak: 235 U/L, normal: 25-115; lipase peak: 228, normal 25-115).

Severe Intensity Local ARs

See Table 3, below.

Table 3: Local Infusion Site ARs (from Sponsor Amended Table 14.3-1)

| | IGSC + rHuPH20 (N=40) | IGSC + LR (N=40) | Albumin + rHuPH20 (N=12) | Albumin + LR (N=12) |
|-----------------|---|---|---------------------------------|----------------------------|
| Severe ARs | 8 -(b)(6)- -(b)(6)- -(b)(6)- -(b)(6)- -(b)(6)- -(b)(6)- -(b)(6)- -(b)(6)- -(b)(6)- | 7 -(b)(6)- -(b)(6)- -(b)(6)- -(b)(6)- -(b)(6)- -(b)(6)- -(b)(6)- | 1 -(b)(6)- | 1 -(b)(6)- |
| Local ARs total | 115 | 149 | 16 | 31 |

6.2 Study #2: 170901 part 4 (phase 1)

Title: “A Phase 1 Study of Immune Globulin Subcutaneous (Human) (IGSC) Administered Either Alone or in Combination with Recombinant Human Hyaluronidase (rHuPH20) Permeation Enhancer for the Evaluation of Safety, Tolerability, and Optimal rHuPH20-to-IGSC Dose Ratio in Healthy Volunteers”

Dosing was halted prematurely on 30 October 2009 due to the occurrence of SAEs and unexpected laboratory findings with onset dates over a 3-week interval from 09 October 2009 to 30 October 2009.

6.2.1 Objectives

To evaluate the safety, tolerability and maximal tolerated flow rate of IGSC 10% infusion with or without rHuPH20.

6.2.2 Design Overview

Prospective, randomized, double blind, controlled single cohort study in healthy volunteers to compare the safety, tolerability, and maximal flow rate of IGSC 10% with or without rHuPH20.

Study 170901 was designed as a 4-part, Phase 1, prospective, randomized, double-blind, controlled, 8-week cross-over study to assess the safety, tolerability, and maximal flow rate of IGSC infusion administered with and without rHuPH20 over a 1-3 week treatment period, and to determine the optimal dose ratio of rHuPH20 and IgG in approximately 47 healthy adult subjects in total.

The study was composed of 4 parts: Study Parts 1 through 3 evaluated IGSC 10% administered either alone or in combination with rHuPH20. Study Part 4 was designed to compare the safety, tolerability, and maximal flow rate of IGSC, 10% infusion given with or without rHuPH20. IGSC, 10% was to be administered at a single infusion site for each treatment. The recommended infusion site was the abdomen in order to accommodate the large volume of solution to be infused subcutaneously.

Study Part 4 Treatments

| Treatment | IGSC, 10% | rHuPH20 |
|-----------|----------------------|----------------------------|
| 4A | 0.3 g/kg BW/infusion | Formulation Buffer Control |
| 4B | 0.3 g/kg BW/infusion | 75 U/g IgG |
| 4C | 0.6 g/kg BW/infusion | Formulation Buffer Control |
| 4D | 0.6 g/kg BW/infusion | 75 U/g IgG |

Note(s): IGSC, 10% was administered sequentially following administration of rHuPH20 or its formulation buffer control at matching volume. BW = body weight.

One cohort: IGSC 10% +/- rHuPH20 sequential administration

- Two IgG doses (0.3 and 0.6 g/kg BW/infusion) were given in a dose-escalating manner (each subject received infusions at 0.3 g/kg BW first, and then followed by infusions at 0.6 g/kg BW). The reasons for this dosing scheme were: (1) the stepwise increase in IgG dose to the full therapeutic dose is commonly practiced clinically for better tolerability and fewer adverse reactions; and (2) these 2 dose levels encompass the therapeutic dose range (0.3 to 0.6 g/kg BW /infusion) typically used in PI and neurology.
- Each subject initially received IGSC 10% infusions at 0.3 g/kg BW/infusion alone (4A) and with rHuPH20 (4B) respectively in a blinded crossover sequence one week (7 ± 2 days) apart. For each individual, the treatment(s) that was/were tolerated and successfully completed within 8 hours were repeated in a blinded fashion at the higher IGSC 10% dose level of 0.6 g/kg BW/infusion (4C, 4D, or both). Thus, a subject could have received a total of 2 to 4 infusions:

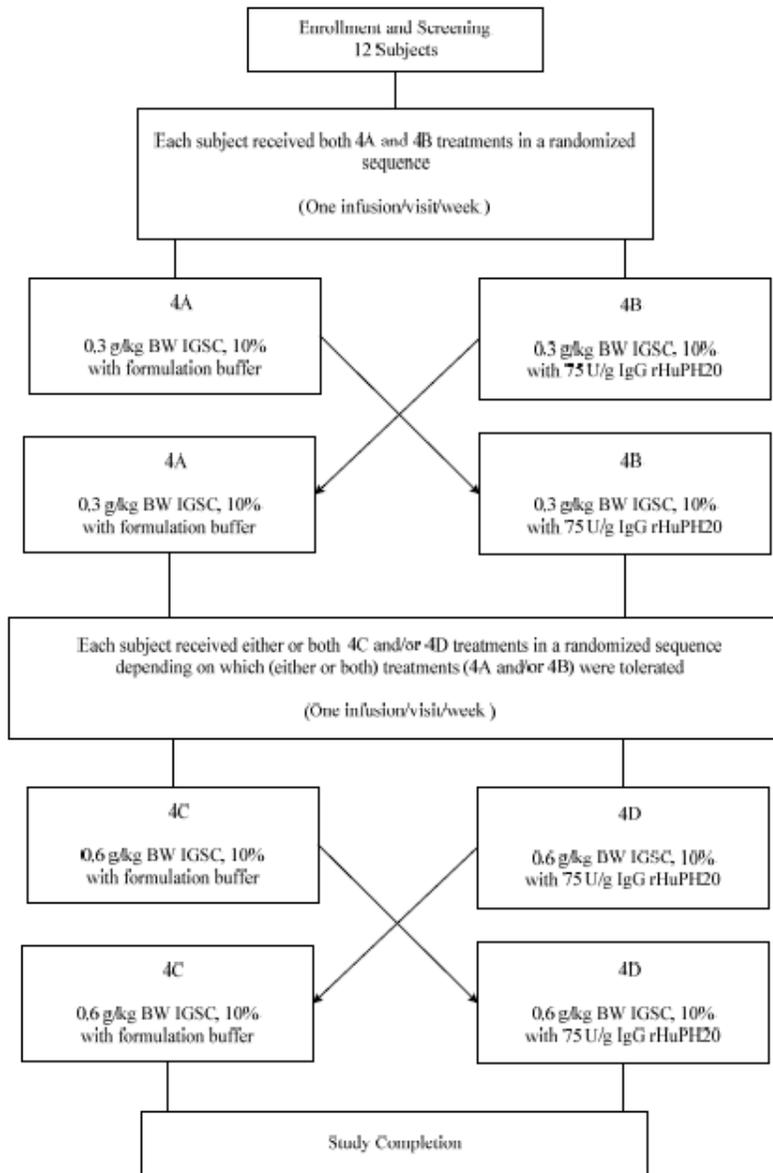
4A: IGSC 10% (0.3 g/kg BW/infusion) + Control

4B: IGSC 10% (0.3 g/kg BW/infusion) + rHuPH20 75 U/g IgG

4C: IGSC 10% (0.6 g/kg BW/infusion) + Control

4D: IGSC 10% (0.6 g/kg BW/infusion) + rHuPH20 75 U/g IgG

See study schematic, below.



6.2.3 Population

Inclusion Criteria

1. Male or female, 18 to 65 years of age.
2. Body mass index (BMI) 19 to 32 kg/m² and body weight ≥ 50 kg. Additionally, for Study Part 3, the subject's body weight did not exceed 90 kg.
3. Healthy subject with no clinical evidence of acute and/or chronic disease and with no clinically significant abnormalities on hematology panel, clinical chemistry panel, urinalysis, ECG.
4. Negative drug screen test at screening. Subject had to agree to refrain from heavy alcohol consumption and use of narcotic drugs or illegal substances, within 2 weeks prior to screening and throughout the study. Subject had to also agree to

drug screen testing at the discretion of the investigator at any time during the course of the study.

5. Nonsmoker or ex-smoker with smoking cessation for a minimum of 6 months prior to screening. Subject had to agree to refrain from smoking throughout the course of the study.
6. For women of childbearing potential, the subject had to have a negative pregnancy test at screening and agree to employ adequate contraceptive measures (intrauterine device, diaphragm or condom with spermicidal jelly or foam, abstinence, or birth control pills) throughout the course of the study.
7. Subject was willing and able to comply with the requirements of the protocol.

Exclusion Criteria

1. Known history of or positive serological evidence for HBV, HCV, or HIV Type 1/2 infection.
2. Known history of thrombophilia and/or thromboembolic episode (DVT, MI, CVA, and PE).
3. Known history of hypersensitivity or persistent adverse reactions (urticaria, breathing difficulty, severe hypotension, or anaphylaxis) following infusions of IGIV, IGSC, ISG, albumin, or other blood components, or currently taking these products within 30 days prior to screening.
4. IgA deficiency (< 7 mg/dL).
5. Known allergy to hyaluronidase of human or animal origin including bee or vesPI.
6. If taking antihistamines or medications with antihistamine properties, sedatives, anxiolytics, systemic steroids, or topical steroids for use on the abdominal region, the subject is unable or unwilling to discontinue these medications for a minimum of 48 hours prior to each infusion visit and through 72 hours post-infusion.
7. Nursing or intends to begin nursing during the course of the study.
8. Subject had not participated in another clinical study involving an investigational product or device within 30 days prior to screening, or intended to participate in another clinical study involving an investigational product or device during the course of this study.

6.2.4 Study Treatments Mandated by the Protocol

IGSC 10%: 0.3 and 0.6 g/kg /infusion

rHuPH20: 0 (rHuPH20 formulation buffer control) or 75 U/g IgG

Lot number:

IGSC 10%: 50 mL-Lot # LE12J118AE; and 100 mL-Lot # LE12J153AC

rHuPH20: Lot # HUC0901CA

rHuPH20 formulation buffer: Lot # 912403

6.2.5 Surveillance/Monitoring

| Event | Screening | Infusion Visits | 48-72 Hour Post Infusion Telephone Follow-up | End of Study* |
|--|-----------|-----------------|--|---------------|
| Informed Consent | X | | | |
| Inclusion/Exclusion | X | | | |
| Demographics | X | | | |
| Medical, Medications, and Non-drug Therapy History | X | | | |
| Body Weight and Height ^b | X | | | |
| Vital Signs ^b | X | X ^c | | X |
| Physical Exam | X | | | X |
| 12-lead Electrocardiogram ^d | X | | | |
| Laboratory Assessments: | | | | |
| Hematology Panel ^e | X | X ^f | | X |
| Clinical Chemistry Panel ^g | X | | | X |
| Hemolytic Panel ^h | | X ^f | | |
| HBsAg, HCV antibody, and HIV-1/HIV-2 antibody | X | | | X |
| Serum IgA | X | | | |
| Urinalysis ⁱ | X | | | |
| Urine Drug/Alcohol Screen ^j | X | | | |
| Urine Pregnancy ^k | X | | | |
| Anti-rHuPH20 Antibodies | X | | | X |
| Investigational Product Infusion | | X | | |
| In-line Pressure Measurements | | X ^c | | |
| Cumulative and Total Volume Infused | | X ^c | | |
| Infusion Site Observations | | X ^c | X ^c | X |
| Subject-rated Categorical Pain/Discomfort Assessment Scale | | X ^c | X ^c | |
| Adverse Events | X | X | X | X |
| Concomitant Medications and Non-Drug Therapies | X | X | X | X |

- a. Subjects who intended to withdraw or were discontinued early from the study after having been exposed to any IP were asked to undergo the end-of-study/early termination visit within 10 ± 3 days after the last IP infusion.
- b. Body weight and height were measured at screening only. Other vital signs including body temperature, pulse rate, sitting blood pressure, and respiratory rate were measured at screening, during each infusion visit (within 30 minutes prior to SC injection of rHuPH20/control; during IGSC or admixture infusion [at the end of each flow rate interval during flow rate ramp-up phase, once constant flow rate was maintained, every 30 minutes till the end of infusion, and at each infusion interruption; at the end of infusion; at 60 minutes and at 24 hours after the end of infusion), and at the end-of-study/early termination visit.
- c. Measurements of in-line pressure and cumulative volume infused were taken at the following time points: during IGSC or admixture infusion (at the end of each flow rate interval during flow rate ramp-up phase; once constant flow rate was maintained, every 15 minutes for the first 2 hours and then every 30 minutes until the end of infusion; and at each infusion interruption, and at the end of infusion (within 5 minutes prior to infusion completion), unless prematurely terminated. Total volume infused was measured at the end of infusion. Infusion site observations were measured at the end of rHuPH20/formulation control injection, during IGSC or admixture infusion (at each infusion interruption), at the end of infusion, at 60 minutes and 24 hours after the end of infusion. Subject-rated pain/discomfort assessment on a 5-point categorical assessment scale were measured at the following time points: at the end of rHuPH20/formulation buffer control injection, during IGSC, at the end of infusion, at 60 minutes and 24 hours after the end of infusion.
- d. Recent records of ECG taken within 3 months prior to screening could be used.
- e. Hematology panel included hemoglobin, hematocrit, erythrocytes, leukocytes with automatic differential (basophils, eosinophils, lymphocytes, monocytes, neutrophils), and platelet counts.
- f. Hematology and hemolytic anemia panels were performed during pre-specified infusion visits. Time points for blood draws for the hematology and hemolytic anemia laboratory assessments were as follows: Infusion Visit 1 (prior to infusion only to obtain baseline measurement), and the last infusion visit at IGSC 10 [20 hours after the end of infusion and 24 hours after the end of infusion]. In addition, the hematology assessment was performed at the screening and end-of-study termination visit.
- g. Clinical chemistry panel included sodium, potassium, bicarbonate, chloride, calcium, phosphorus, total bilirubin, direct bilirubin, alkaline phosphate, AST, ALT, gamma-glutamyl-transferase, LDH, BUN, creatinine, creatine phosphokinase, total protein, albumin, globulin, serum IgA, creatine phosphokinase, and glucose. The clinical chemistry panel was assessed at screening and at the end-of-study termination visit.
- h. Hemolytic anemia panel included direct Coombs test, haptoglobin, LDH, reticulocyte count, and plasma free hemoglobin.
- i. Urinalysis included color, specific gravity, pH, protein, glucose, ketones, bilirubin, urobilinogen, blood, nitrite, leukocyte esterase, and microscopic examination.
- j. Urine drug/alcohol screen test included marijuana, cocaine metabolites, amphetamines, opiates, phencyclidine, barbiturates, benzodiazepines, propoxyphene, ethanol, and creatinine.
- k. For women of child bearing potential only.

6.2.6 Endpoints and Criteria for Study Success

- In-line pressure exerted to infuse IGSC 10% subcutaneously at each flow rate
- In-line pressure exerted to infuse IGSC 10% subcutaneously in relation to cumulative volume infused
- Maximum volume infused and maximum tolerated flow rate at the end of an infusion
- Time required to complete an infusion
- Number (proportion) of SC infusions completed
- Number (proportion) of SC infusions tolerated and completed at the maximum flow rate
- Cumulative volume infused at the time of each infusion interruption (including reduction in flow rate and temporarily stopping the infusion) due to intolerability, local, and/or systemic-related ARs
- Infusion site observations: Catheter leakage; area of swelling; area of induration; area of discoloration (redness); degree of discoloration (redness); severity of local tenderness
- Subject-rated 5-point categorical assessment of pain/discomfort
- Correlation between in-line pressure exerted by SC infusion and complaints of discomfort/pain categorized by pain scores

Safety Endpoints

- Number (proportion) of subjects/infusions experiencing any ARs and/or SARs
- Number (proportion) of subjects/infusions experiencing related AR(s) and/or SAR(s)
- Number (proportion) of infusions with temporally associated (during or within 72 hours of completion of an infusion) AR(s) and/or SAR(s)
- Number (proportion) of infusions that were discontinued, slowed, or interrupted due to an AR
- Number (proportion) of infusions not tolerated: due to any serious related AR; any severe non-serious local or systemic-related AR(s); any severe non-serious local or systemic-related AR(s) that occurred within 60 ± 5 minutes of completion of the infusion
- Number (proportion) of infusions associated with local infusion site reactions by severity and systemic-related AR(s)
- Number (proportion) of subjects who developed antibodies to rHuPH20

6.2.7 Statistical Considerations and SAP

Sample size: based on the assumption that infusion time without rHuPH20 would be 50% longer with a SD of 50%. A sample of 12 subjects would provide 84% power in a two-sided superiority test at the 4% level of statistical significance for testing at the 0.3 g/kg BW dose level.

Planned Statistical Analysis:

The cross-over designs at 0.3 g/kg and at 0.6 g/kg were analyzed separately.

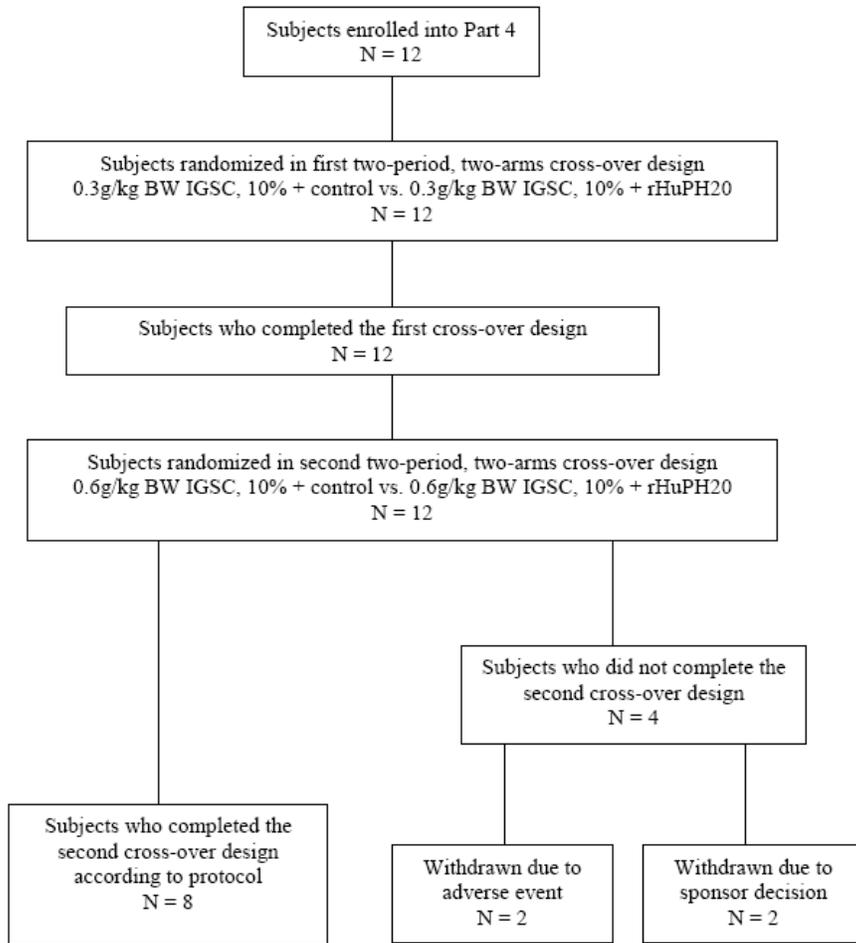
The null hypothesis of no difference in infusion times at the 0.3 g/kg BW dose level was tested against the two-sided alternative of superiority at the 4% level of statistical

significance. The analysis of the crossover design by analysis of variance (ANOVA) used the error variance from a model with fixed effect terms for the sequence effect, the period effect, the subject effect nested in sequences and the drug effect.

The same analysis was performed for the 0.6 g/kg BW at the 1% level of statistical significance for an overall type I error rate of 5%.

6.2.8 Subject Disposition

Additional Table
Flowchart - Subject Disposition
 (Study 170901 Part 4)



6.2.9 SAFETY

Both Study Parts 4 and 1 were terminated early due to the occurrence of 2 SARs (hemolytic anemia, Subjects ----(b)(6)----- and unexpected laboratory findings leading to subject withdrawal (Subject -(b)(6)--- due to a nonserious AR of flu-like illness. A total of 12 subjects (8 male, 4 female) were enrolled in Part 4 and analyzed for safety. Parts 2 and 3 were not conducted.⁴

SARs (see Table 4, next page)

- Hemolytic anemia (sponsor)
 1. **Subject (b)(6)** (treatment 4C, nadir Hb: **11.0** g/dL) was a 32 y/o previously healthy male who experienced moderate hemolytic anemia and severe lymphopenia accompanied by fever, malaise, and sweating 2 days after receiving the 3rd dose of Treatment 4C. At screening, RBC was 5.51 (normal: 4.50-6.0 x 10⁶/uL), declining to 3.91 three weeks after initial dosing. LDH was elevated at 659). At the time of the Final Study Report, the subject had recovered subjectively but still had laboratory evidence of ongoing hemolysis and elevated serum creatinine values.
 2. **Subject (b)(6)** (treatment 4A, nadir Hb: **10.2** g/dL) was a 48 y/o previously healthy male who experienced severe hemolytic anemia accompanied by productive cough, myalgia, fever, chills, and orthostasis following the 4th infusion of Treatment 4A. Hb was 14.5 g/dL at screening and 10.7 at end of study. Peak elevations were noted for LDH (669 U/L), ALT (177 U/L), AST (203 U/L), amylase (200 U/L) and lipase (317 U/L). Hemolytic anemia resolved 7 weeks after the final dose.

Reviewer comment

Not mentioned by the sponsor is Grade 3 hemolytic anemia reported for subject **(b)(6)** (36 y/o male, treatment 4C, nadir Hb: **12.2**), #-(b)(6)- (44 y/o female, treatment 4D, nadir Hb: **11.8**), and (b)(6) (45 y/o male, treatment 4C, nadir Hb: **11.8**)

Clinically Significant Systemic ARs (Grade 2 or higher, Tables 4 and 5, below)

- “Flu-like illness” (sponsor): subject **(b)(6)** (Treatment 4C) was a previously healthy male who was withdrawn from the study 4 days after receiving Treatment 4C. This was accompanied by elevations of ALT (499 U/L), AST (136 U/L), and GGT (87 U/L). Liver function values resolved 22 days after onset (ALT=44 U/L), AST=29 U/L).

⁴ In terms of efficacy, there was no difference in (a) in-line pressure vs. flow rate and in-line pressure vs. cumulative volume infused curves, (b) total volume of IGSC 10% infused with and without rHuPH20 preadministration for both IGSC doses (0.3 g/kg and 0.6 g/kg), (c) maximum tolerated flow rate (300 mL/h), and (d) time needed to complete an infusion

- Lymphopenia: subject -(b)(6)-- (Treatment 4B); -(b)(6)-- (Treatment 4C), -(b)(6)-- (Treatment 4C), -(b)(6)-- (Treatment 4D), and -(b)(6)-- (Treatment 4A)
- Leukopenia: subject -(b)(6)-- (Treatment 4C), -(b)(6)-- (Treatment 4C), and -(b)(6)-- (Treatment 4D)
- Elevated liver transaminases: subject -(b)(6)-- (Treatment 4C), -(b)(6)-- (Treatment 4D), and -(b)(6)-- (Treatment 4C)
- Elevated pancreatic enzymes: subject -(b)(6)-- (Treatment 4C), -(b)(6)-- (Treatment 4D), and -(b)(6)-- (Treatment 4C)

Table 4: Grade 2 or Higher Chemistry & Hematology Values Color-coded by Degree of Toxicity Severity (Source: sponsor)

| ID | Serum Chemistry | | | | Hematology | | | |
|----------|-----------------|------------|-----------|-----|------------|--------------|-----------|-----|
| | Analyte | Peak (ULN) | Tox Grade | Trt | Analyte | Trough (LLN) | Tox Grade | Trt |
| -(b)(6)- | LDH | 468 (259) | 1 | 4C | Hg | 12.2 (14) | 3 | 4C |
| | ALT | 197 (50) | 2 | 4C | WBC | 2.5 (4) | 2 | 4C |
| | AST | 138 (45) | 2 | 4C | LYMPH | 0.9 (1) | 3 | 4C |
| | Amylase | 163 (115) | ** | 4C | | | | |
| -(b)(6)- | | | | | LYMPH | 0.9 (1) | 3 | 4C |
| -(b)(6)- | CPK | 334 (294) | ** | 4C | Hg | 11.0 (14) | 3 | 4C |
| | LDH | 659 (259) | 2 | 4C | LYMPH | 0.6 (1) | 3 | 4C |
| -(b)(6)- | | | | | Hg | 11.8 (12) | 3 | 4D |
| | | | | | WBC | 3.7 (4) | 1 | 4D |
| | | | | | WBC | 2.8 (4) | 2 | 4C |
| -(b)(6)- | | | | | WBC | 2.7 (4) | 2 | 4D |
| | | | | | LYMPH | 0.9 (1) | 3 | 4D |
| -(b)(6)- | CPK | 4190 (294) | **** | 4D | Hg | 10.2 (14) | 4 | 4A |
| | ALT | 177 (50) | 2 | 4D | LYMPH | 0.7 (1) | 3 | 4A |
| | AST | 263 (45) | 3 | 4D | | | | |
| | LDH | 669 (259) | 2 | 4D | | | | |
| | Amylase | 200 (115) | ** | 4D | | | | |
| | Lipase | 317 (60) | *** | 4D | | | | |
| -(b)(6)- | LDH | 361 (259) | 1 | | Hg | 10.9 (14) | 3 | 4D |
| -(b)(6)- | CPK | 1181 (294) | *** | 4C | | | | |
| -(b)(6)- | | | | | Hg | 13.8 (14) | 2 | 4C |
| -(b)(6)- | ALT | 499 (50) | 3 | 4C | Hg | 11.8 (14) | 3 | 4C |
| | AST | 136 (45) | 2 | 4C | | | | |
| | GGT | 87 (57) | ** | 4C | | | | |
| | LDH | 323 (259) | 1 | 4C | | | | |
| | T BILI | 1.4 (1.2) | 2 | 4C | | | | |
| | GGT | 87 (57) | ** | 4C | | | | |

** : toxicity score column missing from sponsor’s data table and imputed by reviewer to grade 2

*** : toxicity score column imputed by reviewer to grade 3

**** : toxicity score imputed by reviewer to grade 4

Trt 4A: IG 0.3 g/kg/infusion + buffer; Trt 4C: IG 0.6 g/kg/infusion + buffer

Trt 4B: IG 0.6 g/kg/infusion + rHuPR20; Trt 4D: IG 0.6 g/kg/infusion + rHuPR20

Table 5: Summary Table of Grade 2 or Higher Toxicity Values

| Chemistry | IG + Buffer | IG + rHuPR20 | Total |
|--|--------------------|---------------------|--------------|
| Grade 2 | 9 | 3 | 12 |
| Grade 3 | 2 | 2 | 4 |
| Grade 4 | 0 | 1 | 1 |
| Total | 11 | 6 | 17 |
| Hematology (including anemia) | | | |
| Grade 2 | 3 | 2 | 5 |
| Grade 3 | 7 | 2 | 9 |
| Grade 4 | 1 | 0 | 1 |
| Total | 11 | 4 | 15 |
| Anemia | | | |
| Grade 2 | 1 | 0 | 1 |
| Grade 3 | 3 | 2 | 5 |
| Grade 4 | 1 | 0 | 1 |
| Total | 5 | 2 | 7 |
| Chemistry + Hematology (including anemia) | 22 | 10 | 32 |

Severe Intensity Local ARs

No subject experienced severe local ARs (NB: mild pain was observed for 1 Treatment 4A subject, 5 Treatment 4B subjects, 0 Treatment 4C subjects, and 1 Treatment 4D subject).

Reviewer comments

1. Hematology: the frequency of Grade 2 (or higher) hemolytic anemia in rHuPR20 subjects was 1/3 the incidence of this event in IG + buffer subjects. Qualitatively similar trends were observed for lymphopenia and leukopenia.
2. Chemistry: the frequency of Grade 2 or higher serum chemistry toxicity was similar to the hematology results.

6.3 Study #3: 160602 (phase 1/2)

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”

6.3.1 Objectives

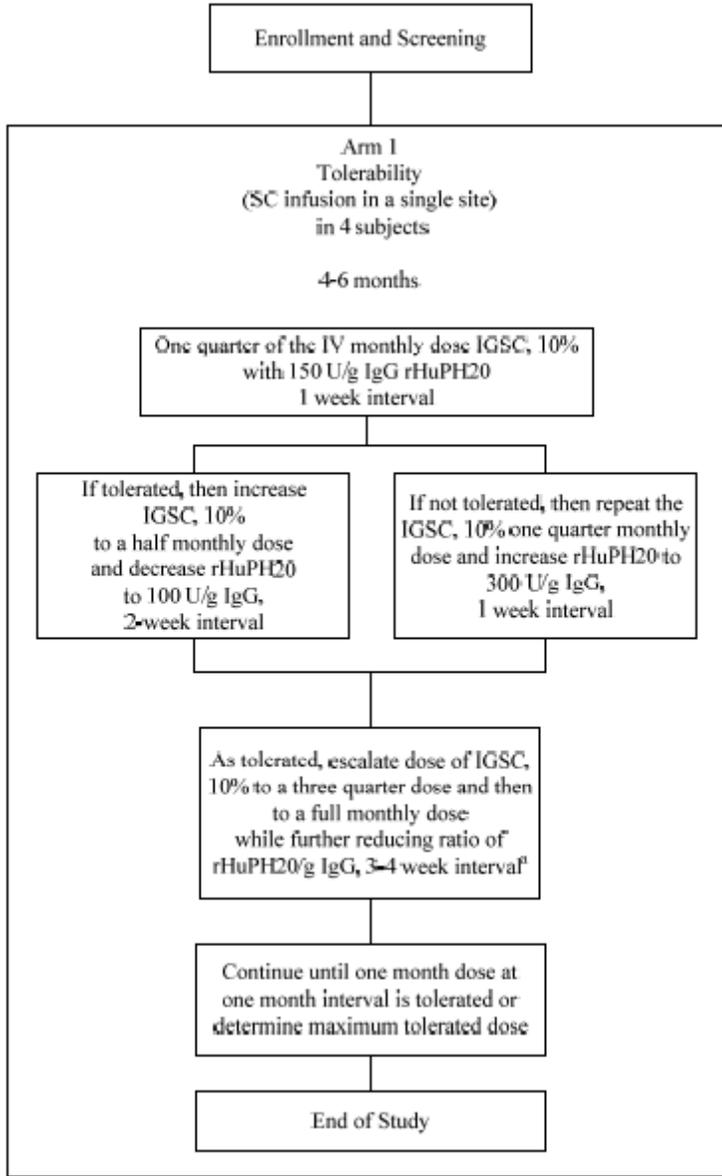
The primary objective was to determine the feasibility of infusing a full 4-week dose of IGIV, 10% in a single SC site and the amount of rHuPH20 needed to infuse that dose (a dose of up to a maximum of 600 mg of IgG/kg BW) with no more than mild local ARs

The secondary objective was to obtain data on the ability of rHuPH20 to improve the bioavailability of SC administered IGIV, 10% to approximate the bioavailability after IV administration

6.3.2 Design Overview

Phase 1/2 prospective, open-label, non-controlled, two-arm multicenter study in PI subjects to determine the dose of rHuPH20 necessary to infuse a full 4-week dose of IGIV, 10%, in a single SC site with good tolerability, and to compare the PK of the rHuPH20-facilitated SC administered IgG with the PK of IV administered IgG. An infusion was defined as having been tolerated if it caused no more than mild local ARs (as for instance minimal swelling, redness or pain) that the investigator did not assess as unacceptable for other medical reasons.

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.



Study Arm 1:

- 4 adult/adolescent subjects received SC infusions of IGIV, 10% to determine tolerability.
- 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. Administration of rHuPH20 was to be completed 5 minutes prior to starting the infusion of the IGIV, 10%.
- Treatment started with 1/4 of a full 4-week dose of IGIV, 10% given SC, which was preceded by 150 U of rHuPH20/g IgG. If that dose was tolerated, 1 week later 1/2 SC dose was administered with a reduced ratio of rHuPH20, 100 U/g IgG. If the 1/4 dose was not tolerated, the same dose of IGIV, 10% was repeated

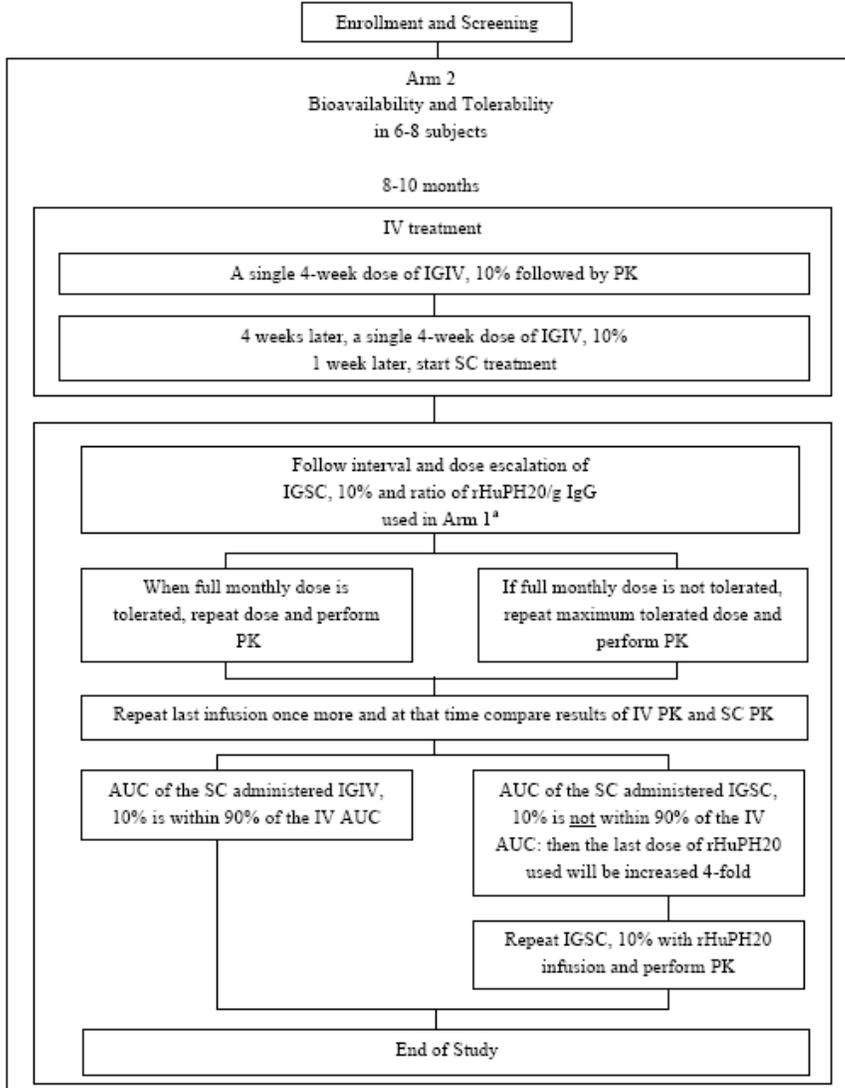
using double the amount of rHuPH20. As tolerated, the dose of IGIV, 10% was increased and the ratio of rHuPH20 was decreased according to the schedule until a full 4-week IgG dose was administered. If the dose of IGIV, 10% was not tolerated, the amount of rHuPH20 was increased until the dose was tolerated or a maximum amount of rHuPH20 was reached and administration was considered a failure. Since subjects completed the study using the minimum amount of 50 U of rHuPH20/g IgG for SC administration of a full 4-week dose of IGIV, 10%, the protocol was amended to allow the amount of rHuPH20 to be decreased to 25 or 10 U/g IgG.

- If a subject was not able to achieve a 4-week dose of IGIV, 10% in a single infusion with the quantity of rHuPH20 allowed per schedule, the amount that was tolerated (2- or 3-week dose) was determined to be the maximum dose tolerated by that subject. This dose was repeated (2 or 3 weeks later) and the study terminated for the subject with an End-of Study visit at the end of the last treatment interval.

Study Arm 2:

- 6 to 8 subjects were scheduled to receive an IV infusion of IGIV, 10% to determine PK over the ensuing 4 weeks. 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 study entry, and was given for a 4-week interval. After completion of the PK study, the subjects received another 4-week dose of IGIV, 10% IV. The first SC infusion was administered 1 week after the second IV infusion. The timing and volume of the SC IGIV, 10% infusions, and the ratio of rHuPH20 and IGIV, 10% followed the schedule that was used for the 4 tolerability subjects in Study Arm 1. Once a full 4-week dose could be infused SC in a single infusion site, the same dose was repeated and a second PK study was conducted. The results were compared to the PK results after IV infusion in terms of bioavailability as determined by AUC of a plot of the IgG concentration versus time.
- If a subject was not able to tolerate a 4-week SC dose of IGIV, 10% in a single infusion site with the quantity of rHuPH20 allowed per schedule, the amount of IGIV, 10% that was tolerated was determined to be the maximum dose tolerated by that subject. This dose was to be repeated (2 or 3 weeks later) and a PK study was performed during the next treatment interval, as was done for the subjects achieving a 4-week infusion interval.
- If the AUC determined after SC administration of IGIV, 10% was below 90% of the AUC determined after IV administration, the last dose of rHuPH20 used was increased 4-fold (the minimum dose being 200 U/g IgG the maximum dose 48,000 U), and another SC infusion of IGIV, 10% was administered followed by a PK study. The subject completed the study with the collection of the last sample for the PK study at the time of the End-of-Study visit. During the interval between the PK infusion and the availability of the PK results, SC administration of IGIV,

10% was continued at the amount and ratio of rHuPH20 to IgG used for the PK infusion.



6.3.3 Population

Inclusion Criteria

1. Written informed consent obtained
2. Subjects had a diagnosis of a PI as defined by WHO criteria for which the subject had been receiving a regimen of weekly or biweekly SC IgG infusions or IGIV infusions every 21 to 28 days over a period of at least 8 weeks pre-study at an equivalent of a 4-week dose of 300 to 800 mg/kg BW
3. 16 years and older
4. If female and capable of bearing children: subject had a negative urine pregnancy test result at study entry and agreed to employ adequate birth control measures for the duration of the study.

Exclusion Criteria

1. Subjects positive at enrollment for HBsAg, PCR for HCV, PCR for HIV Type 1
2. Subjects with levels of ALT or AST $> 2.5 \times$ the ULN for the testing laboratory
3. Subjects with neutropenia ($ANC \leq 500/mm^3$)
4. Subjects with serum creatinine levels $> 1.5 \times$ the ULN for age and gender
5. Subjects with current history of malignancy
6. Subjects with a history of thrombotic episodes (DVT, MI, CVA)
7. Subjects with abnormal protein loss (protein losing enteropathy, nephritic syndrome, severe lung disease)
8. Subjects with anemia that precluded phlebotomy for laboratory studies
9. Subjects who had been exposed to any blood or blood product other than an IGIV, IGSC, immune serum globulin (ISG) preparations, or albumin within the 6 months prior to study entry.
10. Subjects with an ongoing history of hypersensitivity or persistent reactions (urticaria, breathing difficulty, severe hypotension, or anaphylaxis) following IGIV, SCIG and/or ISG infusions.
11. Subjects with IgA deficiency and known anti IgA antibodies.
12. Subjects who had received antibiotic therapy for the treatment of infection within 7 days prior to enrollment.
13. Subjects who had participated in another clinical study involving an investigational product or device within 28 days prior to study entry.
14. Subjects with inability or unwillingness to meet all the requirements of this study.
15. If female, pregnancy or lactation at time of study entry.

6.3.4 Study Treatment Mandated by the Protocol

IGIV, 10%:

- A ready-to-use 10% liquid preparation
- A 4-week dose of 300-800 mg/kg were to be administered depending on the subject's pre-study dose
- Subjects were treated SC (Study Arm 1) or SC treatment was preceded by an IV treatment period (Study Arm 2).

rHuPH20:

- Provided in concentrations of 150 U/mL and 1,500 U/mL in a volume of 1 mL
- SC injection prior to SC infusion of IGIV, 10%. The initial dose was calculated on the basis of 150 U/g IgG. The amount and ratio of rHuPH20 to IGIV, 10% during subsequent administrations was adjusted according to a predetermined scheme to facilitate tolerability.

Lot numbers:

IGIV, 10%: 10.0 g vials: LEI2F033AE

rHuPH20: 150 U/mL: 905089 and 1,500 U/mL: HUC0601CA, HUC0601CB

6.4.5 Surveillance/Monitoring

Study Arm 1 (SC tolerability)

| Procedure/Assessment | Screening/ Baseline Visit | Treatment/Visit No. | | | |
|-------------------------------------|------------------------------|---------------------|---|-------------------------|--|
| | | SC Infusion 1 | All Following Infusions Adjustment of rHuPH20 Dose | Final Infusion Visit | End-of-Study Visit at End of Last SC Infusion Period |
| Location | Study Site | Study Site | Study Site | Study Site | Study Site |
| Informed Consent | x | | | | |
| Inclusion/Exclusion | x | | | | |
| Medical History | x | x | x | x | x |
| Physical Exam | x | x | x | x | x |
| Vital Signs | x | x | x | x | x |
| Laboratory Assessments ^a | x | | | | x |
| Concomitant Medication | x | x | x | x | x |
| Adverse Events | | x | x | x | x |
| Study Product Treatment | | x | x | x | |

Study Arm 2 (PK and SC tolerability)

| Procedure/ Assessment | Screening/ Baseline Visit | Treatment/Visit No. | | | | | | | |
|-------------------------------------|---------------------------------|--|--|--|---|--|--|--|---|
| | | 1 IV Infusion #1 PK Study | 2 (4 Weeks Later) IV Infusion #2 Full 4- Week Dose | 3 (1 Week Later) SC Infusion #1 | 4 - ? SC Adjustment of Dose of rHuPH20 to Maximum Tolerated IgG Dose | Maximum Dose Repeated, Same Dose of rHuPH20 PK Study | Repeat Maximum IgG Dose, Same Dose of rHuPH20 | If AUC Below 90% of AUC After IV Infusion: Infuse Maximum Dose of IGIV, 10% with Adjusted Dose of rHuPH20 | End-of-Study Visit at the End of the Last Treatment Period |
| Location | Study Site | Study Site | Study Site | Study Site | Study Site | Study Site | Study Site | Study Site | Study Site |
| Informed Consent | x | | | | | | | | |
| Inclusion/Exclusion | x | | | | | | | | |
| Medical History | x | x | x | x | x | x | x | x | x |
| Physical Exam | x | x | x | x | x | x | x | x | x |
| Vital Signs | x | x | x | x | x | x | x | x | x |
| Laboratory Assessments ^a | x | PK only | | | | PK only | | PK only | x |
| Concomitant Medication | x | x | x | x | x | x | x | x | x |
| Adverse Events | | x | x | x | x | x | x | x | x |
| Study Product Treatment | | x | x | x | x | x | x | x | |

6.3.5 Endpoints and Criteria for Success

Primary endpoint:

Ability to administer, after rHuPH20, at least 1/2 of a 4-week dose (200 mg/kg) of IgG in a single infusion site via the SC route. A minimum of 90% of the subjects had to tolerate 1/2 of the 4-week and a minimum of 50% had to tolerate a full 4-week dose (400 mg/kg) of IgG in a single site with no more than mild local ARs.

Safety endpoint

- The proportion of SC infusions that were not interrupted or stopped for ARs per subject
- The proportion of SC infusions associated with 1 or more systemic ARs (excluding infections) during or within 72 hours (h) of completion of infusion
- The proportion of SC infusions associated with 1 or more local ARs during or within 72 h of completion of infusion
- The number of moderate or severe local ARs
- The number and proportion of infusions associated with moderate or severe systemic ARs

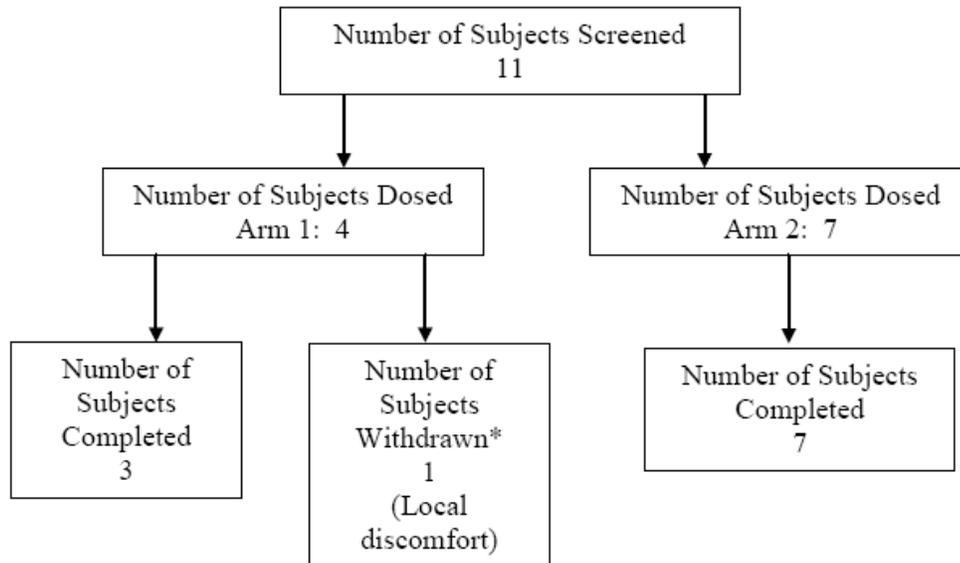
6.3.5 Statistical Considerations and SAP

- No sample size calculations were performed for this study. The primary endpoint was analyzed descriptively.
- PK parameters were summarized over the set of subject in Study Arm 2. The AUC_{0-τ} was calculated by the trapezoidal rule and was standardized for dose. To determine PK equivalence of IV and SC routes of administration, the 90% CI for the difference of the mean logarithms of AUC_{0-τ}/dose was calculated.

6.3.6 Disposition of Subjects

A total of 11 adult subjects (4 male, 7 female) participated in this phase 1/2 study. The purpose was 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 a dose of up to a maximum of 600 mg of IgG/kg BW with no more than mild local ARs.

Figure 1.
Disposition of Subjects in Study 160602



Arm 1: HyQ only
Arm 2: IV followed by HyQ

6.3.6 SAFETY

SARs

Anaphylaxis: the only severe and potentially life-threatening AR that occurred in the study was an anaphylactic reaction in Subject -(b)(6)- that was attributed to an antibiotic drug taken immediately prior to onset of the symptoms. This SAR occurred more than 24 hours after an infusion and was not considered by the sponsor/investigator to be related to the use of the study drugs.

By way of background, hyaluronidase is added to local anesthetics in ocular, dental, and plastic surgery procedures in order to enhance dispersal into tissues, and hypersensitivity reactions with its use have been reported for over half a century. A Medline search using the terms “hyaluronidase” and “anaphylaxis” reported 30 publications in the scientific literature. Although isolated reports of acute (immediate) anaphylaxis subsequent to hyaluronidase administration have been published (*Korean J Pain* 2011;24:221-225; *Allergy* 2005;10:1333-1334), delayed reactions also have been observed 1 week to 4 months post subcutaneous injection (*Orbit* 2011;30:54-7). It is possible, therefore, that this case resulted from the test product, rather than from an antibiotic administered one day post-treatment, as claimed by the sponsor.

Clinically Significant Systemic ARs

Sinusitis: Subject -(b)(6)--- experienced exacerbation of her sinusitis and recovered completely.

Neutrophil decrease (normal: 3.5-5.7): Subject -(b)(6)--- had a neutrophil count of 3.3 at baseline and 2.9 by the end of the study. Subject -(b)(6)-- had a neutrophil count of 4.0 at baseline and 2.3 at end of study. Subject -(b)(6)--- had a neutrophil count of 3.0 at baseline and 1.5 at end of study, followed by a follow-up value of 2.4. Subject -(b)(6)--- had a neutrophil count of 9.6 at baseline and 3.9 at end of study. Subject -(b)(6)--- had a neutrophils count of 3.1 at baseline and 3.2 at end of study. Subject -(b)(6)--- had a neutrophils count of 6.5 at baseline and 3.8 at end of study.

Leukocyte decrease (normal: 4.0-9.2): Subject -(b)(6)--- had a leukocyte count of 6.6 at baseline and 3.9 at end of study. Subject -(b)(6)-- had a leukocyte count of 5.1 at baseline and 3.8 at end of study. Subject -(b)(6)--- had a leukocyte count of 11.8 at baseline and 7.5 at end of study.

AST elevation: Subject -(b)(6)--- had an AST value of 34 at baseline and 53 by the end of the study.

Severe Intensity Local ARs

None reported.

6.1 Study #4: 160601 (phase 2/3)

Title: “Tolerability and Pharmacokinetic Comparison of Immune Globulin Intravenous (Human), 10% (IGIV, 10%) Administered Intravenously or Subcutaneously in Subjects with Primary Immunodeficiency Diseases”

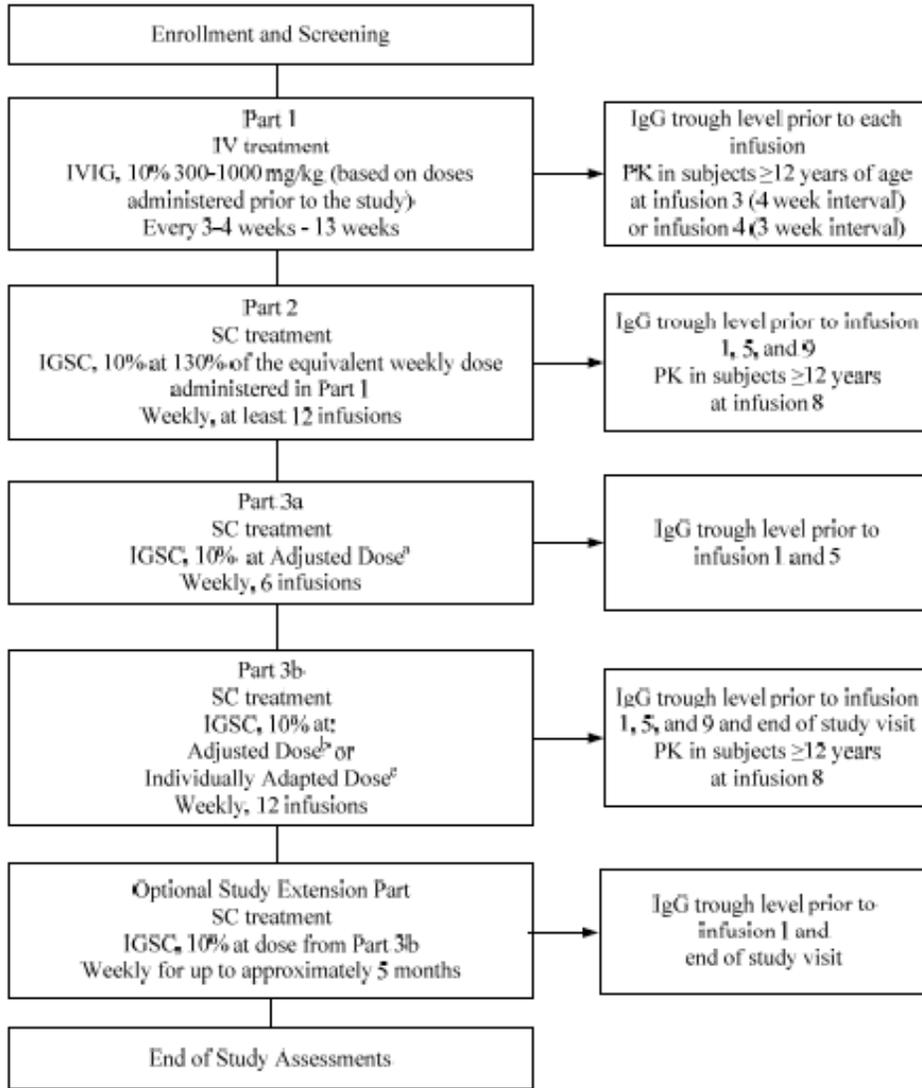
6.4.1 Objectives

To evaluate the tolerability and PK of IGI 10% SC in PI subjects. The PK was compared to those receiving IGIV. A secondary aim was to evaluate efficacy in terms of acute serious bacterial infections.

6.4.2 Design Overview

Prospective, open-label, uncontrolled, multi-center study in 49 PI subjects. PK was compared to subjects administered IGI,10% by the IV route of administration.

The study consisted of 4 parts plus an optional Study Extension Part.



- a. The Adjusted dose was calculated based upon PK assessment from the first 15 subjects aged 12 years and older in study Part 1 and 2.
- b. If trough level increase was within 15% of expected level, then the Adjusted dose was administered.
- c. If trough level increase was not within 15% of expected level, then the Adapted dose was administered.

Study Part 1

Subjects received IV infusions of GAMMAGARD LIQUID (q 3 or 4 weeks) for **12 weeks** at the dose and schedule that they were on prior to the study (0.3-1 g/kg/4 weeks). Trough levels were evaluated before every infusion. Blood for full PK analysis was taken from subjects aged ≥ 12 years after the 3rd or 4th IV infusion, depending on treatment interval. One week after a further regular IV treatment (4th or 5th infusion) given at the end of the PK evaluation, subjects began SC treatment.

- If a subject had been on a pre-study treatment interval of 4 weeks (IV or SC with rHuPH20), 3 infusions of GAMMAGARD LIQUID were administered at 4-week intervals.
- If a subject had been on a pre-study treatment interval of 3 weeks (IV or SC with rHuPH20), 4 infusions of GAMMAGARD LIQUID were administered at 3-week intervals.
- If a subject had been on a pre-study 1 to 2-week SC treatment interval, 4 infusions of GAMMAGARD LIQUID at 3-week intervals were administered.

Study Part 2

Subjects received weekly SC GAMMAGARD LIQUID infusions at a dose 130% of the weekly equivalent of the IV dose administered in Part 1 for ≥ 12 weeks, to begin 1 week after the last IV infusion and until the first 15 subjects aged ≥ 12 years had completed PK assessment with results available. Trough levels were evaluated monthly and blood for full PK analysis taken from subjects aged ≥ 12 years following the 8th infusion. 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 . The Adjusted Dose was expressed as a ratio of the weekly IV dose.

The expected increase in IgG trough levels during Part 3a relative to the trough level during IV infusions (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 3a:

Subjects were treated SC for 6 weeks using the “Adjusted Dose” calculated based on the PK assessments from the first 15 subjects aged 12 years and older in Study Parts 1 and 2. As a single Adjustment Factor was used for deriving the SC dose from the weekly IV dose, further dose correction might be required for individual subjects. To determine whether each subject received an adequate dose, trough levels were determined at Week 5. The trough levels on SC (Study Part 3a) and IV (Study Part 1) treatment were compared over the next 2 weeks, during which the subject received 2 more 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.

Study Part 3b:

Subjects received weekly SC infusions for 12 weeks at doses determined as follows:

- If the increase in trough levels was within 15% of the expected increase over the trough level determined in Part 1, the subject would receive the same “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 Part 1, the subject would receive the “Individually Adapted Dose”.

Following Infusion No. 8, blood sampling for a full PK analysis was done in subjects aged ≥ 12 years.

Study Extension Part:

At the end of Study Part 3b, subjects were offered the opportunity to extend participation in the study by entering a Study Extension Part offered to bridge the time (with weekly infusions with the same dose as in Study Part 3b) until Baxter Study 160603 was opened for enrollment. The duration of the Study Extension Part was estimated to be up to 5 months.

6.4.3 Population

Inclusion Criteria

1. Written informed consent from subject or legally acceptable representative prior to any study-related procedures and study product administration; when appropriate, assent of minor child.
2. Diagnosis of a PI disorder as defined by WHO criteria for which the subject had been receiving regular IGIV or SC with rHuPH20: at mean intervals of 21 ± 3 days or 28 ± 3 days, or SC at mean intervals of 6 - 15 days over at least 3 months pre-study, at a dose of 0.3-1 g/kg BW/4 weeks.
3. Age of ≥ 2 .
4. Serum trough level of IgG >4.5 g/L at last documented determination.
5. Negative serum pregnancy test for any female subject of childbearing potential.
6. Female subjects of childbearing potential agreeing to practice birth control measures for duration of study.

Exclusion Criteria

1. Positive for one or more of the following: HBsAg, PCR for HCV, PCR for HIV-1
2. Levels of ALT or AST >2.5 x the ULN for the testing laboratory
3. Neutropenia ($ANC \leq 1,000/mm^3$)
4. Serum creatinine levels >1.5 x ULN for age and gender
5. Malignancy other than adequately treated basal cell or squamous cell carcinoma of skin or carcinoma *in situ* of the cervix
6. History of thrombotic episodes (DVT, MI, CVA)
7. Abnormal protein loss (protein losing enteropathy, nephrotic syndrome, severe lung disease)
8. Anemia that would preclude phlebotomy for laboratory studies
9. Having received blood or blood product other than immune globulins (IV or SC), ISG preparation, or albumin within the 6 months prior to study entry
10. Ongoing history of hypersensitivity or persistent reactions (urticaria, breathing difficulty, severe hypotension, or anaphylaxis) following immune globulins (IV or SC), and/or ISG infusions
11. IgA deficiency and known anti-IgA antibodies
12. Receiving antibiotic therapy for treatment of infection within 7 days prior to entry
13. Participation in another clinical study involving investigational product or device - with the exception of Baxter Study 160603 - within 28 days prior to study enrollment
14. Bleeding disorders or use of anti-coagulation therapy

6.4.4 Study Treatments or Agents Mandated by the Protocol

IV Administration of GAMMAGARD LIQUID (Study Part 1)

- The dose to be infused was 0.3-1 g/kg q3-4 weeks depending on the subject's previous dose and previous treatment interval.
- Subjects were dosed at increasing rates of infusion, starting at 0.5 mL/kg/h and up to a maximum rate of 5.0 mL/kg/h, as tolerated, at the discretion of the investigator.
- If an AR of at least moderate severity⁵ occurred, the infusion rate was to be reduced to the rate immediately below that at which the AR occurred. If the AR resolved in response to reduction in rate, the infusion was to continue at the adjusted rate for the remainder of the infusion. If the AR continued, the infusion was to be stopped and the AR treated in accordance with the standard of care at the investigational site. The infusion could be restarted at a lower rate once the AR resolved. For hypersensitivity reactions, the infusion was to be stopped immediately and subject treated according to standard of care.
- Phone follow-up (by the investigator/designee) to document ARs occurred within 72 hours after completion of each infusion (also to be logged in the subject diaries). ARs that occurred after the 72-hour phone follow-up contact were also to be logged in the subject diaries.

SC Administration of GAMMAGARD LIQUID (Study Parts 2, 3a, 3b, Study Extension)

- SC administration was used in Study Parts 2 (dose per administration: 130% of the weekly equivalent of the dose used during IV treatment) and Parts 3a and 3b (dose adjusted for Study Parts 3a and 3b based on AUC determined in Study Parts 1 and 2, or dose individually adapted for Study Part 3b, if necessary, according to IgG trough level increase in Study Part 3a). The subjects could also be treated SC in the optional Study Extension Part, where the dose would be the same as in Part 3b.
- The first SC infusions were to be administered at the study. Afterwards, treatment could be performed at home under observation by a home care nurse.
- Infusions were conducted with a portable IV pump or syringe pump. Patients were free to choose their infusion sites but abdomen and anterior thighs were recommended.
- Phone follow-up with the subject by the investigator/designee (if the infusion had been performed at the study site) or by the home care nurse (if the infusion had been performed at home) was done within 72 hours after completion of each infusion to document ARs that might have occurred (to be logged in the diaries). ARs occurring after phone contact were also to be logged in the diaries.
- Multiple infusion sites could be used simultaneously. Up to 10% overage per site was permitted to avoid starting a new site for only a few milliliters. Up to 30 mL could be administered per infusion site for subjects with BW of ≥ 40 kg, and 20 mL per infusion site for subjects with BW < 40 kg. The initial infusions were to start at 5

mL/h/infusion site and could increase to a maximum of 20 mL/h/site for subjects with a BW of ≥ 40 kg and to a maximum of 15 mL/h/site for subjects with a BW < 40 kg, as tolerated (i.e., until the occurrence of AR of at least moderate severity).

- If AR of at least moderate severity occurs during infusion, the maximum rate used to complete this infusion was to be the rate immediately below that at which the AR occurred. If the patient tolerated the first 1 or 2 infusions at the scheduled rate, subsequent infusions could be started at 10 mL/h/site and increased every 15 to 20 minutes to a maximum of 30 mL/h/site for subjects with a BW of ≥ 40 kg and 20 mL/h/site for subjects with a BW < 40 kg. The decision to increase the rate was up to the subject and investigator and was to be made at the study site or under the supervision of a home care nurse trained in SC infusions.

Calculation of Dose Adjustment and Individual Adaptation: Immediately after the last analysis of the PK data (IgG levels) in Study Part 2 for the first 15 subjects aged 12 years and older, a “Dose Adjustment Factor” (DAF) was calculated for the determination of the adjusted dose for all subjects in Study Part 3a:

- $Dose_{P3a} = DAF \times dose_{P1}$, where P1, and P3a refer to Study Part 1 and Study Part 3a.

The Expected IgG Trough Level Factor, based on expected IgG trough levels per dose per kg BW when subjects were dosed as in Study Part 3a, was estimated from the first 15 subjects aged ≥ 12 years. If the IgG trough level of a subject in Study Part 3a deviated by $> 15\%$ from the expected value, an “Individually Adapted Dose” was used in Study Part 3b:

- $Dose_{P3b} = IAF \times dose_{P1}$, where the Individual Adaptation Factor (IAF) was read from a nomogram relating the IAF to the actual IgG trough level in Study Part 3a expressed as a percentage of the IgG trough level expected. The nomogram was derived from the first 15 subjects aged ≥ 12 .

Lot number:

Seven lots of GAMMAGARD LIQUID were used in this study: LE12G011AC, LE12G011AD, LE12G145AC, LE12G174AC, LE12H163AB, LE12H203AB, and LE12H309AC.

6.4.7 Endpoints and Criteria for Study Success

PK

In subjects ≥ 12 years old, bioavailability of IgG after administration of GAMMAGARD LIQUID, via IV, SC, and SC at an Adjusted/Individually Adapted Dose, as measured by AUC per week.

In subjects aged 2 to < 12 years, bioavailability of IgG after administration of GAMMAGARD LIQUID, IV, SC and SC at an Adjusted/Individually Adapted Dose, as measured by IgG trough levels

Efficacy

- Infections were reported as ARs. SABIs were defined as bacteremia/sepsis, bacterial meningitis, osteomyelitis/septic arthritis, bacterial pneumonia and bacterial visceral abscess.
- Rates of infections and SABI were calculated per subject.

Safety

Ability to tolerate GAMMAGARD LIQUID administered IV or SC. Tolerability was measured as proportion of subjects and proportion of infusions for which the infusion rate was reduced at any infusion and/or the infusion was interrupted or stopped for (i) any reason and (ii) for tolerability concerns or ARs.

SAFETY

A total of 226 ARs were reported during the IV treatment period and 634 ARs during the SC treatment; 85 ARs were considered related to use of IGIV, 10% during IV treatment, and 150 ARs were considered related during SC treatment.

Serious Infections

Three subjects experienced acute serious bacterial infections while on SC treatment with IVIG, 10%. All 3 infections were bacterial pneumonias. Those affected included a 53 y/o subject -(b)(6)----, a 10 y/o subject -(b)(6)----, and a 48 y/o subject -(b)(6)----. No acute serious bacterial infections were reported during the 12-week period of IV replacement.

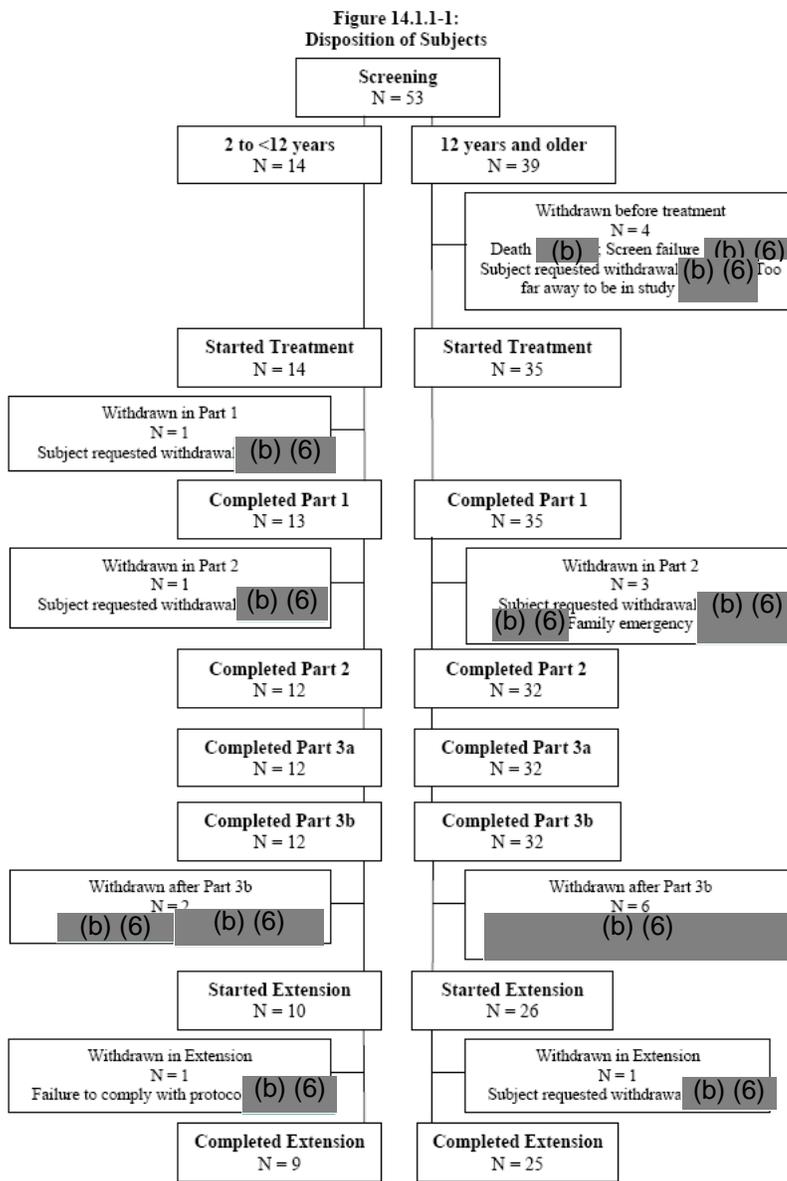
SARs

- **Acute cholecystitis:** Subject -(b)(6)---- was a 40 y/o female without prior gallbladder Hx who experienced acute cholecystitis 15 days after receiving IGIV, 10% SC.
- **Sinusitis:** Subject -(b)(6)-- was a 5 y/o female hospitalized for sinusitis diagnosed by sinus CT 8 days after receiving IGIV, 10% intravenously.
- **Left-sided chest pain:** Subject -(b)(6)--- was a 42 y/o female who developed left-sided chest pain and malaise 2 days after receiving her last infusion of IVIG, 10% SC and was admitted to R/O left arm thrombosis. Although PMH included asthma, cholecystectomy and gastric bypass, no cardiac workup was performed. The investigator proposed that the pain resulted from the subject's Mediport situated in the left chest.
- **Seizure:** Subject -(b)(6)---- was a 19 y/o male who experienced a seizure 23 days after receiving IGIV, 10% intravenously. The subject had been diagnosed with a seizure disorder 4 y previously and had been taken off anti-epileptic medication a year prior to the SAR.

Table 1: SARs Stratified by IGIV or IGSC

| Event | Subject Number | IGIV or IGSC |
|-----------------------------------|----------------|--------------|
| Acute cholecystitis | --(b)(6)---- | IGSC |
| Sinusitis | --(b)(6)---- | IGIV |
| Left chest pain, etiology unknown | --(b)(6)---- | IGSC |
| Seizure | --(b)(6)---- | IGIV |

6.4.9.1.3 Subject Disposition



6.5 Study #5: 160603 (pivotal phase 3)

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 (PI)”

6.5.1 Objectives

The primary objective was to evaluate the efficacy of IGI 10% administered monthly via the SC route when facilitated by pre-administration of rHuPH20 in preventing acute serious bacterial infections (ASBI) in PI subjects.

The secondary objective was to evaluate the tolerability of SC administration of IGI,10% and rHuPR20.

6.5.2 Design Overview

Prospective, open-label, single-arm, Phase 3 study in 80 PI subjects at 14 centers in the US and one site in Canada.

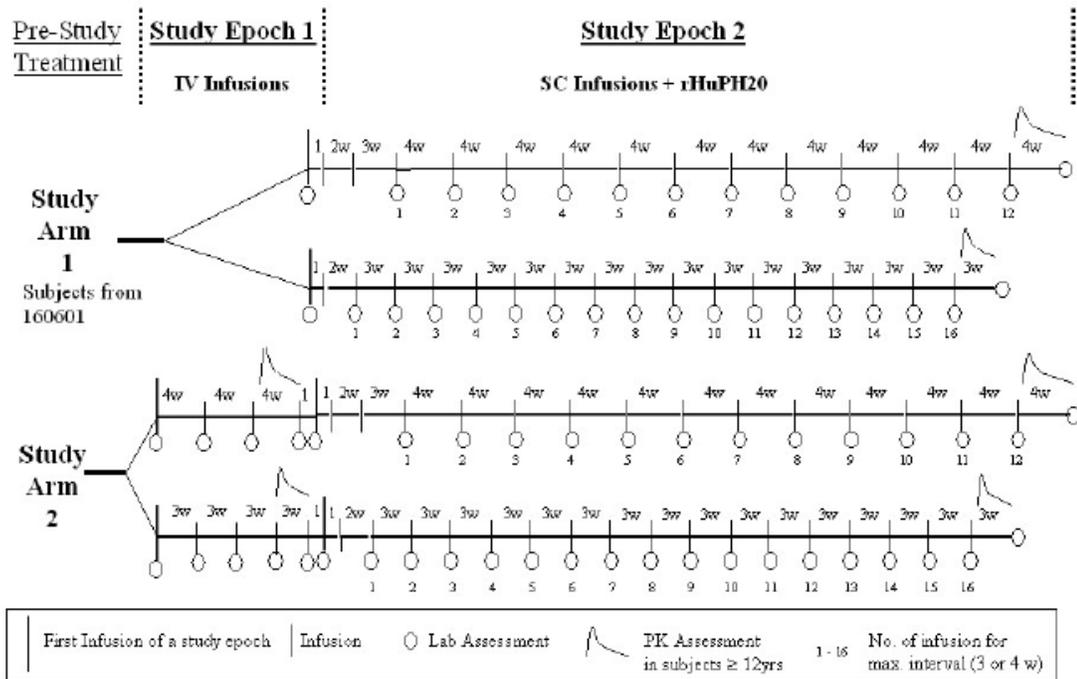
The study consisted of 2 study Epochs:

Epoch 1: IV treatment with IGI 10% at 3- or 4-week treatment intervals

Epoch 2: SC treatment with IGI 10% after administration of 75 U/g IgG rHuPH20, at 3- or 4-week treatment intervals

Subjects were enrolled into one of 2 study arms.

- **Arm 1** enrolled subjects who had previously participated in Study 160601. These subjects participated only in **Epoch 2 (SC)**. The subjects’ IV and SC PK data were used for PK comparison.
- **Arm 2:** subjects enrolled in this arm completed both **Epoch 1 (IV)** and **Epoch 2 (SC)**.



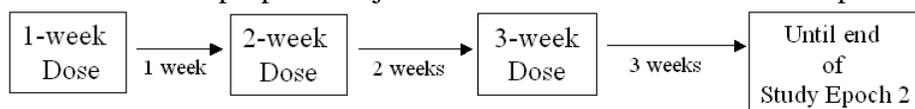
Epoch 1:

- PK assessment (including AUC) of IV IGI 10%.
- Subjects who had previously participated in Study 160601 were not included
- Subjects received IGI 10% for 12 weeks at the same dose and frequency as they previously received before the PK assessment. For subjects on prior SC treatment, the treatment interval in Epoch 1 was 3 or 4 weeks as determined by the investigator.
- For subjects aged 2 to < 12 years, IgG trough levels were the only PK parameter evaluated.
- Following the PK assessment, 1 week after a final 3 or 4 week IV dose of IGI 10%, Epoch 2 (SC treatment) began.

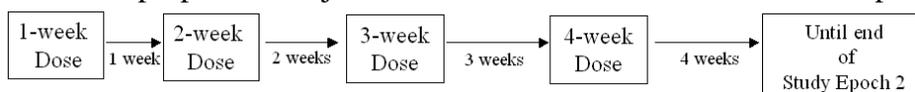
Epoch 2:

- All subjects were treated with SC IGI 10% at 108% of the IV dose used during Epoch 1. The value of 108% was derived from Study 160602. Prior to each SC infusion, rHuPH20 was administered at a minimum dose of 75 U/g IgG, which was also determined in Study 160602.
- The treatment intervals and doses used for the initial infusions were gradually increased during the first weeks of treatment to allow the subjects to adjust to increasing volume administered SC. The aim was to treat subjects SC at the same intervals (every 3 or 4 weeks) that they had been previously treated IV.
- The initial IGI 10% SC dose was 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.

- For all subjects, the 1st SC dose was a 1-week dose given 1-week after the last IV dose. If the 1 week SC infusions was tolerated, for each subsequent treatment the interval (and dose) was to be increased by 1 week, until the treatment interval was the same as the pre-study IV treatment interval (3 or 4 weeks). If the infusions were tolerated, subjects remain on the treatment interval.
- An infusion was determined as tolerated if no serious ARs, no non-serious moderate or severe local ARs that prevent completion of the infusion, and no non-serious moderate or severe systemic ARs during or within 60 minutes of completion of the infusion occurred.
- Dose ramp-up for subjects with 3 week treatment interval prior to the study



Dose ramp-up for subjects with 4 week treatment interval prior to the study:



6.5.3 Population

Inclusion Criteria

1. Subject was 2 years or older at the time of screening
2. Written informed consent obtained from either the subject or the subject's legally acceptable representative prior to any study-related procedures and study product administration
3. Subject had been diagnosed with a PI disorder requiring antibody replacement
4. Subject had completed or was about to complete Study 160601 or had been receiving a regular IGIV-treatment at mean intervals of 21 ± 3 days or 28 ± 3 days, or SC at mean intervals of 5 to 16 days, over a period of at least 3 months prior to enrollment at a minimum dose of 300 mg/kg BW/4 weeks
5. Subject had a serum trough level of IgG > 4.5 g/L at the last documented determination
6. If female of childbearing potential, subject presented with a negative urine pregnancy test and agreed to employ adequate birth control measures for the duration of the study
7. Subject was willing and able to comply with the requirements of the protocol

Exclusion Criteria

1. Subject had a known history of or was positive at enrollment or screening for one or more of the following: hepatitis B surface antigen (HBsAg), polymerase chain reaction (PCR) for hepatitis C virus (HCV), PCR for human immunodeficiency virus (HIV) type 1/2
2. Subject had levels of alanine aminotransferase (ALT) or aspartate amino transferase (AST) > 2.5 times the upper limit of normal (ULN) for the testing laboratory
3. Subject had persistent severe neutropenia (absolute neutrophil count $\geq 500/\text{mm}^3$)
4. Subject had creatinine clearance (CLcr) values < 60% of normal for age and gender

5. Subject had been diagnosed with, or had a malignancy (other than adequately treated basal cell or squamous cell carcinoma of the skin or carcinoma in situ of the cervix) within the last 12 months prior to enrollment; subjects treated with immunosuppressive chemotherapeutic agents were excluded
6. Subject had a history of thrombotic episodes [including deep vein thrombosis (DVT), myocardial infarction (MI), cerebrovascular accident (CVA), pulmonary embolism (PE)] within the last 12 months
7. Subject had abnormal protein loss (protein losing enteropathy, nephritic syndrome)
8. Subject had anemia that would have precluded phlebotomy for laboratory studies
9. Subject had received any blood or blood product other than an IGIV, IGSC, immune serum globulin (ISG) preparation, or albumin within the 6 months prior to enrollment
10. Subject had an ongoing history of hypersensitivity or persistent reactions (urticaria, breathing difficulty, severe hypotension, or anaphylaxis) following IGIV, SC immunoglobulin, and/or ISG infusions
11. Subject had IgA deficiency and known anti IgA antibodies
12. Subject was on prophylactic systemic antibiotics and was not able to stop
13. Subject had active infection and started on antibiotic within 7 days prior to screening
14. Subject had a bleeding disorder or was on anti-coagulation therapy with platelet count < 20,000/ μ L or International Normalized Ratio (INR) > 2 x control, or who, in the opinion of the investigator would have been at significant risk of increased bleeding or bruising as a result of SC therapy
15. Subject had total protein > 9 g/dL and subjects with myeloma, macroglobulinemia (IgM) and paraproteinemia
16. Subject had a known allergy to hyaluronidase
17. If female, subject was pregnant or lactating at the time of study enrollment
18. Subject had participated in another clinical study and had been exposed to an investigational product (IP) or device within 2 weeks prior to study enrollment (exception: Baxter Study No. 160601) or was scheduled to participate in another non-Baxter clinical study involving an IP or device during the course of this study
19. Severe dermatitis that would have precluded adequate sites for safe product administration

6.5.4 Study Treatments Mandated by the Protocol

IGI 10% IV (Epoch 1):

- IGI 10% IV treatment at 3 or 4 week intervals at the same dose and frequency as they previously received. Trough IgG level to be maintained over 4.5 g/L
- For subjects on prior SC treatment, the treatment interval in Epoch 1 was 3 or 4 weeks determined by the investigator.

IGI 10% SC (Epoch 2):

- SC treatment with IGI 10% at 108% of the IV dose used during Epoch 1 after 75 U/g IgG rHuPH20 every 3 or 4 weeks

rHuPH20 SC Infusions:

- Administered at 75 U/g IgG before the SC infusion of IGI 10%.

Lot numbers:

IGI 10%:

LE12H249AB; LE12J074AB; LE12J074AM; LE12H235AC; LE12J045AB;
 LE12J118AD; LE12J155AC; LE12J257AB; LE12J308AD; LE12H091AF;
 LE12H229AC; LE12J058AC; LE12J129AC; LE12H195AD; LE12G174AC;
 LE12G011AD; LE12H163AB; LE12H309AC; LE12G011AC; LE12H163AB and
 LE12G145AC

rHuPH20: 911130; 911529; 911131 and 911530

6.5.5 Surveillance/Monitoring

| Procedure/Assessment | Screening Baseline Visit All Subjects | Treatment/Visit No. in Study Epoch 1 Only Study Arm 2 Subjects Complete Study Epoch 1 | | | | |
|-------------------------------------|---|--|------|------|------|------|
| | | 1 | 2 | 3 | 4 | 5 |
| Location | Site | Site | Site | Site | Site | Site |
| Informed Consent | X | | | | | |
| Inclusion/Exclusion | X | | | | | |
| Medical History | X | | | | | |
| Physical Exam | X | X | X | X | X | X |
| Vital Signs | X | X | X | X | X | X |
| Laboratory Assessments ^b | X ^c | X | X | X | X | X |
| Concomitant Medication | X | X | X | X | X | X |
| Adverse Events | | X | X | X | X | X |
| Collection/Review Diaries | | X | X | X | X | X |
| Study Product Treatment | | X | X | X | X | X |

| Procedure/Assessment | Screening Baseline Visit All Subjects | Treatment/Visit No. in Study Epoch 1 Only Study Arm 2 Subjects Complete Study Epoch 1 | | | |
|-------------------------------------|---|--|------|------|------|
| | | 1 | 2 | 3 | 4 |
| Location | Site | Site | Site | Site | Site |
| Informed Consent | X | | | | |
| Inclusion/Exclusion | X | | | | |
| Medical History | X | | | | |
| Physical Exam | X | X | X | X | X |
| Vital Signs | X | X | X | X | X |
| Laboratory Assessments ^b | X ^c | X | X | X | X |
| Concomitant Medication | X | X | X | X | X |
| Adverse Events | | X | X | X | X |
| Collection/Review Diaries | | X | X | X | X |
| Study Product Treatment | | X | X | X | X |

6.5.6 Endpoints and Criteria for Study Success

A total of 41 subjects received IGSC 10% treatment with rHuPH20 for at least 1 year in Study 160603.

Primary endpoint

Acute Serious Bacterial Infections (ASBI) (bacteremia/sepsis, bacterial meningitis, osteomyelitis/septic arthritis, bacterial pneumonia, and visceral abscess) rate: mean number of acute serious bacterial infections per subject per year in the intent to treat population.

Secondary Endpoints**Efficacy:****PK:**

- Bioavailability of IgG after IV or SC administration as measured by AUC for subjects ≥ 12 years old and by trough IgG levels for subjects 2-12 years old
- Comparison of bioavailability of IgG after SC administration of IGI 10% without rHuPH20 (Study 160601) and with rHuPH20 (Study 160603, Study Arm 2) as measured by AUC/trough IgG levels

Trough IgG levels:

- IgG trough levels and specific antibody titers
- Specific antibody levels to Tetanus, H. Flu, measles and hepatitis B
- PK of IgG, anti-tetanus antibody, and at least one antibody to a PI-relevant pathogen (H. Flu.) for IV and SC treatment

Infections: The annual rate of all infections per subject

Days off school/work, on antibiotics, acute physician visits and in hospital

SAFETY

- Proportion of subjects/infusions for which the infusion rate was reduced and/or the infusion interrupted or stopped for tolerability concerns or for ARs.
- The number of all temporally associated ARs (including and excluding infections) that began during infusion or within 72 hours of completion of an infusion divided by the number of infusions/subjects.
- The proportion of subjects/infusions reporting one or more moderate or severe temporally associated ARs (including and excluding infections).
- The percentage of SC doses of IGI 10% and rHuPH20 tolerated at 1 infusion site.
- Proportion of infusions/subjects associated with one or more temporally associated systemic or local ARs (including and excluding infections).
- The proportion of infusions/subjects with one or more local ARs (including and excluding infections), at any time during the study.
- The number of related ARs (including and excluding infections) determined by the investigator divided by the number of infusions/subjects.
- The frequency of dose corrections based on IgG trough levels < 4.5 g/L IgG for each study epoch.

- The number and rate of all ARs categorized by MedDRA preferred terms, seriousness, relatedness to the study drug, and severity.
- The proportion of infusions associated with one or more related ARs (including and excluding infections).
- The proportion of infusions tolerated with IV and SC administration at the dose used in Study Epoch 2.
- The total number of all temporally associated ARs plus the total number of related ARs (including and excluding infections) starting after 72 hours, divided by the total number of infusions.
- Number and proportion of all subjects who develop neutralizing antibodies to rHuPH20. The coincidence of the presence of antibodies with the occurrence of ARs, were to be assessed.
- Number and proportion of subjects who experienced a decline in hemoglobin of > 2.0 g/dL over the course of the study with evidence of hemolysis on laboratory evaluation.

6.5.7 Statistical Considerations and SAP

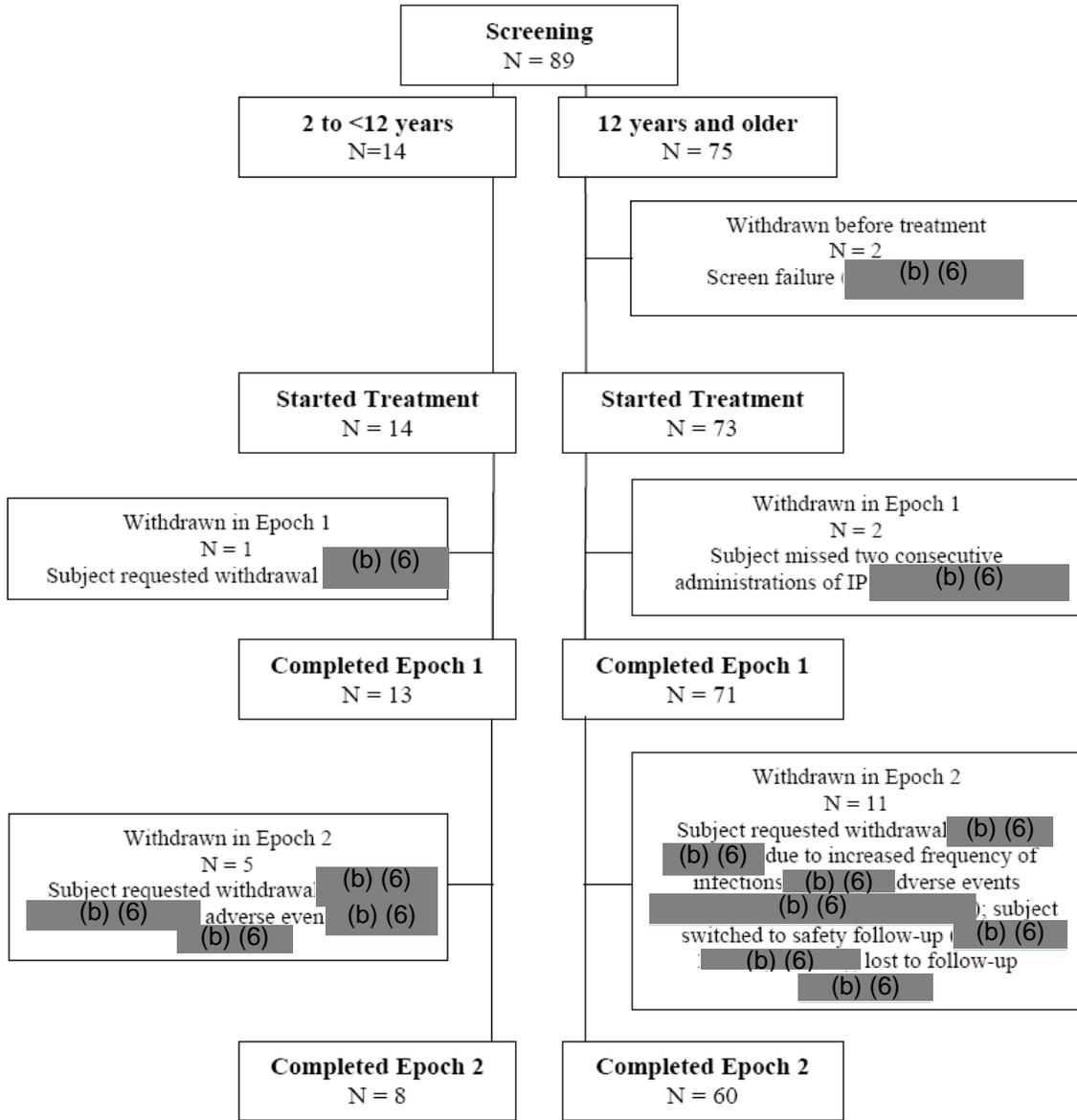
Sample size: a total of 80 subjects was determined by the desire to collect safety data in a sufficient number of subjects (a minimum of approximately 30) who were naïve to SC administration, in addition to the subjects rolling over from study 160601 (about 45).

Primary endpoint: analyzed using a Poisson model on the per-protocol analysis data set.

Hypotheses: the null hypothesis of one or more validated ASBI per subject per year was tested against the alternate hypothesis of less than 1 ASBI per subject per year at the 1% level of statistical significance.

6.5.8 Disposition of Subjects

Figure 10.1-1.
Disposition of Subjects



6.5.9 EFFICACY

The primary endpoint (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) of the study was met: the rate of validated acute serious bacterial infections per year during IGSC, 10% administration with rHuPH20 was 0.025 with an upper limit of the 99% CI of 0.046. The upper limit of the 99% CI was significantly lower than the pre-defined limit of 1.0 ($p < 0.0001$).

6.5.10 SAFETY**Severe Intensity ARs**Epoch 1 (IV)

Extremity pain: Subject (b)(6) (Epoch 1) related to IGIV infusion

Vomiting: Subject (b)(6) (Epoch 1) experienced severe vomiting.

Elevated free plasma Hb: Subject (b)(6) (Epoch 1)

Epoch 2 (SC)

Infusion site hypersensitivity: Subject (b)(6) (Epoch 2)

Myalgia: Subject (b)(6) (Epoch 2)

Adverse event rates in Epoch 2 subjects

AR rates between subjects naïve to SCIG vs. subjects not naïve to SCIG are presented in Table 5, below. Results were comparable.

Table 5: Subcutaneous IG Naïve (SNDS) vs. non-Naïve (Non-SNDS) Subjects
(source: Table 13, OBE reviewer's memo)

| Dataset | Age Group | N | Mean | SD | Min | Median | Max |
|---|------------------------------|----|-------|-------|-----|--------|-----|
| Duration of treatment [days] | | | | | | | |
| Non-SNDS | Subjects aged 2 to <12 years | 8 | 388.8 | 110.5 | 169 | 411 | 505 |
| | Subjects aged ≥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 ≥12 years | 37 | 326.6 | 104.7 | 42 | 337.0 | 449 |
| Number of infusions | | | | | | | |
| Non-SNDS | Subjects aged 2 to <12 years | 8 | 15.8 | 5.7 | 6 | 16 | 24 |
| | Subjects aged ≥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 ≥12 years | 37 | 12.2 | 4.1 | 3 | 12 | 20 |
| Number of temporally associated ARs including infections | | | | | | | |
| Non-SNDS | Subjects aged 2 to <12 years | 8 | 3.5 | 3.9 | 0 | 2.5 | 12 |
| | Subjects aged ≥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 ≥12 years | 37 | 7.1 | 8.5 | 0 | 4 | 29 |

| Rate of temporally associated ARs including infections | | | | | | | |
|---|------------------------------|----|------|------|-----|-----|-----|
| Non-SNDS | Subjects aged 2 to <12 years | 8 | 0.31 | 0.41 | 0 | 0.1 | 1.0 |
| | Subjects aged ≥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 ≥12 years | 37 | 0.68 | 0.97 | 0 | 0.3 | 5 |
| Number of temporally associated ARs excluding infections | | | | | | | |
| Non-SNDS | Subjects aged 2 to <12 years | 8 | 2.9 | 3.3 | 0 | 1.5 | 10 |
| | Subjects aged ≥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 ≥12 years | 37 | 6.6 | 8.3 | 0 | 3 | 28 |
| Rate of temporally associated ARs excluding infections | | | | | | | |
| Non-SNDS | Subjects aged 2 to <12 years | 8 | 0.3 | 0.3 | 0 | 0.1 | 0.8 |
| | Subjects aged ≥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 ≥12 years | 37 | 0.6 | 1.0 | 0 | 0.2 | 5 |

| Dataset | Age Group | N | Mean | SD | Min | Median | Max |
|---|------------------------------|----|------|-----|-----|--------|-----|
| Number of related ARs including infections | | | | | | | |
| Non-SNDS | Subjects aged 2 to <12 years | 8 | 2.6 | 3.5 | 0 | 1.5 | 10 |
| | Subjects aged ≥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 ≥12 years | 37 | 6.5 | 8.7 | 0 | 3 | 28 |
| Rate of related ARs including infections | | | | | | | |
| 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 | 1.1 | 0 | 0.2 | 5.5 |
| Number of related ARs excluding infections | | | | | | | |
| Non-SNDS | Subjects aged 2 to <12 years | 8 | 2.6 | 3.5 | 0 | 1.5 | 10 |
| | Subjects aged ≥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 ≥12 years | 37 | 6.4 | 8.6 | 0 | 3 | 27 |
| Rate of related ARs excluding infections | | | | | | | |
| 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 |
| Rate of infusions with local ARs excluding infections | | | | | | | |
| 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 |

SARs

SARs are presented in Table 6, below.

Table 6: SARs

| Subject ID | SAR | Route of Admin | Additional Comments ⁶ |
|------------|--|----------------|---|
| (b)(6) | Status epilepticus followed by respiratory failure | SC | 15 y/o with PMH of seizures receiving Hyqvia since JUN 2009 experienced a Grand mal seizure NOV 2009 |
| | Tonsillar hypertrophy | SC | Scheduled for tonsillectomy but surgery cancelled after resolution of condition |
| (b)(6) | Thrombosis | SC | 19 y/o with positive family Hx of thrombosis received his 7 th dose of Hyqvia on 30-NOV-2009 in the abdomen and experienced RUE thrombosis on 13-DEC-2009, the same extremity in which a venous access device was replaced 40 days prior |
| (b)(6) | Upper GI hemorrhage | IV | 56 y/o receiving Gammagard Liquid IV since 11-MAY-2009 experienced an upper GI bleed on 15-MAY-2009 |
| | Asthma | IV | 56 y/o receiving Gammagard Liquid starting from 11-MAY-2009 experienced an asthma attack on 4-JUN-2009 |
| (b)(6) | Intervertebral disc degeneration | SC | 62 y/o with PMH of cervical disc disease + nerve root compression received Hyqvia on 11-MAY-2009 and underwent c-spinal surgery on 13-MAY-2009 |
| (b)(6) | Severe headache | SC | 16 y/o with PMH of headache received Hyqvia on 12-FEB-2010 and experienced a severe headache on 21-FEB-2010 |
| (b)(6) | Gastroenteritis | SC | 18 y/o received Hyqvia on 27-MAY-2010 followed by nausea, vomiting, and diarrhea on 12-JUN-2010 after “consuming fast food” |
| (b)(6) | Acute adrenal insufficiency | SC | 36 y/o with PMH of Addison’s disease since MAY 1999 received Hyqvia on 3-FEB-2010 PMH and experienced an Addisonian crisis on 23-FEB-2010 |
| (b)(6) | Lobar pneumonia | SC | 15 y/o with PMH of chronic lung disease received Hyqvia on 9-NOV-2009 and |

⁶ SARs in subjects receiving Hyqvia was considered “not related” or “probably not related” to the product by the investigator.

| | | | |
|--------|----------------------|-------|--|
| | | | experienced RLL pneumonia on 17-NOV-2009 |
| (b)(6) | Leukoplakia oral | SC | 61 y/o received Hyqvia from 14-JUL-2009 to 6-OCT-2009 and underwent surgery for leukoplakia on 16-OCT-2009 |
| (b)(6) | Cervical dysplasia | SC | 35 y/o with Hx of cervical dysplasia since FEB 2009 received Hyqvia and subsequently underwent LEEP procedure (DEC 2009) |
| (b)(6) | Grand mal convulsion | SC | 37 y/o with Hx of Grand mal convulsion (APR 2004) received Hyqvia (OCT 2009) and experienced seizures |
| | Petit mal epilepsy | | |
| (b)(6) | Back injury | SC/IV | 66 y/o with PMH of spinal fusion experienced partial paralysis requiring surgery (JAN 2010) and long term rehabilitation; last Hyqvia on 21-DEC-2009; switched to Gamunex q weekly on 18-JAN-2010. Died from AMI on ---(b)(6)----- |

7. INTEGRATED OVERVIEW OF EFFICACY

7.1 Indication #1

Treatment of PI.

7.1.1 Methods of Integration

Not applicable for efficacy, since only a single phase 3 trial was conducted and the four remaining phase 1/2 trials were small and exploratory.

7.1.2 Demographics

Subjects 3-78 years of age

7.1.3 Subject Disposition

A total of 216 subjects were enrolled. There were 26 subjects age 2 to <12 exposed to product: 14 subjects in Study 160603 and 12 subjects in Study 160601.

Please see “Disposition of Subjects” for each of the studies in this memo.

7.1.4 Analysis of Primary Endpoint(s)

Phase 3 trial (Study #160603)

IGI 10% administered SC with rHuPH20 was effective in reducing the rate of acute serious bacterial infections (ASBI, defined as bacteremia/sepsis, bacterial meningitis, osteomyelitis/septic arthritis, bacterial pneumonia, and visceral abscess): mean number of acute serious bacterial infections per subject per year.

In the ITT population, the ASBI rate 0.025 (upper limit of the 99% CI: 0.046) per subject-year; this is lower than the rate (0.067; upper limit of the 99% CI: 0.134)

observed in phase 1 study 160601 using SC administration of IGI 10% without rHuPH20 was significantly lower ($p < 0.0001$) than the 1.0 rate threshold considered to provide substantial evidence of efficacy. No serious bacterial infections occurred when this product was administered SC at 137% of the IV dose. Compared to IV infusion, SC administration with rHuPH20 was able to be administered at the same dosing interval and resulted in similar IgG trough levels. SC administration with rHuPH20 demonstrated higher bioavailability as determined by AUC per dose/kg than when infused SC without rHuPH20.

7.1.5 Analysis of Secondary Endpoint(s)

Phase 3 trial

- (a) Annualized number of hospital days due to infection was slightly lower for IGSC + rHuPR20 subjects (0.04; 99% confidence interval: 0.02, 0.06) than for IGIV, 10% subjects (0.49; 0.27, 0.79);
- (b) Number of days on antibiotic treatment was similar in subjects >12 years of age but lower in the 2-12 year subgroup;
- (c) Number of days off work or school per subject per year was similar (range: 3.31 to 3.95).

7.1.6 Efficacy Conclusions

When administered at 108% of the IV dose, IGSC 10% treatment with rHuPH20 resulted in minor reductions in the rate of ASBI per subject per year and comparable trough levels to IGIV, 10%.

Study #160603: compared to IVIG (Epoch 1) at bioequivalent doses, Hyqvia PI subjects >12 years old (N=73; Epoch 2) experienced a 10-min reduction in median duration of infusion (2.13 vs. 2.33 h); subjects 2-12 years old (N=14) experienced a 45-min reduction (1.73 vs. 2.49 h). Tolerability was virtually identical, i.e., 86% of subjects in Epoch 1 and 84% of subjects in Epoch 2 did not require a reduction in flow rate, interruption, or termination due to intolerance or ARs.

In other studies, the rHuPH20 component exerted even less of an effect, i.e, no difference in terms of (a) in-line pressure vs. flow rate, (b) in-line pressure vs. cumulative volume infused curves, (c) total volume of IGSC 10% infused with and without rHuPH20 preadministration, (d) maximum tolerated flow rate (300 mL/h), and (e) time needed to complete an infusion.

8. INTEGRATED OVERVIEW OF SAFETY

8.1 Safety Assessment Methods

Review of subject line listings for safety.

8.2 Studies/Clinical Trials Used to Evaluate Safety

160601, 161001, 170901 (part 4), 160602, 160603

8.2.2 Overall Exposure, Demographics of Pooled Safety Populations

Duration of exposure ranged from 6 weeks (Study #161001) to 17 months (Study #160603).

Age of subjects ranged from a low of 14 months (Study #160603) to 78 years of age (Study 160603). See Table 7, below.

Table 7: Age of Subjects

| Study # | 2 to <12 years | 12 to <16 | ≥16 years |
|---------|----------------|-----------|-----------|
| 160601 | 12 | 4 | 31 |
| 160602 | | | 11 |
| 160603 | 14 | 9 | 64 |

8.2.3 Categorization of Adverse Events

Adverse events were stratified by: Cumulative frequency of SARs; severe intensity local ARs, and clinically significant systemic ARs.

8.3 Safety Results

Across the five studies,

1. There were no deaths.
2. **Study #170901** (N=12; prematurely terminated for safety by the sponsor)
 - a. Six cases (Grade 2: one case; Grade 3: five cases; Grade 4: one case) of **anemia** Grade 2 or higher were reported (Final Study Report, Listing 16.2.8).⁷ In addition, there were five cases of Grade 3 **lymphopenia** and six cases of **abnormally elevated enzyme levels** from muscle (CPK), liver (ALT, AST), and pancreas (amylase, lipase) attributed to a “flu-like” illness by the sponsor.
3. **Study #160603** (N=87)
 - a. Two **thrombotic events** (one unrelated, one probably unrelated according to the investigator) occurred during treatment with IGSC + rHuPR20: **acute myocardial infarction** in a 66 y/o male and an upper extremity **thrombosis** in a 19 y/o male.
 - b. The overall rate of **temporally associated ARs per infusion** (0.25 in the IGIV cohort [Epoch 1] vs. 0.21 in the IGSC + rHuPR20 [Epoch 2] cohort) was not different between treatment cohorts (N=87) in the pivotal phase 3 trial. This included subjects who required a reduction in flow rate, interruption, or termination due to intolerance or ARs (86% in Epoch 1

⁷The sponsor indicates in the text (“Serious Adverse Events”) of their Final Study Report that only two anemia SAEs were observed.

and 84% in Epoch 2). Product administration temporally associated with systemic ARs was higher in the IGIV cohort (headache, chills, nausea, fatigue, pyrexia, vomiting), whereas local ARs were higher in the IGSC + rHuPR20 cohort (infusion site pain, infusion site erythema, infusion site discomfort, headache, infusion site pruritus, infusion site edema, and infusion site swelling).

4. Study #160602

- a. One IGSC + rHuPR20 subject in Study 160602 experienced **anaphylaxis** more than 24 h post-study drug injection.

8.3.1 Dropouts and/or Discontinuations

Please refer to “Disposition” for each study reviewed in this memo.

8.3.2 Immunogenicity (Therapeutic Proteins)

Thirteen subjects in Study 160603 had positive titers ($\geq 1:160$) for total rHuPH20-reactive antibodies, but none developed neutralizing antibodies against rHuPH20.

According to the sponsor, “comparison of subjects who produced rHuPH20-reactive antibodies and observed SARs showed no correlation in Studies 160603, 170901 Part 4, and 161001. In Study 160603, none of the 14 SARs was considered to be related to either of the investigational products by the clinical investigators. The most frequently observed ARs attributed to the rHuPH20 were infusion site pain or discomfort, infusion site erythema, infusion site edema or pruritus, and headache. Based upon data available to date, the incidence of treatment emergent rHuPH20-reactive binding antibodies was low and neutralizing antibodies have not been observed in any subjects. In addition, no clinical signs or symptoms have been associated with the development of positive rHuPH20-reactive binding antibody titers” (page 6, ISS/ISE).

8.6 Safety Conclusions

The safety profile of Hyqvia vs. IGIV is acceptable, although there is a theoretical concern about the long-term effect of anti-rHuPH20 antibodies (currently under investigation by the sponsor).

Summary of Adverse Reactions (all studies)

Local ARs

- *Studies enrolling volunteers vs. PI subjects*
The incidence of Local ARs was more frequent in volunteer studies #161001 and #170904 Part 4 than in PI studies #160601 and #160603.
- *Studies using Hyqvia vs. IGSC 10% alone in PI subjects and volunteers*
PI subjects: except for more frequent local ARs of mild (0.235 vs. 0.054) and moderate (0.101 vs. 0.010) severity at the end of infusion, PI subjects receiving Hyqvia every 3-4 weeks (Study #160603) exhibited a safety profile similar to that

of weekly IGSC 10% (Study #160601; N=49). The most commonly reported reactions included infusion site pain, headache, infusion site erythema, and induration. The median time required for the induration ARs to resolve in PI subjects (Study #160601) was 1:01 h (95% CI: 0:20; 1:39) for Hyqvia vs. 4:39 h (95% CI: 4:09; 5:01) for IGSC 10% with control. None of the induration ARs using Hyqvia was moderate or severe, whereas 54.5% were moderate or severe in the IGSC 10% + control group.

Volunteers: 7 of 12 volunteers in Study 170901 Part 4 had measurable induration with Hyqvia at a dose of 0.3 g/kg BW compared to 9/12 for IGSC 10% with buffer control. At the 0.6 g/kg BW dose of IgG, 6/10 Hyqvia subjects had measurable induration at the end of infusion compared to 10/10 who received IGSC 10% with control. Similar results were obtained in Study 161001 (N=57): for Epoch 1 and 2 combined (n=40), Hyqvia volunteers experienced 4 induration ARs compared to 44 induration ARs using IGSC 10% with lactated Ringer's control.

Systemic ARs

- *Hyqvia vs. IVIG infusion*

In study #160603 (N=87), the frequency of systemic safety events temporally associated with product administration was higher in Epoch 1 (IVIG: headache, chills, nausea, fatigue, pyrexia, vomiting), whereas the frequency of local events was higher in Epoch 2 (Hyqvia: infusion site pain, infusion site erythema, infusion site discomfort, headache, infusion site pruritus, infusion site edema, and infusion site swelling). Similar trends were evident in the smaller trials as well.

9. CONCLUSIONS

Compared to IV administration, there is a modest net benefit in using Hyqvia in terms of convenience (subcutaneous vs. intravenous) and frequency of administration.

10. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

See table, below.

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| Decision Factor | Evidence and Uncertainties | Conclusions and Reasons |
|------------------------------|---|---|
| Analysis of Condition | Current treatment of PI using IVIG is safe and effective but requires administration every 3-4 weeks. A product that was equally safe and effective as IVIG but was easier to administer could improve patient satisfaction and compliance. | Hyqvia is effective but potential downstream effects of antibodies to the hyaluronidase component are ill-defined. |
| Unmet Medical Need | Effective treatment already is available but requires intravenous administration. | While the level of patient satisfaction would be expected to be higher with Hyqvia than IGIV, especially in the pediatric population, this is not an unmet medical need. |
| Clinical Benefit | <p>Clinical benefit was investigated in PI subjects (N=87), including pediatric subjects 2-12 years of age (N=14) and 12-16 years of age (9), in an open-label, single-arm, Phase 3 study at 14 centers in the US and one site in Canada.</p> <p>Hyqvia was effective in reducing acute serious bacterial infections. The rate of validated acute serious bacterial infections per subject-year was 0.025 (upper limit of the 99% CI: 0.046), which is lower than the rate (0.067; upper limit of the 99% CI: 0.134) observed in a phase 1 study 160601 using SC administration of IGI 10% without rHuPH20 and significantly lower (p<0.0001) than the 1.0 rate threshold considered to provide substantial evidence of efficacy. Compared to IV infusion, SC administration with rHuPH20 was able to be administered at the same dosing interval and resulted in similar IgG trough levels. Compared to SC administration without rHuPH20, Hyqvia demonstrated higher bioavailability as determined by AUC per dose/kg.</p> | The degree of benefit is similar to IV administration. Except for the mitigation of IGSC-related induration at the site of administration, the rHuPH20 component did not contribute to efficacy in terms of (a) in-line pressure vs. flow rate, (b) in-line pressure vs. cumulative volume infused curves, (c) total volume of IGSC 10% infused with and without rHuPH20 preadministration, (d) maximum tolerated flow rate (300 mL/h), and (e) time needed to complete an infusion. |
| Risk | <p>Risks associated with Hyqvia appear to result primarily from the immunoglobulin component. Rates of mild, moderate and severe ARs per infusion were 0.235, 0.101 and 0.004 respectively, compared to 0.054, 0.010 and 0.001 respectively for IGSC 10% alone.</p> <p>An AERS database search reported only three safety events. The first was a seizure in a 61 y/o male receiving lidocaine infusion for pain control. The second involved a fatal mixed drug toxicity in a 58 y/o subject enrolled in the phase 3 trial (Subject (b)(6)) that occurred two months after the trial had been completed. The third was an 8 y/o male with moderate-severe dehydration who experienced infiltrated fluid in the subcutaneous space where the infusion was being administered, resulting in presumed hyponatremia due to continued vomiting and diarrhea.</p> | <p>Hyqvia has a safety profile similar to that of weekly IGSC 10%, with the exception of <u>more frequent</u> mild and moderate local ARs with Hyqvia infusions given every 3-4 weeks.</p> <p>With respect to potential risk from the rHuPH20 component, evidence from a small (N=12) phase 1 crossover trial indicates that the frequency of Grade 2 or higher toxicity for clinical chemistry + hematology values in healthy volunteers receiving IG 10% + rHuPR20 is only one-third the rate when these same volunteers receive IG 10% + buffer (i.e., without rHuPR20).</p> |

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| | | |
|------------------------|--|---|
| Risk Management | <p>Most injection site reactions are mild in severity and resolve relatively quickly and without sequelae. Additional risks attributable to human rHuPR20 appear to be minimal based on an AERS database search, but preclinical data from guinea pig suggests the possibility of fertility suppression due to anti-PH20 antibodies binding.</p> <p>FDA has requested additional information on potential immunogenicity risk: a tissue cross-reactivity study and a study to evaluate complement binding by rHuPH20-antibody complexes.</p> | <p>A CR letter will be issued asking the sponsor to evaluate whether rHuPH20-antibody complexes are capable of fixing complement.</p> <p>If anti-rHuPH20 antibodies strongly bind to tissues <i>in vitro</i> and/or bind complement, additional data will be required before licensing can be considered.</p> |
|------------------------|--|---|

11.2 Risk-Benefit Summary and Assessment

Hyqvia resulted in a 10-min reduction in median duration of infusion (2.13 vs. 2.33 h) compared to IVIG. Short-term risk was acceptable, but long-term risks associated with antibodies to rHuPR20 are unknown.

11.3 Recommendations on Regulatory Actions

I recommend a CR letter so that the effects of anti-rHuPH20 can be investigated further. If no major concerns are identified, approval with appropriate safety language is recommended. This does not necessarily obviate the need for a PMR at time of approval in order to further understand the immunogenic potential of rHuPR20.

11.4 Labeling Recommendations

N/A until FDA's concerns over rHuPH20 have been satisfactorily addressed.

11.5 Recommendations on Postmarketing Actions

See above.