Cliniical Review Memorandum: BLA STN 125105/708, Baxter's Immune Globulin Infusion (Human) 10%, 10, 25, 50, 100, 200 and 300 mL Solutions for Subcutaneous Administration

DATE: February 21, 2010

FROM: Hon-Sum Ko, Medical Officer, CBER/DH/CRB, HFM-392

THROUGH: Nisha Jain, Chief, CBER/DH/CRB, HFM-392

TO: The File for BLA STN 125105/708

SUBJECT: Clinical Review of Gammagard Liquid, 10%, for subcutaneous administration (Baxter Healthcare Corporation)

Application Type	BLA supplement
Application Number(s)	STN 125105/708
Received Date(s)	4/29/2010
PDUFA Goal Date	2/27/2011
Division / Office	Hematology/Blood
Reviewer Name(s)	Hon-Sum Ko
Review Completion Date	2/18/2011
Applicant	Baxter Healthcare Corporation
Proper Name (Established Name)	Immune Globulin Infusion (Human); previously Immune Globulin Intravenous (Human)
Trade Name	GAMMAGARD LIQUID
Pharmacologic Class	Human immune globulin
Formulation(s), including Adjuvants, etc	10% IgG solution, with excipient of glycine at 0.25M, and pH range 4.6 to 5.1
Dosage Form(s) and Route(s) of Administration	Liquid, for subcutaneous administration (new use) and intravenous administration (previously approved use)
Dosing Regimen	For subcutaneous administration: start at 1.37 x IGIV dose, adjusted to weekly infusion as per clinical response and IgG trough levels
Proposed Indication(s) and Usage	Primary humoral immunodeficiency

Recommendation: Approval recommended

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1 Executive Summary

Baxter submitted a new BLA (STN 125378) to support use of its 10% immune globulin liquid formulation (GAMMAGARD LIQUID) for subcutaneous (SC) administration in the replacement therapy of primary humoral immunodeficiency (PI) disorders. This BLA has been converted to the current efficacy supplement to BLA STN 125105 (supplement 708) because the product is identical to that under BLA 125105.

This submission cross-references CMC data from the original BLA STN 125105/0 and contains no new CMC information. The product is the same as the currently marketed GAMMAGARD LIQUID approved for intravenous (IV) use in the treatment of PI. The clinical data consist of one pivotal study, 160601, to support efficacy and safety in SC use, and in addition, a previous IV use study, 160101, to additionally support product safety. Since Study 160601 contains an IV phase preceding SC use of the product, this part of the study also affords comparison for safety between the two routes of administration.

Pivotal Study Design. Study 160601, entitled "*Tolerability and Pharmacokinetic Comparison of Immune Globulin Intravenous (Human), 10% (GAMMAGARD LIQUID) Administered Intravenously or Subcutaneously in Subjects with Primary Immunodeficiency Diseases*", is a prospective, open-label, uncontrolled, multi-center study in approximately 50 subjects with PI to determine the tolerability and pharmacokinetics (PK) of GAMMAGARD LIQUID under SC administration. The PK of GAMMAGARD LIQUID by SC administration was compared to its PK upon IV administration. The study consisted of 4 parts plus an optional extension:

- Study Part 1: IV infusions of GAMMAGARD LIQUID (q 3 or 4 weeks) for 12 weeks at dose and schedule that the subject was on prior to the study (0.3 to 1 g/kg/3 or 4 weeks).
- Study Part 2: weekly SC GAMMAGARD LIQUID infusions at a dose 130% of the weekly equivalent of the IV dose administered in Part 1 for ≥12 weeks
- Study Part 3a: weekly SC infusions of GAMMAGARD LIQUID for 6 weeks using the "Adjusted Dose" calculated based on the PK assessments from the first 15 subjects aged 12 years and older in Study Parts 1 and 2.
- Study Part 3b: weekly SC infusions of GAMMAGARD LIQUID for 12 weeks at doses further adapted in accordance to the individual's target IgG trough level determined based on the trough level in the IV phase of the study (Part 1).
- Study Extension Part: At the end of Study Part 3b, subjects were offered the opportunity to extend participation in the study to bridge the time (with weekly infusions with the same dose as in Study Part 3b) until Baxter Study 160603 was opened for enrollment (up to 5 months).

Endpoints. The primary endpoint of Study 160601 is based on PK comparison for bioavailability (AUC) between the IV and SC routes of administration. Secondary endpoints include rates for serious acute bacterial infections, all infections, antibiotic use, hospitalizations due to infections, and days out of work, school, day care or inability to perform normal activities.

Efficacy. There were 53 PI subjects screened, with 49 entering Part 1 (IV) of the study, and 47 having had SC treatment (Part 2 and later) with GAMMAGARD LIQUID. A comparison of the area under the curve (AUC) for IV and SC infusions done on the first 15 adult subjects determined that the SC dose required to provide an exposure from SC administration that was not inferior to the exposure from IV administration was 137% of the IV dose. The infection and associated event information can be summarized in the following Table:

Summary of Infections and Associated Events with Subcutaneous Use of GAMMAGARD LIQUID

Number of subjects (efficacy phase)/ Total number of subject-years	47/44
Infections ▪ Serious acute bacterial infections (SABI) ▪ Annual rate of any infections	 0.067* (95% CI 0 to 0.134) SABI/subject year 4.1 (95% CI 3.2 to 5.1) infections/subject year
Antibiotic use§ (prophylaxis or treatment) ▪ Number of subjects (%) ▪ Annual rate	 40 (85.1%) 50.2 (95% CI 33.4 to 71.9) days/subject year
Days out of work/school/ day care or unable to do normal activities ▪ Number of subjects (%) ▪ Annual rate	 25 (53.2%) 4.0 (95% CI 2.5 to 6.1) days/subject year
Hospitalizations due to infections ▪ Number of subjects (%) ▪ Annual rate	 0 (0.0%) 0.0 (95% CI 0.0 to 0.1) days/subject year

*three pneumonia events in 3 subjects

Safety. There were 47 subjects exposed to SC treatment with GAMMAGARD LIQUID, with a total of 2294 infusions and a mean dose between 180 to 190 mg/kg/week over study parts 2, 3a, 3b and extension.

No serious adverse reactions occurred during SC treatment parts of the study. The most common adverse reactions observed with SC treatment (≥5% of study subjects) were local infusion site reactions (e.g., swelling, redness, pain), as well as systemic reactions of headache, fever, fatigue, increased heart rate, increased systolic blood pressure, and upper abdominal pain.

When compared to IV treatment in Part 1, the SC treatment parts of the study offered lower frequency and severity of systemic reactions, but there was a higher frequency of local reactions. There were no pertinent clinical laboratory abnormalities or trends seen in Study 160601.

Of 632 non-serious AEs, the most frequent AEs, regardless of causality, which occurred in ≥5% subjects, are shown below:

AEs, *Excluding Infections* Reported in >5% of Subjects During SC Treatment				
AE	Number of Subjects	Percent of Subjects	Number of Infusions	Rate per Infusion[a]
Infusion site (local) event	21	44.7%	56	2.8%
Headache	23	48.9%	45	2.0%
Nausea	8	17.0%	20	1.0%
Pyrexia	14	29.8%	22	1.0%
Diarrhea	5	10.6%	13	0.6%
Heart rate increased	3	6.4%	12	0.6%
Abdominal pain upper	5	10.6%	12	0.5%
Vomiting	7	14.9%	12	0.5%
Fatigue	7	14.9%	11	0.5%
Blood pressure systolic increase	3	6.4%	9	0.4%
Arthralgia	3	6.4%	9	0.4%
Asthma	6	12.8%	9	0.4%
Myalgia	4	8.5%	9	0.4%
Oropharyngeal pain	6	12.8%	8	0.3%
Ear pain	4	8.5%	5	0.2%
Migraine	4	8.5%	4	0.2%
Aphthous stomatitis	3	6.4%	4	0.2%
Constipation	3	6.4%	4	0.2%
Eczema	3	6.4%	4	0.2%
Musculoskeletal pain	4	8.5%	4	0.2%
Nasal congestion	3	6.4%	4	0.2%
Abdominal discomfort	3	6.4%	3	0.1%
Abdominal pain	3	6.4%	3	0.1%
Contusion	3	6.4%	3	0.1%
Epistaxis	3	6.4%	3	0.1%
Insomnia	3	6.4%	3	0.1%
Lymphadenopathy	3	6.4%	3	0.1%
Pain in extremity	3	6.4%	3	0.1%
Sinus headache	3	6.4%	3	0.1%
Urticaria	3	6.4%	3	0.1%

[a] Rate per infusion= total number of events divided by total number of infusions; rates provided as percentages

The frequencies of local adverse reactions during GAMMAGARD LIQUID subcutaneous treatment are shown below:

Local AEs, *Excluding Infections*[a] Occurring with 1 or More Infusions During SC Treatment	
Infusion site pain	22 (1.0%)
Infusion site hematoma	14 (0.6%)
Infusion site pruritus	6 (0.3%)
Infusion site rash	4 (0.2%)
Infusion site erythema	3 (0.1%)
Infusion site edema	3 (0.1%)
Infusion site hemorrhage	2 (0.1%)
Infusion site irritation	2 (0.1%)
Infusion site swelling	2 (0.1%)
"Infusion related" reaction	1 (0.0%)
Infusion site reaction	1 (0.0%)
Infusion site vesicles	1 (0.0%)
Injection site hematoma	1 (0.0%)
Edema, peripheral	1 (0.0%)
Rash	1 (0.0%)

[a] Rates per infusion are provided as percentages

The overall safety data of GAMMAGARD LIQUID for SC use in Study 160601 are similar to those seen with other approved IGSC products.

Conclusion and Recommendation.

- The data from Study 160601 support the safety and efficacy of GAMMAGARD LIQUID in the SC treatment of PI.
- From a clinical standpoint, this supplement is recommended for approval pending acceptance of labeling revisions by Baxter and resolution of compliance issues at Baxter's Lessines facility in Belgium.

2 CLINICAL AND REGULATORY BACKGROUND

2.1 Disease or Health-Related Condition Studied

- Primary humoral immunodeficiency (PI)

2.2 Available Treatments for Proposed Indication

- Current treatment of PI is replacement therapy with human immune globulin products, usually administered intravenously (IV). There are three marketed products in the U.S. that allow for subcutaneous (SC) administration: Vivaglobin (CSL-Behring), Hizentra (CSL-Behring) and Gamunex-C (Talecris).

2.3 Safety and Efficacy of Pharmacologically Related Products

- The safety profiles and effectiveness of human immune globulin products for replacement therapy of PI have been well documented for the IV preparations. Immune globulin products for SC use should have similar efficacy as the IV preparations as long as adequate dosing can be assured. SC immune globulin differs from IV immune globulin in the safety profile, as there is greater tendency to local infusion site reactions, but lower likelihood of severe systemic reactions.

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

- GAMMAGARD LIQUID has been licensed in the U.S. for IV use in the treatment of PI since 2005, based on a study in the U.S. and a study in Europe. Baxter has explored SC use of this product and filed the current efficacy supplement for SC administration in the same indication. In addition, Baxter is studying combination use of the product with recombinant human hyaluronidase for PI, as well as preparing a ----------(b)(4)----------.
- Although the SC use of GAMMAGARD LIQUID is new, experience on IV use of immune globulin products has accumulated over many years for several indications, including PI, with safety and efficacy well demonstrated (see 2.3)

2.5 Summary of Pre-submission Regulatory Activity Related to Submission

- Baxter submitted a pre-BLA meeting request with FDA in 2009. The meeting was canceled upon FDA responding to the firm's questions and subsequent clarifications. FDA agreed with Baxter in the submission of a new BLA for subcutaneous use of the product, together with new package insert.

2.6 Other Relevant Background Information

- After BLA submission, Baxter has been notified that the submission should have been an efficacy supplement[1] and this was to be rectified by changing the nature of the submission and partial refund of user fees. In addition, as the product for SC use is actually the same as the marketed product for IV use, Baxter may not have separate package inserts for different routes of administration, nor would there be separate packaging for the product for SC use. The established name (proper name) can no longer be Immune Globulin Intravenous (Human), and Baxter proposed Immune Globulin Infusion (Human), which is acceptable. The proprietary name, GAMMAGARD LIQUID, remains unchanged.

[1] See *Guidance for Industry: Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees*

3 ETHICS AND GOOD CLINICAL PRACTICE

3.1 Submission Quality and Integrity

- This supplement has been submitted electronically in compliance with *Guidance for Industry: Providing Regulatory Submissions to the Center for Biologics Evaluation and Research (CBER) in Electronic Format — Biologics Marketing Applications*. The submission is also compliant with ICH guideline M4E, *Common Technical Document for the Registration of Pharmaceuticals for Human Use*, using appropriate numbering within the Modules. An Index provides links to the relevant sections.

3.2 Compliance with Good clinical Practices

- Baxter has attested to ethical conduct of the clinical study 160601 and compliance with Good Clinical Practice, in accordance to 21 CFR Parts 50 and 56, as well as ICH's GCP (E6 Consolidated Guidance).

3.3 Financial Disclosure

- Financial certification and disclosure information (Form 3454) have been submitted. The applicant certifies that there have been no arrangements where the value of the compensation could have been affected by the outcome of the study. A list of Investigators for Study 160601 is included in the "Financial" folder of the original supplement submission.

4 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

4.1 Chemistry, Manufacturing and Controls

- This submission has no new CMC information. CMC information is by cross-reference to the original BLA STN 125105/0.
- The compliance check conducted on Baxter's Lessines facility in Belgium between 1/10/11 and 1/21/11 has pending issues which are being reviewed. The Office of Compliance and Biologics Quality recommends not approving this supplement until the issues are resolved.

4.2 Assay Validation

- See Clinical Pharmacology review memo on assay validation for IgG in clinical samples.

4.3 Statistics

- See Dr. Chinying Wang's memo. Dr. Wang has verified the efficacy data presented by Baxter for SC use in the draft package insert. There are no statistical issues with the safety data.

4.4 Preclinical Pharmacology/Toxicology, including Reproductive Toxicology

- There are no preclinical pharmacology/toxicology or reproductive issues; the supplement does not include a preclinical pharmacology/toxicology section, but cross-references to the original BLA STN 125105/0.

4.5 Clinical Pharmacology

- See Dr. I. Mahmood's memo. The pivotal trial is a PK study and primary efficacy is based on PK comparison of SC use of GAMMAGARD LIQUID with IV use. Dr. Mahmood finds the pharmacokinetic data acceptable and supportive of product efficacy. Together with the Statistical Reviewer, Dr. Mahmood has also reviewed the

dose-adjustment methodology proposed for labeling and worked out the derivation of target IgG trough level for SC administration.

4.6 Pharmacovigilance

- See Dr. A. Ou's memo. The pharmacovigilance plan (PVP) proposed by Baxter needed strengthening with quarterly periodic reporting for the first 3 years upon approval for SC use, together with enhanced reporting for adverse events with off-label use (immune thrombocytopenic purpura) and for hemolytic events. Baxter has agreed and revised the PVP.

5 SOURCES OF CLINICAL DATA

5.1 Table(s) of Studies/Clinical Trials

- There is one clinical trial supporting this supplemental application, 160601. Baxter has also used Study 160101, the U.S. pivotal trial supporting licensure of the product for IV use in 2005 to support safety of the product. The following is a Table on the design of Study 160601.

	Study Part 1	**Study Part 2**	**Study Part 3a**	**Study Part 3b**
IG Route	**IV**	**SC**	**SC**	**SC**
Administration intervals	3 or 4 weeks (± 2 days), last infusion (No. 4 or 5, depending on treatment intervals in Part 1): 1 week	Weekly (± 1 day) (To begin one week (± 1 day) after the last infusion of Study Part 1)	Weekly (± 1 day)	Weekly (± 1 day)
Dose	300 – 1,000 mg/ kg BW/ 4 weeks, depending on pre-study dosing	Dose calculation: If subject had been on a 4-week treatment interval in Part 1, 130% of the 4-week IV dose was divided by 4 to calculate the weekly SC dose. If subject had been on a 3-week interval in Study Part 1, 130% of the 3-week IV dose was divided by 3 to calculate the weekly SC dose.	The Adjusted Dose as calculated from PK derived from the first 15 subjects aged ≥12 in Part 1 and Part 2 was used.	Dose was either the same (Adjusted Dose) as in Study Part 3a (trough level inc within 15% of expected in) or the Individually Adapted Dose (inc in trough levels not within 15% of expected inc).
PK evaluation in subjects aged ≥12: • AUC, half-life (for IV treatment only), • clearance, C_{max}, C_{min}, T_{max} (for SC treatment only)	After IV infusion No. 4 (for 3-week treatment interval) or after IV infusion No. 3 (for 4-week treatment interval)	After SC infusion No. 8	No PK evaluation	After SC infusion No. 8, at Adjusted or Individually Adapted Dose
	Sampling before infusion (ie, trough level of previous infusion) and at 30' (±3') after infusion completion, and on Days 1, 4, 9 (±1 day), 14 (±2 days) and 21 (±2 days, = before next infusion in 3-week treatment interval) and Day 28 (±2 days, = before next infusion in 4-week treatment interval) after infusion.	Sampling before infusion (trough level of previous infusion) and on Days 1, 3, 5, and 7 (= blood draw before next infusion)		Serum samples were collected before infusion (trough level of previous infusion) and on Days 1, 3, 5, and 7 (= blood draw before next infusion)
IgG trough levels tested in all subjects.	On the day of each IV infusion.	On the days of SC infusions No. 1, 5, and 9*.	On the days of SC infusions No. 1 and 5.	On the days of SC infusions No. 1, 5, and 9* and at End-of-Study Visit.

*For subjects aged ≥12, there would be an additional sampling for IgG trough level on days of SC infusion No. 8 (sections 9.1.2.2 and 9.1.4.2 of study report)

5.2 Review Strategy

- The review of this supplement 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*. The datasets are in SDTM-like format and jReview has also been used to explore the datasets.

5.3 BLA/IND Documents which Serve as the Basis for the Clinical Review

- This review is based primarily on Module 5 (Clinical) of the submission, together with clinical summaries in Module 2, and administrative documents in Module 1, including labeling. The review also includes Baxter's responses to Information Request after mid-cycle review (submitted 11/15/10) and subsequent discussions (submitted 1/11/11, 1/14/11, 1/26/11, 2/1/11, and 2/11/11).

5.4 Literature Reviewed

- The literature reviewed includes articles submitted in Module 5 of this supplement.

6 DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Background

- Individuals with PI require replacement therapy with immune globulins to prevent or reduce the severity of infections. The majority of immune globulin products in the United States are licensed for IV administration. SC use of immune globulins has become more widespread and there are three approved products in the U.S. for SC administration: Vivaglobin (CSL-Behring), Hizentra (CSL-Behring) and Gamunex-C (Talecris). After adequate training by healthcare professionals, subcutaneous administration of immune globulin products (IGSC) can easily be performed in home therapy.
- GAMMAGARD LIQUID is a ready-to-use IgG preparation with intact Fc regions licensed for IV replacement therapy of PI. It contains no added sugars, sodium, or preservatives, and is formulated with glycine for stabilization at a pH of 4.6 to 5.1. Its manufacturing process employs a modified Cohn-Oncley cold ethanol fractionation procedure and further purification by a continuous process through the use of weak cation and weak anion exchange chromatography. Three dedicated virus reduction steps are included in the purification: solvent/detergent (S/D) treatment, nanofiltration, and incubation at low pH/elevated temperature in the final formulation.
- Two clinical studies evaluating the safety, efficacy and pharmacokinetics of GAMMAGARD LIQUID by the IV route in PI patients were conducted in the US (Baxter Study 160101) and Europe (Baxter Study 160001).

Study 160101 was a phase 3, multi-center, randomized, uncontrolled evaluation of safety and efficacy in 61 patients >2 years of age in the U.S. GAMMAGARD LIQUID was administered at a dose of 300-600 mg/kg at 3 to 4 week intervals for at least 12 months.

- None of the 61 treated subjects reported validated acute serious bacterial infections (bacteremia/sepsis, bacterial meningitis, osteomyelitis/septic arthritis, bacterial pneumonia, and bacterial visceral abscess) during the study. The annualized rate of validated acute serious bacterial infections was less than the acceptable rate of <1 infection per patient per year.
- Four other validated bacterial infections commonly occurring in PI subjects (1 case of urinary tract infection, 1 case of gastroenteritis, and 2 cases of otitis media) were reported, none of which were serious or severe, or resulted in hospitalization. The mean rate of these validated bacterial infections commonly occurring in PI subjects was 0.07 per subject per year. For non-validated infections, the

mean rate was 3.4 infections per patient per year. These consisted primarily of recurrent episodes of commonly observed infections in this patient population; the most frequent being: sinusitis, nasopharyngitis, bronchitis, upper respiratory tract infections, and urinary tract infections.

- PK data demonstrated that the dosing regimens maintained serum trough IgG levels considerably >450 mg/dL. Median total IgG trough levels varied from 960 to 1120 mg/dL.
- A total of 826 infusions of GAMMAGARD LIQUID were administered. The median number of infusions administered per subject was 13. The adverse event profile of GAMMAGARD LIQUID in this study is consistent with that in other immune globulin studies on IV administration (see Section 8).

Study 160001 was a phase 2, multi-center, open-label evaluation of PK, efficacy and safety in 22 patients aged ≥18 with PI in Europe, who received infusions of 300-450 mg of IgG/kg at 3-week intervals for ~ 9 months.

- A total of 59 infection episodes started at or after the first infusion with GAMMAGARD LIQUID. None of them were serious. The severity was reported as mild for 39, and as moderate for 20 episodes. The median infection rate per month was 0.48.
- Median steady state trough level of total IgG was 851 mg/dL.
- There were 194 infusions of GAMMAGARD LIQUID, with 3 SAEs observed during treatment, none assessed as being related to product by the investigators. There were 14 non-serious AEs assessed as being related to product use in 7 subjects. The most commonly reported "related" AEs occurring during treatment were urticaria (N=6, observed in 1 subject), headache (N=2), and pyrexia (N=2). Baxter states that the proportion of infusions followed by AE(s) was low (4%).

6.2 Pivotal Trial in Support of SC Administration of GAMMAGARD LIQUID in the Treatment of PI

The pivotal trial presented in this supplement, Baxter's Study 160601, is a phase 3 study conducted under ------(b)(4)------, with the aim of evaluating the PK, efficacy and safety of GAMMAGARD LIQUID upon SC administration in PI patients.

Protocol 160601. Tolerability and Pharmacokinetic Comparison of Immune Globulin Intravenous (Human), 10% (GAMMAGARD LIQUID) Administered Intravenously or Subcutaneously in Subjects with Primary Immunodeficiency Diseases. (first subject enrolled: 10/03/07, and last subject completed: 07/08/09)

Baxter states: "This study was conducted in accordance with the standards of Good Clinical Practice (GCP) in effect at the time of the study."

Investigators and Study Centers:

Site #	Investigator	Site	Address
34	Melamed, Isaac	1st Allergy & Clinical Research Center	7286 S. Yosemite St., Suite 180 Centennial, CO 80112
39	Stein, Mark	Allergy Associates of the Palm Beaches	840 US Highway 1, Suite 235 North Palm Beach, FL 33408
40	Wasserman, Richard	Pediatrics Allergy/Immunology Assoc., PA	7777 Forest Lane, Suite B332 Dallas, TX 75230
50	Kobrynski, Lisa	Emory Children's Center	2015 Uppergate Dr., Atlanta, GA 30322
52	Buckley, Rebecca (formerly Larry Williams >formerly Laurie Lee)	Duke University Medical Center	Box 2898, Rm 363 Jones Building Research Drive, DUMC Durham, NC 27710
53	Roberts, Robert L.	UCLA Medical Center Dept of Pediatrics	Dept Pediatrics, Rm 12-430 MDCC UCLA Medical Center, 10833 Le Conte Avenue Los Angeles, CA 90095
54	Strausbaugh, Steven D. (formerly Melvin Berger)	University Hospitals of Cleveland	Pediatric Pulmonary Division Rainbow Babies and Children's Hospital 11100 Euclid Ave, Cleveland, OH 44106
55	Grant, Andrew	University of Texas Medical Branch	Medical Research, 301 University Blvd. Galveston, TX 77555-1083
58	Routes, John M.	Medical College of Wisconsin	9000 W. Wisconsin Ave. Milwaukee, WI 53226-4874

6.2.1 Protocol of Study 160601

Objectives: To evaluate the tolerability of SC administration of GAMMAGARD LIQUID and the PK of immunoglobulin G (IgG) following SC use of GAMMAGARD LIQUID in subjects with PI. A further aim was to evaluate efficacy in terms of acute serious bacterial infections.

Study Design: Prospective, open-label, uncontrolled, multi-center study in ~50 subjects with PI to determine tolerability and PK of GAMMAGARD LIQUID SC administration. The PK of GAMMAGARD LIQUID administered SC was compared to its PK when administered IV. See below for enrollment strategy (under "Number of Subjects" section)

- The study was administered centrally by the Global Clinical and Medical Affairs Department at Baxter Healthcare Corporation (Westlake Village, CA, US). On-site data and compliance monitoring was carried out by contract clinical research associates ----------(b)(4)----------, with oversight provided by Baxter. Testing of blood and urine was done at a ---------- ----------(b)(4)---------- including safety lab and PK assessments.
- ----------(b)(4)---------- provided the home care nurse services and central pharmacy services. Various SC infusions could be administered at the clinical study site or at home. When given at home by the subject/parents, a home care nurse was there to observe or assist with infusions as necessary, collect vital signs and document total dose given, infusion rate, rate changes, and occurrence of AEs. The ----------b)(4)--- provided supplies for the home care nurse to deliver to the subject's home. Packaging and distribution of the investigational product were done by ----------(b)(b)----------.

The study consisted of 4 parts plus an optional Study Extension Part. The four parts of the original study (Parts 1, 2, 3a and 3b) have been summarized above in Table format (see Section 5.1).

Study Part 1:
Subjects received IV infusions of GAMMAGARD LIQUID (q 3 or 4 weeks, ± 2 days) for ***12 weeks*** at the dose and schedule that they were on prior to the study (0.3 to 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 (± 1 day) after a further regular IV treatment (i.e., 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 recombinant human hyaluronidase [rHuPH20]), 3 infusions of GAMMAGARD LIQUID were administered at 4-week intervals (± 2 days).
- 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 (± 2 days).
- 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 (± 2 days) were administered.

Study Part 2:
Subjects received weekly (± 1 day) 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 ± 1 day after the last IV infusion and until the first 15 subjects aged ≥12 years had completed PK assessment with results available. Trough levels were evaluated monthly and blood for **full PK analysis** taken from subjects aged ≥12 years following the 8th infusion. ***PK analysis was used to determine the "Adjusted Dose" to be administered in Study Part 3a for all subjects, including subjects aged 2 to <12.*** The Adjusted Dose was expressed as a ratio of the weekly IV dose.

The expected increase in IgG trough levels during Part 3a relative to the trough level during IV infusions (Part 1) was estimated and a nomogram was derived to individually adapt the dose in Study Part 3b, in case the expected IgG trough level increase was not attained in Study Part 3a.

Study Part 3a:
Subjects were treated SC for ***6 weeks*** using the "Adjusted Dose" calculated based on the PK assessments from the first 15 subjects aged 12 years and older in Study Parts 1 and 2. As a single Adjustment Factor was used for deriving the SC dose from the weekly IV dose, further dose correction might be required for individual subjects. To determine whether each subject received an adequate dose, trough levels were determined at Week 5 (after 4 weekly infusions in Study Part 3a). The trough levels on SC (Study Part 3a) and IV (Study Part 1) treatment were compared over the next 2 weeks, during which the subject received 2 more infusions of the "Adjusted Dose". If the increase in trough levels was not within 15% of the expected increase, the dose was individually adapted ("Individually Adapted Dose")

using an Individual Adaptation Factor read from the nomogram derived from the analysis of the first 15 PK subjects in Study Part 2.

Study Part 3b:
Subjects received weekly SC infusions for ***12 weeks*** at doses determined as follows:
- If the increase in trough levels was within 15% of the expected increase over the trough level determined in Part 1, the subject would receive the same "Adjusted Dose" as during Study Part 3a;
- If the increase in trough levels was not within 15% of the expected increase over the trough level in Part 1, the subject would receive the "Individually Adapted Dose".

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

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

Product Administration:
Each subject was to receive product from a single batch for the duration of the study, except for the optional Study Extension Part. Seven lots of GAMMAGARD LIQUID were used in this study: LE12G011AC, LE12G011AD, LE12G145AC, LE12G174AC, LE12H163AB, LE12H203AB, and LE12H309AC.

IV Administration of GAMMAGARD LIQUID (Study Part 1)
- The dose to be infused was 0.3-1 g/kg BW q3-4 weeks depending on the subject's previous dose and previous treatment interval. The dose (on a gram IgG/kg BW basis) was to be kept constant during the whole study part. If the subject's BW changed by more than 5%, the dose administered was to be adjusted accordingly.
- 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 AE of at least moderate severity[2] occurred, the infusion rate was to be reduced to the rate immediately below that at which the AE occurred. If the AE resolved in response to reduction in rate, the infusion was to continue at the adjusted rate for the remainder of the infusion. If the AE continued, the infusion was to be stopped and the AE treated in accordance with the standard of care at the investigational site. The infusion could be restarted at a lower rate once the AE 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 AEs occurred within 72 hours after completion of each infusion (also to be logged in the subject diaries). AEs that occurred after the 72-hour phone follow-up contact were also to be logged in the subject diaries.

Comments
- The protocol for 160601 was amended on November 16, 2007 to allow for entry of subjects with previous use of IGSC in combination with rHuPH20. It is not clear from the datasets submitted which patients had previous IGSC alone and which had the combination. Baxter had a submission on 1/11/11 indicating that 7 subjects from Study 160602 (IGSC and rHuPH20) were enrolled and treated in Study 160601. They had completed Study 160602 4 to 6 months prior to starting Study 160601 and reverted back to their previous IV regimen (no rHuPH20) in the interim. They were included in the group of SC-experienced subjects, but not evaluated separately because the number of subjects was too small for useful analysis.
- It is also not clear from the protocol how subjects previously on IGSC were transitioned back to IGIV in Study Phase 1. In a submission dated 1/11/11, Baxter explained that when Study 160601 began, prior SC dosing was the same as was given IV, and so the Phase 1 IV dose was either the previous IV dose or the SC dose adjusted to a 4 week interval. Subjects were not on an adjusted SC dose and no algorithm was needed to recalculate the IV dose back for Phase 1 from the SC dose or the SC dose with rHuPH20.

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

[2] Adverse event severity was graded as (a) Mild: transient discomfort not interfering significantly with normal functioning and resolving spontaneously or with minimal intervention, (b) Moderate: limited function impairment and can require intervention but no sequelae, and (c) Severe: marked impairment of function and can lead to temporary inability to resume usual life pattern; producing sequelae, which require prolonged intervention.

determined in Study Parts 1 and 2, or dose individually adapted for Study Part 3b, if necessary, according to IgG trough level increase in Study Part 3a). The subjects could also be treated SC in the optional Study Extension Part, where the dose would be the same as in Part 3b.

- The first SC infusions were to be administered at the study site (number of infusions at study site was left to the discretion of the investigator). Afterwards, treatment could be performed at home by subject or parents after documented training to the satisfaction of the Investigator. Adjustments in infusion rate were only permitted under direct supervision at the study site *or* by home care nurse trained in SC infusions. Home treatment was only permitted under observation by a home care nurse, who also completed the documentation and signed for it in the subject's diary.
- Infusions were conducted with a portable IV pump or syringe pump capable of holding syringes of up to 60 mL volume. 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 AEs that might have occurred (to be logged in the diaries). AEs occurring after phone contact were also to be logged in the diaries.
- Multiple infusion sites could be used simultaneously. Up to 10% overage per site was permitted to avoid starting a new site for only a few milliliters. Up to 30 mL could be administered per infusion site for subjects with BW of ≥40 kg, and 20 mL per infusion site for subjects with BW <40 kg. The initial infusions were to start at 5 mL/h/infusion site and could increase to a maximum of 20 mL/h/site for subjects with a BW of ≥40 kg and to a maximum of 15 mL/h/site for subjects with a BW <40 kg, as tolerated (i.e., until the occurrence of AE of at least moderate severity).
- If AE 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 AE occurred. If the patient tolerated the first 1 or 2 infusions at the scheduled rate, subsequent infusions could be started at 10 mL/h/site and increased every 15 to 20 minutes to a maximum of 30 mL/h/site for subjects with a BW of ≥40 kg and 20 mL/h/site for subjects with a BW <40 kg. The decision to increase the rate was up to the subject and investigator and was to be made at the study site or under the supervision of a home care nurse trained in SC infusions.

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

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

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

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

Number of Subjects:

Planned:

~50 subjects with PI were planned. The evaluable population was to include -

- ~23 subjects with PI aged ≥12 years (including a minimum of 4 subjects aged between 12 to <16) previously been treated with IV administration of immune globulin; and
- ~12 subjects aged 2 to <12 years previously treated with IV administration of immune globulin; while
- ~12 subjects aged 2 years and older previously treated with SC administration of immune globulin could be enrolled at the discretion of the investigator and the Sponsor.

Analyzed:

- A total of 49 subjects who received treatment were included in the safety analysis: 14 were aged 2 to <12 years old, and 35 were ≥12 (of these 35, 4 were between 12 and <16 and 4 were ≥65).
- A total of 38 subjects were naïve to IGSC replacement therapy: 14 in the lower age group (2 to <12) and 24 in the higher (≥12).

Eligibility Criteria:

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 immunoglobulin treatment IV or SC with rHuPH20: at mean intervals of 21 ± 3 days or 28 ± 3 days, or SC at mean intervals of 6 - 15 days over at least 3 months pre-study, at a dose of 0.3-1 g/kg BW/4 weeks.
3. Age of ≥2.
4. Serum trough level of IgG >4.5 g/L at last documented determination.
5. Negative serum pregnancy test for any female subject of childbearing potential.

6. Female subjects of childbearing potential agreeing to practice birth control measures for duration of study.

Exclusion Criteria

1. Positive at enrollment or screening 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 upper limit of normal for the testing laboratory
3. Neutropenia (defined as an ANC $\leq$1,000/mm^3)
4. Serum creatinine levels >1.5 x upper limit of normal 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 (deep vein thrombosis, myocardial infarction, cerebrovascular accident)
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), immune serum globulin (ISG) preparation, or albumin within the 6 months prior to study entry
10. Ongoing history of hypersensitivity or persistent reactions (urticaria, breathing difficulty, severe hypotension, or anaphylaxis) following immune globulins (IV or SC), and/or ISG infusions
11. IgA deficiency and known anti-IgA antibodies
12. Receiving antibiotic therapy for treatment of infection within 7 days prior to entry
13. Participation in another clinical study involving investigational product or device - with the exception of Baxter Study 160603 - within 28 days prior to study enrollment
14. Bleeding disorders or use of anti-coagulation therapy

Withdrawal Criteria

- Any subject could voluntarily withdraw informed consent for any reason at any time. The investigator could withdraw any subject if, in his/her judgment, continued participation would pose unacceptable risk for the subject. The investigator was to provide the Sponsor with a written account of reasons for early withdrawal. In this event, all unused investigational product provided to the subject was to be returned to study site.
- Subjects could be withdrawn from further participation for failing to comply with requirements of the protocol.
- For subjects who prematurely terminated the study, every effort was to be made for the subject to complete the End-of-Study Visit. Evaluations to be performed at this visit included physical examination, interval medical history, concomitant medication use, collection/review of diary, occurrence of AEs, and clinical lab assessment.
- For premature termination due to AE, clinical and/or laboratory investigations beyond the scope of the required study observation could be performed as part of the evaluation of the event. These investigations would take place under the direction of the investigator in consultation with the Sponsor. If applicable, the details of the outcome were reported to the appropriate regulatory authorities by the Sponsor.

Criteria for Evaluation:

Pharmacokinetics:

Primary Endpoint:

- In subjects aged 12 years and older, bioavailability of IgG after administration of GAMMAGARD LIQUID, via IV, SC, and SC at an Adjusted/Individually Adapted Dose, as measured by area under the IgG concentration versus time curve (AUC) per week
- In subjects aged 2 to <12 years, bioavailability of IgG after administration of GAMMAGARD LIQUID, IV, SC and SC at an Adjusted/Individually Adapted Dose, as measured by trough levels of IgG

Secondary Endpoints:

- In subjects aged 12 years and older
  - trough levels of IgG, and levels of antibody to tetanus, *H. influenzae*, measles and hepatitis B for IV and SC treatment in Study Parts 1, 2, 3a and 3b.
  - IgG half-life (IV administration only), clearance (Cl), concentration maximum (Cmax), concentration minimum (Cmin), time to Cmax (Tmax; for SC treatment only)
- In subjects aged 2 to <12 years
  - trough antibody levels to tetanus, *H. influenzae*, measles, and hepatitis B for IV and SC treatment

Efficacy:

- Infections were to be reported as adverse events (AEs) and coded as Infections and Infestations in MedDRA. They were reported as a separate variable. Serious acute bacterial infections were defined according to *FDA's Guidance for Industry* as bacteremia/sepsis, bacterial meningitis, osteomyelitis/septic arthritis, bacterial pneumonia and bacterial visceral abscess.
- Rates of infections and serious acute bacterial infections were to be calculated per subject.

Safety:

Safety analyses were to be performed for the (a) full safety dataset, (b) subset of subjects naïve to IGSC and (c) subset of subjects with prior experience with IGSC. Separate analyses were to be done for IV and SC administrations in all study parts (1, 2, 3a 3b, and Study Extension Part).

Primary Safety Endpoint:

- Ability to tolerate GAMMAGARD LIQUID administered IV or SC. Tolerability was measured as 4 numbers: (a) proportion of subjects and (b) proportion of infusions (for infusion proportions - estimation using the negative binomial model) 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.

Secondary Safety Endpoints:

- Total number of AEs that begin during infusion or within 72 hours of completion of an infusion ("temporally associated") divided by the total number of infusions
- Total number of AEs determined by the investigator to be related to the investigational product that occur at any time during the study ("related") divided by the total number of infusions
- Frequency of dose adjustments based on IgG trough levels <4.5 g/L, if any, for each study part
- Proportion of subjects reporting ≥1 moderate or severe AEs that begin during infusion or within 72 hours of completion of an infusion
- Number of AEs categorized by MedDRA preferred terms, seriousness, relatedness to the investigational product, and severity
- Rate of AEs defined as the number of AEs categorized by MedDRA preferred terms, seriousness, relatedness to the investigational product, and severity, divided by the number of infusions
- Proportion of IV and SC infusions associated with ≥1 AEs related to the investigational product
- Proportion of IV and SC infusions associated with ≥1 AE that begin during infusion or within 72 hours of completion of infusion
- Proportion of IV and SC infusions associated with ≥1 AEs excluding infections that begin during infusion or within 72 hours of completion of infusion
- Proportion of IV and SC infusions associated with ≥1 systemic AE excluding infections that begin during infusion or within 72 hours of completion of infusion
- Proportion of IV and SC infusions associated with ≥1 local AEs (coded as Application Site Disorders in MedDRA) that begin during infusion or within 72 hours of completion of infusion

Statistical Methods:

Sample Size: Sample size considerations were based on PK assumptions. These are addressed by Dr. Iftekhar Mahmood.

Pharmacokinetics and Pharmacokinetic Equivalence: See review by Dr. I. Mahmood.

- Baxter also had exploratory analyses of AUCs vs. IgG trough levels, including xy-plots of AUC ratios vs. IgG trough level ratios with IV and SC administration and linear/non-linear regression analyses as appropriate of these ratios. The aim was to investigate the extent to which IgG trough levels could be used to guide dose adjustments aiming at providing comparable AUCs.

Infections: Monthly rate of infections and of serious acute bacterial infections were calculated per subject. Point estimates and confidence intervals for the annual rates were calculated using a Poisson model.

Seasonal Effect Analysis: In addition to the analyses specified in the SAP, Baxter did two types of sensitivity analyses for infections to address the potential bias due to seasonal imbalances.

- An analysis by season: the year was divided into 4 meteorologic seasons for the northern hemisphere as: winter=December, January, February; spring=March, April, May; summer=June, July, August; fall=September, October, November. The infection rate per season was calculated by the number of infections per season divided by the number of observation days per season. The overall rate, accounting for season, was then calculated as the average of the 4 seasonal rates. For comparison, the overall rate disregarding season was calculated as the number of infections divided by the number of observation days. For the sake of simplicity, the sensitivity analysis used crude rates whereas the pre-specified analyses used a Poisson model accounting for the different lengths of observation per subject. The rates of the sensitivity analyses should therefore be compared to each other (winter, spring, summer, fall; overall rate accounting for season; overall rate disregarding season), but not to the results of the pre-specified analyses.
- Analysis was performed on the first 365 days following the first SC infusions in the 26 subjects who had been treated subcutaneously for 1 year (or longer). While being a subset of the study population, seasonal balance for each subject was achieved by selection of the data.

Safety: Separate analyses were performed as described in the primary and secondary safety endpoints for the (a) full safety dataset, (b) subset of subjects naïve to immune globulin SC therapy and (c) subset of subjects with prior experience with SC therapy. All safety analyses were performed for the 3 datasets. Separate analyses were also to be done for IV and SC administrations in all study parts. The primary and secondary safety endpoints are described above under Criteria for Evaluation. Descriptive statistics were used for other safety data, including changes in vital signs.

Interim Analysis: There was an interim analysis of the PK and IgG trough levels from Parts 1 and 2 of the first 15 subjects aged ≥12 years to determine the "Dose Adjustment Factor", "Expected IgG Trough Level

Factor" and the nomogram for "adjusting" dose in Part 3a and individually "adapting" dose in Part 3b. The interim analysis had in 3 steps:

- The dose that would have resulted in equal AUCs per week was estimated for each of the 15 subjects in the interim analysis based on the observed AUCs in Study Parts 1 and 2. A robust estimate (eg, trimmed mean) was used to identify the Dose Adjustment Factor.
- The IgG trough levels expected for the 15 subjects in the interim analysis in Study Part 3a were predicted. A robust estimate (e.g., trimmed mean) was used to identify the Expected IgG Trough Level Factor.
- The relationship between the dose needed for equal AUC and the predicted deviation from the IgG trough levels was explored to derive the nomogram. In the simplest case, a linear regression model could be sufficient, but in general, a monotonic, non-linear regression model was required.

The dataset used for the interim analysis contained a total of 15 subjects aged ≥12 (Subjects ----------(b)(6)----------. Ten (10) subjects were female and 5 were male; 2 subjects ---------(b)(6)------- were on 3-weeks IV infusion intervals, and the remaining 13 subjects were on 4-week IV infusion intervals.

Changes in the Conduct of the Study or Planned Analyses: The original protocol was dated 3/20/07. Four amendments to the study protocol were performed. The first amendment of 07/03/07 was made prior to subject enrollment, based on FDA's pre-IND input. Subsequent amendments are as follows:

- Amendment 2: 16 NOV 07: Major changes to the previous version of the protocol including those suggested by FDA in a teleconference on 02 OCT 2007 upon IND submission.
- Amendment 3: 04 JUN 08: Replacement of ">2 to <12 years" by "2 to 12 years" and change in sample size to include ~ 50 subjects with ~ 23 subjects aged ≥12 years (including 4 subjects between 12 and <16 years), who had previously been treated with immune globulin IV therapy, and ~ 12 subjects aged 2 to <12 years previously treated also via the IV route, as well as ~12 aged ≥2 years having previously received SC therapy at the discretion of the investigator and the Sponsor. In addition, the upper limit of the pre-study IV dose was raised to 1 g/kg/4 weeks to include subjects on doses ≤1 g/kg/4 weeks. It was specified that observable swelling following the SC infusion of GAMMAGARD LIQUID not causing discomfort was not to be considered an AE, because infusion of large volumes of liquid into the SC space would always be expected to cause a degree of swelling.
- Amendment 4: 13 AUG 08: This amendment allows SC treatment with GAMMAGARD LIQUID until initiation of follow-up study (160603) by adding an optional Study Extension Part lasting for up to ~5 months.

  Changes in Planned Analyses
  - General. In addition to Study Parts 1, 2, 3a, and 3b mentioned in the statistical analysis plan (SAP), the extension phase was analyzed as a separate study part.
  - Subgroups for Age. The age group of 2 to <5 years was merged with the age group of 5 to <12 years because only one subject was younger than 5 years of age. For some analyses, additional subgroups of "12 to <16 years" and of "65 years and older" were analyzed in addition to the SAP-specified subgroups for age. These analyses were limited to the full dataset (FSDS) as only 4 subjects were in the additional age groups.
  - Primary Safety Endpoints. Analyses of the primary safety endpoints used a binomial model rather than the negative binomial model because SAS procedure GENMOD failed to converge for some of the study parts and datasets. For consistency and comparability of the results, the binomial model was used throughout.
  - Secondary Safety Endpoints. Rates of adverse events per infusion were calculated per SAP as the number of AEs divided by the number of infusions of the subject. These rates relating to each subject were further summarized by medians over the set of subjects in the study part and dataset.
  - Analysis of Serious Acute Bacterial Infections. Serious acute bacterial infections were reported on the CRF throughout the study, but the observation times in the individual study parts would have been too short to warrant statistical analysis. While this assessment remained unchanged for the 3 months of IV treatment (Study Part 1) where no serious acute bacterial infection was reported, the combined SC study parts (Study Parts 2, 3a, 3b, and Extension) during which 3 serious acute bacterial infections occurred, allowed for a formal analysis at least for the full dataset (FSDS).

6.2.2 Results

6.2.2.1 Study Subjects

Disposition of Subjects. A total of 53 subjects were screened for the study at 9 study sites; of these, 4 withdrew before treatment:

- death (Subject ---(b)(6)--
- screen failure (Subject ---(b)(6)--
- subject request (Subject ---(b)(6)--
- subject request due to long commute to study site (Subject ---(b)(6)--

Among the 49 subjects who received treatment in the study (Full Safety Dataset [FSDS]), between 2 and 13 subjects were enrolled and treated per study site.

Of the 49 subjects enrolled and treated, 14 were aged 2 to <12 years and 35 were aged ≥12 years. Five (5) of them terminated the study prematurely: 4 were naïve and 1 had previously IGSC therapy –

- During Study Part 1, one subject in the 2 to <12 age group ---(b)(6)-- requested withdrawal because the upcoming SC treatment schedule conflicted with the subject's vacation plans.
- After completion of Study Part 1, one subject in the 2 to <12 age group ---(b)(6)-- was withdrawn by the subject's parent, before transitioning to SC replacement.
- Of the 47 subjects who continued into Study Part 2, three (3) subjects in the aged ≥12 requested withdrawal during Part 2:
  - subject did not wish to continue with study ---(b)(6)-- ,
  - family emergency ---(b)(6)-- ,
  - subject felt quality of life had decreased on IGSC, with complaint of increased fatigue and general malaise---(b)(6)--. The subject reported one instance each of - mild fatigue and moderate malaise considered possibly related to the use of treatment in Study Part 2.

Of the 44 subjects (89.8% of the 49 enrolled subjects in the FSDS) who completed Study Part 2, none withdrew during Study Part 3, but 2 subjects aged 2 to <12 ---------(b)(6)---------- and 6 aged ≥12 ----------(b)(6)---------- did not participate in the Study Extension Part, resulting in 36 subjects continuing into the Extension Part. During Extension, one subject in each age group ---(b)(6)-- and ---(b)(6)-- terminated the study prematurely, with a total of 69.4% of subjects in the FSDS (34/49) completing the Study Extension Part.

Protocol Deviations. A total of 30 protocol deviations were classified as major deviations:

- 12 major deviations of dosing errors or inadvertent administration of wrong lot
- 7 instances of not obtaining PK samples
- 1 subject receiving prohibited concomitant treatment.
- 10 major deviations were reported during the screening period:
  - 4 subjects had not been on regular IgG replacement therapy for at least 3 months prior to screening ----------(b)(6)----------
  - in 1 subject the pre-study regimen was too low ---(b)(6)--
  - in 2 subjects the pre-study regimen was too high -------(b)(6)---------
  - in 1 subject PCR for HCV had not been done in time---(b)(6)--
  - 1 subject ---(b)(6)-- had antibiotic therapy for infection within 7 days prior to enrollment
  - 1 subject---(b)(6)-- had secondary immune deficiency diagnosed after inclusion in the study.

One significant deviation occurred with Subject ---(b)(6)-- the nurse performing home visits for this subject falsified temperature data at 2 home visits on 23 JUN 2008 and 30 JUN 2008. The nurse was terminated and the falsified data deleted from the database.

6.2.2.2 Efficacy

A. Datasets Analyzed

1 Full Safety Dataset (FSDS)

The FSDS comprises all subjects who received any amount of investigational product regardless of completing all 4 study parts. Of these 49 subjects, 45 (91.8%) met all inclusion/exclusion criteria: in the group of subjects aged 2 to <12 years, 85.7% (12/14) met all criteria, in the group of subjects aged 12 years and older, 94.3% (33/35) met all criteria.

Four (4) subjects in the FSDS did not meet all inclusion/exclusion criteria. All 4 were naïve to SC IgG replacement. Three (3) subjects did not fulfill Inclusion Criterion 2, i.e., diagnosis of a PI disorder as defined by World Health Organization criteria,1 for which the subject had been receiving regular immunoglobulin treatment either intravenously or subcutaneously with rHuPH20 at mean intervals of 21 ±3 days or 28 ± 3 days or subcutaneously at mean intervals of 6 to 15 days over a period of at least 3 months pre-study at a dose of 300-1,000 mg/kg BW/4 weeks (or of 300-800 mg/kg for subjects enrolled before protocol Amendment 3 was implemented). Of these, 2 subjects ---------(b)(6)---------- had been on replacement therapy for less than 12 weeks prior to the study. One subject --(b)(6)- did not have PI but a secondary immune deficiency that was diagnosed after inclusion into the study. The fourth subject---(b)(6)-- had been receiving antibiotic therapy for the treatment of infection within 7 days prior to enrollment and therefore met Exclusion Criterion 12. Subjects enrolled who failed to fulfill all inclusion/exclusion criteria are listed by age group and experience with SC replacement prior to the study (naïve/non-naïve).

2 Dataset of Subjects Naïve to Subcutaneous Administration of Immunoglobulins (SNSC)

The SNSC comprises all subjects who received any amount of investigational product regardless of completing all 4 study parts and who had never received immunoglobulins subcutaneously before. The SNSC is a subset of the FSDS. A total of 38 subjects were naïve to SC immunoglobulin replacement, 14 in the 2 to <12 years age group, and 24 in the 12 years and older age group. Four of these naïve subjects (2 per age group) did not meet all inclusion/exclusion criteria.

3 Dataset of Subjects with Prior Experience with Subcutaneous Administration of Immunoglobulins (SESC)

The SESC comprises subjects who received any amount of investigational product regardless of completing all 4 study parts and who had previously received IGSC. The SESC is a subset of the FSDS. The SESC includes 11 subjects aged 12 years and older who had pre-study experience with SC immunoglobulin replacement. None of the subjects aged 2 to <12 years had prior experience with SC immunoglobulin treatment. All of the subjects in the SESC met all inclusion criteria.

4. Pharmacokinetic Datasets

PK Datasets consist of IV-treated subjects aged ≥12 Years (PKIV), and SC-treated subjects aged ≥12 Years (PKSC).

B. Demographic and Other Baseline Characteristics

The following pertain to the Full Safety Dataset in which all subjects had received investigational product.

- Demographics

  Of all subjects treated, 44.9% (22/49) were female, and 55.1% (27/49) were male.
  - In the age group of 2 to <12, the ratio of females and males was 42.9% (6/14) and 57.1% (8/14), respectively.
  - In the age group of ≥12 years, the ratio was 45.7% (16/35) and 54.3% (19/35), respectively.

  Of all subjects treated, 93.9% (46/49) were Caucasian, 4.1% (2/49) were Black, and 2.0% (1/49) were of Hispanic ethnicity.
  - In the age groups of 2 to <12, 92.9% (13/14) were Caucasian, 7.1% (1/14) Black.
  - In the age group of ≥12 years, 94.3% (33/35)were Caucasian, 2.9% (1/35) Black, 2.9% (1/35).

  The median age at enrollment in the FSDS was 20 years with a range of 3 to 77 years.
  - In the age groups of 2 to <12, median age was 7.5 at enrollment (range 3-11).
  - In the age group of ≥12 years, median age was 36 at enrollment (range 14-77).

  The median height of subjects in the FSDS was 164 cm with a range 99 to 191 cm.
  - In the age groups of 2 to <12, median height was 132 cm (range 99-144 cm).
  - In the age group of ≥12 years, median height was 168 cm (range 150-191 cm).

  The median weight of subjects in the FSDS was 61 kg (range 18 to 133 kg)
  - In the age groups of 2 to <12, median weight was 23 kg (range 18-46 kg).
  - In the age group of ≥12 years, median weight was 66 kg (range 45-133 kg).

- Other Baseline Characteristics

  Medical history showed that in addition to PI, the vast majority of subjects treated had a history of disease in the system categories eyes, ears, nose and throat (98%; 48/49), neurological (79.6%; 39/49), respiratory (77.6%; 38/49), dermatological and gastrointestinal (63.3%; 31/49 each).

  Physical examination at baseline revealed abnormal conditions in the system categories nose and throat (18.4%; 9/49), eyes and ears (6.1%; 3/49), head and neck (4.1%; 2/49), lungs (4.1%; 2/49), and extremities and joints, general appearance, neurological, and skin (2.0%; 1/49 each).

  The median systolic blood pressure at baseline was 115 mmHg (mean 115.49 [±15.14] mmHg); median diastolic blood pressure 71 mmHg (mean 70.61 [±11.38] mmHg); median pulse rate 80 beats per minute (mean 81.27 [±15.10] beats per minute); the median body temperature 36.6°C (mean 36.51 [±0.42]°C), and the median respiratory rate 18 breaths per minute (mean 19.53 [±3.36] breaths per minute).

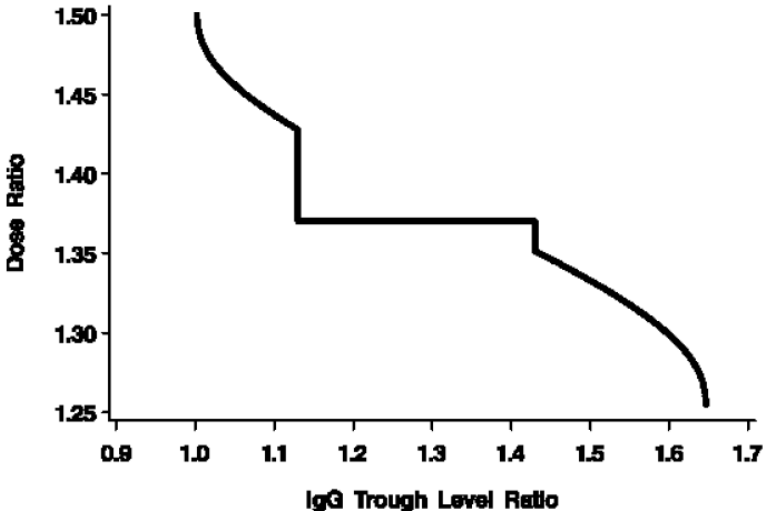
  Median trough levels for the period up to 6 months prior to enrollment (N=36) were 10.65 g/L with a range of 2.96 g/L to 17.3 g/L.

C. Primary Endpoint

Analysis of the primary endpoint, PK equivalence has been conducted by the Clinical Pharmacology Reviewer, Dr. Iftekhar Mahmood, and he concludes that equivalence has been demonstrated.

According to the study report, PK equivalence would require dose adjustment from the IV dose recalculated for weekly SC administration by multiplication with a dose adjustment factor (DAF) valued at 1.37 (DAF = 137%). Also, the individual ratios of the subject's expected IgG trough level in Study Part 3a over the subject's trough level in Study Part 1 ranged from 1.00 to 1.65, with a 40%-trimmed mean of the individual ratios to estimate the expected average IgG trough level factor (EATLF) valued at 1.28 (EATLF = 128%). The report provides a nomogram (Figure 11-1 of study report) to give the ***dose ratio*** of the SC dose required for equivalent AUC relative to the adjusted weekly IV dose as a function of the IgG ***trough level ratio*** of SC over IV expected for a SC dose of 137% of the weekly IV dose:

Nomogram: Dose Ratio of SC Dose Required for Equivalent AUC Relative to Weekly IV Dose



Comment The use of the "expected average IgG trough level factor" (EATLF) assumes a linear relationship without intercept between target trough IgG level under SC administration (Study Part 3a) and trough IgG level under IV administration (Study Part 1). Data to support this assumption of a linear relationship with no intercept is lacking. Baxter was requested to address this issue via an Information Request after mid-cycle review of this supplement (see below).

The study uses a nomogram to obtain a dose ratio of the SC dose required for equivalent AUC relative to the weekly IV dose as a function of the IgG tough level ratio of SC over IV administration, whereas proposed labeling uses a table to find the dose increment for dose adjustment. There does not seem to be a clear relationship between the two methods. Moreover, the table in proposed labeling uses a slope of 7 kg/dL for trough level change vs dose change based on linear relationship without intercept. This no-intercept assumption may underestimate the dose increment required. Baxter was also requested to address this issue via an Information Request after mid-cycle review of this supplement (see below).

D. Infections

1. Acute serious bacterial infections. A total of 3 subjects had acute serious bacterial infections while on SC treatment with GAMMAGARD LIQUID, and all were bacterial pneumonias:

- 53-year old subject non-naïve to IGSC ---(b)(6)-- in Study Part 3a
- 10-year old subject naïve to IGSC ---(b)(6)-- in the Study Extension Part
- 48-year old subject non-naïve to SC treatment ---(b)(6)-- in Study Part 3b.

The annual rate of acute serious bacterial infections while on SC treatment with GAMMAGARD LIQUID was calculated to be 0.067 per person; the 99% upper confidence limit was 0.134.

No acute serious bacterial infections were reported during the 12-week period of IV replacement.

2. Infection rates. A summary of annual infection rates (point estimates and 95% CIs) calculated by a Poisson model is presented below for the FSDS including subjects of all ages (N=49).

	Annual Infection Rate (# per subject per year) and 95% C.I.						
Study Part	**All ages**	**Age <12**	**Age 12-<16**	**Age 16-<65**	**Age ≥65**	**Age ≥16**	**Age ≥12**
1 (IV)	5.1 (3.7-6.9)	5.0 (2.3-9.3)	12.0 (6.9-19.2)	4.8 (3.1-6.9)	1.7 (0.3-5.2)	4.3 (2.9-6.2)	5.2 (3.6-7.2)
2 (SC)	4.5 (3.1-6.3)	5.6 (2.7-10.0)	12.2 (5.0-22.1)	3.1 (1.8-4.9)	3.0 (0.5-9.1)	3.1 (1.9-4.7)	4.1 (2.6-6.1)
3a (SC)	4.3 (2.7-6.4)	3.5 (1.4-7.1)	10.9 (3.7-24.0)	3.9 (2.0-6.9)	2.2 (0.1-9.2)	3.7 (1.9-6.3)	4.6 (2.6-7.3)
3b (SC)	3.9 (2.6-5.5)	3.9 (1.6-7.8)	7.5 (1.7-20.3)	3.6 (2.0-5.7)	2.0 (0.4-5.8)	3.3 (2.0-5.2)	3.8 (2.4-5.8)
Extension (SC)	3.8 (2.9-5.0)	4.0 (2.4-6.2)	11.0 (7.0-16.3)	3.6 (2.4-5.2)	1.5 (0.4-4.1)	3.3 (2.2-4.6)	3.8 (2.6-5.3)
2, 3a, 3b, Ext (SC)	4.1 (3.2-5.1)	4.3 (2.8-6.4)	10.3 (5.4-17.6)	3.5 (2.6-4.6)	2.0 (1.2-3.0)	3.3 (2.5-4.3)	4.0 (3.0-5.2)

The majority of infections were of mild or moderate severity. Subject ---(b)(6)-- (aged 2 to <12 years) and Subject ---(b)(6)-- (aged 12 years and older) each had 1 severe infection during the IV treatment period (Study Part 1). Monthly infection rates per subject ranged from 0.0 to 1.8.

The report also presents the annual infection rates in the SNSC and the SESC for the age groups of 2 to <12 years and ≥12 years, as well as cumulatively for all ages. These are similar to the rates for the FSDS and will not be further elaborated on here.

3. Sensitivity analysis of infection data by season. Sensitivity analysis of annual infection rates by season while on treatment with GAMMAGARD LIQUID was conducted to address the potential bias due to seasonal imbalances.

Study Part	Annual Infection Rate by Season								Average rate	Disregarding Season	
	Winter		Spring		Summer		Fall				
	Days	Rate	Days	Rate	Days	Rate	Days	Rate		Days	Rate
1 (IV)	2796	4.3	906	3.6	433	5.1	422	3.5	4.1	4557	4.2
2 (SC)	410	0.9	2734	2.9	737	3.0	334	10.9	4.4	4215	3.4
3a (SC)	23	0.0	256	2.9	1250	3.2	346	7.4	3.4	1875	3.9
3b (SC)	587	4.4	6	0.0	1720	1.9	1469	3.5	2.4	3782	2.9
Extension (SC)	2656	2.1	1946	2.3	211	3.5	1551	2.4	2.5	6364	2.2
2, 3a, 3b, Ext (SC)	3676	2.3	4942	2.7	3918	2.6	3700	4.0	2.9	16236	2.9
Annual infection rates are crude rates (number of infections divided by number of observational days)											

The majority of the IV infusions in Study Part 1 were administered in winter. Similarly, the majority of infusions in Study Part 2 were given in spring, whereas Study Part 3a fell into the summer season and 3b extended over summer and fall. The annual infection rate disregarding season for all study parts of SC treatment was 2.9, while overall, the incidence of infection was similar during all study parts (0 to 5.1 infections per subject per year), with exceptions for the rates in the fall for Study Parts 2 and 3a:

- The annualized infection rates in the fall for Study Parts 2 and 3a were 10.9 and 7.4, respectively. It was noted, however, that only 334 of a total of 4,215 observation days for Study Part 2 and 346 of 1,875 observation days for Study Part 3a fell into this season. Baxter postulates that low number of observation days in fall might have biased the infection rates in these study parts. The number of observation days per season was similar when calculated for the entire SC treatment period (3,700 in fall compared to 3,676 in winter, 4,942 in spring, and 3,918 in summer). The rate of infection in fall calculated to include all SC treatment parts (2, 3a, 3b, and Extension) was 4.0, which seems to be comparable to the infection rates of 2.3, 2.7, and 2.6 observed in winter, spring and summer.

Seasonal effect was also addressed by analyzing subjects who had at least 365 days of IGSC therapy. There were 26 subjects having received IGSC treatment for ≥53 weeks, 17 for 30 to 52 weeks, and 4 for up to 29 weeks. An unplanned sensitivity analysis of infection rates (determined using Poisson model) within the first 365 days of SC treatment with GAMMAGARD LIQUID (in 26 subjects with at least 366 days on SC treatment) resulted in an annual infection rate of 3.1 (95% CI for annual rate 2.3 to 4.0).

Comment It appears that bias due to seasonal effect is not pronounced in this study.

E. Patient Diary Information regarding Infections, Hospitalizations due to Infections, Antibiotic Use and Loss of Work or School Days.

In the Clinical Section of this supplement, Baxter includes an Addendum to the Clinical Study Report of Study 160601, which presents the data relating to infections, hospitalizations due to infections, antibiotic use, and loss of work or school days, etc. as derived from recordings in the study subject diaries. This information is also partly in the datasets mh.xpt and ae.xpt.

Because of differences in recording in the diaries, the numbers of study days were not uniformly identical for these parameters in the same subject. Thus, instead of total subject-days, total subject-years have been used for estimating the event rates, because the differences in subject-years among these parameters from the diaries would be extremely small. The information may be summarized as follows:

Summary of Infections and Associated Events with Subcutaneous Use of GAMMAGARD LIQUID

Number of subjects (efficacy phase)/ Total number of subject-years	47/44
Any infections ▪ Annual rate of any infections	4.1 (95% CI 3.2 to 5.1) infections/subject year

Summary of Infections and Associated Events with Subcutaneous Use of GAMMAGARD LIQUID

Number of subjects (efficacy phase)/ Total number of subject-years	47/44
Antibiotic use§ (prophylaxis or treatment) ▪ Number of subjects (%) ▪ Annual rate	 40 (85.1%) 50.2 (95% CI 33.4 to 71.9) days/subject year
Days out of work/school/ day care or unable to do normal activities ▪ Number of subjects (%) ▪ Annual rate	 25 (53.2%) 4.0 (95% CI 2.5 to 6.1) days/subject year
Hospitalizations due to infections ▪ Number of subjects (%) ▪ Annual rate	 0 (0.0%) 0.0 (95% CI 0.0 to 0.1) days/subject year

§ Included systemic and topical antibacterial, anti-fungal, anti-viral, and anti-protozoal antimicrobials.

Comment The original submission miscoded some hospitalizations that were not due to infections and suggested there were 5 subjects who had been hospitalized due to infections. Two of the subjects actually had hospitalization in the IV phase of the study, and the other three were hospitalized for events not related to infections. Baxter submitted clarification on 1/26/11, establishing the lack of hospitalization due to infections during the SC phase of the study.

F. Efficacy Conclusions

- Pharmacokinetic comparison between IV and SC dosing with GAMMAGARD LIQUID shows equivalence when appropriate dose adjustment is made upon switch from IV to SC administration, with the SC dose at 1.37 x the weekly equivalent of the IV dose.
- The annual rate of acute serious bacterial infections while on SC treatment with GAMMAGARD LIQUID was 0.067 per person; its 99% upper confidence limit was 0.134. This confidence limit is below 1 serious bacterial infection per person-year, and is acceptable.
- The annual rate of infection calculated by a Poisson model for all subjects of all age groups during IV (5.1, 95% CI 3.7 to 6.9) and during SC (4.1, 95% CI 3.2 to 5.1) treatment is within the range seen in similar studies. It was similar in children aged 2 to <12 years (5.0 during IV and 4.3 during SC treatment) and in adult subjects aged 16 to <65 years (4.8 during IV and 3.5 during SC treatment) as well as in those aged 65 years and above (1.7 during IV and 2.0 during SC treatment).
- The annual rate of infection in the 26 subjects who completed a full year of SC therapy was 3.1 (95% CI 2.3 to 4.0) and is not appreciably different from the annual rate for all subjects of all age groups. Overall, the rate of infection per season was similar during all study parts, ranging from 0 to 5.1 infections per subject per year, with 2 exceptions: the rates in the fall for Study Parts 2 and 3a were 10.9 and 7.4, respectively, which might have been associated with low subject days for study. At this point, a seasonal bias on infection rates has not been established.
- The study report lacks presentation on antibiotic use, hospitalization days, loss of days for work/school/day care or inability to perform normal activities. These data are presented in an addendum to the study report and are comparable to those seen with other SC immune globulin products.
- Dose adjustment in Study 160601 uses methodology (expected average IgG trough level factor and normogram) different from that in proposed labeling (table with volume increments according to body weight and trough level difference). Dose adjustment issues for labeling have been discussed with Baxter subsequent to the mid-cycle review resulting in Baxter's clarification and revision of labeling (see below).

6.2.2.3 Safety

A. Extent of Exposure

- In a total of 26 subjects, the duration of SC treatment with GAMMAGARD LIQUID was ≥53 weeks, 17 subjects received SC treatment for 30 to 52 weeks, and 4 for ≤29 weeks.
- In the FSDS, 207 IV and 2294 SC infusions were administered:
    - 162 IV and 1757 SC infusions to the population naïve to SC therapy
    - 45 IV and 537 SC infusions to the population who had pre-study experience with SC therapy.

Number of Infusions and Total Amount of Investigational Product Administered

Study Part	# of infusions	Range in Total Product Administered (mg per kg BW per subject)
1 (IV)	3=1 subject 4=36 subjects 5=12 subjects	1121.5 to 3952.7
2 (SC)	12=25 subjects Range 1-18	253.8 to 4051.9
3a (SC)	6=Majority 7=2 subjects 8=1 subject	541.9 to 1719.0

Study Part	# of infusions	Range in Total Product Administered (mg per kg BW per subject)
3b (SC)	11=1 subject 12= all but 5 14=1 subject 15=3 subjects	1413.6 to 3857.1
Extension (SC)	20-30=majority Range 1-36	173.6 to 9738.7

- Doses Per Week Per kg BW: In the FSDS, subjects in the age group of 2 to <12 years received a variably higher mean dose of investigational product per week per kg than subjects aged ≥12.

	Mean Dose Investigational Product (mg/kg BW)		
Study Part	**Age 2 - <12**	**Age ≥12**	**All Subjects**
1	192.2	134.2	151.0
2	198.0	176.1	181.9
3a	213.4	181.8	190.5
3b	214.6	181.8	190.7
Extension	219.4	178.6	189.8

- Infusion Characteristics for Different Age Groups: Duration

			Infusion Duration (Hrs)		
Study Part	**Age Group**	**N (Subjects)**	**Min**	**Median**	**Max**
1	Subjects aged 2 to <12	14	1.7	2.5	5.0
	Subjects aged ≥12	35	1.0	2.3	5.3
	All subjects	49	1.0	2.4	5.3
2	Subjects aged 2 to <12	12	0.7	1.2	2.7
	Subjects aged ≥12	35	0.8	1.3	3.7
	All subjects	47	0.7	1.3	3.7
3a	Subjects aged 2 to <12	12	0.7	1.1	2.2
	Subjects aged ≥12	32	0.9	1.3	2.6
	All subjects	44	0.7	1.2	2.6
3b	Subjects aged 2 to <12	12	0.8	1.1	2.2
	Subjects aged ≥12	32	0.8	1.3	2.3
	All subjects	44	0.8	1.2	2.3
Extension	Subjects aged 2 to <12	10	0.8	1.2	2.9
	Subjects aged ≥12	26	0.6	1.3	2.2
	All subjects	36	0.6	1.2	2.9

- Infusion Characteristics for Different Age Groups: Initial and Maximum Infusion Rate*

Study Part	**Age Group**	**N (Subjects)**	**Min**	**Median**	**Max**
			Initial Infusion Rate (mL/hr)		
1	Subjects aged 2 to <12	14	4.0	12.0	23.0
	Subjects aged ≥12	35	10.0	35.0	75.0
	All subjects	49	4.0	31.0	75.0
2	Subjects aged 2 to <12	12	5.0	10.0	10.0
	Subjects aged ≥12	35	2.0	10.0	10.0
	All subjects	47	2.0	10.0	10.0
3a	Subjects aged 2 to <12	12	5.0	10.0	10.0
	Subjects aged ≥12	32	5.0	10.0	10.0
	All subjects	44	5.0	10.0	10.0
3b	Subjects aged 2 to <12	12	5.0	10.0	10.0
	Subjects aged ≥12	32	5.0	10.0	10.0
	All subjects	44	5.0	10.0	10.0
Extension	Subjects aged 2 to <12	10	5.0	10.0	10.0
	Subjects aged ≥12	26	2.0	10.0	10.0
	All subjects	36	2.0	10.0	10.0
			Maximum Infusion Rate (mL/hr)		
1	Subjects aged 2 to <12	14	25.0	80.0	141.0
	Subjects aged ≥12	35	60.0	250.0	668.0
	All subjects	49	25.0	189.0	668.0
2	Subjects aged 2 to <12	12	15.0	20.0	30.0
	Subjects aged ≥12	35	8.0	30.0	30.0
	All subjects	47	8.0	30.0	30.0
3a	Subjects aged 2 to <12	12	15.0	20.0	30.0
	Subjects aged ≥12	32	15.0	30.0	30.0
	All subjects	44	15.0	30.0	30.0

Study Part	Age Group	N (Subjects)	Min	Median	Max
			Initial Infusion Rate (mL/hr)		
3b	Subjects aged 2 to <12	12	15.0	20.0	30.0
	Subjects aged ≥12	32	15.0	30.0	40.0
	All subjects	44	15.0	30.0	40.0
Extension	Subjects aged 2 to <12	10	10.0	20.0	30.0
	Subjects aged ≥12	26	15.0	30.0	30.0
	All subjects	36	10.0	30.0	30.0

*For SC infusions, the rates are not provided as total volumes/hr but volumes/hr/infusion site.

- Infusion Characteristics: Number of Infusion Sites. The study protocol originally limited the maximum number of infusion sites to three. A protocol amendment in July 2007 removed the limitation to 3 sites. The following Table shows the number of infusions in relation to number of sites used.

# of sites	Frequency
2	47
3	444
4	353
5	875
6	305
7	203
8	7
9	2
10	56
14	2

  Thus, 1719 of the 2294 subcutaneous infusions used 5 sites or fewer (75%). A minority of infusions used 6 or more sites.

- Adjusted Doses Administered in Study Part 3a. In Study Part 3a, the ratio of SC doses administered (Adjusted Dose) compared to the IV dose used during Study Part 1 (=100%) in the FSDS was: (a) 100.5% to 160.0% in subjects aged 2 to <12, and (b) 128.3% to 148.0% in subjects aged >12. Also, the "Adjusted Doses" were similar between subjects who were naïve to and those not naïve to IGSC replacement.

- Doses Administered in Study Part 3b. In the FSDS, the median ratio of the dose administered in Study Part 3b compared to Study Part 1 was (a) 141.0% (range 100.5% to 160.0%) for subjects aged 2 to <12 years, (b) 137.3% (range 125.7% to 150.8%) for subjects aged >12, and (c) 137.4% (range 100.5% to 160.0%; quartiles 136.8% and 144.0%) with all age groups combined.
  - SC doses had to be individually adapted in Study Part 3b in 13 instances: in 7 of them the Individually Adapted Dose was ***higher*** and in 6 it was ***lower*** than the Adjusted Dose administered in Study Part 3a.

B. Adverse Events (AEs)

The following discussion on AE data are based on the population FSDS (full safety dataset)..

A total of 226 AEs were reported during the IV treatment period (Study Part 1), among which 85 AEs were considered related to the use of the investigational product. There were 2 SAEs not related to treatment and 632 non-serious AEs reported during the SC treatment periods (Study Parts 2, 3a, 3b, and Extension), among which 150 AEs were considered related during SC treatment. The proportion of subjects with non-serious AEs can be summarized in the following Table:

		Frequency of AEs			
		Age 2 - <12		Age ≥12	
Study Part		**Subjects (n/N)**	**Percent**	**Subjects (n/N)**	**Percent**
1 (IV)	All AEs	12/14	85.7	32/35	91.4
	Related AEs	9/14	64.3	14/35	40.0
	Mild	3/14	21.4	5/35	14.3
	Moderate	5/14	35.7	7/35	20.0
	Severe	1/14	7.1	2/35	5.7
2 (SC)	All AEs	11/12	91.7	31/35	88.6
	Related AEs	6/12	50.0	20/35	57.1
	Mild	4/12	33.3	13/35	37.1
	Moderate	1/12	8.3	7/35	20.0
	Severe	1/12	8.3	0/35	0
3a (SC)	All AEs	8/12	66.7	22/32	68.8
	Related AEs	4/12	33.3	9/32	28.1

Study Part		Frequency of AEs			
		Age 2 - <12		Age ≥12	
		Subjects (n/N)	Percent	Subjects (n/N)	Percent
	Mild	4/12	33.3	6/32	18.8
	Moderate	0/12	0	3/32	9.4
	Severe	0/12	0	0/32	0
3b (SC)	All AEs	10/12	83.3	25/32	78.1
	Related AEs	3/12	25.0	8/32	25.0
	Mild	2/12	16.7	5/32	15.6
	Moderate	1/12	8.3	3/32	9.4
	Severe	0/12	0	0/32	00
Extension (SC)	All AEs	10/10	100.0	22/26	84.6
	Related AEs	7/10	70.0	9/26	34.6
	Mild	6/10	60.0	6/26	23.1
	Moderate	1/10	10.0	2/26	7.7
	Severe	0/10	0	1/26	3.8

- Serious Adverse Events (SAEs)
  Study Part 1. There were 2 SAEs during IV immunoglobulin replacement; one in the age group of 2 to <12 years (sinusitis, Subject ---(b)(6)--), the other in the age group of ≥12 years (convulsion/seizure, Subject ---(b)(6)--). Both SAEs were considered unrelated to the use of the investigational product.
  Study Part 2. One subject in the age group of ≥12 years experienced an SAE (cholecystitis due to gallstones, Subject --(b)(6)--) which was considered unrelated to the use of the investigational product.
  Study Part 3a. No SAEs were reported in Study Part 3a (FSDS).
  Study Part 3b. One subject in the age group of ≥12 years experienced an SAE (chest pain, Subject ---(b)(6)--) which was considered unrelated to the use of the investigational product.
  Study Extension Part. No SAEs occurred during the Study Extension Part.

- Analysis and Display of Adverse Events
  The analysis and display of AEs are best illustrated in the following series of Tables which show the most frequent AEs (which occurred with a frequency of ≥5%) in the FSDS (excluding infections).

AEs, *Excluding Infections* Reported in ≥5% of Subjects During SC Treatment

AE	Number of Subjects	Percent of Subjects	Number of Infusions	Rate per Infusion[a]
Infusion site (local) event	21	44.7%	56	2.8%
Headache	23	48.9%	45	2.0%
Nausea	8	17.0%	20	1.0%
Pyrexia	14	29.8%	22	1.0%
Diarrhea	5	10.6%	13	0.6%
Heart rate increased	3	6.4%	12	0.6%
Abdominal pain upper	5	10.6%	12	0.5%
Vomiting	7	14.9%	12	0.5%
Fatigue	7	14.9%	11	0.5%
Blood pressure systolic increase	3	6.4%	9	0.4%
Arthralgia	3	6.4%	9	0.4%
Asthma	6	12.8%	9	0.4%
Myalgia	4	8.5%	9	0.4%
Oropharyngeal pain	6	12.8%	8	0.3%
Ear pain	4	8.5%	5	0.2%
Migraine	4	8.5%	4	0.2%
Aphthous stomatitis	3	6.4%	4	0.2%
Constipation	3	6.4%	4	0.2%
Eczema	3	6.4%	4	0.2%
Musculoskeletal pain	4	8.5%	4	0.2%
Nasal congestion	3	6.4%	4	0.2%
Abdominal discomfort	3	6.4%	3	0.1%
Abdominal pain	3	6.4%	3	0.1%
Contusion	3	6.4%	3	0.1%
Epistaxis	3	6.4%	3	0.1%
Insomnia	3	6.4%	3	0.1%
Lymphadenopathy	3	6.4%	3	0.1%
Pain in extremity	3	6.4%	3	0.1%
Sinus headache	3	6.4%	3	0.1%
Urticaria	3	6.4%	3	0.1%

[a] Rate per infusion= total number of events divided by total number of infusions; rates provided as percentages

For infusional AEs (temporally associated), which have been collected during or within 72 hours after the end of an SC infusion of the product, the following Table shows the frequencies of events with a frequency of ≥5% in the FSDS (excluding infections).

Temporally Associated AEs, *Excluding Infections*, Reported in ≥5% of Subjects During SC Treatment

AE	Number of Subjects	Percent of Subjects	Number of Infusions	Rate per Infusion[a]
Infusion site (local) event	21	44.7%	53	2.7%
Headache	18	38.3%	27	1.2%
Pyrexia	9	19.1%	11	0.5%
Fatigue	6	12.8%	10	0.4%
Abdominal pain upper	5	10.6%	9	0.4%
Heart rate increased	3	6.4%	8	0.3%
Vomiting	5	10.6%	7	0.3%
Asthma	4	8.5%	6	0.3%
Nausea	3	6.4%	6	0.3%
Blood pressure systolic increase	3	6.4%	5	0.2%
Ear pain	3	6.4%	4	0.2%
Aphthous stomatitis	3	6.4%	3	0.1%
Diarrhea	3	6.4%	3	0.1%
Migraine	3	6.4%	3	0.1%
Oropharyngeal pain	3	6.4%	3	0.1%

[a] Rate per infusion= total number of defined events divided by total number of infusions; rates provided as percentages

AEs considered by the Investigator to be related to treatment with the investigational product are "adverse reactions" (21 CFR 201.57). There were 150 adverse reactions, 124 (83%) were mild, 24 (16%) were moderate, and 2 were severe, but neither of the 2 severe adverse reactions required hospitalization or resulted in sequelae. The frequencies for adverse reactions are displayed below.

Adverse Reactions, *Excluding Infections,* in ≥5% of Subjects During SC Treatment

Adverse Reactions	Number of Subjects	Percent of Subjects	Number of Infusions	Rate per Infusion[a]
Infusion site (local) event	21	44.7%	53	2.7%
Headache	13	27.7%	20	0.9%
Heart rate increased	3	6.4%	9	0.4%
Fatigue	5	10.6%	8	0.3%
Systolic bp increase	3	6.4%	6	0.3%
Pyrexia	6	12.8%	7	0.3%
Abdominal pain upper	3	6.4%	4	0.2%

[a] Rate per infusion= total number of events divided by total number of infusions; rates are provided as percentages

Local adverse events at the infusion site are among the more common AEs in SC therapy with immune globulin products. The frequencies of such events in the study are as follows.

Rate[a] of Local AEs, *Excluding Infections*, During SC Treatment

Severity	Subjects Naïve to SC Therapy with Immune Globulin Products: N=1757	Subjects with Experience of SC Therapy with Immune Globulin Products: N=537	FSDS N=2294
Mild	2.6%	1.1%	2.3%
Moderate	0.7%	0.0%	0.5%
Severe	0.0%	0.0%	0.0%
Total	3.3%	1.1%	2.8%

N = total number of infusions;
[a] Rate of local AEs = number of local AEs / total number of infusions; rates are provided as percentages

Local AEs, *Excluding Infections*[a] Occurring with 1 or More Infusions During SC Treatment

Local AE	Number of Infusions (Rate per Infusion[a])			
	Mild	Moderate	Severe	Total
Infusion site pain	14 (0.6%)	8 (0.3%)	0 (0.0%)	22 (1.0%)
Infusion site hematoma	13 (0.6%)	1 (0.0%)	0 (0.0%)	14 (0.6%)
Infusion site pruritus	4 (0.2%)	2 (0.1%)	0 (0.0%)	6 (0.3%)
Infusion site rash	4 (0.2%)	0 (0.0%)	0 (0.0%)	4 (0.2%)
Infusion site erythema	3 (0.1%)	0 (0.0%)	0 (0.0%)	3 (0.1%)
Infusion site edema	3 (0.1%)	0 (0.0%)	0 (0.0%)	3 (0.1%)
Infusion site hemorrhage	2 (0.1%)	0 (0.0%)	0 (0.0%)	2 (0.1%)

Local AEs, *Excluding Infections*[a] Occurring with 1 or More Infusions During SC Treatment				
Local AE	Number of Infusions (Rate per Infusion[a])			
	Mild	Moderate	Severe	Total
Infusion site irritation	2 (0.1%)	0 (0.0%)	0 (0.0%)	2 (0.1%)
Infusion site swelling	1 (0.0%)	1 (0.0%)	0 (0.0%)	2 (0.1%)
"Infusion related" reaction	1 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.0%)
Infusion site reaction	1 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.0%)
Infusion site vesicles	1 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.0%)
Injection site hematoma	1 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.0%)
Edema, peripheral	1 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.0%)
Rash	1 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.0%)

[a] Rates per infusion are provided as percentages

- Primary Safety Endpoint
  The primary safety endpoint was the ability to tolerate GAMMAGARD LIQUID administered IV or SC, measured as four parameters: the 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.

  The following Table provides the analysis by ***subjects***.

			Infusion Rate Reduced and/or Infusion Interrupted or Stopped			
			For Any Reason		For Tolerability/AE	
Age Group	Study Part	Total Number of Subjects	Number of Subjects	Percent	Number of Subjects	Percent
All Ages	Study Part 1 (IV)	49	9	18.4	8	16.3
All Ages	Study Part 2 (SC)	47	14	29.8	2	4.3
All Ages	Study Part 3A (SC)	44	7	15.9	1	2.3
All Ages	Study Part 3B (SC)	44	6	13.6	1	2.3
All Ages	Study Extension (SC)	36	5	13.9	0	0.0
All Ages	Study Part 2, 3A, 3B, Study Extension (all SC)	47	19	40.4	2	4.3
Age <12 Years	Study Part 1 (IV)	14	4	28.6	3	21.4
Age <12 Years	Study Part 2 (SC)	12	5	41.7	2	16.7
Age <12 Years	Study Part 3A (SC)	12	3	25.0	1	8.3
Age <12 Years	Study Part 3B (SC)	12	3	25.0	1	8.3
Age <12 Years	Study Extension (SC)	10	1	10.0	0	0.0
Age <12 Years	Study Part 2, 3A, 3B, Study Extension (all SC)	12	7	58.3	2	16.7
Age >=12 Years	Study Part 1 (IV)	35	5	14.3	5	14.3
Age >=12 Years	Study Part 2 (SC)	35	9	25.7	0	0.0
Age >=12 Years	Study Part 3A (SC)	32	4	12.5	0	0.0
Age >=12 Years	Study Part 3B (SC)	32	3	9.4	0	0.0
Age >=12 Years	Study Extension (SC)	26	4	15.4	0	0.0
Age >=12 Years	Study Part 2, 3A, 3B, Study Extension (all SC)	35	12	34.3	0	0.0

Comment The percentage of subjects with infusion rate reduced and/or the infusion interrupted or discontinued for tolerability reasons was highest for IV treatment in Study Part 1. For the group of subjects aged between 2 and <12, the percentage of subjects with reduction, interruption or discontinuation for tolerability reasons declined with the duration of SC therapy while in the age group of ≥12 years, no rate changes, interruptions or discontinuations for tolerability reasons were observed. The analysis of subjects naïve to SC immune globulin therapy showed similar behavior as with the FSDS. The subjects non-naïve to SC therapy did not have infusion rate reduction, interruption, or discontinuation for tolerability reasons.

The following Table provides the analysis by ***infusions***.

			Infusion Rate Reduced and/or Infusion Interrupted or Stopped			
			For Any Reason		For Tolerability/AE	
Age Group	Study Part	Total Number of Infusions	Rate (%)	95% Confidence Interval	Rate (%)	95% Confidence Interval
All Ages	Study Part 1 (IV)	207	6.7	3.6 to 11.3	6.2	3.2 to 10.5
All Ages	Study Part 2 (SC)	595	4.2	2.7 to 6.2	0.5	0.1 to 1.3
All Ages	Study Part 3A (SC)	268	3.1	1.4 to 5.8	0.4	0.0 to 1.7
All Ages	Study Part 3B (SC)	538	1.1	0.4 to 2.3	0.2	0.0 to 0.8

Age Group	Study Part	Total Number of Infusions	Infusion Rate Reduced and/or Infusion Interrupted or Stopped For Any Reason Rate (%)	95% Confidence Interval	For Tolerability/AE Rate (%)	95% Confidence Interval
All Ages	Study Extension (SC)	893	0.6	0.2 to 1.2	0.0	NAP
All Ages	Study Part 2, 3A, 3B, Study Extension (all SC)	2294	1.9	1.4 to 2.5	0.2	0.1 to 0.5
Age <12 Years	Study Part 1 (IV)	60	11.1	4.3 to 23.8	9.1	3.2 to 20.6
Age <12 Years	Study Part 2 (SC)	159	8.2	4.3 to 14.1	1.9	0.5 to 5.1
Age <12 Years	Study Part 3A (SC)	74	4.2	1.0 to 11.3	1.4	0.1 to 6.2
Age <12 Years	Study Part 3B (SC)	147	2.1	0.5 to 5.5	0.7	0.0 to 3.1
Age <12 Years	Study Extension (SC)	244	0.4	0.0 to 1.8	0.0	NAP
Age <12 Years	Study Part 2, 3A, 3B, Study Extension (all SC)	624	3.1	1.9 to 4.8	0.8	0.3 to 1.7
Age >=12 Years	Study Part 1 (IV)	147	5.0	2.1 to 9.9	5.0	2.1 to 9.9
Age >=12 Years	Study Part 2 (SC)	436	2.8	1.5 to 4.8	0.0	NAP
Age >=12 Years	Study Part 3A (SC)	194	2.6	0.9 to 5.8	0.0	NAP
Age >=12 Years	Study Part 3B (SC)	391	0.8	0.2 to 2.0	0.0	NAP
Age >=12 Years	Study Extension (SC)	649	0.6	0.2 to 1.4	0.0	NAP
Age >=12 Years	Study Part 2, 3A, 3B, Study Extension (all SC)	1670	1.5	0.9 to 2.1	0.0	NAP

Comment With analysis by infusions, the proportion of infusions during which a reduction of the infusion rate and/or interruption or discontinuation of the infusion was required for tolerability reasons decreased over time. The analysis of subjects naïve to SC immune globulin therapy showed similar behavior as with the FSDS. Subjects non-naïve to SC therapy did not have infusion rate reduction, interruption, or discontinuation for tolerability reasons.

The change in reduction of infusion rate and/or discontinuation over time is also reflected by the change in local reaction rate over time. Thus, the rate of all local AEs per infusion immediately after switching from IV to SC therapy was 4.9% (29/595), decreasing to 1.5% (8/538) by the end of the study and to 1.1% (10/893) in the Study Extension. In fact, during the first SC infusion, 17% of the subjects experienced a local adverse reaction, but this decreased to 2.1% for subsequent SC infusions (range of 0 to 6.8% in the first year of SC therapy). During the last 18 months of the study and Study Extension, one local AE was reported for any infusion.

- Secondary Safety Endpoint

  This study has 11 secondary safety endpoints. These provide analyses which overlap and may be confusing. Only the most relevant analyses are discussed here, including the following:
  - Proportion of IV and SC infusions associated with ≥1 AEs that begin during infusion or within 72 hours of completion of infusion
  - Proportion of IV and SC infusions associated with ≥1 AEs excluding infections that begin during infusion or within 72 hours of completion of infusion
  - Proportion of IV and SC infusions associated with ≥1 systemic AE excluding infections that begin during infusion or within 72 hours of completion of infusion
  - Proportion of IV and SC infusions associated with ≥1 local AEs that begin during infusion or within 72 hours of completion of infusion

These data can be summarized as follows (adapted from Table 14.3.2-19 of the study report):

	Proportion of infusions associated with one or more temporally associated AEs		Proportion of infusions associated with >1 temporally associated AEs excluding infections		Proportion of infusions associated with >1 temporally associated systemic AEs excluding infections		Proportion of infusions associated with >1 temporally associated local AEs excluding infections	
	IV	SC	IV	SC	IV	SC	IV	SC
FSDS	64/207 (30.9%**)	251/2294 (10.9%***)	59/207 (28.5%)	201/2294 (8.8%)	58/207 (28.0%)	155/2294 (6.8%)	2/207 (1.0%)	53/2294 (2.3%)
SNSC*	58/162 (35.8%)	207/1757 (11.8%)	53/162 (32.7%)	164/1757 (9.3%)	52/162 (32.1%)	123/1757 (7.0%)	2/162 (1.2%)	47/1757 (2.7%)
SESC*	6/45 (13.3%)	44/537 (8.2%)	6/45 (13.3%)	37/537 (6.9%)	6/45 (13.3%)	32/537 (6.0%)	0/45 (0.0%)	6/537 (1.1%)

*SNSC – subjects naïve to IGSC, and SESC – subjects with past experience in IGSC therapy.
**95% C.I. = 24.6%, 37.2%, ***95% C.I. = 9.7%, 12.2%

Comment The proportion of infusions associated with one or more temporally associated AEs excluding infections was only slightly lower than the overall proportion of infusions with temporally associated AEs. In general, subjects who had past experience with SC therapy showed lower frequencies of temporally associated AEs, especially with IV administration. As well (not shown in the above Table, but present in Table 14.3.2-9 of the study report) there is a trend of decreasing AE frequency from Study Part 2 (switch from IV to SC) over time towards the Extension Study Part. For instance, the proportion of infusions associated with temporally associated local AEs (excluding infections) was highest in Study Part 2 (4.9%) and declined to 1.1% at the Study Extension Part.

The data on the proportion of infusions with temporally associated AEs are consistent with those on the rate of temporally associated AEs per infusion (in Table 14.3.2-11 of study report but not shown here). The rate of temporally associated AEs per infusion is low. The median rate of temporally associated AEs per infusion for FSDS was 0.25 after IV and 0.08 after SC infusions. The median rate of "related" AEs per infusion for FSDS was actually 0 for both (Table 14.3.2-11 of study report)

Also not shown in the above Table are the proportions of infusions associated with "related" AEs. This was higher after IV than after SC infusion of the product (22.2% vs. 5.5%). The proportion of infusions associated with one or more local AEs (excluding infections) that began during infusion or within 72 h of completion of infusion was highest in Study Part 2, which marked the change from IV to SC infusions, and the proportion of local AEs was lowest in Study Part 1 (IV infusion).

The upper bound of the 95% confidence interval for the proportion of infusions with temporally associated AEs was 12.2% over the SC administration phases. This is substantially lower than the upper bound desired for IGIV products when administered intravenously (40%). Indeed, the IV administration phase gave a corresponding upper bound of 37.2% in this study.

- Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

There were no deaths in the FSDS, although one subject died without having had any administration of investigational product. See above for discussion of SAEs: a total of 4 SAEs were reported from the subjects who received investigational product and all 4 SAEs were considered unrelated to the use of the investigational product by the investigator. Narratives of the SAEs are as follows:

Two SAEs occurred in subjects who did not receive investigational product, including one death:

- Subject --(b)(6)-- did not receive study treatment. She was a 52-year-old Caucasian female who died on----------(b)(6)--- from cardiorespiratory failure prior to initiation of study treatment. The investigator judged the event as unrelated to the study product or procedures.
- Subject -(b)(6)- did not receive treatment in the context of the study. The subject was a 15-year-old African-American male with hypogammaglobulinemia (diagnosed 1992) and had been on chronic IV therapy with immune globulin products (usually a non-GAMMAGARD LIQUID product). He developed a sickle cell pain crisis on 26 FEB 2008 during routine care with GAMMAGARD LIQUID. The infusion had to be stopped due to back and leg pain which were described as severe. IV fluids, Tylenol, and Benadryl were administered. Naprosyn was also given. The pain decreased and the subject was discharged home. As the pain increased again during the evening of that day, the subject was admitted to hospital for IV fluids and pain medication on 27 FEB 2008. The subject recovered and was discharged from hospital on 29 FEB 2008. According to the discharge summary, the subject developed generalized musculoskeletal pain associated with GAMMAGARD LIQUID infusion, possibly from rapid infusion and exacerbated by upper respiratory infection.
- Subject --(b)(6)-- was a 40-year-old Caucasian female with PI who presented at the emergency room on 08 MARCH 2008 with abdominal pain. Examination revealed two gallstones. On 22 MAR 2008, the subject underwent surgery to remove her gallbladder. The subject had received SC GAMMAGARD LIQUID on 07 MAR 2008. Medical history was also significant for recurrent sinusitis, recurrent urinary tract infection, chronic fatigue, migraine headaches, depression, irritable bowel syndrome, fibromyalgia, osteoarthritis, common variable immune deficiency, corrective mandible surgery, Cesarean section (X2), tubal ligation, endoscopy, colonoscopy, endometrial ablation, ruptured disc in the neck, gastroesophageal reflux disease (GERD), and insomnia.
- Subject --(b)(6)- a 5-year-old Caucasian female, was hospitalized on 04 APR 2008 for sinusitis after a sinus CT on 03 APR 2008 had suggested an acute infection. On 09 APR 2008, the subject recovered and was discharged from hospital. The subject had received IV GAMMAGARD LIQUID on 26 MAR 2008. Medical history of the subject included chronic sinusitis. No action was taken on the investigational product or trial procedure.
- Subject --(b)(6)- , a 42-year-old Caucasian female, developed chest pain after SC administration of GAMMAGARD LIQUID. The last administration of GAMMAGARD LIQUID before the event was on 01 SEP 2008. She was not feeling well on the evening of 03 SEP 2008 and went to the emergency room (ER), and was admitted on 04 SEP 2008 to rule out blood clot in the left arm. On the same day, the subject was discharged from the hospital and considered recovered. Per discharge summary, she presented with chest

pain at the side of her mediport (left side) on her chest. Medical history included asthma, umbilical hernia repair, cholecystectomy, and gastric bypass. Family history included diabetes mellitus and increased clot production. No action was taken on the investigational product.

- Subject --(b)(6)- , a 19-year-old Caucasian male, had a seizure which required hospitalization. He had received IV GAMMAGARD LIQUID in the context of Study 160601 on 04 FEB 2007. For the SAE, the subject was treated with Depakote and Keflex. On 29 FEB 2008, he had recovered and was released from hospital. The subject had been diagnosed with a seizure disorder 4 years previously and had been taken off anti-epileptic medication a year prior to the SAE. No action was taken on the investigational product.

C. Clinical Laboratory Evaluation

Laboratory parameters including hematology and clinical chemistry were determined at baseline, at each 3 or 4-week study visit in Study Part 1, at Visits 1, 5, and 9 in Study Part 2, at Visit 1 in Study Part 3a, at Visits 1, 5, and 9 in Study Part 3b, at Visit 1 in the Study Extension Part and at the end-of-study evaluation. Urinalysis was performed at baseline, at the first visit in each study part and at end of study. There were no consistent clinically relevant laboratory abnormalities from investigational product administration in this study.

Although decreases in hemoglobin after administration of the investigational product of more than 20 g/L, which could be indicative of hemolysis, were observed in 3 isolated instances --(b)(6)- at study extension Visit 1, --(b)(6)- at Study Part 1 Visit 2, and --(b)(6)- at Study Part 1 Visit 2), none of the subjects had appreciable changes in LDH at the same time or corresponding AEs reported.

D. Other Observations Related to Safety

Concomitant medications. All medications taken for up to 2 weeks prior to study entry and all concomitant medications administered during study were documented. Prophylactic treatment with antibacterial antibiotics was not allowed during the study. Pre-medication with antihistamines, antipyretics, and/or steroids in subjects prone to AEs following IG product administration was to be avoided and their use of permitted only under specified conditions.

Vital signs and physical findings. For each infusion, vital signs including sitting BP, pulse, respiratory rate and body temperature were monitored and recorded pre-infusion (within 30 minutes prior to infusion), 30 minutes after initiation of infusion, and hourly (after initiation of the infusion) during and after infusion (within 30 minutes of completion). Vital sign changes considered clinically significant by the investigator were recorded, handled as an AE, and monitored until returning to baseline. Vital signs and physical exams did not give rise to safety concerns.

E. Safety Conclusions

- Median maximum infusion rates of 20.0 mL/h and of 30.0 mL/h were achieved for SC infusion of GAMMAGARD LIQUID in the age groups of 2 to <12 and of ≥12, respectively. The proportion of infusions in the entire SC treatment period associated with rate reduction, interruption or discontinuation for tolerability reasons was low (0.2%) [primary safety endpoint]. This parameter also decreased with the duration of SC treatment.
- The rate of temporally associated AEs per infusion and the rate of related AEs per infusion were low. The median rate of temporally associated AEs per infusion for the entire population treated was 0.25 after IV and 0.08 after SC infusions.
- This study included mainly subjects who were naïve to SC immunoglobulin replacement (38/49). The proportion of infusions with temporally associated ***local*** AEs (excluding infections) was highest in Study Part 2 (4.9% upon switch from IV to SC treatment) and decreased to 1.1% in the Study Extension Part (2.3% for the entire IGSC period). The proportion of infusions with temporally associated ***systemic*** AEs (excluding infections) was instead highest during the IV treatment period (28.0%) but still decreased to 6.8% during the entire period of SC replacement therapy.
- The proportion of infusions associated with "***related***" AEs was also higher after IV than after SC infusion of GAMMAGARD LIQUID (22.2% vs. 5.5%), corroborating the findings with temporally associated AEs. The reported symptoms related to the use of GAMMAGARD LIQUID are consistent with symptoms reported in the literature. The major symptom/AE reported after SC administration was injection-site reactions. The most frequently reported related systemic AE was headache. Most of the subjects reporting ***related*** AEs during SC treatment had symptoms of mild severity. The most frequently reported ***related*** symptoms during SC replacement were infusion site reactions, followed by headache, increased heart rate, and fatigue.
- There were 4 SAEs reported during the IV and SC treatment periods, but they were considered by the investigator to be not related to the use of GAMMAGARD LIQUID.

- Clinical laboratory parameters (hematology, clinical chemistry, and urinalysis) evaluated during the study did not show findings that would impact the safety profile of GAMMAGARD LIQUID. Vital signs and physical findings throughout the study did not give rise to new safety concerns.

6.2.3 BIMO Inspection Findings

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6.2.4 Conclusions from Study 160601

- Efficacy of GAMMAGARD LIQUID as a SC treatment of PI is demonstrated by (a) PK equivalence to its use as IV treatment for the same indication and (b) an acceptable rate of serious acute bacterial infections (0.067 per subject per year; with 99% C.I. upper bound of 0.134 per subject per year) in this population.
- The safety profile of GAMMAGARD LIQUID as SC treatment of PI is similar to that of its use as IV treatment for the same indication, except for a higher frequency of local adverse events but a lower frequency and severity of systemic events.

7 OVERVIEW OF EFFICACY

- Efficacy for SC administration of GAMMAGARD LIQUID in the treatment of PI is based on one pivotal trial, 160601, discussed in Section 6 of this memo. No overview is necessary.

8 OVERVIEW OF SAFETY

- Safety of SC administration of GAMMAGARD LIQUID in the treatment of PI is primarily supported by data in the pivotal study, 160601, discussed in Section 6 of this memo. In addition, there are data from studies on IV administration of the same product for the same indication which formed the basis of licensure of GAMMAGARD LIQUID in 2005: Baxter's studies 160101 and 160001. Description of these studies can be found in Section 6.1 of this memo. Baxter has submitted the study report of 160101 and its datasets to support product safety.
- Baxter's clinical study 160101 was a phase 3, randomized, double-blinded, non-controlled, multicenter clinical trial designed to evaluate the safety and efficacy of IV administration of GAMMAGARD LIQUID in subjects >24 months of age with PI. Safety in this study was assessed in subjects treated with at least 1 infusion of

investigational product. The dose to be administered per protocol was 300 to 600 mg/kg body weight (BW) every 21 to 28 days for 12 months. The primary safety endpoint was the proportion of infusions with temporally associated AEs, which was compared to 2 times the historical background rate of 20% (ie, 40%). Secondary safety endpoints included the following:

- The percentage of subjects with investigational product (IP)-related AEs.
- The proportion of infusions with 1 or more causally associated AEs, (ie, deemed by the investigator to be related to IGIV, 10%).
- The proportion of infusions with 1 or more temporally and causally associated AEs.
- The overall number and frequency of AEs in MedDRA terms.
- Other safety assessments included: examination of clinically significant laboratory parameters, changes in vital signs, and serology for HBV, HCV, and HIV.

o There were 61 subjects treated with 826 IV infusions of GAMMAGARD LIQUID. The median weight-adjusted dose per infusion was 455 (range: 262 to 710) mg/kg. The majority of subjects (78.69%, 48/61) achieved a maximum rate of >2 mL/kg/h and ≤4 mL/kg/h, 12 (19.67%) achieved >2 mL/kg/h and ≤6 mL/kg/h, and 1 achieved 8 mL/kg/h.

o A total of 911 AEs were reported in 61 of 61 subjects, of which 15 events in 8 subjects were serious, 896 were non-serious. There were no deaths. One subject withdrew in the optional post-efficacy phase due to AE (pruritic paular rash). Among the 15 SAEs, 1 (2 episodes of aseptic meningitis in 1 subject) was considered related to GAMMAGARD LIQUID treatment. None of the subjects withdrew from the study during the efficacy period due to an AE. Among the 896 non-serious AEs, 204 were possibly and 54 were probably considered product-related and the majority (880/896) were mild or moderate events. The following Table shows the rates of "related" AEs and AEs temporally associated with infusions (during or within 72 hrs after the end of an infusion).

Study 160101. Infusions with ADRs or Temporally Associated AEs

Category	Total [N/X (%)]	P-Value [a]
Causally "related"		
Including 1st Infusion	141/826 (17.07%)	NAP
Excluding 1st Infusion	125/756 (16.34%)	NAP
Temporally-Associated		
Including 1st Infusion	206/826 (24.94%)	p << 0.0001
Excluding 1st Infusion	180/765 (23.53%)	p << 0.0001

Abbreviations: N/X = (N) number of infusions with associated AEs and (X) the total number of infusions; (%) = percent of infusions; NAP = not applicable.
[a] Compared with the hypothesized percentage of 40%

o The following Table on temporally-associated AEs in Study 160101 is adapted from the approved package insert of GAMMAGARD LIQUID:

Study 160101. Temporally Associated AEs, *Excluding Infections* in >5% of Subjects

Event	By Infusion		By Subject	
	N	%	N	%
Headache	57	6.90	22	36.1
Fever	19	2.30	13	21.3
Fatigue	18	2.18	10	16.4
Vomiting	10	1.21	9	14.8
Chills	14	1.69	8	13.1
Infusion site events	8	0.97	8	13.1
Nausea	9	1.09	6	9.8
Dizziness	7	0.85	6	9.8
Pain in Extremity	7	0.85	5	8.2
Diarrhea	7	0.85	5	8.2
Cough	5	0.61	5	8.2
Pruritus	5	0.61	4	6.5
Pharyngeal Pain	5	0.61	4	6.5

Comment The safety profile of GAMMAGARD LIQUID administered IV in the treatment of PI is similar to those of other immune globulin products administered IV. These data are supportive of the safety of GAMMAGARD LIQUID for SC use in the treatment of the same indication.

- Since the pivotal study in this supplement, 160601, contains a phase with IV administration of GAMMAGARD LIQUID for 12 weeks, there are actual data on IV

use to compare with safety in SC use of the product. This has been discussed in Section 6 of this memo. Essentially, SC administration of GAMMAGARD LIQUID as compared to IV use is associated with higher frequency of local injection site AEs, but also lower frequency and severity of systemic events.

- The safety and risks of the administration of human immune globulin products have been well documented, and are discussed in the package inserts of the licensed human immune globulin products. The risks include hypersensitivity, renal dysfunction, thromboembolism, aseptic meningitis syndrome, hemolysis, transfusion-related acute lung injury (TRALI), transmission of infectious agents, interference with clinical laboratory tests, and interference of live vaccine effects. These risks can generally be managed with labeling. Since GAMMAGARD LIQUID is a licensed product for IV use, post-marketing data are available to assess these risks for that route of administration. There does not appear to be major differences between GAMMAGARD LIQUID and other immune globulin products in the postmarket reporting of adverse reactions in the IV treatment of PI.

Comments There have been an accumulation of reports of hypersensitivity resulting from the use of GAMMAGARD LIQUID. Baxter has discussed with FDA on this issue in a teleconference on 7/26/10. As yet, no root cause has been found. Baxter was requested to address this issue via an Information Request after mid-cycle review of this supplement (see below).

The study on GAMMAGARD LIQUID as SC therapy for the treatment of PI, 160601, has not documented evidence of hemolytic disease. However, it is possible that the evaluation in PI studies is generally not timed for the optimal collection of information on hemolysis. Since the use of GAMMAGARD LIQUID together with recombinant human hyaluronidase in healthy volunteers in a SC study resulted in reports of hemolysis (Baxter's Study170901, Part 4; hemolysis attributed by Baxter to be due to intercurrent viral infection), adequate postmarket surveillance on the occurrence of hemolysis is warranted. Baxter was requested to address this issue via an Information Request after mid-cycle review of this supplement (see below).

There is a risk of thromboembolism in the use of immune globulin products by IV administration especially in susceptible individuals. This risk is stated in the package inserts of immune globulin products. Postmarket data on GAMMAGARD LIQUID has not revealed a propensity to this risk for IV use. For SC use, the risk of thromboembolic phenomenon is expected to be even lower.

An additional risk that has been considered concerns the off-label use for immune thrombocytopenia (ITP) patients, because of the potential of hematoma formation if the product is administered to them subcutaneously. Although the dose and clinical setting for ITP treatment would make this use unlikely, there is still a possibility that should be mitigated. Since GAMMAGARD LIQUID does not have an indication for ITP use by either the IV or the SC route, the approach must be sensitive to the fact that any communication to the healthcare provider about this issue may inadvertently promote off-label use for ITP with GAMMAGARD LIQUID via the IV route. Thus, it would be inappropriate to institute an "education program" to healthcare providers on this issue. Instead, Baxter has been requested to implement in the PVP measures to address this possibility by enhanced reporting. Baxter agreed (see below, section 11.1).

9 SPECIAL POPULATIONS

- There are no data in pregnant women, lactating mothers, or pediatric patients aged 2 or under regardinig the SC use of GAMMAGARD LIQUID in PI. Study 160601 included 4 geriatric subjects aged 65 to 77 with PI, and this sample size is too small to draw conclusions on differences with other subjects.
- Study 160601 has included 18 pediatric subjects treated with SC administration of GAMMAGARD LIQUID (14 aged 2 to <12, and 4 aged 12 to <16: see Section 6 for safety and efficacy data). At the pre-BLA meeting, FDA recognized Baxter's pediatric database as adequate, and agreed that waiver or deferral would not be necessary

for the age groups 2 to <12 and 12 to <16. Only waiver for neonates and children up to 2 years of age needs to be requested, and such a waiver has been submitted.

- The pediatric assessment for SC use of GAMMAGARD LIQUID in this supplement was presented to the Pediatric Review Committee (PeRC) on 12/15/10. The PeRC endorsed the waiver for pediatric patients below 2 years of age. Between 2 to 16 years of age, Baxter has provided safety and efficacy data to support use in children and adolescent age groups, but within the pediatric age group, PK data were only obtained in the adolescent subjects in Study 160601. The PeRC agreed that SC use in patients between 2 and 16 years of age is supported by the assessment submitted by Baxter, but would encourage future PK studies in pediatric subjects below 12 years of age.

10 POSTMARKET EXPERIENCE

- GAMMAGARD LIQUID has not been licensed for Sc use in the treatment of PI. It has been available since 2005 for IV use for the same indication. See OBE Review on post-market experience of this product used as IV therapy for PI.

11 REVIEW ISSUES ADDRESSED AFTER MID-CYCLE

11.1 Mid-Cycle Review Issues and Baxter's Response on 11/15/10

The issues from the Review Disciplines at mid-cycle were conveyed to Baxter in an Information Request (IR) on 10/26/10 to which Baxter responded on 11/15/10. The following are the comments conveyed and Baxter's responses.

1. In the teleconference held on July 26, 2010 regarding hypersensitivity reactions to Gammagard 10% Liquid, you informed us that you were investigating the root cause for these reactions. Please submit your investigation results and case analysis for predisposing factors, and propose how this risk can be adequately managed for subcutaneous use in the home treatment of primary immunodeficiency with Gammagard 10% Liquid.

Baxter responded that the 7/26/10 teleconference was held to discuss two withdrawn lots of the product with an increased rate of hypersensitivity reactions. Baxter initiated a Corrective and Preventative Action (CAPA) investigation on these lots, LE12J370 and LE12J379, including all aspects of the manufacturing process, review of all in-process and final product testing results, additional testing characterization of the impacted lots, and pharmacovigilance investigation of the adverse events. All quality requirements and specifications were met by the impacted lots. Baxter determined there were no quality issues with Lots LE12J370 and LE12J379 that could be associated with the increased incidence in adverse event reporting of hypersensitivity reactions.

As of the end of October 2010 there were 53 reactions reported: 17 in Lot LE12J370 (3 serious), and 36 in Lot LE12J379 (8 serious). There was no apparent pattern with regard to age, sex, indication, or dose. The majority of events for which the event time is known occurred during or soon after infusion. Baxter has not received reports of an unusually high number of allergic events for other lots of GAMMAGARD LIQUID. No allergic local or systemic reactions occurred in the clinical trial that included 2294 subcutaneous infusions (Study 160601).

Baxter recognized that SC administration is of potential home use and possibly without medical supervision; thus there is concern that should an acute reaction occur there would be a delay in obtaining medical assistance. These actions are being taken to address the risk:

- *The proposed package insert will advise prescribers that patients with a history of allergic reactions to blood products should not be treated subcutaneously at home until they have been treated under controlled conditions and until they have been shown to tolerate the infusions without adverse reactions.*
- *Information to patients will contain language alerting them to the potential risk of allergic reactions and to seek medical attention immediately should they develop skin rashes, especially hives, difficulty breathing or swallowing, or if they become faint or light-headed.*

Comment The risk of significant systemic reactions with SC use of immune globulin products is low and much less than following IV administration (Gardulf A., etal. J Clin Immunol. 2006; 26:177-85). There were no severe allergic reactions in the Baxter Study 160601 which evaluated the SC administration of GAMMAGARD LIQUID or in the clinical studies of other FDA approved subcutaneously administered gammaglobulin products. Despite the low risk of systemic reactions, especially allergic events, associated with SC infusions of gammaglobulin, the risk cannot be eliminated entirely. Baxter's plans are reasonable. However, the occurrence of hypersensitivity reaction could be unpredictable, especially with the change of product lots. Thus, for self-administration, there should be measures for immediate management should a severe reaction occur. This was brought to Baxter's attention in a communication on 12/27/10 (see below).

2. Please submit all reported information and your investigations regarding hemolysis associated with the use of Gammagard 10% Liquid product, and propose how this risk can be adequately managed for subcutaneous use in the home treatment of primary immunodeficiency with Gammagard 10% Liquid.

Baxter discussed the two episodes of hemolysis that occurred in Baxter Study 170901, which evaluated GAMMAGARD LIQUID or a similar 20% formulation administered with recombinant human hyaluronidase (rHuPH20). These episodes were in association with flu-like symptoms shown to be associated with seroconversion to H1N1 Influenza A. The investigations on these adverse events have previously been submitted under -------(b)(4)-------- and evaluated by CBER without discovery of any relevant risk factors predisposing to the hemolysis. No similar reactions have occurred in any of the other Baxter studies evaluating IV or SC administration of gammaglobulin. Baxter provided a summary table and narrative of hemolysis events reported since the 2005 approval of GAMMAGARD LIQUID, and showed there have not been an increased number of hemolysis events reported in Baxter's pharmacovigilance database. Literature search has also not uncovered any report of hemolysis associated with SC infusions of gammaglobulin.

Baxter will mitigate the risk of hemolysis with warning in the proposed package insert and as information to patients concerning the risk of hemolysis, noting that should patients develop dark colored urine, decreased urination, back or abdominal pain, light headedness or fatigue, they must contact their healthcare provider immediately.

Comment The risk of significant hemolysis is also addressed in Baxter's pharmacovigilance plan. Although the above measures may not necessarily mitigate the risk of hemolysis, they appear to be adequate for management should such an event occur, even for home use of the product to be administered subcutaneously.

3. Regarding dose adjustment upon attainment of steady state with subcutaneous administration of your IGIV 10% LIQUID product, please address the following:

• The use of the "expected average IgG trough level factor" (EATLF) in Study 160601 assumes a linear relationship without intercept between target trough IgG level under SC administration and trough IgG level under IV administration (Study Part 1). Data supporting this assumption of a no-intercept linear relationship are lacking. Please reevaluate this relationship and address its role in dose adjustment in proposed labeling.

Baxter contends that the dose in Study Part 2 (130% of IV dose) was close to the dose required in Study Part 3a (137% of IV dose), the loss of accuracy due to the linear approximation was accepted, because the limiting factors at the interim analysis were believed to be measurement errors in the IgG trough levels and the small sample size.

Comment Baxter has not addressed the no-intercept assumption. This was brought to Baxter's attention in a communication on 12/27/10 (see below).

• Study 160601 uses a nomogram to obtain a dose ratio of the SC dose required for equivalent AUC relative to the weekly IV dose as a function of the IgG trough level ratio of SC over IV administration, whereas proposed labeling uses a table to find the dose increment for dose adjustment. Please clarify how proposed labeling is supported by the nomogram method.

Baxter states that the nomogram method used in Study 160601 is not used to establish the dose-adjustment Table in the package insert, which is based on a similar approach as in currently approved package inserts.

Comment Although it is acceptable to have a similar approach as in other package inserts with the use of the proposed dose-adjustment Table (Table 1 in the package insert), construction of the Table must be based on data from Baxter's study. See comment under next bullet.

• The dose adjustment table in proposed labeling uses a slope of 7 kg/dL for trough level change vs. dose increment based on linear relationship without intercept. Please provide data to support this no-intercept assumption, as forcing the slope through the origin may underestimate the dose increment required.

Baxter discussed the issues relating to over- and under-correction of IgG trough level, but did not provide data to support the 7 kg/dL slope.

Comment Baxter has been asked again to provide data supporting the slope in a communication on 12/27/10.

4. Please submit analysis-ready files of individual datasets that provide infection data that correspond to tables of infection rates (such as Tables 14.2.2-14, 14.2.2-15) in the Clinical Study Report, and the datasets that support Table 7 "Summary of Infections and Associated Events" in the proposed package insert. In addition, please submit the datasets used for the Poisson model in SAS program (i.e. "sabactsum" and "infsum1a").

Baxter submitted analysis-ready datafiles for the Statistical Reviewer to review.

Comment The submitted material contains inconsistencies from patient diary records, resulting in further communication on 1/6/11 to Baxter for reconciliation of the information (see below and Statistical Review).

5. In Baxter responses received by FDA on August 10, 2010, Baxter supplied the following facilities that have bearing on the Immune Globulin Subcutaneous (Human) (IGSC) product:

Los Angeles Facility 4501 Colorado Blvd. Los Angeles, CA 90039 CFN #2011021	Lessines Facility Baxter S.A. Boulevard Rene Branquart 80, B-7560 Lessines, Belgium CFN #9611642
Vienna Facility Baxter AG, Industriestrase 131 4-1220 Vienna, Austria CFN #9610020	---------- ---------- ----------(b)(4)---------- ----------

Please clarify what part of the product manufacturing is completed at each of these locations.

The manufacture of Precipitate G is performed at the Baxter Los Angeles, Vienna and (b)(4) facilities. Precipitate G is then shipped to the Baxter Lessines facility for further manufacture into the IGSC final product.

Comment The DMPQ Reviewer has reviewed the inspection history of the above sites in conjunction with other pertinent factors regarding this supplement, and has recommended waiving inspection. However, a compliance check of the Belgian facility at Lessines by the Division of Case Management of Office of Compliance and Biologics Quality (OCBQ) between 1/10/11 and 1/21/11 revealed issues that are pending resolution by the time this memo is being finalized. OCBQ has recommended that the efficacy supplement not be approved at this time.

6. Please submit a plan for the implementation of routine monitoring and reporting of adverse events, including the submission of 15-day expedited reports for serious, unlabeled adverse events and Periodic Safety Update Reports (PSURs), quarterly for the first three years after licensure and yearly thereafter, as required under 21 CFR 600.80.

Baxter cites a waiver (25 August 2008 letter) from reporting in the PAER format per 21 CFR 600.80 and to instead report in the PSUR format for the currently licensed "intravenously"

administered GAMMAGARD LIQUID IGIV, 10% product on a yearly basis. Since the SC administration is an efficacy supplement and not a new BLA, Baxter proposes to continue to submit a yearly PSUR and will include reports of adverse events for both SC and IV administration of GAMMAGARD LIQUID.

Comment Baxter's proposal is not acceptable to OBE and this was communicated to Baxter on 12/23/10 (See below).

7. Please provide expanded adverse experience reporting for subcutaneous use of Gammagard 10% Liquid (in addition to complying with the requirements under 21 CFR 600.80) to the Adverse Reporting System for one year following product licensure with submission of 15-day expedited reports, regardless of seriousness, the case reports for:

- all adverse events in patients who have had off-label use of the product for immune thrombocytopenia (ITP), and
- all hemolysis adverse events

Baxter agrees and has updated the pharmacovigilance plan.

Comment Issue resolved.

8. Please identify in specific subsections of the annual Periodic Safety Update Reports (PSURs) any bleeding events in ITP patients who have had off-label, subcutaneous treatment with Gammagard 10% Liquid. In addition, please identify all occurrences of subcutaneous administration in ITP patients as either (a) medication error reports (if no associated adverse event) or (b) adverse event case reports associated with subcutaneous use.

Baxter agrees and has updated the pharmacovigilance plan.

Comment Issue resolved.

9. Please consider measures to expand the safety database, given the limited study duration and the small number of subjects systematically evaluated, especially in certain groups (pregnant and lactating women, children younger than 2 years, and individuals older than 65 years).

Baxter did not believe that an independent database of SC use is justified.

Comment This comment was provided by OBE, and OBE does not intend to pursue further on the issue.

11.2 Resolution of Pending Issues from Mid-Cycle Comments and Baxter's 11/15/10 Response

The following remained to be resolved despite Baxter's 11/15/10 response:

- Risk of severe hypersensitivity reactions and their management during home treatment.
- The no-intercept assumption for the relationship between IgG trough levels during IV and SC administration of GMMAGARD LIQUID.
- Support for dose-adjustment Table in draft package insert (slope of IgG trough level change vs dose change).
- Data inconsistencies to support Table in draft package insert on infections, hospitalizations, antibiotic use and time away from work and school.
- Quarterly periodic safety reports for the first three years after licensure
- Compliance issues at Baxter's Lessines facility in Belgium

1. Risk of severe hypersensitivity reactions and their management.

FDA and Baxter held a teleconference on 12/27/10 to discuss the risks of severe hypersensitivity reactions and management of such risks in a home use setting for SC administration of GAMMAGARD LIQUID. Although such a risk is low, it is recognized that Baxter has had recent withdrawals of product lots due to hypersensitivity reactions, and thus the risk can be unpredictable.

On 1/11/11 Baxter submitted more detailed information regarding the lot withdrawals. It is also noted that none of the events reported for the two lots in question were associated with SC administration of GAMMAGARD LIQUID.

Baxter states that other manufacturers, such as Talecris and Octapharma, have had similar withdrawals of specific lots of their immune globulin products due to allergic reactions. Their investigations, as well as Baxter's, have never identified a root cause. Such lots appear to be exceptions, and not indicative of the overall safety profile of the product. Nevertheless, Baxter has proposed strengthening warnings and instructions for care providers and patients as detailed previously in their response to IR on 11/15/10, and further revised in the submission of 1/11/11 by advising patients to have responsible persons and rescue medications available to treat serious reactions or summon help, should such reactions occur.

Comment Issue resolved.

2. No-intercept assumption for the relationship between IgG trough levels during IV and SC administration of GMMAGARD LIQUID.

At a teleconference dated 12/27/10, FDA discussed with Baxter about the relationship between IgG trough levels during IV and SC administration, and advised Baxter that although the relationship is linear, the straight line does not go through zero, and thus using a factor to link the trough levels would be unwarranted. Other approved package inserts of immune globulin products for SC administration have now been revised to add a specific value to the IgG trough level under IV administration in deriving the target IgG trough level with SC administration. Similar methodology should apply to GAMMAGARD LIQUID. Baxter responded on 1/11/11 without adopting the no-intercept methodology.

Another teleconference was held on 1/24/11 to discuss the relationship between IgG trough levels during IV and SC administration. Baxter subsequently presented a draft package insert on 1/28/11 revising this relationship to be: "To calculate the target trough IgG level, add 281 to the last IgG trough level obtained during intravenous therapy." FDA requested Baxter to provide data supporting the figure 281 mg/dL, and this was provided by Baxter in a submission on 2/1/11. At another teleconference dated 2/10/11, FDA and Baxter discussed the methodology used by Baxter ---------(b)(4)---------- in arriving at the figure to be added (281 mg/dL). Baxter provided further analyses using different variance ratio assumptions on 2/11/11 for FDA's review. After further clarifications and corrections, it was determined that it would be appropriate to add 300 mg/dL to the IgG trough level under IV administration in order to derive the target IgG trough level for SC administration.

Comment Issue resolved.

3. Data supporting construction of Table 1 of the draft package insert (slope of IgG trough level chagne vs dose change).

At a teleconference dated 12/27/10, FDA again asked Baxter for data supporting the slope for the IgG change vs dose change curve in constructing the dose-adjustment Table in the package insert.

Baxter submitted the data used for deriving the slope of 7 kg/mL for this Table on 1/11/11 (file named dosetab.xpt), and explained that the slope was calculated as median of the SLOPE variable and rounded to 1 significant digit. Since the dosetab.xpt file defines "slope" for each individual subject on single datapoints with IgG trough level at phase 3b of Study 160601 divided by the dose, such "slope" is not based on changes in trough level or dose. This was discussed with Baxter at a teleconference on 1/24/11.

Baxter subsequently presented a draft package insert on 1/28/11 revising the slope for the dose-adjustment Table to be 5.3 kg/dL, and supporting data were presented in a submission dated 2/1/11. This slope of 5.3 kg/dL is based on changes in trough level and changes in dose and is deemed satisfactory.

Comment Issue resolved.

4. Data inconsistencies to support Table in draft package insert on infections, hospitalizations, antibiotic use and time away from work and school.

Baxter provided explanations in submissions dated 1/14/11 and 1/26/11, including the correction of errors coding for hospitalization due to infections. The explanations are deemed satisfactory and the Statistical Reviewer was able to verify Baxter's data in the Tables in the Clinical Studies section of the draft package insert.

Comment Issue resolved.

5. Quarterly periodic safety update reports for the first three years after licensure
In a teleconference dated 12/23/10, OBE communicated to Baxter that for SC administration, quarterly reporting of adverse events should be implemented approval of the supplement for 3 years. Baxter indicated that this would create a discrepancy between the reporting for IV use and for SC use. Subsequently OBE had internal discussion on this issue, and determined that Baxter should submit Periodic Adverse Experience Reports (PAERs) for SC administration quarterly for 3 years upon approval of the supplement, and then Periodic Safety Update Reports (PSURs) on an annual basis, while the safety reporting for IV administration can continue on a yearly basis in the form of PSURs because of the waiver granted to Baxter in 2005. Baxter agreed and incorporated this into the pharmacovigilance plan.

Comment Issue resolved.

6. Compliance issues at Baxter's Lessines facility in Belgium
Compliance issues at Baxter's Lessines facility are pending resolution by the time this memo is being finalized. OCBQ has recommended that the efficacy supplement not be approved at this time.

Comment Non-approval of this supplement will be based on establishment issues at the Lessines facility.

12 CONCLUSIONS - OVERALL

- Efficacy of GAMMAGARD LIQUID as a subcutaneous treatment of primary immunodeficiency is demonstrated by (a) pharmacokinetic equivalence to its use as intravenous treatment for the same indication and (b) an acceptable rate of serious acute bacterial infections (0.067 per subject per year; with 99% C.I. upper bound of 0.134 per subject per year) in this population.
- The safety profile of GAMMAGARD LIQUID as a subcutaneous treatment of primary immunodeficiency is similar to that of its use as an intravenous treatment for the same indication, except for a higher frequency of local adverse events but a lower frequency and severity of systemic events.

13 RISK-BENEFIT ASSESSMENT/RECOMMENDATIONS

13.1 Risk Benefit Assessment
- The risks of GAMMAGARD LIQUID as a subcutaneous treatment of primary immunodeficiency are outweighed by its benefits.

13.2 Discussion of Regulatory Options
- From a clinical perspective, this efficacy supplement is approvable with new proper name for the product: Immune Globulin Infusion (Human), pending acceptance of revised labeling by Baxter and resolution of compliance issues at Baxter's Lessines facility in Belgium.

13.3 Recommendations on Regulatory Action(s)
- From a clinical perspective, this efficacy supplement is approvable with new proper name for the product: Immune Globulin Infusion (Human), pending acceptance of revised labeling by Baxter and resolution of compliance issues at Baxter's Lessines facility in Belgium.

13.4 Labeling Recommendations
- A package insert submitted on July 13, 2011 is the final approved PI

13.5 Recommendations on Postmarketing Actions

- None