BLA Clinical Review Memo

Application Type	Original BLA
Application Number(s)	125402
Received Date(s)	30-JUN-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% IG (100 mg/mL) and 160 U/mL Recombinant Human Hyaluronidase
Dosage Form(s) and Route(s) of Administration	Subcutaneous
Dosing Regimen	*For Patients on Intravenous Treatment*: Administer HYQVIA at the same dose and frequency as the previous intravenous treatment, after the initial dose ramp-up. *For Patients Naïve to IG treatment or Receiving Subcutaneous Treatment:* Administer HYQVIA at 300 to 600 mg/kg every 3 to 4 weeks, after initial ramp up.
Indication(s) and Intended Population(s)	Treatment of adult patients with Primary Immunodeficiency (PI)

<u>GLOSSARY</u>

ASBI: acute, serious, bacterial infections
AE: adverse event (untoward medical occurrence not necessarily considered drug related)
AR: adverse reaction (adverse event known to be caused by a drug)
rHuPH20: Recombinant Human Hyaluronidase
HYQVIA: IG 10% with rHuPH20 (administered subcutaneously)
IG: immunoglobulin G
IGIV 10%: Immune Globulin Infusion 10% (Human) administered intravenously
IGSC 10%: Immune Globulin Infusion 10% (Human) administered subcutaneously
IV: intravenous
PI: primary immunodeficiency disease
SAR: serious adverse reaction
SC: subcutaneous

1. EXECUTIVE SUMMARY
Background
Baxter's BLA for HYQVIA [IG 10% with rHuPH20, 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 IG 10% and rHuPH20 and is for subcutaneous (SC) administration initially using rHuPH20, followed by IG 10%. The 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 IG 10% to be infused SC than would be possible with IG 10% alone, thereby necessitating less frequent administration (q 3-4 weeks as opposed to q weekly SC administration without rHuPH20); a second rational is that subcutaneous administration will improve patient comfort by obviating the need for intravenous administration.

The IG 10% component is a 10% liquid formulation of Immunoglobulin G (IG), 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.

Materials reviewed
- Pivotal Study 160603 (N=87) and extension study 160902 (N=66) were open label, sequential, multicenter trials that compared HYQVIA with IGIV 10% in PI subjects.
- Exploratory studies 161001 (N=53) and 170901 part 4 (N=12) were randomized, controlled trials in healthy volunteers that compared HYQVIA with placebo (lactated Ringer's, human serum albumin, or buffer control).

- Exploratory studies 160602 (N=11) and 160601 (N=49) were open label, sequential, multicenter trials in PI subjects that compared HYQVIA with IGIV 10% and IGSC 10%, respectively.

BLA Clinical Study Roster

Study ID	Study Phase and Design	No. of Subjects Age Range Duration/Subject	Study Objectives	Products
Healthy adult volunteers				
161001	Phase 1, prospective, lactated Ringer's/human serum albumin -controlled, within subject-between subjects, single-center RCT	N=53 19-65 years 6 weeks	Evaluate effectiveness of rHuPH20 in enhancing IGSC administration	IGSC 10% HYQVIA
170901 Part 4*	Phase 1, prospective, sequential, RCT	N=12 26-64 years 8 weeks	Assess safety, tolerability, infusion pressure, and maximal flow rate of IGSC infused with and without prior infusion of rHuPH20	IGSC 10% HYQVIA
PI subjects				
160602	Phase 1/2, prospective, open-label, sequential, two-arm, multicenter study	N=11 20-76 years 8-65 days (Arm1) 133-165 days (Arm 2)	Determine dose of rHuPH20 enabling up to 600 mg/kg IGIV 10% to be administered SC in a single infusion site	IGIV 10% HYQVIA
160601	Phase 2/3, prospective, open-label, sequential, multi-center study	N=49 3-77 years ≥10 months	Evaluate tolerability, PK, and efficacy of IGSC 10%	IGIV 10% IGSC 10%.
160603	Phase 3, prospective, open-label, sequential, multi-center study	N=87 4-78 years 14 months (Arm1) 17 months (Arm 2)	Evaluate efficacy, tolerability and PK of IGIV 10% vs. IGSC 10% following rHuPH20	IGIV 10% HYQVIA
160902†	Extension study of 160603	N=66	Long term safety	HYQVIA

*Trial halted prematurely by Baxter due to hemolytic anemia SAEs and flu-like syndrome AE
†Trial halted at FDA request over concerns about anti-human hyaluronidase antibody formation

SUBJECT DEMOGRAPHICS

Pivotal study 160603 evaluated efficacy, tolerability and pharmacokinetics (PK) of the combination product in PI subjects > 2 years of age, with subjects 2 to <12 years of age comprising 16% of the total. The following table describes the demographic characteristics of the population.

Table 1: Subject Demographics

Parameter	Category	Age 2 to 12 Years N (%)	Age ≥12 Years N (%)	Total N (%)
Population	Subgroup	14 (16)	73 (84)	87 (100)
Gender	Male	8 (57)	36 (49)	44 (51)
	Female	6 (43)	37 (51)	43 (49)
Race	White	14 (100)	65 (89)	79 (92)
	Black/African American	0	2 (3)	2 (2)
	Asian	0	3 (4)	3 (3)
	American Indian/ Alaska Native	8	1 (1)	1(1)
	Pacific Islander	0	0	0
	Multiple	0	2 (3)	2 (2)
Ethnicity	Hispanic	1 (7)	7 (10)	8 (9)
	Non-Hispanic	13 (93)	66 (90)	79 (91)

The small number of subjects in study 160603 precludes subset or trend analyses and inferences based on the following information should be interpreted with caution.

- Safety: a small number of serious adverse events (N=12), all assessed as unrelated to the product, was observed only in the ≥12 year old subgroup. There was no evidence that nonserious adverse reactions differed among subgroups based on age or gender. Most subjects were Caucasian and non-Hispanic so no conclusions can be drawn regarding safety differences according to race and ethnicity. There were no safety signals except for the development of non-neutralizing antibodies against the hyaluronidase component of the drug. These antibodies present a theoretical risk in patients of reproductive age and are of unknown clinical significance. The occurrence of antibodies did not appear to be related to age or gender.

-   Efficacy: the study drug was uniformly effective and there was no evidence of a difference in reduction of acute serious bacterial infections (ASBI) based on age, gender, race or ethnicity.

SUBJECT DISPOSITION
Withdrawal from studies enrolling healthy volunteers

Study 161001
2/53 randomized subjects were discontinued for the following reasons: hypotension AE following rHuPH20 administration but prior to IGSC 10% administration; lost to follow-up)

Study 17091 part 4
4/12 randomized subjects were discontinued for the following reasons: hemolytic anemia SAE after IGSC administration (2 subjects); applicant's request for withdrawal (2)

Withdrawal from studies enrolling PI subjects

IGIV 10%
5/150 (3%) subjects were discontinued for the following reasons: missing 2 consecutive visits (2); conflict with vacation; refusal to continue; difficult IV access.

IGSC 10%
3/49 (6%) subjects were discontinued for the following reasons: family emergency; refusal to continue; increase fatigue

HYQVIA
41/193 (21%) subjects were discontinued for the following reasons: local discomfort (4); lost to follow-up; geographical factors (4); inconvenience of home care; grand mal seizure; back injury; closure of study site (9); subject relocation (3); death from drug overdose; scheduled for bone marrow transplantation; rigors of study visits; nonserious adverse event (3); HYQVIA arm terminated by applicant (8); status epilepticus; abdominal pain (2)

EFFICACY
Synopsis: HYQVIA was effective in reducing ASBI, i.e., the annual rate of validated ASBI was significantly ($p<0.01$) lower than 1.0 (threshold for demonstrating substantial evidence of efficacy, FDA Guidance), thereby meeting its primary endpoint.

Table 2: Primary Endpoint (ASBI)

Study ID	Point Estimate	Upper Limit of 99% CI	P-value
160603 – pivotal study	0.025	0.046	<0.0001
160902 – extension study	0.020	0.045	<0.0001

Secondary efficacy endpoints − days off school/work, on antibiotics, acute physician visits, days in hospital and days in hospital due to infection − also were met: See Table 3 below.

Table 3: Secondary Efficacy Endpoints (Annualized Monthly Rates; Pivotal Study 160603)

Parameter	Treatment	Point Estimate (95% CI)
Days off school/work	IV HYQVIA	0.23 (0.15 to 0.34) 0.28 (0.20 to 0.37)
Days on antibiotics	IV HYQVIA	3.15 (2.19 to 4.35) 1.69 (1.29 to 2.16)
Acute physician visits	IV HYQVIA	0.33 (0.23 to 0.45) 0.40 (0.32 to 0.49)
Days in hospital	IV HYQVIA	0.06 (0.03 to 0.10) 0.02 (0.01 to 0.03)
Days in hospital due to infection	IV HYQVIA	0.03 (0.01 to 0.05) 0.00 (0.00 to 0.01)

Contribution of rHuPH20 to efficacy

Studies 161001 (N=57) and 170901, part 4 (N=12)

Except for mitigation of IGSC-related induration at the administration site and a small shortening of infusion duration, the rHuPH20 component did not appear to contribute to efficacy with respect to total volume of IGSC 10% infused, maximum tolerated flow rate, or time needed to complete an infusion in the two healthy volunteer studies, Study 161001 and Study 170901, part 4, which was prematurely terminated.

Study 160603 (N=87 PI subjects)

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 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 was acceptable. Risks associated with acute exposure to HYQVIA were similar to risks of IGSC alone.

NB: none of the serious adverse drug experiences reported in clinical trials of PI subjects was attributed to the product by the investigators, sponsor, or FDA, and thus, they were

classified by FDA as *serious adverse events*.[1] This contrasts with the large number of local and systemic adverse drug experiences reported in sequential-design clinical trials that were determined either to be caused by the drug (*adverse reaction*), or the temporal relationship between event and drug exposure made it reasonably possible that the drug caused the experience (*suspected adverse reaction*). For the purposes of this review, nonserious adverse reactions and nonserious suspected adverse reactions were aggregated and classified as *adverse reactions*.

Serious Adverse Events (SAE)
Studies enrolling healthy volunteers
- Phase 1 Study 161001
  No cases reported.

- Phase 1 Study 17091 part 4
  IGSC 10%: 2 cases of hemolytic anemia, moderate were reported, one in the 0.3 g/kg cohort (peak LDH: 659 U/L) and a second in the 0.6 g/kg cohort (peak LDH: 669 U/L). NB: this trial was terminated prematurely subsequent to these 2 SARs and a nonserious AR of flu-like illness in an IGSC 10% 0.6 g/kg subject).

Studies enrolling PI subjects
- Phase 1/2 Study 160602
  HYQVIA: 1 case of severe (non-lethal), unrelated anaphylaxis reported.

- Phase 2/3 Study 160601
  IGSC 10%: 1 case of cholecystitis, biliary tract infection, both moderate and 1 case of chest pain, severe reported.
  IGIV 10%: 1 case of sinusitis, moderate and 1 case of seizure, moderate reported.

- Pivotal Study 160603
  HYQVIA
    14 cases in 11 subjects reported:
      Grand mal, severe + petit mal epilepsy, severe
      Thrombosis right upper extremity, moderate
      Headache, severe

---

[1] 21 CFR 312.32(a): an *adverse event* means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An *adverse reaction* means any adverse event caused by a drug. A s*uspected adverse reaction* means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, 'reasonable possibility' means there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug. *FDA Guidance on Safety Reporting Requiring Requirements for INDs and BA/BE Studies.*

Status epilepticus, severe + respiratory failure, severe, + tonsillar hypertrophy, mild
Acute adrenocortical insufficiency, moderate
Gastroenteritis, moderate
Cervical dysplasia, mild
Back injury requiring surgery, severe
Exacerbation of tonsillar enlargement, mild + status epilepticus, severe + respiratory failure, severe

IGIV 10%
4 cases in 3 subjects reported:
Peptic ulcer, severe + bronchitis, moderate in one subject
Viral infection, mild
Cervical dysplasia, mild

Nonserious Adverse Reactions (AR)
- **Pivotal Study 160603**

The AR *rate per infusion* overall in pivotal Study 160603 was similar across the two treatment cohorts: 1.05 in the IGIV 10% cohort (Epoch 1) vs. 0.94 in the HYQVIA (Epoch 2) cohort. See Table 4 below.

Table 4: AR Rate per Infusion in Pivotal Study 160603

Treatment Cohort	No. of ARs	AR Rate per Infusion
IGIV 10% (365 infusions; N=87)	383	1.05
HYQVIA (1129 infusions; N=83)	1074	0.94

The AR rate per infusion stratified by *AR intensity* was virtually identical between the IGIV and HYQVIA cohorts. See Table 5 below.

Table 5: AR Rate per Infusion Stratified by AR Intensity in Pivotal Study 160603*

Treatment Cohort	No. of ARs (Percent of Total ARs)		
	Mild	Moderate	Severe
IGIV 10%	240 (63%)	132 (34%)	11 (3%)
HYQVIA	688 (64%)	371 (35%)	15 (1%)

*Based on the Common Toxicity Criteria of the Eastern Cooperative Oncology Group
Mild: transient discomfort; does not interfere in a significant manner with normal function
Moderate: limited impairment of function; produces no sequelae
Severe: marked impairment of function; produces sequelae requiring therapeutic intervention

In contrast, rates per infusion for mild and moderate *local ARs* using HYQVIA were disproportionately greater (e.g., 0.01 vs. 0.15, IGIV 10% vs. HYQVIA, respectively) and

in the opposite direction compared with rates per infusion for mild and moderate *systemic ARs* (e.g., 0.64 vs. 0.46). See Table 6 below.

Table 6: AR Rate per Infusion – Local vs. Systemic ARs in Pivotal Study 160603

Site Treatment Cohort	No. of ARs (Rate per Infusion)			
	Mild	Moderate	Severe	Total
Local ARs				
IGIV 10% (365 infusions)	5 (0.01)	0	0	5 (0.01)
HYQVIA (1129 infusions)	166 (0.15)	66 (0.06)	3 (0)	235 (0.21)
Systemic ARs				
IGIV 10% (365 infusions)	235 (0.64)	132 (0.36)	11 (0.03)	378 (1.03)
HYQVIA (1129 infusions)	522 (0.46)	305 (0.27)	12 (0.01)	839 (0.74)

Potential risks of anti-rHuPH20 antibodies

Theoretical concerns have been raised that chronic rHuPH20 exposure could elicit anti-rHuPH20 antibodies and that anti-rHuPH20 antibody-complexes could bind complement, resulting thereby 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 rHuPH20, PH-20.[2]

In pivotal Study 160603 + extension Study 160902, 15 of 87 subjects (17%) developed 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 cut-off attributable to passive transfer noted by the sponsor, the clinical implications of this finding are <u>unknown</u>.

At FDA request, the sponsor conducted two *in vitro* studies to address this issue. The first evaluated binding of anti-rHuPH20 antibodies in a normal human tissue panel; the second evaluated whether rHuPH20-antibody complexes are capable of fixing complement. See the preclinical reviewer's memo for a more complete discussion of this topic.

RISK-BENEFIT ASSESSMENT

Prior assessments of currently licensed IG products have concluded that the clinical benefit of IG therapy outweighs potential risks arising from product immunogenicity. Although HYQVIA demonstrates a (favorable) benefit-to-risk profile that is similar to the "gold standard", IGIV, HYQVIA'S calculus is more nuanced because the main

---

2 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

immunogenic component of concern (rHuPH20) is not the life-saving therapeutic; rather, subcutaneous administration of rHuPH20 is designed primarily to increase comfort and convenience of treatment in PI patients. See the Benefit-to-Risk panel below.

Benefits	Risks

– Compared with IGIV
    • Just as effective
        – Number of acute serious bacterial infections (ASBI)
        – Days hospitalized, on antibiotics, off school/work
    • Lower rate of <u>systemic</u> AEs
    • More convenient for home use
– Compared with IGSC
    • Requires less frequent dosing
        – IGIV: 3-4 weeks (= IGIV)
        – IGSC alone: 1-2 weeks
	– Short term
	    • Higher rate of mild-moderate <u>local</u> AEs than with IGIV
	    • Indirect comparison suggests rate of local and systemic AEs for HyQvia <u>*may*</u> be higher than for IGSC alone
	– Long term
	    • Uncertainty over clinical relevance of reports indicating anti-human hyaluronidase antibody binds to neural, GI, and reproductive tissue in experimental animals

PI patients who elect to receive HYQVIA in order to take advantage of a reduction in infusion duration and dosing frequency could be exposed to theoretical risks associated with life-long exposure to rHuPH20. While HYQVIA administration every 3-4 weeks in clinical trials of comparatively short duration was associated with a safety profile similar to that of weekly IGSC 10% (with the exception of more frequent SARs considered unrelated to HYQVIA as well as more frequent mild-moderate local ARs), it is unknown whether longer exposures will elicit anti-rHuPH20 antibodies and anti-rHuPH20 antibody-complexes in target organs (testicular tissue, mesenteric tissue and brain tissue; see the preclinical reviewer's memo).

To address these concerns, the sponsor has committed to conducting an adequately sized PMC safety study(ies) with adequate follow-up to detect adverse events.

Addendum #1
April 10, 2014 Update
A resubmission to the BLA was received on 12-DEC-2013. The resubmission contained Pharmacology/Toxicology Study Protocols and Final Reports, Revised Labeling, and a Pharmacovigilance Plan originally submitted in response to FDA's 27-JUL-2012 CR letter. No additional clinical safety data were received from the Applicant.

Addendum #2
August 4, 2014 Update
The BPAC met on 31-JUL-2014 to discuss this BLA. By a 15-to-1 vote, the Committee voted that HYQVIA had a favorable benefit: risk profile.

RECOMMENDATION

Approval of the product with a requirement for one (or more) PMC safety studies of adequate size conducted over an adequate study period to capture AEs and antibody cross-reactivity with other hyaluronidases.

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 PI. It is most often reflected by a decrease in serum IG, which in turn leads to increased susceptibility to bacterial infections. Individuals with these diseases require replacement therapy with IG to prevent or reduce the severity of infections. For many years, IG replacement therapy was given intramuscularly, and then by the IV route. Currently, the vast majority of IG products 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 IG preparations has been introduced in many countries. The primary disadvantage of SC therapy has been the limited volume that can be infused into 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 taken by manufacturers to address 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) indication(s)

2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/Interventions(s) for the Proposed Indications(s)

Current treatment of PI is replacement therapy with human IG products, usually administered IV every 3-4 weeks. There are four marketed products in the U.S. that allow for 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. IGSC differs from IGIV 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-APR-2005 (STN 125105) for the treatment of PI by IV route of administration. The SC route of administration (STN 125105/708) was licensed in 2011.

rHuPH20-HYLENEX
HYLENEX Hyaluronidase was licensed on 2-DEC-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 IG 10% product.

2.5 Summary of Pre-submission Regulatory Activity Related to Submission
- 27-APR-2005: GAMMAGARD LIQUID was approved by FDA (STN 125105) for the treatment of PI by IV route of administration.
- 2-DEC-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.
- 20-AUG-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.
- 30-SEP-2008: IND 13840, a Phase 3 study to evaluate the combination product in the treatment of PI, was submitted.
- 30-JUN-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 IG 10% infusion given alone or sequentially following SC injection of rHuPH20.
- 6-OCT-2009: Pre-BLA Type B meeting discussed the data requirement to support the license of the combination product.

- 20-JUL-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.
- 31-AUG-2010: Type A meeting discussed the data requirements to support the independent contribution of rHuPH20 in the combination product.
- 6-OCT-2010: Type C CMC meeting discussed the related CMC issues.
- 16-DEC-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 14-MAR-2011.
- 25-JUN-2011: Pre-BLA Type B meeting discussed the results of clinical studies performed to support the BLA.
- 22-JUL-2011: GAMMAGARD LIQUID was approved (STN 125105/708) for the treatment of PI by SC route of administration.

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 indicates 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 pivotal 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 rHuPH20** 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-DEC-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 IG 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. rHuPH20 is intended to improve dispersion and absorption of the IG. The IG of HYQVIA supplies a broad spectrum of opsonizing and neutralizing IG 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, absorption and bioavailability of IG 10%.

- IG 10% supplies a broad spectrum of opsonizing and neutralizing IG 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 IG have not been fully elucidated.

- rHuPH20 is intended to facilitate increased bioavailability of IG10% 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 IG 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 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 IG is required for tolerability of a full 4-week SC dose of IG 10%. The mean duration of administration of a tolerated full 4-week dose was 2.9 h. Bioavailability of IG 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.

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

6. DISCUSSION OF INDIVIDUAL STUDIES (see Table 1, Clinical Trial Roster)

6.1 Study 161001 (phase 1)
<u>Synopsis</u>: Study 161001 was a human volunteer study (N=53) that found rHuPH20 administered prior to IGSC 10% (a) improved frequency, size, time-to-resolution and severity of induration but (b) exerted no effect on total volume infused, maximum tolerated flow rate or time to completion of infusion.

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 administration of IGSC 10% solution.

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

Study 161001 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 IG) 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/m^2 (inclusive) and body weight $\geq$ 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 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 infusion of IGSC 10% or albumin control (75 U/g IG or 7.5 U/mL of albumin control solution)

Human albumin 0.25% in LR solution
- Single administration immediately preceding infusion of IGSC 10% or albumin control (75 U/g IG or 7.5 U/mL of albumin control solution)

LR solution (placebo control for rHuPH20)
- Single administration immediately preceding infusion of IGSC 10% or albumin control (at matching volume to that of rHuPH20 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 8, below.

Table 8: 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

a. Infusion visit includes subject check-in at the study site on Day -1 through 48 (± 6) hours after both infusions are completed/terminated.
b. 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.
c. Written informed consent must be obtained prior to any study procedures including screening.
d. Body weight measured at check-in (Day -1) will be used for the calculation of doses to be administered.
e. For laboratory assessments, see Table below.
f. 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 follow 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)
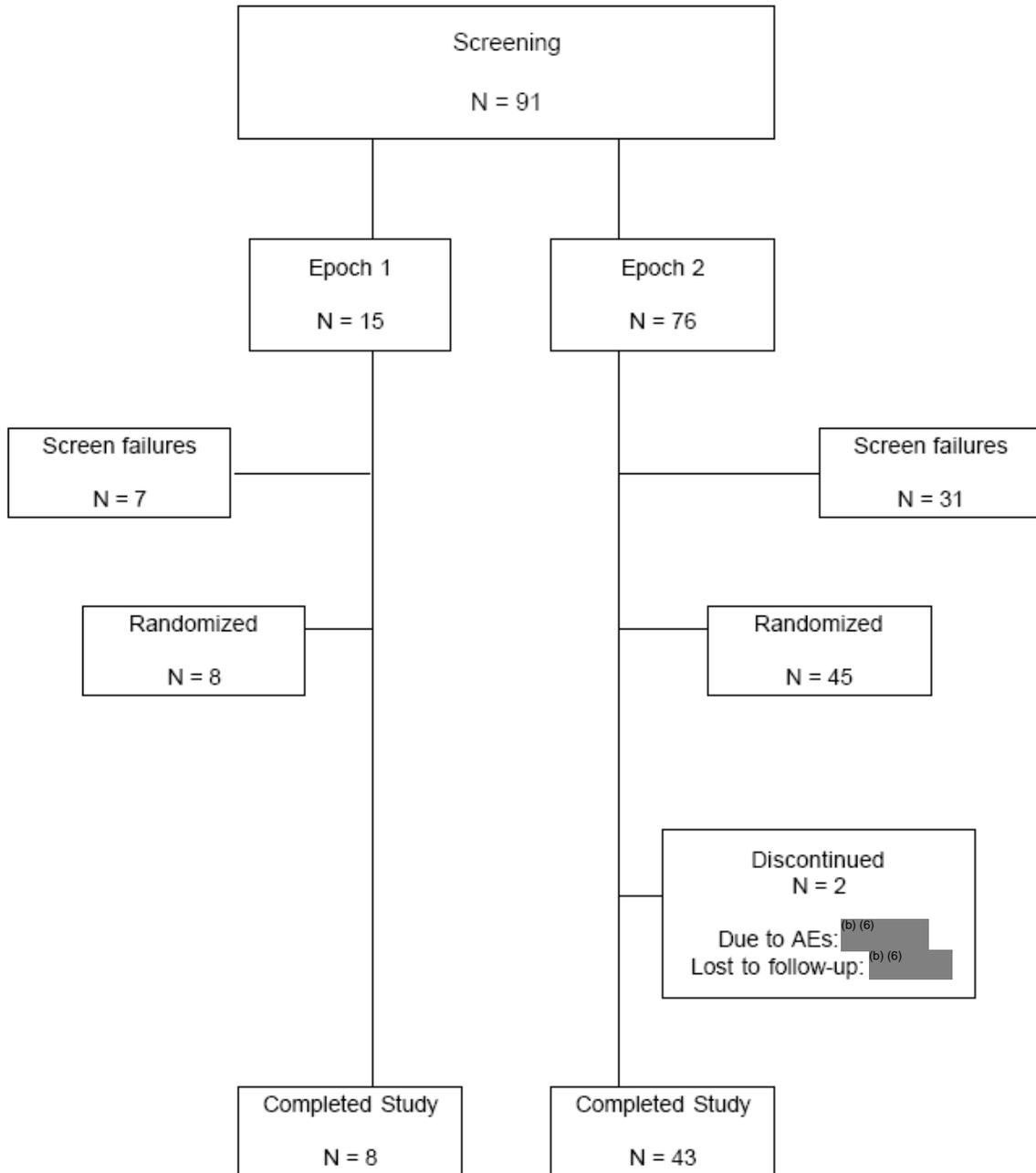
6.1.9 Safety

A total of 363 AEs 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 anti-rHuPH20 antibodies.

Serious Adverse Events (SAE)

There were no deaths or other SAEs in the study.

Systemic Nonserious Adverse Events (severe intensity)

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

- **Leukopenia**: Subject (b)(6) (IGSC + rHuPH20) had a normal leukocyte level (4.7 x 10^9/L; normal: 4.0-11.0/L) at screening which subsequently declined to 2.7 one week post infusion and then returned to 3.9 at study end.

- **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).

Local Adverse Reactions (severe intensity)

See Table 9, below.

Table 9: Local Infusion Site AEs (from Sponsor Amended Table 14.3-1)

	IGSC + rHuPH20 (N=40)	IGSC + LR (N=40)	Albumin + rHuPH20 (N=12)	Albumin + LR (N=12)
Severe AEs	8 -(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 AEs total	115	149	16	31

6.2 Study 2: 170901 part 4 (phase 1)
Synopsis: this trial was prematurely terminated after two reports of hemolytic anemia SAEs.

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-OCT-2009 due to the occurrence of SAEs and unexpected laboratory findings with onset dates over a 3-week interval from 9-OCT-2009 to 30-OCT-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 IG in approximately 47 healthy adult subjects in total.

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

See study schematic, below.
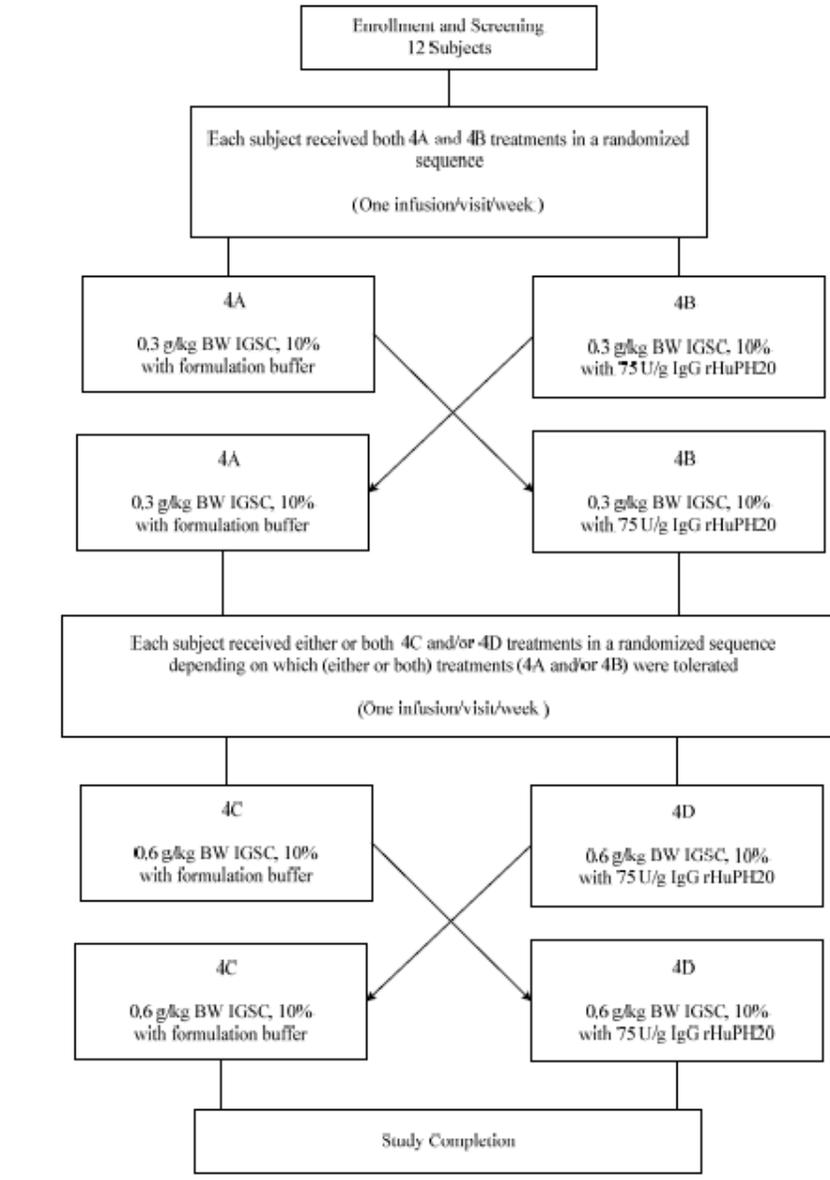
6.2.3 Population
Inclusion Criteria
1. Male or female, 18 to 65 years of age.
2. Body mass index (BMI) 19 to 32 kg/m^2 and body weight $\geq$ 50 kg. Additionally, for Study Part 3, the subject's body weight did not exceed 90 kg.
3. Healthy subject with no clinical evidence of acute and/or chronic disease 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.

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 IG

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[a]
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 E 20 (with PBW prior to 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 AEs and/or SAEs
- Number (proportion) of subjects/infusions experiencing related AE(s) and/or SAE(s)
- Number (proportion) of infusions with temporally associated (during or within 72 hours of completion of an infusion) AE(s) and/or SAE(s)
- Number (proportion) of infusions that were discontinued, slowed, or interrupted due to an AE
- Number (proportion) of infusions not tolerated: due to any serious related AE; any severe non-serious local or systemic-related AE(s); any severe non-serious local or systemic-related AE(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 AE(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)

Subjects enrolled into Part 4
N = 12

Subjects randomized in first two-period, two-arms cross-over design
0.3g/kg BW IGSC, 10% + control vs. 0.3g/kg BW IGSC, 10% + rHuPH20
N = 12

Subjects who completed the first cross-over design
N = 12

Subjects randomized in second two-period, two-arms cross-over design
0.6g/kg BW IGSC, 10% + control vs. 0.6g/kg BW IGSC, 10% + rHuPH20
N = 12

Subjects who did not complete the
second cross-over design
N = 4

Subjects who completed the
second cross-over design
according to protocol
N = 8

Withdrawn due to
adverse event
N = 2

Withdrawn due to
sponsor decision
N = 2

6.2.9 Safety

Both Study Parts 4 and 1 were terminated early due to the occurrence of 2 SAEs (hemolytic anemia, Subjects ---------(b)(6)------------) and unexpected laboratory findings leading to subject withdrawal (Subject -(b)(6)-) due to a nonserious AE 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.[3]

Serious Adverse Events (see Table 10, 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 10^6/uL), declining to 3.91 three weeks after initial dosing. LDH was elevated at 659 U/L. 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

Since attribution of hemolytic anemia to rHuPH20 could not be ruled out, these two events were classified as serious adverse *events*. Nonserious cases of anemia also were 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).

Systemic Adverse Events (Grade 2 or higher, Tables 10 and 11, 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).

---

[3] 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 rHuPH-20 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 10: Grade ≥2 Chemistry & Hematology Values by 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
Treatment 4A: IG 0.3 g/kg/infusion + buffer; Trt 4C: IG 0.6 g/kg/infusion + buffer
Treatment 4B: IG 0.6 g/kg/infusion + rHuPH20; Trt 4D: IG 0.6 g/kg/infusion + rHuPH20

Table 11: Summary Table of Grade 2 or Higher Toxicity Values

Chemistry	IG + Buffer	IG + rHuPH20	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 AEs

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 rHuPH20 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)
Synopsis: Study 160602 was a pilot tolerability study that found an rHuPH20 dose ≥50 U/g IG was required to tolerate a 4-week dose of IGSC 10%.

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 IGSC 10% in a single site and the amount of rHuPH20 needed to infuse that dose (a dose of up to a maximum of 600 mg of IG/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 IGSC 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 IGSC 10% in a single site with good tolerability, and to compare the PK of the rHuPH20-facilitated SC administered IG with the PK of IV administered IG. 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.
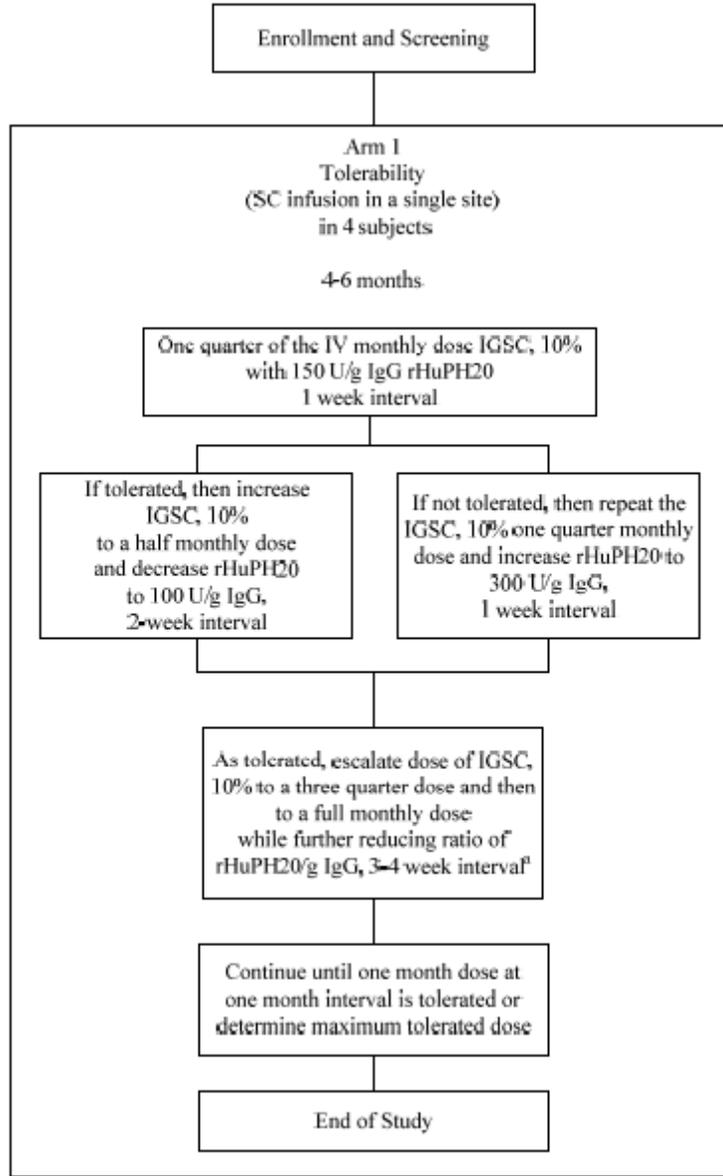
Study Arm 1

- 4 adult/adolescent subjects received IGSC 10% to determine tolerability.
- The initial dose of rHuPH20 was calculated on the basis of 150 Units (U)/g IG in IGSC 10%, rounded up to the next higher gram of IG. Administration of rHuPH20 was to be completed 5 minutes prior to starting the infusion of the IGSC 10%.
- Treatment started with 1/4 of a full 4-week dose of IGSC 10% which was preceded by 150 U of rHuPH20/g IG. If that dose was tolerated, 1 week later 1/2 SC dose was administered with a reduced ratio of rHuPH20, 100 U/g IG. 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 IG dose was administered. If the dose of IGSC 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 IG for SC administration of a full 4-week dose, the protocol was amended to allow the amount of rHuPH20 to be decreased to 25 or 10 U/g IG.

- If a subject was not able to achieve a 4-week dose of IGSC 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 IGIV infusion 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%.
- The first IGSC infusion was administered 1 week after the second IV infusion. The timing and volume of the IGSC 10% infusion and the ratio of rHuPH20 and IGSC 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 IG concentration versus time.
- If a subject was not able to tolerate a 4-week IGSC 10% in a single infusion site with the quantity of rHuPH20 allowed per schedule, the amount of IGSC 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 IGSC 10% administration was below 90% of the AUC determined after IGIV administration, the last dose of rHuPH20 used was increased 4-fold (the minimum dose being 200 U/g IG the maximum dose 48,000 U), and another IGSC infusion 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, IGSC 10% administration was continued at the amount and ratio of rHuPH20 to IG used for the PK infusion.

```
┌─────────────────────────────┐
│   Enrollment and Screening  │
└─────────────────────────────┘

              Arm 2
      Bioavailability and Tolerability
            in 6-8 subjects

              8-10 months

  ┌──────────────────────────────────────────────────┐
  │                  IV treatment                      │
  │  ┌──────────────────────────────────────────────┐  │
  │  │  A single 4-week dose of IGIV, 10% followed    │  │
  │  │  by PK                                          │  │
  │  └──────────────────────────────────────────────┘  │
  │  ┌──────────────────────────────────────────────┐  │
  │  │  4 weeks later, a single 4-week dose of IGIV,  │  │
  │  │  10%  1 week later, start SC treatment          │  │
  │  └──────────────────────────────────────────────┘  │
  └──────────────────────────────────────────────────┘

  ┌──────────────────────────────────────────────────┐
  │        Follow interval and dose escalation of      │
  │     IGSC, 10% and ratio of rHuPH20/g IgG           │
  │               used in Arm 1[a]                      │
  │                                                     │
  │ ┌────────────────────────┐ ┌────────────────────┐ │
  │ │ When full monthly dose  │ │ If full monthly    │ │
  │ │ is tolerated, repeat    │ │ dose is not        │ │
  │ │ dose and perform PK     │ │ tolerated, repeat  │ │
  │ │                         │ │ maximum tolerated  │ │
  │ │                         │ │ dose and perform PK│ │
  │ └────────────────────────┘ └────────────────────┘ │
  │ ┌────────────────────────────────────────────────┐ │
  │ │ Repeat last infusion once more and at that time │ │
  │ │ compare results of IV PK and SC PK              │ │
  │ └────────────────────────────────────────────────┘ │
  │ ┌───────────────────────┐ ┌──────────────────────┐│
  │ │ AUC of the SC          │ │ AUC of the SC        ││
  │ │ administered IGIV, 10% │ │ administered IGSC,   ││
  │ │ is within 90% of the   │ │ 10% is not within    ││
  │ │ IV AUC                 │ │ 90% of the IV AUC:   ││
  │ │                        │ │ then the last dose of││
  │ │                        │ │ rHuPH20 used will be ││
  │ │                        │ │ increased 4-fold     ││
  │ │                        │ └──────────────────────┘│
  │ │                        │ ┌──────────────────────┐│
  │ │                        │ │ Repeat IGSC, 10% with││
  │ │                        │ │ rHuPH20 infusion and ││
  │ │                        │ │ perform PK           ││
  │ │                        │ └──────────────────────┘│
  │ ┌────────────────────────────────────────────────┐ │
  │ │                  End of Study                    │ │
  │ └────────────────────────────────────────────────┘ │
  └──────────────────────────────────────────────────┘
```

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 IGSC 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 x the ULN for the testing laboratory
3. Subjects with neutropenia (ANC ≤ 500/mm^3)
4. Subjects with serum creatinine levels > 1.5 x 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
- Injection prior to IGSC infusion 10%. The initial dose was calculated on the basis of 150 U/g IG. 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		
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 IG 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 IG in a single site with no more than mild local AEs.

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

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 $AUC0-\tau$ 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 $AUC0-\tau$ /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 IG/kg BW with no more than mild local AEs.

Figure 1.
Disposition of Subjects in Study 160602
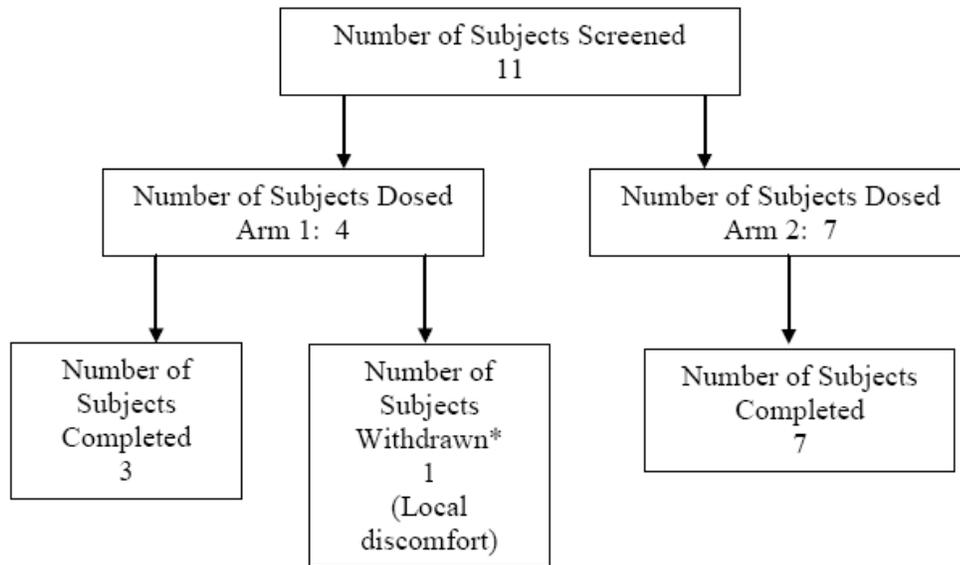
Arm 1: HyQ only
Arm 2: IV followed by HyQ

6.3.6 Safety
Serious Adverse Events
- **Anaphylaxis**: the only severe and potentially life-threatening AE that occurred in the study was an immediate anaphylactic reaction in Subject ---(b)(6)--- that was attributed to moxifloxicin taken prior to onset of the symptoms.

Systemic Nonserious Adverse Events
- *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 Adverse Reactions
None reported.

6.1 Study 4: 160601 (phase 2/3)

Synopsis: Study 160601 (N=49) was a comparative PK study that found 108% of the IGIV dose was required to achieve PK equivalence using HYQVIA compared with 137% of the IGIV dose using IGSC 10% alone.

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

The primary objective was to evaluate the tolerability and PK of IGSC 10% compared to those receiving IGIV. A secondary objective was to evaluate efficacy in terms of acute serious bacterial infections.

6.4.2 Design Overview

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

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

```
┌─────────────────────────────────┐
│      Enrollment and Screening   │
└─────────────────────────────────┘
                 │
┌─────────────────────────────────┐      ┌──────────────────────────────────┐
│             Part 1              │      │ IgG trough level prior to each    │
│           IV treatment          │      │            infusion               │
│  IVIG, 10% 300-1000 mg/kg (based on doses │──▶│ PK in subjects ≥12 years of age   │
│  administered prior to the study) │      │   at infusion 3 (4 week interval) │
│      Every 3-4 weeks - 13 weeks │      │   or infusion 4 (3 week interval) │
└─────────────────────────────────┘      └──────────────────────────────────┘
                 │
┌─────────────────────────────────┐      ┌──────────────────────────────────┐
│             Part 2              │      │ IgG trough level prior to infusion│
│           SC treatment          │      │           1, 5, and 9             │
│  IGSC, 10% at 130% of the equivalent weekly dose │──▶│  PK in subjects ≥12 years         │
│       administered in Part 1    │      │          at infusion 8            │
│     Weekly, at least 12 infusions │      └──────────────────────────────────┘
└─────────────────────────────────┘
                 │
┌─────────────────────────────────┐      ┌──────────────────────────────────┐
│            Part 3a              │      │  IgG trough level prior to        │
│           SC treatment          │──▶│        infusion 1 and 5           │
│   IGSC, 10% at Adjusted Dose^a  │      │                                   │
│       Weekly, 6 infusions       │      └──────────────────────────────────┘
└─────────────────────────────────┘
                 │
┌─────────────────────────────────┐      ┌──────────────────────────────────┐
│            Part 3b              │      │ IgG trough level prior to infusion│
│           SC treatment          │      │  1, 5, and 9 and end of study visit│
│           IGSC, 10% at:         │──▶│  PK in subjects ≥12 years         │
│        Adjusted Dose^b or       │      │          at infusion 8            │
│    Individually Adapted Dose^c  │      └──────────────────────────────────┘
│       Weekly, 12 infusions      │
└─────────────────────────────────┘
                 │
┌─────────────────────────────────┐      ┌──────────────────────────────────┐
│     Optional Study Extension Part │      │  IgG trough level prior to        │
│           SC treatment          │      │         infusion 1 and            │
│  IGSC, 10% at dose from Part 3b │──▶│       end of study visit          │
│  Weekly for up to approximately 5 months │      └──────────────────────────────────┘
└─────────────────────────────────┘
                 │
┌─────────────────────────────────┐
│      End of Study Assessments   │
└─────────────────────────────────┘
```

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 IG 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 IG 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 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 $\geq$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 pivotal 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 $\pm$ 3 days or 28 $\pm$ 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 $\geq$2 y.
4. Serum trough level of IG >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 pivotal 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 severity 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 IG 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 $\geq$40 kg, and 20 mL per

infusion site for subjects with BW <40 kg. <u>The initial infusions</u> 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, <u>subsequent infusions</u> 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.

<u>Calculation of Dose Adjustment and Individual Adaptation;</u> Immediately after the last analysis of the PK data (IG 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 IG Trough Level Factor, based on expected IG 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 IG 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 IG trough level in Study Part 3a expressed as a percentage of the IG 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
<u>PK</u>
In subjects ≥ 12 years old, bioavailability of IG 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 IG after administration of GAMMAGARD LIQUID, IV, SC and SC at an Adjusted/Individually Adapted Dose, as measured by IG trough levels

Efficacy
- Infections were reported as ARs. ASBIs were defined as bacteremia/sepsis, bacterial meningitis, osteomyelitis/septic arthritis, bacterial pneumonia and bacterial visceral abscess.
- Rates of infections and ASBI 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 AEs.
-

6.4.9.1.3 Subject Disposition

Figure 14.1.1-1:
Disposition of Subjects
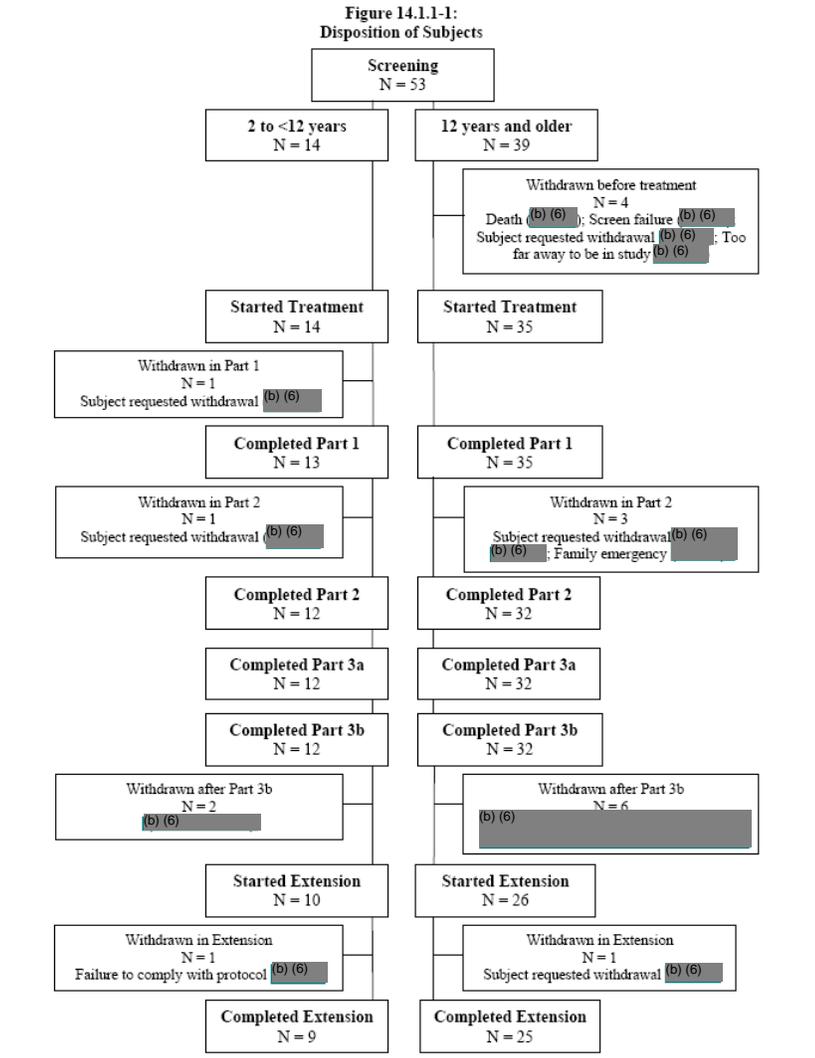
Serious Adverse Events

- **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, <u>no cardiac workup was performed</u>. 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 SAE.

Table 12: Serious Adverse Events Stratified by Treatment Cohort

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

Nonserious Adverse Reactions

A total of 226 AEs were reported during the IV treatment period and 634 AEs 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.

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 year old subject (-(b)(6)-), a 10 year old subject (-(b)(6)-), and a 48 year old subject (-(b)(6)-). No acute serious bacterial infections were reported during the 12-week period of IV replacement.

6.5 Study 5: 160603 (pivotal phase 3)
Synopsis: HYQVIA was effective in decreasing annualized ASBI rate to <1.0. No serious adverse events were attributed to the product by the investigators, sponsor or FDA.

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 IG 10% administered monthly via the SC route when facilitated by pre-administration of rHuPH20 in preventing ASBI in PI subjects. The secondary objective was to evaluate the tolerability of SC administration of IGI 10% and rHuPH20.

6.5.2 Design Overview
Prospective, open-label, single-arm, phase 3 study in 87 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 IG 10% at 3- or 4-week treatment intervals
Epoch 2: SC treatment with IG 10% after administration of 75 U/g IG 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)**.
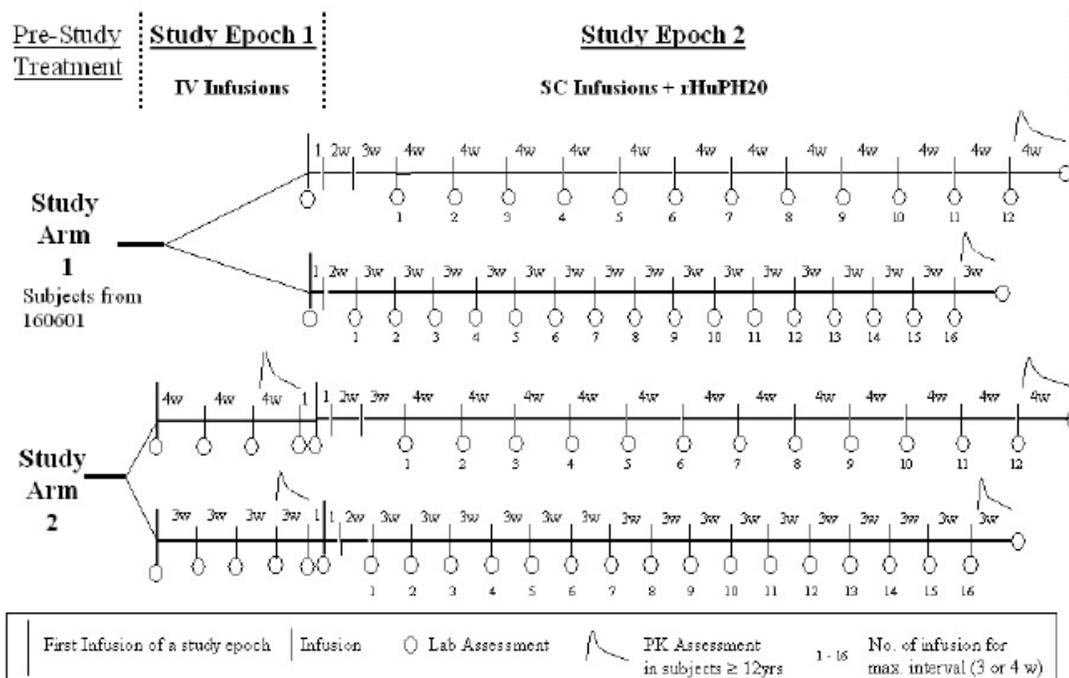
Epoch 1:

- PK assessment (including AUC) of IV IG 10%.
- Subjects who had previously participated in Study 160601 were not included
- Subjects received IG 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, IG trough levels were the only PK parameter evaluated.
- Following the PK assessment, 1 week after a final 3 or 4 week IV dose of IG 10%, Epoch 2 (SC treatment) began.

Epoch 2:

- All subjects were treated with SC IG 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 IG, 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 IG 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
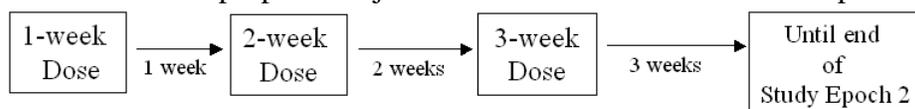
Dose ramp-up for subjects with 4 week treatment interval prior to the study:
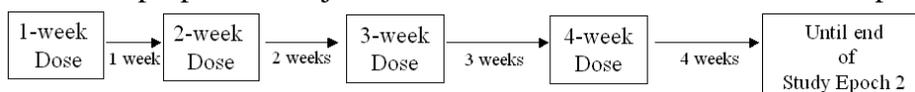
6.5.3 Population
Inclusion Criteria
1. Subject was 2 years or older at the time of screening
2. Written informed consent obtained from either the subject or the subject's legally acceptable representative prior to any study-related procedures and study product administration
3. Subject had been diagnosed 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 IG > 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 aminotransferase (AST) > 2.5 times the upper limit of normal (ULN) for the testing laboratory
3. Subject had persistent severe neutropenia (absolute neutrophil count $\geq 500/mm^3$)
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/μL 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
IGIV 10% (Epoch 1):
- IG 10% IV treatment at 3 or 4 week intervals at the same dose and frequency as they previously received. Trough IG 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.

IGSC 10% (Epoch 2):
- SC treatment with IG 10% at 108% of the IV dose used during Epoch 1 after 75 U/g IG rHuPH20 every 3 or 4 weeks

rHuPH20 SC Infusions:

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

Lot numbers:
IG 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.

Primary endpoint
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 IG after IV or SC administration as measured by AUC for subjects $\geq$ 12 years old and by trough IG levels for subjects 2-12 years old
- Comparison of bioavailability of IG after SC administration of IG 10% without rHuPH20 (Study 160601) and with rHuPH20 (pivotal Study 160603, Study Arm 2) as measured by AUC/trough IG levels

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

Infections: 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 AEs.
- The number of all temporally associated AEs (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 AEs (including and excluding infections).
- The percentage of SC doses of IG 10% and rHuPH20 tolerated at 1 infusion site.
- Proportion of infusions/subjects associated with one or more temporally associated systemic or local AEs (including and excluding infections).
- The proportion of infusions/subjects with one or more local AEs (including and excluding infections), at any time during the study.
- The number of related AEs (including and excluding infections) determined by the investigator divided by the number of infusions/subjects.
- The frequency of dose corrections based on IG trough levels < 4.5 g/L IG for each study epoch.

- The number and rate of all AEs categorized by MedDRA preferred terms, seriousness, relatedness to the study drug, and severity.
- The proportion of infusions associated with one or more related AEs (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 AEs plus the total number of related AEs (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 AEs 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
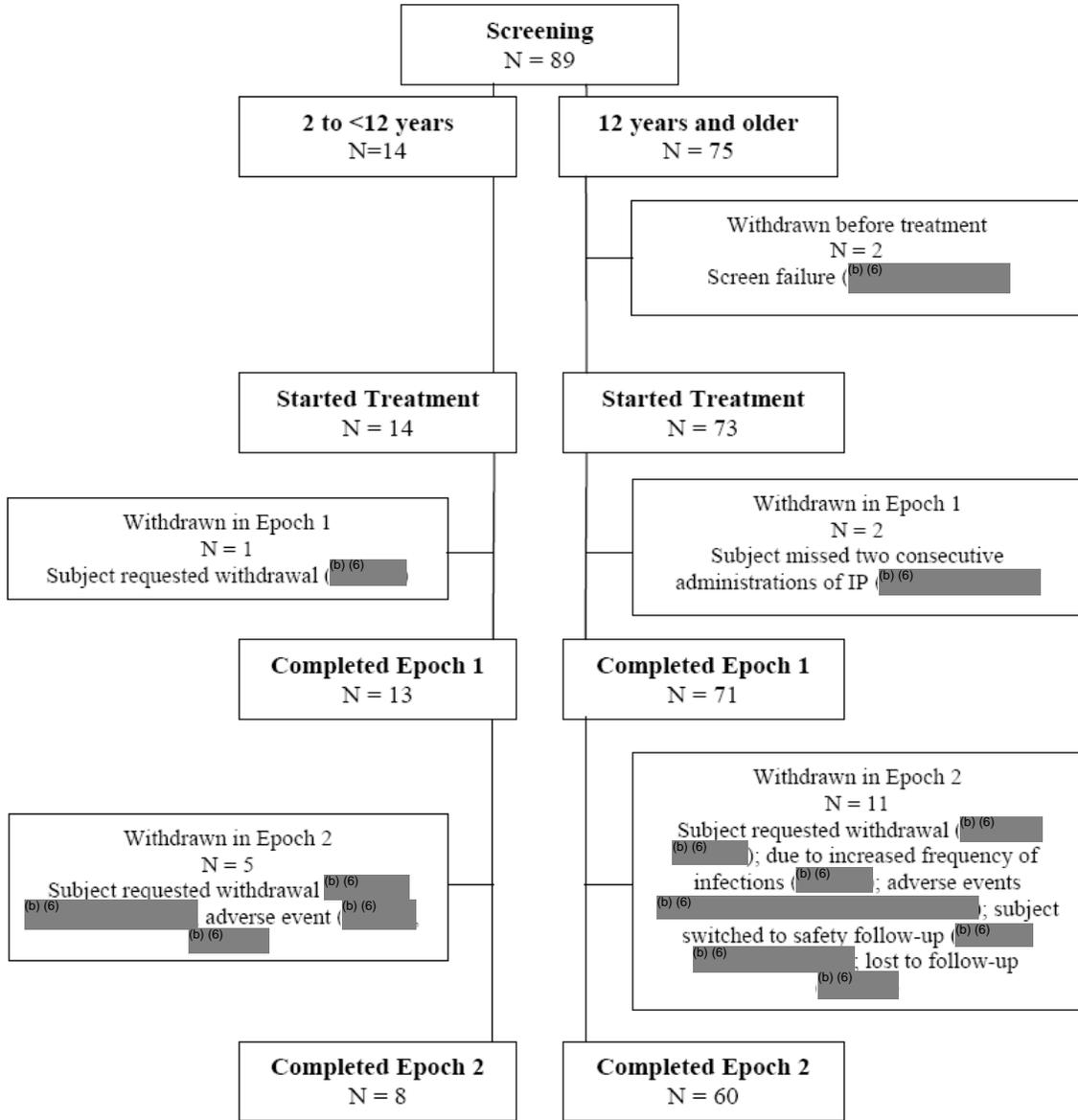
6.5.9 Efficacy
The primary endpoint (validated ASBI, defined as the mean number of validated acute serious bacterial infections per subject per year in the intent-to-treat population) of the study was met: the rate of validated acute serious bacterial infections per year during IGSC, 10% administration 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 Local and Systemic Adverse Reactions
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 Reaction Rates in Epoch 2 subjects
AR rates between subjects naïve to SCIG vs. subjects not naïve to SCIG are presented in Table 13, below. Results were comparable.

Table 13: IGSC Naïve vs. IGSC non-Naïve Datasets
(Source: Table 13, OBE reviewer's memo)

Dataset	Age Group	N	Mean	SD	Min	Median	Max
Duration of treatment [days]							
Non-Naïve IGSC	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
IGSC Naive	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-Naïve IGSC	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
IGSC Naive	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-Naïve IGSC	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
IGSC Naive	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-Naïve IGSC	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
IGSC Naive	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-Naïve IGSC	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
IGSC Naive	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-Naïve IGSC	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
IGSC Naive	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-Naïve IGSC	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
IGSC Naive	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-Naïve IGSC	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
IGSC Naive	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-Naïve IGSC	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
IGSC Naive	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-Naïve IGSC	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
IGSC Naive	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-Naïve IGSC	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
IGSC Naive	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

Serious Adverse Events

None of the serious adverse drug experiences was considered to be related to the product. See Table 14 below for details..

Table 14: Serious Adverse Events

Subject ID	Event	Route of Admin	Additional Comments[4]
-(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 7th 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-

---

[4] SARs in subjects receiving HyQvia was considered "not related" or "probably not related" to the product by the investigator.

			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 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 Petit mal epilepsy	SC	37 y/o with Hx of Grand mal convulsion (APR 2004) received HYQVIA (OCT 2009) and experienced seizures
-(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
Treatment of PI.

7.1.1 Methods of Integration
Except for data integration of a subgroup of pivotal Study 160603 subjects who elected to continue in extension study 160902, none of the data was aggregated.

7.1.2 Demographics
Male and female subjects 2-78 years of age.

7.1.3 Subject Disposition
A total of 213 PI subjects (160602: N=11; 160601: N=49; 160603: N=87; 160902: N=66) were enrolled, including 32 subjects aged 2 to <12 (Study 160601: N=14; 160603: N=14; 160902: N=4). Not all enrolled subjects were unique to a given study. For example, subjects (N=31) from study 160601 were rolled over into pivotal Study 160603 whereas the remaining 160603 subjects (N=56) were recruited *de novo*.

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

7.1.4 Analysis of Primary Endpoint(s): Pivotal Study 160603
HYQVIA was effective in reducing the rate of 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 per subject-year was lower than the rate observed in phase 1 study 160601 using IGSC 10% alone and significantly lower (p<0.0001) than the 1.0 rate threshold considered to provide substantial evidence of efficacy. Compared to IGIV, HYQVIA was able to be administered at the same dosing interval and resulted in similar IG trough levels. HYQVIA demonstrated higher bioavailability as determined by AUC per dose/kg than when infused SC without rHuPH20.

7.1.5 Analysis of Secondary Endpoint(s)
Pivotal Study 160603
(a) Annualized number of hospital days due to infection was slightly lower for IGSC + rHuPH20 subjects than for IGIV, 10% subjects
(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

7.1.6 Efficacy Conclusions
When administered at 108% of the IV dose, HYQVIA resulted in minor reductions in the rate of ASBI per subject per year and comparable trough levels to IGIV 10%.

Compared with IVIG (Epoch 1) at bioequivalent doses, HYQVIA PI subjects >12 years old (N=73; Epoch 2) in pivotal Study 160603 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 little effect, i.e., no difference in (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 (pivotal Study 160603).

Age of subjects ranged from 2 years (pivotal Study 160603) to 78 years of age (pivotal Study 160603). See Table 15, below.

Table 15: Age of Subjects

Study Number	2 to <12 years	≥12 years	≥16 years
160601	14	35	31
160602	0	11	11
160603	14	73	64

8.2.3 Categorization of Adverse Events

Adverse events were stratified by (a) cumulative frequency, (b) intensity (mild, moderate, severe), (c) seriousness (serious or nonserious) and (d) site (local *vs* systemic)

8.3 Safety Results

Across the five studies, there were no deaths.

1. 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).[5] 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.

2. Pivotal Study 160603 (N=87)
    a. Two thrombotic events (one unrelated, one probably unrelated according to the investigator) occurred during treatment with HYQVIA: 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 + rHuPH20 [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 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 + rHuPH20 cohort (infusion site pain, infusion site erythema, infusion site discomfort, headache, infusion site pruritus, infusion site edema, and infusion site swelling).

3. Study 160602
    a. One HYQVIA subject in Study 160602 experienced anaphylaxis immediately after receiving moxifloxacin and > 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)

Fifteen subjects (13 in pivotal Study 160603 and 2 in extension Study 160902) 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 SAEs showed no correlation in Studies 160603, 170901 Part 4, and 161001. In pivotal Study 160603, none of the SAEs was considered to be related to either of the investigational products by the clinical investigators. The most frequently observed AEs attributed to the rHuPH20 were infusion site pain or discomfort, infusion

---

[5] The sponsor indicates in the text ("Serious Adverse Events") of their Final Study Report that only two anemia SAEs were observed.

site erythema, infusion site edema or pruritus, and headache. 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 compared with the "gold standard", IGIV.

Summary of Adverse Reactions (all studies)

Local ARs

- *Studies using HYQVIA vs. IGSC 10% alone in PI subjects and volunteers*
  Except for more frequent local ARs of mild and moderate severity at the end of infusion, PI subjects receiving HYQVIA every 3-4 weeks (pivotal 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.

  Seven 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 IG, 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 10% infusion*
  The frequency of systemic safety events temporally associated with product administration in Study 160603 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 net benefit in using HYQVIA in terms of patient convenience (subcutaneous *vs.* intravenous) and frequency of administration. These benefits may be associated with risks potentially arising from chronic, life-long exposure to rHuPH20.

10. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

See Table, below.

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	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. 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 IG 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, HYQVIA was able to be administered at the same dosing interval and resulted in similar IG trough levels. Compared to SC administration without rHuPH20, HYQVIA demonstrated higher bioavailability as determined by AUC per dose/kg.	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	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. An AERS database search for hyaluronidase 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.	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. 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% + rHuPH20 is only one-third the rate when these same volunteers receive IG 10% + buffer (i.e., without rHuPH20).
Risk Management	Most injection site reactions are mild in severity and resolve relatively quickly and without sequelae. Additional risks attributable to human rHuPH20 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. 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.	A CR letter was issued asking the sponsor to evaluate whether rHuPH20-antibody complexes are capable of fixing complement. This issue was taken before the BPAC in July 2014.

11.2 Risk-Benefit Summary and Assessment

HYQVIA met the FDA definition of efficacy and resulted in a 10-min reduction in median duration of infusion (2.13 vs. 2.33 h) compared with IVIG 10%. Short-term risks were acceptable, but potential long-term risks are unknown.

11.3 Recommendations on Regulatory Actions

Approval.

11.4 Labeling Recommendations

Amended labeling has been submitted according to FDA advice and is acceptable. .

11.5 Recommendations on Postmarketing Actions

An adequately sized PMC safety study of sufficient follow-up duration will be conducted by the sponsor.

.