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Application Type	Original Application
STN	125596/0
CBER Received Date	September 14, 2015
PDUFA Goal Date	September 13, 2016
Division / Office	DHRR /OBRR
Priority Review	No
Reviewer Name(s)	Laurence Landow
Review Completion Date / Stamped Date	
Supervisory Concurrence	
Applicant	Baxalta US Inc.
Established Name	Immune Globulin Subcutaneous (Human), 20% Liquid
(Proposed) Trade Name	Cuvitru
Pharmacologic Class	Immune Globulin Subcutaneous (human)
Formulation(s), including Adjuvants, etc	Liquid; 0.2 g/ml solution for injection
Dosage Form(s) and Route(s) of Administration	IGSC 20%, subcutaneous; 5 mL, 10 mL, 20 mL, 40 mL vials
Dosing Regimen	300-1000 mg/kg monthly; dosed weekly, biweekly, or 2-7 times/week
Indication(s) and Intended Population(s)	Replacement therapy for primary humoral immunodeficiency (PI) in adults and pediatric subjects >2 years of age
Orphan Designated (Yes/No)	No

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GLOSSARY

AESI: AE of special interest
AE: AE (an untoward medical occurrence associated with use of a drug whether or not considered drug related)
AR: adverse reaction (AE known to be caused by a drug)
AR: alternate response (in Study NGAM-02: elevation in platelet count to $\geq 30 \times 10^9$/L and at least double the baseline platelet count, confirmed on at least 2 separate occasions at least 7 days apart, and absence of bleeding)
CI: confidence interval
CSR: clinical study report
CVID: common variable immunodeficiency
Ig: immunoglobulin
ICF: informed consent form
IGIV: Immune Globulin Infusion (Human) administered intravenously
IGSC: Immune Globulin Infusion (Human) administered subcutaneously
PI: primary immunodeficiency
PT: MedDRA preferred term
QoL: quality of life
SAR: serious adverse reaction
SBI: serious bacterial infection
SC: subcutaneous
SOC: MedDRA system organ class
TEAE: treatment emergent AE (untoward medical occurrence not necessarily considered drug related)
XLA: X-linked agammaglobulinemia

1. Executive Summary

BLA 125596/0 is intended to support use of Cuvitru (IGSC, 20%), Baxalta's subcutaneous immunoglobulin (Ig) replacement product for the treatment of primary immunodeficiency (PI) disease. Cuvitru is essentially the same product as the applicant's licensed GAMMAGARD LIQUID, 10% product (STN BL 125105) except for the (b) (4) and formulation steps (20% protein concentration instead of 10%). GAMMAGARD LIQUID is licensed for intravenous (IV) and SC administration in PI subjects.

To date, three IGSC products (one 20% product and two 10% products) have been licensed for the PI indication: (*a*) Hizentra (IGSC, 20%; CSL Behring), (*b*) HYQVIA (IGSC 10% co-administered with recombinant hyaluronidase; Baxalta U.S. Inc), and (*c*) GAMUNEX-C (IGSC 10%; Grifols Therapeutics Inc). The primary advantage of IGSC treatment over IGIV is convenience, i.e., IGSC can be self-administered at home; a disadvantage is that only small volumes can be infused over a given time, mandating multiple infusion sites per weekly treatment.

Three clinical studies were included in this original submission.

1. **Study 170904**
   Study 170904 was a phase 2/3, prospective, open-label, historic-controlled, multicenter (U.S., Canada) study designed to evaluate the efficacy, safety, tolerability, and pharmacokinetics of Cuvitru in subjects with PI (N=77). In this 4-part ("Epoch") study, subjects received GAMMAGARD LIQUID intravenously in Epoch 1 and Cuvitru subcutaneously during Epoch 2 through Epoch 4. To account for lower bioavailability with SC *versus* IV administration, Cuvitru dose-finding was an iterative process that progressed from Epoch 2 (fixed SC dose equivalent to 145% of IV dose) to Epoch 3 ("Adjusted Dose" of Cuvitru every 7 days for 3 months based on pharmacokinetic (PK) data from Epoch 1 and Epoch 2) to Epoch 4 ("Individually Adapted Dose" based on a comparison of measured trough levels in Epoch 1 and Epoch 3). The primary endpoint of Study 170904 was the annualized number of serious bacterial infections (SBI).

2. **Study 170903**
   Study 170903 (N=49) was a phase 2/3 study conducted in Europe with objectives similar to Study 170904. In Epoch 1, subjects received (*a*) KIOVIG[1] administered intravenously every 3 or 4 weeks for 13 weeks or (*b*) SUBCUVIA[2] administered subcutaneously every week or every other week for 12 weeks. In Epoch 2, all subjects received Cuvitru. When transitioning to Epoch 2, Epoch 1 subjects in the KIOGIV cohort received Cuvitru at the same dose of IGIV 10% as in Epoch 1, adjusted to a weekly-equivalent dose over a period of 51-weeks. The primary endpoint of Study 170903 was annualized number of SBI.

1 GAMMAGARD LIQUID is marketed by Baxalta ex-U.S. under the name KIOVIG
2 SUBCUVIA (IGSC, 16%; CSL Behring) is licensed by the EMA but not by FDA.

3. Study 160601

Study 160601 was a phase 2/3, prospective, open-label, historic-controlled, multicenter (U.S.) study in male and female subjects aged 2 years and older with PI (N=49) that was designed to determine the tolerability and pharmacokinetics of GAMMAGARD LIQUID, 10% when administered IV and SC. A further aim was to evaluate efficacy in terms of acute serious bacterial infections (SBI) and total infections during SC administration.

EFFICACY

Table 1 shows that Study 170904 and Study 170903 both met their primary endpoint: the point estimate of the annualized SBI rate among all subjects who received at least one dose of Cuvitru regardless of whether they completed the study (Safety Analysis Set), was 0.01 and 0.02, respectively, i.e., well below the threshold (SBI rate ≥1.0 per person year at the 1% level of significance) needed to reject the null hypothesis. Similar values were obtained for the pediatric subpopulation aged <16 years (0.06 for Study 170904 and 0.00 for Study 170903).

Table 1: Analysis of SBI by Study (Safety Analysis Set)*

Study	Epoch	Treatment Cohorts	Point Estimate	Upper Limit 99% CI	p-value
170904	2-4	Cuvitru	0.012	0.024	<0.0001
170903	2	Cuvitru	0.022	0.049	<0.0001

*Subjects who received at least one dose of Cuvitru

Adapted from text in the CSRs for Study170904 (page 61 of 885) dated 26 June 2015 and Study 170903 (page 52 of 737) dated 23 September 2014

The annual rate of acute serious bacterial infections in the GAMMAGARD LIQUID SC treatment cohort of Study 160601 was 0.067 (99% upper confidence limit: 0.134). This CI was substantially lower than the goal of achieving a rate of <1 SBI per person-year.

Several unrelated SBIs necessitating hospitalization were reported. One adult subject in Study 170904, a 78 year old White male with a specific antibody deficiency, experienced bilateral pneumonia during treatment with Cuvitru (Epoch 4) that lasted 6 days and required hospitalization. One pediatric subject in Study 170903 aged 11 years with XLA experienced 2 episodes of bacterial pneumonia (moderate severity); the first occurred during treatment with SUBCUVIA and the second during treatment with Cuvitru. Both subjects recovered with antibiotic therapy.

Secondary endpoints (Days off school/work, Days on antibiotics, Number of hospitalizations, Days in hospital, and Acute physician/ER visits) were consistent with achievement of the primary endpoint.

SAFETY

A total of 6675 Cuvitru infusions were administered in Study 170904 and 170903.

Serious Adverse Events (SAE)

SAEs (N=10), all unrelated to study drug, were reported in 8 subjects (6.6%): 2 subjects in Study 170904 and 6 subjects in Study 170903. These events included lung adenocarcinoma, myocardial infarction, ventricular fibrillation, nasal septum deviation, brainstem infarction, enteritis, chronic sinusitis, pneumonia and rhinorrhea (the last three likely representing treatment failures due to underlying disease).

Treatment Emergent Adverse Events (TEAE)

Table 2 shows that a high proportion of Cuvitru subjects experienced one or more TEAEs, regardless of age. All but 4 of these events were mild-moderate in intensity.

Table 2: TEAEs Reported in Association with Cuvitru Regardless of Causality (Safety Analysis Set)*

Classification	Subjects Affected n (%) (N=122)
Number of subjects experiencing ≥1 TEAE	111 (90.9)
Number of subjects experiencing TEAEs by intensity*	
Mild	64 (52.5)
Moderate	65 (53.3)
Severe	4 (3.3)
Number of subjects experiencing TEAEs by age cohort (years)	
<6 to 16 (N=39)	33 (84.6)
16 to <65 (N=71)	66 (93.0)
≥65 (N=12)	12 (100.0)
Number of subjects experiencing TEAEs within 72 hours	95 (77.9)
<6 to <16 year cohort (N=39)	27 (69.2)

*The same subject could have experienced ≥1 TEAE of different intensities

Adapted from Integrated Summary of Safety Tables 14 and 34, page 29 and 634 of 1575, date not indicated

Table 3 summarizes causally related and/or temporally associated TEAEs reported at a frequency ≥5% in the Cuvitru cohort of Study 170903 and Study 170904. It shows that a substantial proportion of subjects experienced local (33.6%) and systemic (60.7%) TEAEs.

Reviewer Comment

The Integrated Summary of Safety tables categorize safety data in three ways: (*a*) causally related, (*b*) temporally associated and (*c*) causally related and/or temporally associated. In this reviewer's opinion, "causally related and/or temporally associated" most closely mimics a patient-oriented outcome.

Table 3: Incidence ≥5% for Causally Related and/or Temporally Associated TEAEs Associated with Cuvitru (Safety Analysis Set)*

Adverse Event	Study 170903 (N=48) Subjects Affected n (%)	Study 170904 (N=74) Subjects Affected n (%)	Studies 170903, 170904 (N=122) Subjects Affected n (%)
Local TEAEs	18 (37.5)	23 (31.1)	41 (33.6)
Infusion/injection site pain/discomfort	10 (20.8)	15 (20.3)	25 (20.5)
Infusion/injection site erythema	10 (20.8)	8 (10.8)	18 (14.8)
Infusion/injection site pruritus	7 (14.6)	4 (5.4)	11 (9.0)
Systemic TEAEs	33 (68.8)	41 (55.4)	74 (60.7)
Headache	14 (29.2)	10 (13.5)	24 (19.7)
Diarrhea	9 (18.8)	5 (6.8)	14 (11.5)
Nausea	2 (4.2)	9 (12.2)	11 (9.0)
Fatigue	6 (12.5)	5 (8.1)	12 (9.8)

Adapted from Table 13, Response to IR, 17 July 2016, page 14 of 19

Table 4 is an indirect comparison of Cuvitru *versus* other licensed IGSC products based on data contained in package inserts of each product. It suggests that the incidence of local reactions is lowest using Cuvitru, even when compared with other, less-concentrated licensed IGSC, 10% products (HYQVIA and GAMMUNEX-C).

Table 4: Incidence ≥5% for Local and Systemic TEAEs: Cuvitru *vs*. Hizentra, HYQVIA and GAMUNEX-C

TEAEs	Cuvitru† No. of Subjects (%) (N=122)	Hizentra* No. of Subjects (%) (N=49)	HYQVIA♯ No. of Subjects (%) (N=81)	GAMUNEX-C↑ No. of Subjects (%) (N=32)
Local TEAEs	41 (33.6)	49 (100)	42 (51.9)	24 (75.0%)
Systemic TEAEs	74 (60.7)	45 (91.8)	55 (67.9)	No information listed
Headache	24 (19.7)	12 (24.5)	17 (21.0)	4 (13.0)

†Study 170903 + Study 170904, Integrated Summary of Safety (Causally Related and/or Temporally Associated within 72 Hours) Tables 20, 26 and 30, page 492 of 1575
*Table 2, Hizentra (IGSC, 20%) Package Insert, Jan 2015
♯Table 4, HYQVIA (IGSC, 10% with recombinant human hyaluronidase) Package Insert, Sep 2014
↑ Table 6, GAMUNEX-C (IGSC, 10%) Package Insert, Sep 2013

Reviewer Comment

Subcutaneous administration of therapeutic agents generally is considered to be easier, requires less time, and provides patients with greater flexibility than IV administration. While Table 3 appears to show that this convenience comes at some cost, i.e., a relatively "high" incidence of local TEAEs (33.6%), Table 4 suggests that Cuvitru actually is associated with fewer TEAEs when compared against other currently licensed IGSC products. Note: These data should be interpreted with caution since none of the products was directly compared with others in a clinical trial.

Risk-Benefit Assessment

The risk-benefit assessment of Cuvitru is favorable and commensurate to other marketed IGSC products. No adverse events of special interest (AESI), e.g., TEE, hemolysis, were reported.

RECOMMENDATION
I recommend an approval action be taken for this BLA.

1.1 Demographic Information: Table 5 presents demographic characteristics of the study populations. The Cuvitru study population (Study 170904 and Study 170903) comprised a total of 122 subjects. Inferences based on subgroups defined by gender, race and age cannot be made because of limited sample size and absence of a contemporaneous control cohort.

Table 5: Demographics of the Aggregate Study Population*

Parameter		Study 170904	Study 170903	Study 160601
Sample size		77	49	49
Age				
	Median	36	17	20
	Min; Max	3; 83	2; 67	3; 77
Gender				
	Male [N (%)]	40 (51.9)	30 (61.2)	27 (55.1)
	Female [N (%)]	37 (48.1)	19 (38.8)	22 (44.9)
Race				
	White [N (%)]	70 (90.9)	48 (98.0)	46 (93.9)
	Black/African American [N (%)]	3 (3.9)	0	2 (4.1)
	Hispanic/Latino [N (%)]	5 (6.5)	0	1 (2.0)
	Asian [N (%)]	2 (2.6)	1 (2.0)	0
	Multiple [N (%)]	2 (2.6)	0	0

**In Study 170904, 5 Hispanic/Latino subjects were displayed/counted under "Race" twice, once as Hispanic and once per their race. Without "Hispanic/Latino", the number of subjects totaled 77.*
Adapted from Table 3, ISE, page 20 of 48

Table 6 shows that a total of 39 pediatric subjects aged <16 years were enrolled in the two Cuvitru studies.

Table 6: Demographics of the Pediatric Population in Study 170904, 170903 and 160601

Study No.	No. of Subjects	<6 Years N (%)	6 to <12 Years N (%)	12 to <16 Years N (%)	Pediatric Subjects Receiving Cuvitru N (%)
160601	49	3 (6.1)	9 (18.4)	4 (8.2)	-
170903	49	5 (10.2)	8 (16.3)	5 (10.2)	18 (36.7)
170904	77	1 (1.3)	14 (18.2)	6 (7.8)	21 (27.3)
Total	175	9 (5.1)	31 (17.7)	15 (8.6)	39 (22.3)

Adapted from Table 3, Integrated Summary of Safety Tables, page 3 of 1575

2. Clinical and Regulatory Background

2.1 Disease or Health-Related Condition(s) Studied

PI diseases comprise a heterogeneous population of disorders that affect 1-2% of the population worldwide[3]. The main antibody deficiency syndromes of clinical significance include X-linked agammaglobulinemia (XLA), Common Variable Immunodeficiency (CVID), Wiskott-Aldrich syndrome, Hyper IgM Syndrome, Severe Combined Immunodeficiency (SCID), Chronic Granulomatous Disease (CGD), and IgG subclass deficiency. Although over 100 different primary immunodeficiencies have been described, fewer than 20 likely account for >90% of cases.[4]

PI is characterized by hypogammaglobulinemia with or without defective antibody production. Children and adults with PI are at increased risk for recurrent bacterial and viral infections that typically affect the respiratory tract (sinusitis, bronchitis and pneumonia) but can also affect the gastrointestinal tract (gastroenteritis). Symptoms can be severe and can lead to substantial morbidity. Response to antibacterial therapy is often poor. At present, most primary immune deficiencies are not curable, but IgG products have been shown to decrease the number of severe infections and duration of hospitalization.

Replacement therapy using Ig provides antibodies to prevent viral and bacterial diseases. Use of IgG replacement therapy to reduce the incidence of viral and bacterial diseases has been applied in three therapeutic domains: (*a*) replacement for subjects with PI syndromes who have significant defects in antibody formation (humoral immunity); (*b*) provision of antibody to subjects with immunodeficiency secondary to a disease, immunosuppressive therapy or losses of IgG; and (*c*) as adjuvant therapy in the treatment of infectious diseases.

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

General therapy for PI involves treating infections with antibiotics and preventing infections. Antibiotics may also be used to prevent infections (e.g. trimethoprim-sulfamethoxazole to prevent *pneumocystis carinii*),[3] but the mainstay of prevention lies in correcting immunodeficiency via replacement therapy using IgG products.

IgG products are licensed for the following indications:

(i) Treatment of primary immunodeficiencies
(ii) Prevention of bacterial infections in subjects with hypogammaglobulinemia and recurrent bacterial infection caused by B-cell chronic lymphocytic leukemia chronic lymphocytic leukemia, CIDP, and multifocal motor neuropathy
(iii) Prevention of coronary artery aneurysms in Kawasaki disease

3 Modell et al. Primary Immunodeficiencies Worldwide. Immunol Res 2016, Jan 22. Epub Ahead of print
4 Lindegren et al. Applying Public Health Strategies to Primary Immunodeficiency Diseases. MMWR Recommen Rep. 2004 Jan 16;53(RR-1):1-29

(iv) Prevention of infections, pneumonitis, and acute graft-*versus*-host disease after bone marrow transplantation
(v) Reduction of SBI in children with human immunodeficiency virus (HIV)
(vi) Increase of platelet count in idiopathic thrombocytopenic purpura (ITP) to prevent or control bleeding

2.3 Safety and Efficacy of Pharmacologically Related Products

Marketed IGIV and IGSC products have demonstrated annualized SBI rates <1.0 SBI/year in BLA clinical studies. The incidence of adverse reactions (AR) reported in BLA clinical studies varies according to product, route of administration, and maximal infusion rate. Because of these differences, the safety profile of each product is determined independently.

2.4 Previous Human Experience with the Product

There is no previous human experience with Cuvitru, and it is not currently licensed in any other country. The manufacturing of Cuvitru is based on the currently licensed liquid Ig Baxalta product, Immune Globulin Infusion (IGI, Human), 10% Solution, marketed under the trade name GAMMAGARD LIQUID. GAMMAGARD LIQUID is licensed for IV and SC replacement therapy in PI.

2.5 Summary of Pre- and Post-submission Regulatory Activity Related to the Submission

Pre-BLA meeting (April 24, 2015)

1) FDA advised Baxalta that the application should include integrated safety analyses of the clinical trials of Cuvitru with and without inclusion of data from IGIV 10% administered subcutaneously, e.g., GAMMAGARD LIQUID.
2) FDA advised Baxalta to define infusional AEs as those whose onset occurred within 72 hours of product infusion. FDA had previously advised that causally related and temporally related associated AEs within 24 hours and within 1 hour of completion of the infusion should be added as safety endpoints.
3) FDA recommended that Baxalta monitor for thrombotic events and hemolytic anemia, including testing for hemolysis at screening/baseline.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The submission was organized adequately to accommodate a thorough clinical review without undue burden. It was submitted electronically and formatted as an electronic Common Technical Document (eCTD) according to FDA guidance for electronic submission. The submission contained the five modules in the common technical document structure.

3.2 Compliance With Good Clinical Practices And Submission Integrity

Protocol deviations were categorized as major if they were violations from the protocol that require evaluation for potential impact to the statistical analysis and/or the

interpretation, safety, and/or efficacy of the Cuvitru (IP). Minor deviations were defined as all deviations without the potential to impact the safety or efficacy of the IP.

There were 1043 reported protocol deviations in 78 subjects reported during the study, of which 47 were qualified as "major". The majority of the minor deviations consisted of "procedure not done" (77.9% of subjects) or variations in "protocol schedule" (84.9% of subjects). No subjects were excluded from the analysis due to a major protocol deviation.

Reviewer comment
Major and minor deviations were reviewed. Minor deviations involved instances such as timing of vital signs falling outside the specified window or late follow-up visits. Major deviations largely pertained to failure to collect laboratory samples.

3.3 Financial Disclosures

Covered clinical study (name and/or number):		
Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 31		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from applicant)

Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from applicant)

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

4.1 Chemistry, Manufacturing, and Controls

Cuvitru is a purified IgG liquid biologic product at 20% w/v protein concentration. This preparation is an isotonic solution containing a concentration of approximately 200 mg of protein per mL, of which at least 98% is gamma globulin, and has a pH of 4.6 to 5.1. The stabilizing agent is glycine and is present in the range of (b) (4). The product contains no preservatives.
The starting material is human plasma intended for the manufacture of plasma derivatives, (b) (4). Each unit of plasma is tested for Hepatitis B Surface Antigen (HBsAg), antibody to Hepatitis C Virus, and antibody to Human Immunodeficiency Virus Types 1 and 2 (anti-HIV-1/2) by FDA-approved tests. In addition, mini-pools of plasma are tested by Nucleic Acid Amplification Technology (NAT) for (b) (4), HCV and HIV-1. Mini-pools are screened to ensure there is (b) (4). Each plasma manufacturing pool is tested for (b) (4)

4.2 Assay Validation
See CMC reviewer's memo.

4.3 Nonclinical Pharmacology/Toxicology

See preclinical reviewer's memo.

4.4 Clinical Pharmacology

Clinical pharmacology was evaluated in two phase 2/3 clinical studies: Study 170904 (N=77) and Study 170903 (N=49). Supportive clinical pharmacology data were obtained from Study 160601 (N=49).

4.4.1 Mechanism of Action

Cuvitru supplies a broad spectrum of opsonizing and neutralizing IgG antibodies against a wide variety of bacterial and viral agents. These antibodies also are capable of interacting with erythrocytes. Unlike the case with IGIV, there is no high initial peak IgG concentration following infusion; however, treatment requires multiple infusions on a weekly or biweekly basis.

4.4.2 Human Pharmacodynamics (PD)
Normal human Ig contains primarily IgG and IgG subclasses proportional to that in native human plasma. Adequate doses of Cuvitru may restore abnormally low Ig levels to the normal range.

4.4.3 Human Pharmacokinetics (PK)
A population PK analysis was performed *post-hoc* on pooled total IgG trough level data obtained in subjects administered GAMMAGARD LIQUID and Cuvitru during Study 170904 and Study 170903. All subjects with reliable dosing and sampling collection date and time information and at least 2 measurable total IgG concentrations for Cuvitru were considered for analysis (N = 102: 70 subjects from Study 17094 and 32 subjects from Study 170903). Cuvitru bioavailability was 82.07% of GAMMAGARD LIQUID by measured analysis and 73.9% when predicted by population PK analysis. Results suggest that Cuvitru administration at 130% of the GAMMAGARD LIQUID IV dose provides comparable exposure as assessed by AUC ratios.

4.5 Statistical

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

4.6 Pharmacovigilance

The pharmacovigilance reviewer has identified no substantive issues for which a PMR is indicated.

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

5.1 Review Strategy

The primary focus of this review is a phase 2/3 prospective, open label, non-controlled global trial assessing efficacy, PK, tolerability and safety (Study 170904) in adults and children >2 years of age with primary immune deficiency disease (PI). A European phase 2/3 multicenter uncontrolled prospective open-label study conducted at 16 sites (170903) as well as safety and efficacy data from a supportive study (160601) also were reviewed. Due to differences in doses and/or product concentrations across the three studies, a comparison of the efficacy results was not considered feasible by Baxalta; however, the studies were described and summarized in parallel, where possible, in the Integrated Summary of Efficacy.

The Integrated Summary of Safety incorporated safety and tolerability results from Study 170904 and Study 170903 with supportive data used from Study 160601.

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

This review is based on the following materials:

- 1.14: Labeling claims (package insert)
- 2.5: Clinical overview
- 2.7.3: Summary of clinical efficacy
- 2.7.4: Summary of clinical safety
- 5.3.3: Reports of human pharmacokinetic studies
- 5.3.5: Reports of efficacy and safety studies

5.3 Table of Studies/Clinical Trials

The table below presents the three phase 2/3 trials reviewed for safety and efficacy.

Table 7: Table of Clinical Studies

Study	Study type	Population	Product	Dose (g/kg)	Exposed to IP	Complete	Country
160601	Phase 2/3, 4-Part, Efficacy, PK, and Tolerability	Subjects aged 2 years and older, with PI	Part 1: GAMMAGARD LIQUID (IGIV, 10%)	0.3-1.0 g/kg BW/4 weeks	49 [47 subjects received Cuvitru]	N = 44	U.S.
			Part 2, 3a, 3b, Extension: GAMMAGARD LIQUID (IGSC, 10%)	130% of weekly dose equivalent of GAMMAGARD LIQUID or adjusted dose based on individual PK			
170903	Phase 2/3, 2-Epoch, Efficacy, PK, Tolerability and Safety	Subjects aged 2 years and older, with PI	Epoch 1: GAMMAGARD LIQUID (IGIV, 10%)	Pre-study dose but within 0.3-1.0 g/kg BW/4 weeks	49 [48 subjects received Cuvitru]	N = 45	Europe
			Epoch 1: SUBCUVIA (IGSC, 16%)	Dose used during Epoch 1 adjusted to weekly equivalent			
			Epoch 2: Cuvitru (IGSC, 20%)	Dose used during Epoch 1 adjusted to weekly equivalent			
170904	Phase 2/3, 4-Epoch, Efficacy, PK, Tolerability and Safety	Subjects aged 2 years and older, with PI	Epoch 1: GAMMAGARD LIQUID (IGIV, 10%)	GAMMAGARD LIQUID: 0.3-1.0 g/kg BW/4 weeks	77 [74 subjects received Cuvitru]	N = 67	U.S., Canada
			Epoch 2, 3, 4 Cuvitru (IGSC, 20%)	145% of the weekly dose equivalent of GAMMAGARD LIQUID or adjusted dose based on individual PK			

Adapted from Table 1, Clinical Overview, page 8 of 75, 25 Aug 2015

5.5 Literature Reviewed

1. Bruton OC. Agammaglobulinemia. Pediatrics. 1952; 9(6):722-728.
2. Fasth A, Nystrom J. Safety and efficacy of subcutaneous human immunoglobulin in children with primary immunodeficiency. Acta Paediatrica. 2007; 96:1474-1478.
3. Jolles S. et al. Current treatment options with immunoglobulin G for the individualization of care in patients with primary immunodeficiency disease. Journal of Translational Immunology. 2014;179: 146-160.
4. Jolles S. et al. New Frontiers in Subcutaneous Immunoglobulin Treatment. Biol Ther. 2011; 1(1):003
5. Wood P. et al. Recognition, clinical diagnosis and management of patients with primary antibody deficiencies: a systematic review. 2007;149:410-423
6. Bharath et al. Incidence and natural history of intravenous immunoglobulin-induced aseptic meningitis: a retrospective review at a single tertiary care center. Transfusion.2015;55(11):2597-2605

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 STUDY 170904

"A clinical study of immune globulin subcutaneous (Human), 20% solution (IGSC, 20%) for the evaluation of efficacy, safety, tolerability, and pharmacokinetics in subjects with primary immunodeficiency diseases"

6.1.1 Objectives

Primary

- To evaluate the efficacy of Cuvitru in preventing the development of acute SBI in subjects with PI.

Secondary

- To evaluate further efficacy assessments as well as the safety, tolerability, and PK characteristics of Cuvitru in subjects with PI and assess quality of life and treatment satisfaction.

6.1.2 Design Overview

Phase 2/3, prospective, open-label, historical-controlled, multicenter, multinational (U.S. Australia, Canada), study.

The study consisted of 4 Epochs. Efficacy, safety and tolerability were determined during Epochs 2 to 4 (up to 12 months).

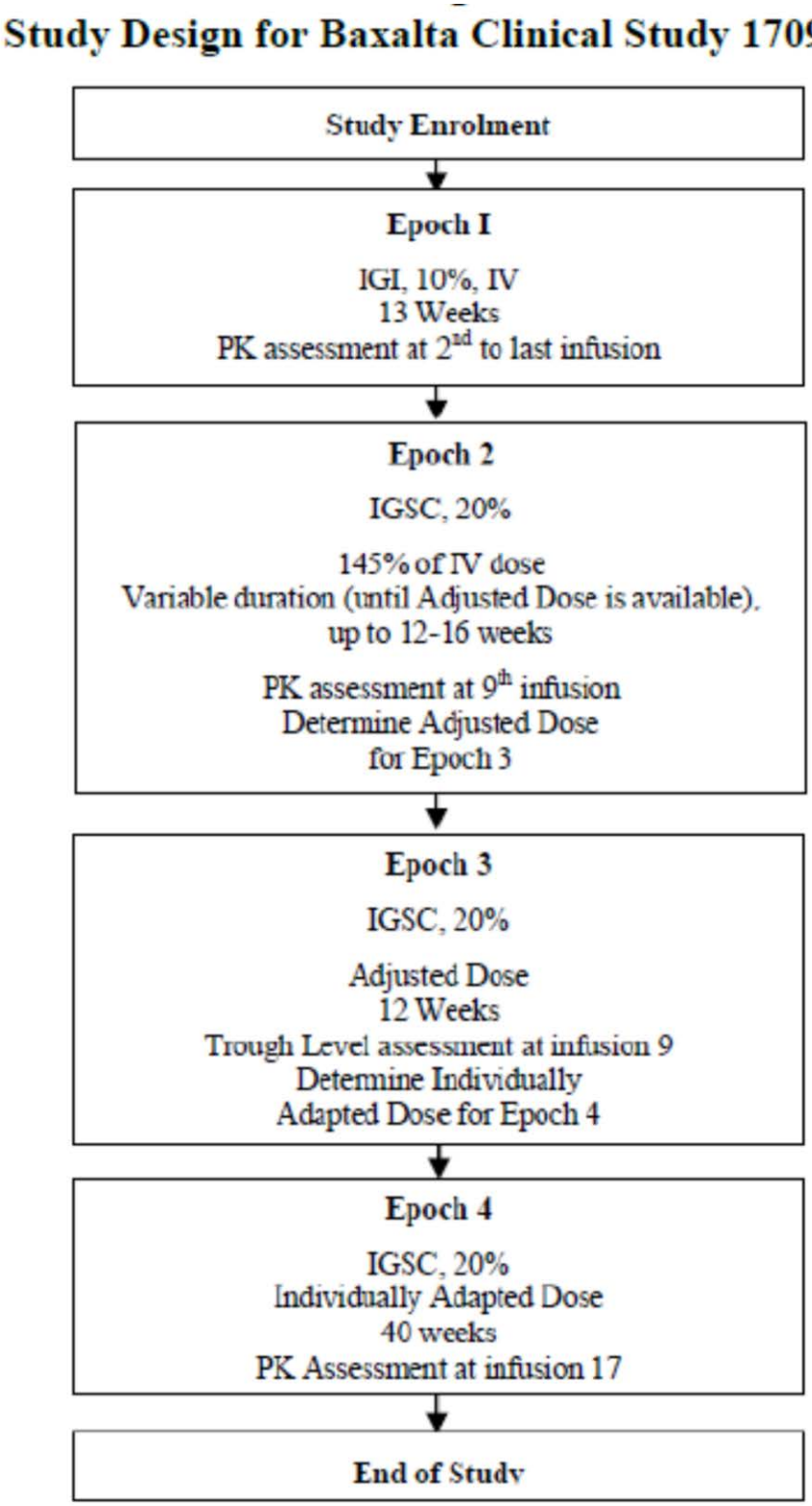

Figure 1: Study design for Study 170904
Source: CSR 170904, page 26 of 885, Jun 26, 2015

6.1.3 Population

Inclusion criteria

1. Documented diagnosis of primary humoral immunodeficiency involving antibody formation requiring IgG replacement.
2. Age 2 years or older.
3. Already receiving a stable (i.e., without need for dose adjustment due to lack of efficacy or low trough IgG levels) monthly equivalent dose of IgG at an average minimum dose of 300 mg/kg BW/4 weeks and a maximum dose of 1.0 gram/kg BW/4 weeks for a minimum of 12 weeks prior to first treatment with Cuvitru in the study.
4. Serum trough level of IgG >500 mg/dL at Screening.

Exclusion criteria

1. History of or positive on Screening for Hepatitis B, Hepatitis C, or HIV
2. Abnormal liver tests
3. Renal failure, defined as creatinine clearance (CLcr) < 60% of normal range for age and gender, either measured, or calculated according to the Cockcroft-Gault formula.
4. Malignancy unless the disease-free period prior to screening exceeded 5 years.
5. Neutropenia
6. Hematologic disease (bleeding or thrombosis)
7. Acute serious bacterial infection within 3 months prior to screening

6.1.4 Study Treatments or Agents Mandated by the Protocol

- **GAMMAGARD LIQUID** (IGIV, 10%)
- **Cuvitru** (IGSC, 20%)

The doses were as follows:

- Epoch 1: Subjects received GAMMAGARD LIQUID intravenously every 3 to 4 weeks depending on pre-study treatment at a monthly dose equivalent to that received prior to the study to determine the AUC (AUC_{IV}) of total IgG. All subjects aged ≥12 years completed a PK assessment.

- Epoch 2: Subjects received Cuvitru at 145% of the IV dose every 7 days in Epoch 1. Subjects (N=15) aged ≥12 years completed a PK assessment.

- Epoch 3: Subjects received an "Adjusted Dose" of Cuvitru every 7 days for 3 months based on PK data from Epoch 1 and Epoch 2.

- Epoch 4: Subjects were treated with an "Individually Adapted Dose" based on a comparison of measured trough levels in Epoch 1 and Epoch 3.

6.1.4.1 Directions for Use

Dosing

When switching from IGIV, 10% or HYQVIA, the following formula was used:

$$\text{Initial weekly dose (g)} = \frac{\text{Previous IGIV dose (g)}}{\text{\# of weeks between IGIV doses}} \times 1.30$$

When switching from other IGSC treatment, the weekly dose was equivalent to the weekly dose of prior IGSC treatment.

Administration

Infusions were conducted with an electronic pump. When multiple infusion sites were used simultaneously, the rate set on the pump was rate/site x number of sites. If an AE, at least moderate in severity, occurred during an infusion, the infusion was to be completed at the infusion rate immediately below that at which the AE occurred or at a lower rate. During home treatment if no ramp-up had been performed at this infusion, it was suggested to reduce to the infusion rate advised by the investigator during the training session(s).

Infusion Rates

The initial two infusions were started at 10 mL/h/infusion site, and could be increased stepwise to a maximum of 20 mL/hr/infusion site. Adjustment of the infusion rate was based on subject tolerability; if well tolerated the infusion rate could be increased at intervals of ≥10 minutes. For subsequent infusions, if well tolerated, the infusion rate could be increased to a maximum of 60 ml/h/site.

If the initial infusions were well tolerated then subsequent infusions could begin at the maximum tolerated rate without ramp-up. If the subject did not achieve the maximum allowable rate during the initial infusions, it was permissible to increase the rate during subsequent infusions, up to the maximum allowable rate, as long as there had been no more than mild local reactions.

IgG Monitoring

Serum trough levels were monitored as follows.

- Screening and Epoch 1: Week 1, 4, 7, 10 and 13 for subjects receiving treatment every 3 Weeks, and Week 1, 5, 9, and 13 for subjects receiving treatment every 4 weeks
- Epochs 2 and 3: Weeks 5 and 9
- Epoch 4: Week 1, 9, 17, 18, 29, and End of Study (170904 Protocol Amendment 3, Feb 21, 2013, p. 100-107/129).

Serum trough levels IgG >5 g/L (i.e., therapeutic nadir) were to be maintained throughout the study. If levels decreased to ≤5 g/L, the subject's dose was adjusted to maintain minimum trough levels. If body weight increased >5% from the weight used for the current dose, then the total dose (grams) - but not the dose per weight (g/kg) – was to be adjusted accordingly. The investigator contacted the sponsor to inform of any change to the dose.

6.1.5 Sites and Centers

Although 18 study sites were opened for the study, 3 did not enroll subjects (indicated by an asterisk in the list below). Fourteen of the active sites were in the U.S., and the remaining site was in Canada.

Site 01: Isaac Melamed MD (U.S.)
Site 02: James N. Moy MD (U.S.)
Site 03: Mark R. Stein MD (U.S.)
Site 04: Sudhir Gupta MD (U.S.)
Site 05: Bruce Mazer MD (Canada)*
Site 06: Daniel Suez (U.S.)
Site 07: John Routes MD (U.S.)*
Site 08: Amy Liebl Darter MD (U.S.)
Site 09: Ralph Shapiro MD (U.S.)
Site 10: Alan P. Knutsen MD (U.S.)
Site 11: Kenneth Paris MD (U.S.)
Site 12: Lisa Kobrynski MD (U.S.)
Site 13: Richard L. Wasserman MD (U.S.)
Site 14: Arye Rubinstein MD (U.S.)
Site 15: Elie Haddad MD (Canada)
Site 16: Douglas H. Jones MD (U.S.)
Site 17: Iftikhar Hussain MD (U.S.)
Site 18: Wesley Sublett MD (U.S.)*

6.1.6 Surveillance/Monitoring

Safety assessments included vital signs, laboratory parameters and AE monitoring. The Common Toxicity Criteria of the Eastern Cooperative Oncology Group, published by Oken et al was used to grade laboratory values. Laboratory values were graded on a scale of 0-4. Abnormal laboratory values that were considered an AE by the investigator were recorded on the AE Case Report Form (CRF). The justification for abnormal values not deemed AEs was recorded by the Investigator on the laboratory form. Additional tests and other evaluations required to establish the significance or etiology of an abnormal laboratory value or to monitor an AE were obtained at investigator discretion.

An electronic subject diary (eDiary) was provided to each subject at enrollment to record the following throughout the study period: occurrence of AEs, including infection; concomitant medications; days of school/work missed or days unable to perform activities of daily living, off-study out-patient visits and hospitalizations; and infusion related data (e.g. rate of infusion). Information from the eDiaries was transferred to electronic CRFs. Follow-up contact with the subject either by the diary system or by the investigator occurred 3-5 days after the completion of every infusion in each Epoch.

No data monitoring committee (DMC) was used in this study. The reasons were 1) the product to be administered subcutaneously (SC) in this study is the same as a product already licensed for this indication, although the product administered SC will be at a

higher concentration 2) SC administration is known to be clinically effective 3) there is a low risk of systemic adverse reactions 4) the main anticipated adverse reactions are local reactions.

> **Reviewer comment**
> Since Cuvitru is similar to already approved products, the applicant's justification for the absence of a DMC is acceptable.

6.1.7 Endpoints and Criteria for Study Success

Efficacy

Primary Endpoint

- Rate of validated acute SBI in the intent-to-treat (ITT) population. Validated SBIs were defined as bacteremia/sepsis, bacterial meningitis, osteomyelitis/septic arthritis, bacterial pneumonia, and visceral abscess, diagnosed according to the Diagnostic Criteria for Serious Acute Bacterial Infections listed in FDA Guidance for Industry.[5]

Secondary Endpoints

- Annual rate of all infections per subject, as well as the number, severity, duration and types of infections
- Annual rate of sinus infections per subject as well as duration, severity, and acute or chronic status
- Annual rate of fever episodes per subject defined as a body temperature of ≥38° C. Fever which recurred after ≥3 afebrile days was counted as a new fever episode. The number of days of fever for a given fever episode was defined as the number of days from the first to the last day with body temperature of ≥ 38 °C
- Annual rate of days off school/work or days unable to perform normal daily activities due to illness or infection per subject
- Annual rate of days on antibiotics per subject
- Annual rate of hospitalizations for illness or infection per subject
- Annual rate of days of hospitalizations for illness or infection per subject
- Annual rate of acute (urgent or unscheduled) physician visits, or visits to the Emergency Room for illness or infection per subject

Safety

- Related SAEs and Related AEs by subject and by infusion
- All SAEs and AEs by subject and by infusion
- Temporally Associated AEs beginning within 72 h of infusion completion by subject and by infusion, beginning within 24 h of infusion completion by subject and by infusion, and beginning within 1 h of infusion completion by subject and by infusion
- Causally related and/or temporally associated AEs, including the total number of all AEs within 72 h of infusion completion plus the total number of related AEs divided by the total number of infusions

5 Safety, Efficacy, and Pharmacokinetic Studies to Support Marketing of Immune Globulin Intravenous (Human) as Replacement Therapy for Primary Humoral Immunodeficiency, June, 2008.

- Local AEs by proportion of infusions and proportion of subjects
- Infusion Tolerability as assessed by infusion rate reduced and/or infusion interrupted or stopped due to tolerability or AEs by subject and infusion respectively, and proportion of infusions tolerated with IV or SC administration
- Short term tolerance, as assessed by vital signs
- Incidence of laboratory confirmed hemolysis following test product

Pharmacokinetics

- Bioavailability of Cuvitru as measured by the ratio of IgG AUC_{SC} in Epoch 4 to IgG $AUC_{IV,\ 0\text{-}\tau}$ in Epoch 1 (standardized to 1 week), adjusted for dose and dosing frequency (for subjects aged 12 years and older)
- Trough levels of IgG (total), IgG subclasses, and specific antibodies to clinically relevant pathogens (such as Clostridium tetani, Haemophilus influenzae type b, and Hepatitis B Virus)
- Other pharmacokinetics parameters for IgG (total) and one specific antibody (anti-Haemophilus influenzae type b):
    - For subjects 12 years of age or older, area under the curve over a dosing interval ($AUC_{0\text{-}\tau}$), clearance (CL; for IV treatment) or apparent clearance (CL/F; for SC treatment), bioavailability (F), maximum observed concentration (Cmax), minimum observed concentration (Cmin), time to Cmax (Tmax) and $T_{1/2}$ (IV only).
    - For subjects aged 2 to <12 years in Epoch 4, area under the curve over a dosing interval, apparent clearance, maximum observed concentration and minimum observed concentration.

Quality of Life Satisfaction

- Quality of Life
    - Pediatric Quality of Life Inventory™ (PEDS-QL™) for the age group 2 to 4 and 5 to 7 years (observer: parent).
    - PEDS-QL™ subjects 8 to 13 years of age
    - Short-Form 36v2 (SF-36v2) for the age group 14 years and older

- Life Quality Index (LQI)
    - As observed by a parent for subjects age 2 to 12 years, and as observed by the subject for ages 13 years and older.

- Treatment Satisfaction
    - Treatment Satisfaction Questionnaire for Medication (TSQM); as assessed by a parent for subjects age 2 to 12 years, and as assessed by the subject for ages 13 years and older.

6.1.8 Statistical Considerations & Statistical Analysis Plan

The rate of validated acute SBIs was calculated as the mean number of SBIs per subject per year in the ITT population. The mean number of SBIs per year and the 99% upper CI was calculated using a Poisson model accounting for the length of the observation

periods per subject. The observation period for each subject began with the day of the first infusion of IGSC 20% in Epoch 2 and ended with the day of the End of Study visit. Secondary endpoints, including rates of infection, fever episodes, days on antibiotics, off work/school/daily activity, hospitalizations, and acute physician visits were analyzed for efficacy using a Poisson model. The data were presented as point estimates and 95% confidence intervals.

Medians and quartiles and non-parametric 95% confidence intervals were used to summarize PK parameters for IgG, IgG subclasses (IgG subclasses in subjects 12 years and older only) and 1 specific antibody (anti-*Haemophilus influenzae* type b).

The AUC between adjacent infusions was calculated by the trapezoidal rule. To allow for comparisons between Epochs 1, 2 and 4; $AUC_{0-\tau}$ was standardized for the infusion intervals (3 or 4 weeks vs. 1 week) and denoted as $AUC_{0-\tau}$;std.

The expected trough level increase and a nomogram to calculate individual dose adjustments were determined in the interim analysis based on the results of the first 15 subjects treated with Cuvitru in Epoch 2.

Safety and QoL endpoints
Descriptive statistics were used to analyze safety and QoL. In addition, a Wilcoxon signed ranks test was used to test the hypothesis of change in QoL perception from Epoch 1 to Epoch 3 or 4, as well as by using Bonferroni adjustment with a nominal significance level of $\alpha = 0.01$.

Determination of Sample Size
A sample size of 59 subjects provided 85% power to reject the null hypothesis of a serious infection rate ≥1.0 using a one-sided test and a Type I error of 0.01 assuming a true SBI rate of 0.6/year. Enrollment was planned for approximately 70 subjects, allowing for a dropout rate of 15%. Enrollment requirements included approximately 30 SC naïve subjects and approximately 16-20 subjects with PI aged 2 to <16 years (age 2 to <5 years: ~ 4-6 subjects; age 5 to <12 years: ~ 4-6 subjects, age group 12 to <16 years: 6-8 subjects).

Missing data
There were no statistical techniques to identify or exclude any missing or spurious data. The reason for exclusion and the analyses from which the data points were excluded was documented.

6.1.9 Study Population and Disposition

6.1.9.1 Populations Enrolled/Analyzed

Safety Analysis Dataset-IGIV, 10% (**SADS-IGIV**; N=77): All subjects who received at least one dose of GAMMAGARD LIQUID

Safety Analysis Dataset-IGSC, 20% (**SADS-IGSC**; N=74): All subjects who received at least one dose of Cuvitru

Analysis cohorts

Epoch 1: N=77
- Subjects treated with GAMMAGARD LIQUID at 3-week infusion intervals
- Subjects treated with GAMMAGARD LIQUID at 4-week infusion intervals
- PK assessment

Epoch 2: N=45
- Subjects treated with Cuvitru in Epoch 2
- PK assessment

Epoch 3: N=74
- Subjects treated with Cuvitru

Epoch 4: N=70
- Subjects treated with Cuvitru
- PK assessment

Age cohorts
- 2 to <5 years: N=1
- 5 to <12 years: N=14
- 12 to <16 years: N=8
- 16 to <65 years: N=45
- ≥65 years: N=9

6.1.9.1.1 Demographics

Table 8 shows that of the 77 treated subjects, 40/77 (51.9%) were male and 37/77 (48.1%) were female. The majority were White (70/77, 90.9%) whereas 5 of the 77 (6.5%) were non-Hispanic/Latino. Median age was 36 years (range: 3-83 years).

Table 8: Study 170904 Population Demographics (Safety Analysis Set)

Parameter	Category	Age 2 to <5 Years N=1 (%)	Age 5 to <12 Years N=14 (%)	Age 12 to <16 Years N=8 (%)	Age 16 to <65 Years N=45 (%)	Age ≥ 65 Years N=9 (%)	Total N=77 (%)
Gender	Male	1 (100.0)	13 (92.9)	7 (87.5)	18 (40.0)	1 (11.1)	40 (51.9)
	Female	0	1 (7.1)	1 (12.5)	27 (60.0)	8 (88.9)	37 (48.1)
Race	White	1 (100.0)	9 (64.3)	7 (87.5)	44 (97.8)	9 (100.0)	70 (90.9)
	Black/AA	0	2 (14.3)	1 (12.5)	0	0	3 (3.9)
	Asian	0	2 (14.3)	0	0	0	2 (2.6)
	Multiple	0	1 (7.1)	0	1 (2.2)	0	2 (2.6)
Ethnicity	Hispanic	0	0	1 (12.5)	4 (8.9) 0	0	5 (6.5)
	Not Hispanic	1 (100.0)	14 (100.0)	7 (87.5)	41 (91.1)	9 (100.0)	72 (93.5)

Adapted from CSR, p. 99-100, 26 Jun 2015

6.1.9.1.2 Medical/Behavioral Characterization of the Enrolled Population

The etiology of infusional TEAEs was confounded by pre-existing medical conditions or symptoms that mimic ARs associated with IgG treatment of PI. Thus, conditions such as headache (n=39 cases), sinusitis (n=31), pain (n=42), fatigue (n=16) and nausea (n=9) occurred at a high frequency (n) in the study population (N=77).

6.1.9.1.3 Subject Disposition

Table 9 shows that of 86 subjects screened for the study, 9 subjects were withdrawn prior to treatment (Screen failure, N=6; subject withdrew consent, N=1; applicant withdrew subject because the 1st infusion would not have been within 30 days of the screening visit, N=2) and 77 (89.5%) started Epoch 1, 74 subjects (86.0%) received Cuvitru, 67 subjects (77.9%) completed the study 22.1% discontinued prematurely. Of the 74 subjects treated with Cuvitru, 45 subjects (52.3%) participated in Epoch 2 and 29 subjects (33.7%) went from Epoch 1 directly on to Epoch 3. All 74 subjects received Cuvitru at the "Adjusted Dose" during Epoch 3 and 70 subjects (81.4%) received the "Individually Adapted Dose" during Epoch 4.

Table 9: Disposition of Subjects

Study Time	Withdrawals	2 to <5 Years N=1	5 to <12 Years N=14	12 to <16 Years N=9	16 to <65 Years N=52	≥ 65 Years N=10	Total N=86
Screening	Withdrew Before Study			1 subject	7 subjects	1 subject	N=9
Started Epoch 1		N=1	N=14	N=8	N=45	N=9	N=77
	Withdrew in Epoch 1			2 subjects	1 subject		N=3
Started Epoch 3		N=1	N=14	N=6	N=44	N=9	N=74
	Withdrew in Epoch 3				2 subjects	2 subjects	N=4
Started Epoch 4		N=1	N=14	N=6	N=42	N=7	N=70
	Withdrew in Epoch 4		1 subject		1 subject	1 subject	N=3
Completed Study		N=1	N=13	N=6	N=41	N=6	N=67

Adapted from Figure 1, CSR, page 57 of 885, 26 Jun 2015

Of the 74 subjects (86.0%) who received Cuvitru, 7 did not complete the study. No subject withdrew from Epoch 2. Reasons cited for discontinuation included withdrawal of consent: Subjects (b) (6) [Epoch 4], (b) (6) [Epoch 3], (b) (6) [Epoch 4], (b) (6) [Epoch 3], (b) (6) [Epoch 3]); fatigue AE (Subject (b) (6) [Epoch 3]); and non-compliance (Subject (b) (6) [Epoch 4]).

- **Subject** (b) (6) was a 66 year old White female with a history of hypothyroidism, migraine, depression, fibromyalgia and hypokalemia who experienced multiple non-serious AEs including diarrhea, dizziness and fatigue on

8 Apr 2014 while receiving Cuvitru. She felt that the fatigue was possibly due to the product and elected to discontinue from the study on 23 Apr 2014. The AEs were assessed by the investigator as non-serious and unrelated to Cuvitru administration and were resolving at the time of study discontinuation.

- **Subject** (b) (6) was a 39 year old White female with a history depression and recurrent respiratory infections who was uncomfortable with weekly subcutaneous injections

- **Subject** (b) (6) was an 8 year old Asian male with a history of ataxia telangiectasia who withdrew because his family was moving to China.

- **Subject** (b) (6) was a 36 year old White female with a history of chronic sinusitis whose reason for discontinuation was that she "felt better on Hizentra".

- **Subject** (b) (6) was a 67 year old White female with a history of chronic rhinitis, GERD, COPD, and CAD who developed an unrelated lung adenocarcinoma SAE and subsequently withdrew from Epoch 3.

- **Subject** (b) (6) was a 66 year old White female with a history of hypothyroidism and atopic dermatitis who experienced two mild, unrelated non-serious events (animal bite, neck abscess).

- **Subject** (b) (6) was a 49 year old White female with a history of chronic allergic rhinitis, chronic fatigue and depression, who was terminated from the study due to noncompliance.

6.1.10 Efficacy Analyses

6.1.10.1 Primary Endpoint

The study met its primary endpoint: the annualized SBI rate was significantly <1.0 SBI/year, with 1 case of pneumonia reported in Epoch 4 (see 6.1.12). The point estimate of the annualized SBI rate was 0.01 (upper limit of 99% CI: 0.02) during Cuvitru administration (Epoch 2 to Epoch 4) and 0.01 (upper limit of 99% CI: 0.02) for all study epochs combined. Similar values were reported for the pediatric Cuvitru subpopulation: 0.00; upper limit of 99% CI: 0.20.

6.1.10.2 Secondary Endpoints

Subject-reported outcomes (annualized)
Table 10 shows subject-reported outcomes in the Cuvitru cohort that were similar to those in the GAMMAGARD LIQUID IV cohort.

Table 10: Subject-Reported Outcomes by Treatment Cohort (Safety Set)

Outcome	Product	Point Estimate	95% Confidence Interval
Infections per subject	GAMMAGARD LIQUID IV	3.9	2.8 to 5.2
	Cuvitru	2.4	1.9 to 3.0
Days on antibiotics	GAMMAGARD LIQUID IV	63.2	43.4 to 88.3
	Cuvitru	57.6	40.7 to 78.6
Days in hospital			
	GAMMAGARD LIQUID IV	0.2	0.1 to 0.4
	Cuvitru	0.1	0.1 to 0.2
Acute physician visits			
	GAMMAGARD LIQUID IV	1.7	1.0 to 2.7
	Cuvitru	0.9	0.5 to 1.3
Missed school/work days			
	GAMMAGARD LIQUID IV	3.2	1.9 to 5.0
	Cuvitru	1.2	0.7 to 1.8

Adapted from Table 10, CSR, page 105 to 885, 26 Jun 2015

Reviewer comment

Clinical outcomes from secondary endpoint analyses support the primary endpoint.

Pharmacokinetics

The bioavailability of Cuvitru estimated from the ratio of the geometric means of AUC/week for total IgG during weekly Cuvitru treatment in Epoch 4 (once every week) versus GAMMAGARD LIQUID (3 or 4-week interval standardized to 1 week) was 1.0855 (90% CI: 1.0394 to 1.1336, N = 49).

Table 11 presents total IgG trough levels at end of treatment stratified by treatment interval, product and age subcohorts. All trough levels were well above the minimum therapeutic level of 5 g/L. A 95% confidence interval was not computed for small sample sizes.

Table 11: Trough Levels at the End of Treatment by Interval, Age and Product (Safety Set)

Age Cohort (Years)	Treatment Interval	N	Median Trough Level (g/L)	95% CI
2 to <5	GAMMAGARD LIQUID 4 weeks	1	8.3	NA
	Cuvitru adjusted 1 week	1	14.6	NA
	Cuvitru individualized 1 week	1	13.6	NA
5 to <12	GAMMAGARD LIQUID 3 weeks	3	10.7	NA
	GAMMAGARD LIQUID 4 weeks	10	8.3	5.4 to 10.5
	Cuvitru 145% 1 week	2	12.5	NA
	Cuvitru adjusted 1 week	11	11.4	10.1 to 14.9
	Cuvitru individualized 1 week	10	13.1	9.3 to15.1
12 to <16	GAMMAGARD LIQUID 3 weeks	3	11.3	NA
	GAMMAGARD LIQUID 4 weeks	2	9.5	8.7 to 10.3
	Cuvitru 145% 1 week	2	16.5	NA
	Cuvitru adjusted 1 week	5	15.6	NA
	Cuvitru individualized 1 week	5	14.5	NA

16 to <65	GAMMAGARD LIQUID 3 weeks	11	12.0	11.0 to14.3
	GAMMAGARD LIQUID 4 weeks	30	10.5	9.8 to 18.5
	Cuvitru 145% 1 week	19	15.3	12.6 to 16.1
	Cuvitru adjusted 1 week	40	14.7	13.8 to 15.9
	Cuvitru individualized 1 week	35	15.8	134.0 to 17.0
≥65	GAMMAGARD LIQUID 3 weeks	2	14.1	NA
	GAMMAGARD LIQUID 4 weeks	7	12.2	8.8 to 14.6
	Cuvitru 145% 1 week	4	16.1	NA
	Cuvitru adjusted 1 week	9	15.7	11.2 to 18.0
	Cuvitru individualized 1 week	6	16.9	12.7 to 18.7
Total	GAMMAGARD LIQUID 3 weeks	19	12.0	11.0 to 14.1
	GAMMAGARD LIQUID 4 weeks	50	10.2	6.1 to 18.5
	Cuvitru 145% 1 week	27	15.3	12.8 to 16.1
	Cuvitru adjusted 1 week	66	14.7	13.8 to 15.6
	Cuvitru individualized 1 week	57	15.1	14.0 to 16.4

Adapted from Table 11, CSR, page 110 of 885, 26 Jun 2015

Quality of Life/Treatment satisfaction

Health-related quality of life was assessed using the Pediatric Quality of Life Inventory™ (PEDS-QL) questionnaire or the self-administered SF-36 survey.

The Life Quality Index (LQI) and treatment satisfaction were assessed using the LQI questionnaire and the Treatment Satisfaction Questionnaire for Medication (TSQM-9), respectively. Assessments were performed immediately prior to infusion 1 of Epoch 1, at the end of Epoch 1, of Epoch 3 and during the End-of-Study visit (or early termination visit). Score changes between End of Epoch 1 and End of Epoch 3 or End of Study visit were analyzed. Higher scores indicated higher satisfaction.

1. **Generic Health-Related Quality of Life** was assessed for the age group 2-7 years (PEDS-QL, observer: parent), 8-13 years (PEDS-QL, observer: subject) and subjects aged 14 and older (SF-36 survey). A total score was calculated for the PEDS-QL and 2 summary scores, the Physical Component and the Mental Component scores for the SF-36 questionnaire. The change in total score for all categories was 3.8 (4.8) and -0.7 (3.6). By Bonferroni-Adjusted and Hierarchical testing, no statistically significant difference in the total score or summary scores was observed when subjects switched from GAMMAGARD LIQUID in Epoch 1 to Cuvitru in Epoch 3 (adjusted dose) or in Epoch 4 (individualized dose) .

2. **Disease-specific Quality of Life** (**Life Quality Index**) was assessed for the age group 2 to 12 years (observer: parent) and the age group 13 years and older (observer: subject) using the LQI questionnaire developed to assess health-related quality of life perception among subjects with PI. A score was calculated for each domain covered by the questionnaire: Treatment interferences, Therapy-related problems, Therapy settings and Treatment costs. The point estimate for change in the Treatment interference score across all age groups was 1.5 ($p = 0.008$) between the end of Epoch 1 and the end of Epoch 4.

3. **Treatment Satisfaction** was assessed in age groups, 2-12 years (TSQM-9, observer: parent) and 13 years and older (TSQM-9, observer: subject) in 3 domains, Effectiveness, Convenience and Global satisfaction. Summary scores were calculated for each domain. The point estimate for change in the treatment convenience score was 11.11 ($p < 0.001$) as assessed by subjects who switched from GAMMAGARD LIQUID to Cuvitru across all age groups.

Reviewer comment
The QoL data indicate an improvement overall with use of Cuvitru.

6.1.10.3 Subpopulation Analyses

No SBIs occurred in the pediatric subpopulations, but one subject in the geriatric subpopulation (78 year old male) experienced an SBI (pneumonia).

During Cuvitru administration, the annualized rate of all infections per subject was

- 0.00 (95% CI: 0.00 to 4.61) for subjects aged 2 to <5 years
- 1.72 (95% CI: 0.85 to 3.05) for subjects aged 5 to <12 years
- 2.00 (95% CI: 0.70 to 4.35) for subjects aged 12 to <16 years
- 2.62 (95% CI: 1.91 to 3.50) for subjects aged 16 to <65 years
- 2.91 (95% CI: 1.67 to 4.65) for subjects aged 65 years and above.

In all subgroups except geriatrics, annualized infection rates were higher during GAMMAGARD LIQUID IV treatment, 3.86 (95% CI: 2.77 to 5.22), than with Cuvitru.

6.1.10.4 Dropouts and/or Discontinuations

Of the 74 subjects who received Cuvitru, 67 completed the study. Of the 7 subjects who did not complete the study, one was due to an AE (fatigue attributed to the product by the subject), 5 were classified as withdrawal of consent, and 1 was withdrawn by physician decision due to noncompliance:

See 6.1.9.1.3 for a brief narrative of each subject who prematurely terminated the study.

6.1.10.5 Exploratory and Post Hoc Analyses

Dose adjustment
Dose adjustment was necessary in 3/77 GAMMAGARD LIQUID subjects (3.9%). Dose adjustment was required for (*a*) all 45 subjects who received Cuvitru at 145% of the GAMMAGARD LIQUID, (*b*) 31/ 74 subjects treated with the adjusted dose, and (*c*) 66/70 (94.3%) subjects who received an individualized dose in Epoch 4. None of the adjustments was due to increased incidence of infections or IgG trough levels lower than the protocol-defined threshold (<5 g/L).

Reviewer Comment
The high proportion of subjects with dose adjustments for "other medical reasons" was expected per protocol because i) all subjects in Epoch 2 had their dose adjusted to 145% of the GAMMAGARD LIQUID dose in Epoch 1 ii) in Epoch

4, doses were adjusted to an individualized dose, if necessary, based on the subject's predicted individual trough levels.

6.1.11 Safety Analyses

6.1.11.1 Methods

Cuvitru subjects were exposed for a median treatment duration of 380.5 days (range: 30 - 629 days) and a mean ± SD of 413.1 ± 116.5 days.

Safety was evaluated in terms of occurrence of AEs and potential hemolysis; infusion tolerability, viral safety; clinically significant laboratory values (hematology and clinical chemistry); physical assessments and vital signs. Safety endpoints included the determination of frequency, per subject and per infusion, of all SAEs and AEs, and of those SAEs and AEs assessed as related to any IP by the investigator. AEs were compiled based on an eDiary filled out by the subject and on investigator observation.

Further safety endpoints were the frequency (per subject and per infusion) of temporally associated AEs and of causally related and/or temporally associated AEs. Temporally-associated AEs were defined as AEs occurring during or within 72 hours, 24 hours or 1 hour after infusion completion. Causally related and/or temporally associated AEs were defined as the sum of all "temporally associated" AEs (that began during or within 72 hours after completion of infusion) plus all "related" AEs (determined by the investigator as at least possibly related to the study drug) that started more than 72 hours following the completion of an infusion.

Local AR endpoints included the proportion of infusions associated with one or more local ARs and the proportion of subjects who experienced one or more local ARs. Infusion tolerability endpoints included the proportion of infusions requiring adjustment, the proportion of subjects with infusions requiring adjustment and the proportion of tolerated infusions.

Descriptive statistics were used for analyses of safety for study Epoch 1 (GAMMAGARD LIQUID) and the combined study Epochs 2, 3 and 4 (Cuvitru) separately.

6.1.11.2 Overview of TEAEs

SAEs

- There were no deaths among the 77 subjects in the Safety Analysis Set.
- In total, 3 SAEs occurred in 3 subjects. One 14 year old White female (Subject (b) (6)) experienced a related headache SAE on Study Day 2 after receiving GAMMAGARD LIQUID (see 6.1.12.4) which necessitated hospitalization for 6 days. No related SAEs were reported in Cuvitru subjects.

  Two SAEs, pneumonia in a man aged 78 years (Subject (b) (6)) and lung adenocarcinoma in a woman aged 67 years (Subject (b) (6)), occurred during Cuvitru administration. See 6.1.12.4.

TEAEs

- Table 12 presents an overview of TEAEs by subject.

Table 12: Subjects Experiencing TEAEs Regardless of Causality (Safety Analysis Set)

Classification	GAMMAGARD LIQUID (%) (N=77)	Cuvitru (%) (N=74)
Number of subjects experiencing ≥1 TEAE	58 (75.3)	65 (87.8)
Number of subjects experiencing TEAEs by intensity		
Mild	49 (63.6)	61 (82.4)
Moderate	28 (36.4)	42 (56.8)
Severe	2 (2.6)	2 (2.7)
Number (%) of subjects experiencing TEAEs by age cohort (years)		
2 to <5	0 (0.0)	0 (0.0)
5 to <12	9 (64.3)	7 (50.0)
12 to <16	6 (75.0)	5 (83.3)
16 to <65	30 (66.7)	36 (81.8)
≥65	6 (66.7)	9 (100.0)
Number (%) of subjects experiencing infusional TEAEs within 72 hours		
All subjects	35 (45.5)	54 (73.0)
Subjects aged 2 to <16 years	11 (14.3)	12 (16.2)

Adapted from Table 26 (page 259 of 885) and Table 31 (page 282 of 885), CSR 170904, 26 Jun 2015

Table 13 presents causally related and/or temporally associated TEAEs reported in ≥5% of subjects. It shows that infusion site pain was the most common local adverse reaction and headache the most common systemic adverse reaction.

Table 13: Incidence ≥5% for Causally Related and/or Temporally Associated TEAEs (Safety Analysis Set)

TEAEs	GAMMAGARD LIQUID (%) (N=77)	Cuvitru (%) (N=74)
Local Adverse Reactions	**-**	**23 (31.1)**
Injection site pain (including Infusion site discomfort and Injection site pain	-	15 (20.3)
Infusion site erythema	-	8 (10.8)
Infusion site pruritus	-	4 (5.4)
Systemic Adverse Reactions	**34 (44.2)**	**41 (55.4)**
Headache	21 (27.3)	10 (13.5)
Diarrhea	-	5 (6.8)
Nausea	6 (7.8)	9 (12.2)
Fatigue	5 (6.5)	6 (8.1)
Somnolence	4 (5.2)	-
Vomiting	4 (5.2)	-

Adapted from Table 1 (page 1 of 710), Response to Information Request received 5 July 2016, CSR 170904, 26 Jun 2015

- Infectious TEAEs

An updated list of the status of unresolved infections at the time of data-lock was requested from the applicant. Table 14 shows details of the 8/202 (4%) unresolved infections in Cuvitru subjects as of 22 Feb 2016. Five events were of mild intensity and three were of moderate intensity. Per protocol, "Recovering/resolving AEs will be followed until resolution, medically stabilized, or 30 days after the study completion/termination visit, whichever comes first" (emphasis added by this reviewer).

Table 14: Ongoing Infections as of Database Lock (Safety Set)

Subject No.	Age (years)	Reported Term	Intensity	Study Day	Status as of 22 Feb 2016	Duration (days)
(b) (6)	50	Acute nasopharyngitis	Moderate	686	Resolving	Unknown
(b) (6)	49	Acute sinusitis	Mild	701	Resolving	Unknown
(b) (6)	63	URI	Mild	610	Ongoing	Unknown
(b) (6)	83	Onychomycosis	Moderate	352	Ongoing	Unknown
(b) (6)	69	Esophageal candida	Mild	580	Ongoing	Unknown
(b) (6)	56	H Pylori infection	Mild	548	Ongoing	Unknown
(b) (6)	52	Onychomycosis	Mild	398	Ongoing	Unknown
(b) (6)	13	Chronic otitis media	Moderate	105	Ongoing	Unknown

Adapted from Response to Request for Information, 22 Feb 2016

Reviewer comment

An IR received from the applicant stated that two of the eight events were resolving at the time of database lock. As noted, none of the TEAEs was assessed as severe.

- Infusion rate modifications
  - The GAMMAGARD LIQUID infusion rate had to be reduced in 1 (1.3%) subject aged 5 to <12 years and interrupted in 5 (6.5%) subjects (2 subjects aged 5 to <12 years, 1 subject aged 12 to <16 years and 2 subjects aged 16 to <65 years). No subject required an infusion to be stopped.
  - The Cuvitru infusion rate had to be reduced in 4 (5.4%) subjects (1 subject aged 5 to <12 years, 1 subject aged 12 to <16 years, and 2 subjects aged 16 to <65 years), interrupted in 1 (1.4%) subject aged 5 to <12 years and stopped in 1 (1.4%) subject aged 5 to <12 years.

Table 15 shows 10 cases (5 GAMMADGARD LIQUID and 5 Cuvitru cases) where the infusion rate needed to be modified because of infusional TEAEs: 2 children aged <16 years (0.9%) and 3 adults (0.6%) in Epoch 1, and 4 children (17%) and 1 adult (2%) in Epoch 2-4.

Table 15: Infusions (n) Where the Infusion Rate was Modified (Safety Analysis Set)

Subject No.	Age (years)	Treatment	Total No. of Infusions	Infusion Rate Reduced n (%)	Infusion Interrupted n (%)	Infusion Stopped n (%)
(b) (6)	55	GAMMAGARD LIQUID	5	0	1 (20.0)	0
(b) (6)	16	GAMMAGARD LIQUID	4	0	1 (25)	0
(b) (6)	13	GAMMAGARD LIQUID	4	1 (25.0)	1 (25.0)	0
(b) (6)	24	GAMMAGARD LIQUID	5	1 (20.0)	00	
(b) (6)	7	GAMMAGARD LIQUID	5	0	1 (20.0)	0
(b) (6)	10	Cuvitru 145% IV	18	1 (5.6)	0	0
(b) (6)	9	Cuvitru – Adjusted	12	0	1 (8.3)	0
		Cuvitru – Individualized	39	0	0	1 (2.6)
(b) (6)	11	Cuvitru – Individualized	40	0	1 (2.5)	0
(b) (6)	13	Cuvitru – Adjusted	12	2 (16.7)	0	0
(b) (6)	36	Cuvitru – Adjusted	7	1 (14.3)	0	0

Adapted from Listing 5, Section 16.2.7, CSR, page 1 of 377,

Reviewer Comment
While it may be tempting to speculate that children aged <16 years (N=4) administered Cuvitru were at higher risk of experiencing infusional site issues than children receiving GAMMAGARD LIQUID (N=2), sample sizes are too small to draw any meaningful conclusions.

6.1.11.3 Deaths

No fatalities were reported.

6.1.11.4 Nonfatal Serious AEs

Three SAEs occurred in three subjects.

NARRATIVES

- **Subject** (b) (6) was a 78 year old White male with specific antibody deficiency who experienced bilateral pneumonia during Epoch 4 on 29 Nov 2014 (Study Day 520) that lasted 6 days and required hospitalization. This was the only SBI reported.

  His medical history was significant for PI, bronchiectasis, recurrent pneumonia, GERD, and chronic bronchitis. His last infusion of Cuvitru prior to the event was 3 days earlier (26 Nov 2014). The pneumonia was treated with Levaquin, Solu-Medrol and unspecified nebulizer treatments. His infection resolved on 4 Dec 2014. The event did not result in his discontinuation of the study. The pneumonia was assessed as unrelated to study treatment by the Investigator.

Reviewer comment
This subject had experienced multiple episodes of pneumonia in the past, and had many predisposing factors including chronic bronchitis and bronchiectasis. While the SAE was unrelated to Cuvitru, it does indicate a treatment failure.

- **Subject** (b) (6) was a 68 year old White female with CVID who entered Epoch 2 on 17 Jan 2014 and Epoch 3 on 17 Feb 2014 (Study Day 124). On 10 Feb 2014 she underwent a chest CT which showed a right lower lobe mass. On 12 Feb 2014 she underwent a bronchoscopy which showed a malignancy consistent with adenocarcinoma of the lung/non-small cell lung cancer. On 17 Feb 2014 the diagnosis was confirmed and she began treatment soon thereafter. She withdrew from the study on 20 Mar 2014.

Reviewer comment
This SAE was unrelated to the study treatment. A causal relationship between lung cancer and IGSC treatment is not biologically plausible.

- **Subject** (b) (6) was a 14 year old White female with CVID with a history of PI and arthritis who developed headache requiring hospitalization on Study Day 2 during treatment with GAMMAGARD LIQUID in Epoch 1. The subject was hospitalized on 12 Nov 2013 lasted 6 days. She withdrew from the study on 19 Nov 2013.

Reviewer comment
This SAE was possibly related to GAMMAGARD LIQUID and could represent aseptic meningitis.

6.1.11.5 AEs of Special Interest (AESI)

No AESIs were reported in Study 170904.

6.1.11.6 Clinical Test Results
Primary concerns for the class of Ig products include thrombosis, hemolysis, and renal failure. There were no reports of thrombosis, hemolysis, or renal failure in the study.

A previous study conducted by Baxalta, 170901, a phase 1 study to evaluate the safety and tolerability of Cuvitru (b) (4) in healthy volunteers was stopped prematurely due to hemolysis events. Therefore, in the development of this study, FDA advised the company to institute additional measures to monitor for the potential of hemolysis. Such measures included the addition of a reticulocyte count (Amendment 3, Feb 21, 2013). In addition, tests for hemolysis were added to the screening procedures, the timing of post-infusion hemolysis tests was modified to include results at 1 hour, 24 hours, and 72 hours, and additional information was added to ensure the Investigator properly instruct subjects on how to recognize hemolytic events (Amendment 1, Sept. 16, 2010). In addition the incidence of laboratory confirmed

hemolysis that occurred following Cuvitru administration was made one of the safety endpoints of the study.

Hemolysis:
Table 17 presents laboratory values for subjects who received at least one Cuvitru infusion and were assessed for potential hemolysis. Of 77 subjects, 6 (7.8%) experienced a decline in hemoglobin ≥2.0 g/dL: Subjects (b) (6)). However, laboratory testing was negative for a hemolytic reaction based on clinically meaningful changes in LDH or haptoglobin.

Table 17: Baseline and Nadir Values for Hemolysis-Associated Parameters

Subject No.	Time Point	Coombs' Test	Plasma Free Hb (mg/L)	Hb (g/L)	Reticulocytes (GI/L)	Serum Hp* (g/L)	LDH (U/L)	Urine Hemosiderin
(b) (6)	Screening	Negative	30.0	149	50.4	0.90	104	None detected
	End of study	Unknown	Unknown	107	102	1.06	75	Unknown
(b) (6)	Screening	Negative	36.0	125	52.2	0.88	137	None detected
	Epoch 3, week 9	Unknown	56.0	110	46.1	0.83	117	Unknown
(b) (6)	Screening	Negative	21.0	135	35.0	0.55	291	None detected
	Epoch 2, week 1	Unknown	Unknown	98	71.3	1.04	145	Unknown
(b) (6)	Screening	Negative	46.0	139	15.0	0.99	190	None detected
	Epoch 3, Week 9	Negative	23.0	128	23.2	1.50	157	None detected
(b) (6)	Screening	Unknown	Unknown	143	77.8	1.56	246	Unknown
	Epoch 3, Week 1	Unknown	Unknown	119	79.7	2.81	274	Unknown
(b) (6)	Screening	Unknown	Unknown	161	39.0	1.25	136	Unknown
	Epoch 3, week 9	Negative	82.0	146	34.5	0.84	90	Unknown

Adapted from Listing 30, page 158 of 377, CSR,
**Hp = haptoglobin*

Reviewer comment
Individual components of a laboratory panel used to detect hemolysis were inconsistent with one another. Subject (b) (6) and Subject 060013 experienced nadir Hb values at study end. While subsequent testing might have revealed evidence of hemolysis, declining trends in LDH values from baseline to end of study suggest the absence of hemolysis.

Urinalysis
Subject (b) (6), a 62 year old White male with a history of CVID, chronic fatigue, chronic sinusitis, hypercholesterolemia, GERD, HTN, and BPH, had an increase in urine protein from 1+ at screening to 2+ in Epochs 3 and 4 but returned to 1+ by the end of the study.

Reviewer comment

The applicant attributes increasing proteinuria followed by decreasing proteinuria to preexisting CVID. However, this is not a common complication of the disease. In addition, proteinuria is not a recognized AR with other IGIVs or IGSCs. The etiology of this event is unclear.

Transfusion-transmitted infections

No evidence of HIV, Hepatitis C, or Hepatitis B was seen in the study.

There were no other clinically significant changes in laboratory values or vital signs.

6.1.11.7 Dropouts and/or Discontinuations

Out of the 86 subjects who signed the ICF, 9 did not receive study drug. Of the remaining 77 subjects (Safety Analysis Set), all were treated with GAMMAGARD LIQUID *vs.* 74 who received Cuvitru. Overall, 67 subjects completed the study.

- In Epoch 1, Subject (b) (6) and Subject (b) (6) were discontinued for non-compliance and Subject 150001 experienced a headache TEAE that led to discontinuation.
- In Epoch 2, 7 subjects terminated participation due to withdrawal of consent (Subjects (b) (6)), a headache TEAE (Subject (b) (6)) and non-compliance (Subject (b) (6)).

Stratified by age, 1 dropout was a child aged 5 to <12 years, 3 were adolescents, 11 were adults aged 16 to <65 years, and 4 were subjects aged ≥65 years.

Two were discontinued due to AEs.

- **Subject** (b) (6) was a 14 year old White female with a history of PI and arthritis who developed headache requiring hospitalization during treatment with IGSC 10%, in Epoch 1. The subject was hospitalized on 13 Nov 2013; the headache resolved and she was discharged on 17 Nov 2013. She withdrew from the study on 19 Nov 2013.
- **Subject** (b) (6), a 66 year old White female with a history of hypothyroidism, migraine, depression, fibromyalgia and hypokalemia experienced multiple AEs including diarrhea, dizziness and fatigue on 8 Apr 2014 while receiving Cuvitru. She felt that the fatigue was possibly due to IGSC 20%, and chose to discontinue from the study on 23 Apr 2014. The AEs were assessed by the investigator as non-serious and unrelated to CUVITRU administration and were resolving at the time of study discontinuation.

6.1.12 Study Summary and Conclusions

The data support the safety and efficacy of Cuvitru as replacement therapy for patients with primary humoral immunodeficiency. Although sample sizes are too small to draw

any meaningful conclusion, pediatric subjects appeared to be at slightly higher risk than adults of experiencing local infusional TEAEs necessitating modification of the infusion.

6.2 STUDY 170903

"A Clinical Study of Immune Globulin Subcutaneous (Human) (IGSC), 20% for the Evaluation of Efficacy, Safety, and Pharmacokinetics in Subjects with Primary Immunodeficiency Diseases"

6.2.1 Objectives

Primary

- To evaluate the efficacy of Cuvitru in subjects with PI.

Secondary

- To evaluate further efficacy assessments as well as the safety, tolerability, and pharmacokinetic characteristics of Cuvitru in subjects with PI.

6.2.2 Design Overview

Prospective, open-label, 2-Epoch, non-controlled, non-randomized, multi-center study.

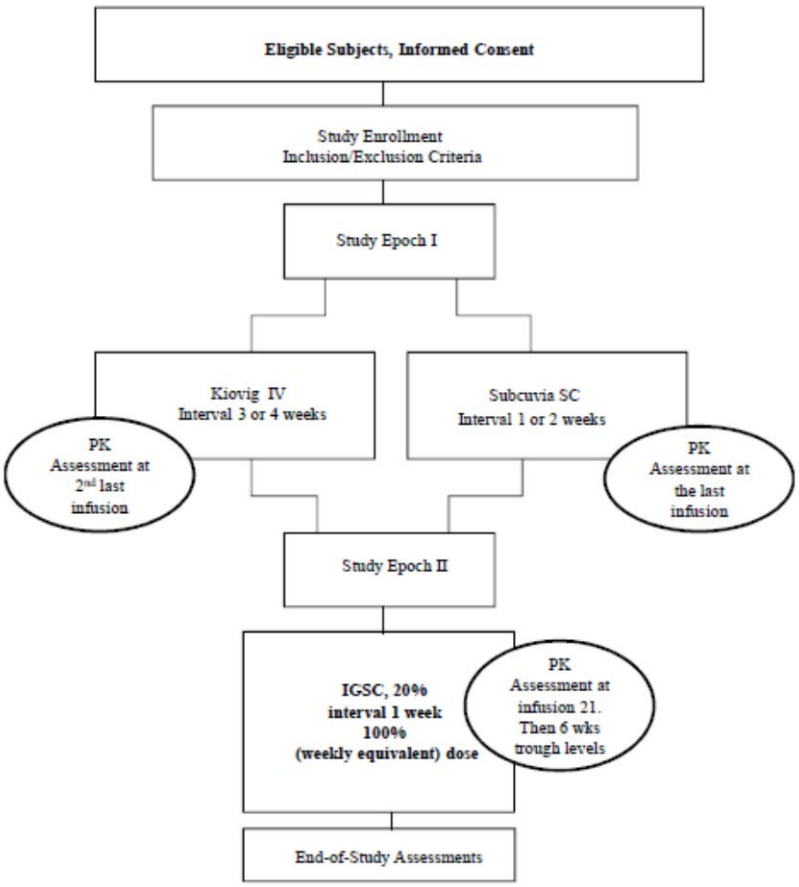

Figure 2: Study design for Study 170903 showing Epoch 1 (KIOVIG or SUBCUVIA) and Epoch 2 (Cuvitru).

Source: Figure 9.2-1, 170903 CSR, page 24 of 737, 23 Sep 2014

Reviewer Comment

KIOVIG is Baxalta's proprietary name for GAMMAGARD LIQUID sold in Europe.

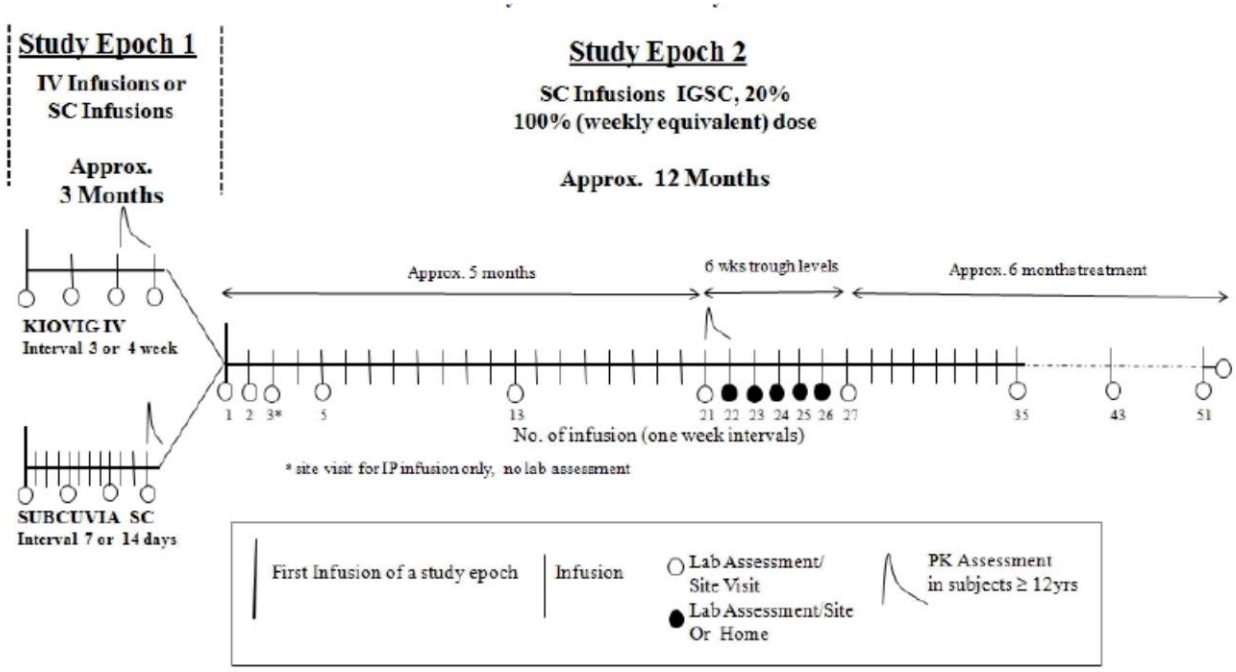

Figure 3: Study schedule for Study 170903 showing the 3-month Epoch 1 treatment schedule and the 12-month Epoch 2 treatment schedule. Note that exposure to KIOVIG and SUBCUVIA lasted approximately 3 months. Also note the measurement of IgG trough levels at Week 6.

6.2.3 Population

Subjects aged 2 years or older with documented diagnosis of a form of primary humoral immunodeficiency involving antibody formation and requiring replacement therapy.

6.2.4 Study Treatments or Agents Mandated by the Protocol

KIOVIG (IGIV, 10%)[6]
SUBCUVIA (IGSC, 16%)
Cuvitru (IGSC, 20%)

6.2.5 Sites and Centers

Site 10: Prof. Dr. Michael Borte (Germany)
Site 11: Dr. Robin Kobbe (Germany)
Site 12: Prof. Dr. Thomas Harrer (Germany)
Site 13: Prof. Dr. Reinhold E. Schmidt (Germany)
Site 20: Prof. Dr. Elisabeth Forster-Waldl (Austria)
Site 30: Prof. Dr. Anders Fasth (Sweden)
Site 32: Dr. Nicholas Brodszki (Sweden)

6 GAMMAGARD LIQUID is marketed in Europe under the trade name KIOVIG.

Site 40: Prof. Dr. P. Martin van Hagen (Netherlands)
Site 60: Dr. Sofia Grigoriadou (UK)
Site 61: Dr. Aarnoud Huissoon (UK)
Site 65: Dr. Stephen Jolles (UK)
Site 70: Jutte Van der Werff ten Bosch (Belgium)
Site 80: Dr. Gergely Kirivan (Hungary)
Site 81: Prof. Dr. Laszlo Marodi (Hungary)
Site 82: Dr. Tasas Bense (Hungary)
Site 83: Dr. Ferenc Dicso (Hungary)

6.2.6 Surveillance/Monitoring

Monitoring of vital signs, laboratory parameters and AE reporting were accepted standard methods for safety evaluation at the time of the study. The Common Toxicity Criteria of the Eastern Cooperative Oncology Group and WHO toxicity grading system (sodium and potassium only).

Two interim analyses of safety and tolerability were performed to evaluate serious AEs, all infections per subject, percentage of infusions requiring adjustment, number and rate per infusion of all AEs and of temporally associated AEs by relatedness and severity and classified as local or systemic and by medical dictionary for regulatory activities (MedDRA) terms, and selected PK parameters such as IgG trough levels. In addition, infusion rates and infusion volume per site administered and their tolerability was assessed in order to determine whether an adaption of the maximum rate/volume per site should be implemented.

Two further interim analyses of the PK and IgG trough levels were performed in subjects who had completed the PK assessments in Epoch 1 and Epoch 2. Both interim analyses compared IgG trough levels, area under the concentration/time curve between subsequent infusions and other PK parameters for Epoch 1 and Epoch 2.

No statistical adjustment or changes to the protocol were made based on data collected during these interim analyses.

6.2.7 Endpoints and Criteria for Study Success

Efficacy
Primary

- SBI rate defined as the mean number of SBIs per subject per year in the ITT population. SBIs included bacteremia/sepsis, bacterial meningitis, osteomyelitis/septic arthritis, bacterial pneumonia, and visceral abscess that were caused by a recognized bacterial pathogen

Secondary

1. Pharmacokinetics
    a. Trough levels of IgG were determined at
        - Baseline
        - Epoch 1:

IV treatment: At each infusion (every 3 weeks or every 4 weeks)
SC treatment: Every 4 weeks

- Epoch 2:
  At infusion numbers 1, 5, 13; then weekly at infusion numbers 21, 22, 23, 24, 25, 26 and 27; then every 8 weeks at infusion numbers 35, 43 and 51.
- End-of-Study Visit

b. Trough levels of specific antibodies to clinically relevant pathogens (*Clostridium tetani* toxoid, *Hemophilus influenzae* and *Hepatitis B* Virus) during 3 months treatment with SUBCUVIA or KOVIG(Epoch 1) and trough levels of these specific antibodies after SC administration of Cuvitru (Epoch 2)

c. Other PK parameters assessed for IgG: area under the curve (AUC), clearance (CL) for IV and apparent clearance (CL/F) for SC administration, maximum concentration (Cmax), minimum concentration (Cmin), and time to maximum concentration (Tmax).

2. Infections
   a. The annual rate of all infections per subject
   b. The annual rate of sinus infections per subject
   c. The annual rate of fever episodes per subject
   d. Days not able to attend school/work or to perform normal daily activities due to illness/infection
   e. Days on antibiotics
   f. Number of hospitalizations and length of stay (in days)
   g. Acute (urgent or unscheduled) physician visits due to illness/infection

Safety

1. Related AEs
   a. Number of AEs (including and excluding infections) determined by the investigator to be related to the study drug that occurred at any time during the study ("related") divided by the number of subjects
   b. Number of AEs (including and excluding infections) determined by the investigator to be related to the study drug that occurred at any time during the study ("related") divided by the number of infusions
2. All AEs
   a. Annual rate of serious AEs (SAEs), related and not related
   b. Rates of AEs (including and excluding infections) defined as number of AEs categorized by MedDRA preferred terms, seriousness, and severity, divided by the number of subjects
   c. Rates of AEs (including and excluding infections) defined as number of AEs categorized by MedDRA preferred terms, seriousness, and severity, divided by the number of infusions

3. Local AEs
    a. Proportion of infusions in Study Epoch 1 and in Study Epoch 2 associated with one or more local AEs (including and excluding infections), at any time during the study
    b. Proportion of subjects in Study Epoch 1 and in Study Epoch 2 reporting one or more local AEs (including and excluding infections), at any time during the study
4. Temporally associated AEs
    a. Number of AEs (including and excluding infections) that began during the infusion or within 72 hours of completion of infusion divided by the number of subjects
    b. Number of AEs (including and excluding infections) that began during or within 72 hours of completion of infusion divided by the number of infusions
5. Short term tolerance
    a. Vital signs
    b. Proportion of infusions for which the infusion rate was reduced and/or the infusion interrupted or stopped for tolerability concerns or for AEs
    c. Proportion of subjects for whom the infusion rate was reduced and/or the infusion interrupted or stopped for tolerability concerns or for AEs
    d. Proportion of infusions tolerated with intravenous (IV) or subcutaneous (SC) administration
6. Hemolysis evaluation
    a. Occurrences of hemolysis at any time during the study

Exploratory Endpoints

1. Dose adjustments: number and proportion of subjects for whom the dose was changed for any reason.
2. Quality of life was analyzed separately for the age groups 2-7 years (PEDS-QL, observer: parent), 8-13 years (PEDS-QL, observer: subject), and 14 years and older (SF-36, observer: subject). Additionally all subjects completed the EQ-5D Health Questionnaire, analyzed separately for the age groups: 2-11 years EQ-5D (observer: parent) and 12 years and older EQ-5D (observer: subject).
3. Treatment satisfaction (Life Quality Index) was analyzed separately for the age groups 2-13 years (observer: parent) and 14 years and older (observer: subject).
4. Treatment preference was analyzed separately for the age groups 2-13 years (observer: parent) and 14 years and older (observer: subject).

6.2.8 Statistical Considerations & Statistical Analysis Plan

- A sample size of 43 subjects provided 84% power to reject the null hypothesis of a serious acute bacterial infection rate greater than or equal to 1.0 by means of a one-sided test and a Type I error of 0.01 assuming a rate of SBIs of 0.6/year. Allowing for a dropout rate of 10%, 47 subjects were planned to be dosed in the study.

- SBI rate and its 99% upper confidence limit were calculated using a Poisson model.
- Point and interval estimates were used for IgG trough levels and other PK parameters.
- Rates of infection, of fever episodes, hospitalizations, and acute physician visits were expressed as observed overall frequency.
- Descriptive statistics were used for analyses of safety.
- For dose adjustment, the number and proportion of subjects with dose increases and decreases was given for any reason and broken down by type of reason (weight change, IgG trough level <=5g/L, frequency of infections, other medical reason).
- Analysis of quality of life and treatment satisfaction were performed using descriptive statistics.

6.2.9 Study Population and Disposition

- Inclusion Criteria
  1. Subject had a documented diagnosis of a form of primary humoral immunodeficiency involving antibody formation and requiring gamma globulin replacement
  2. Subject was ≥2 years of age at the time of screening
  3. Written informed consent was obtained from either the subject or the subject's legally authorized representative prior to any study-related procedures and study product administration
  4. Subject had received a consistent monthly equivalent dose of IgG over a period of at least 3 months prior to first treatment with Cuvitru at (average dose range over that interval equivalent to 0.3g/kg -1.0 g/kg BW/4 weeks). Examples of pre-study dosing frequency:
     a. IV at mean intervals of approximately 3 or 4 weeks or
     b. SC at mean intervals of approximately 1 or 2 weeks
     c. SC alternative treatment schedule (e.g. 2x/week)
  5. Subject had a serum trough level of IgG >5 g/L at screening
  6. Subject did not have a serious bacterial infection within the 3 months prior to screening.
  7. Subject was willing and able to comply with the requirements of the protocol

- Exclusion Criteria
  1. Subject had a known history of, or was positive at screening for, one or more of the following: hepatitis B surface antigen (HBsAg), polymerase chain reaction (PCR) for hepatitis C virus (HCV), PCR for human immunodeficiency virus (HIV) Type 1/2
  2. Abnormal laboratory values at screening met any one of the following criteria (abnormal tests could be repeated once to determine if they persisted):
     a. Persistent alanine aminotransferase (ALT) and aspartate amino transferase (AST) >2.5 times the upper limit of normal for the testing laboratory
     b. Persistent severe neutropenia (absolute neutrophil count [ANC] ≤500/mm3)

3. Subject had creatinine clearance (Clcr) value that was <60% of normal for age and gender either measured, or calculated according to the Cockcroft-Gault formula
4. Subject had been diagnosed with or had a malignancy (other than adequately-treated, basal-cell or squamous-cell carcinoma of the skin or carcinoma in situ of the cervix), unless the disease-free period prior to screening exceeded 5 years
5. Subject was receiving anti-coagulation therapy or had a history of thrombotic episodes within 12 months prior to screening or a history of thrombophilia
6. Subject had abnormal protein loss
7. Subject had anemia that precluded phlebotomy for laboratory studies, according to standard practice at the site
8. Subject had an ongoing history of hypersensitivity or persistent reactions following IGIV, IGSC and/or Immune Serum Globulin (ISG) infusions
9. Subject had severe Ig A (IgA) deficiency (IgA < 0.07g/L) with known anti IgA antibodies and a history of hypersensitivity
10. Subject was on preventative (prophylactic) systemic antibacterial antibiotics at doses sufficient to treat or prevent bacterial infections, and could not stop those antibiotics at the time of screening
11. Subject had active infection and was receiving antibiotic therapy for the treatment of infection at the time of screening
12. Subject had a bleeding disorder or a platelet count < 20,000/μL, or in the opinion of the investigator, was at significant risk of increased bleeding or bruising as a result of SC therapy
13. Subject has total protein >9 g/dL or myeloma, or macroglobulinemia (IgM) or paraproteinemia
14. Women of childbearing potential met any one of the following criteria
    a. subject presented with a positive pregnancy test
    b. subject was breast feeding
    c. subject intended to begin nursing during the course of the study
    d. subject did not agree to employ adequate birth-control measures throughout the study
15. Subject had participated in another clinical study and had been exposed to an investigational product (IP) or device within 30 days prior to study enrollment (exception: treatment with Ig pre-study)
16. Subject was scheduled to participate in another (non-Baxter) non-observational (interventional) clinical study involving an IP or device during the course of the study
17. Subject had severe dermatitis that would preclude adequate sites for safe product administration

6.2.9.1 Populations Enrolled/Analyzed

- Safety Analysis Dataset (N=49): all subjects who received at least one dose of any study drug.
- Pharmacokinetic Dataset (N=31)

6.2.9.1.1 Demographics

Table 18 shows that a majority of the population was male, with virtually no minority representation.

Table 18: Study 170903 Population Demographics (Safety Analysis Set)

Parameter	Category	Age 2 to <6 Years N=5 (%)	Age 6 to <12 Years N=8 (%)	Age 12 to <18 Years N=12 (%)	Age 18 to <65 Years N=21 (%)	Age ≥ 65 Years N=3 (%)	Total N=49 (%)
Gender	Male	4 (80.0)	6 (75.0)	8 (66.7)	12 (57.1)	0	30 (61.2)
	Female	1 (20.0)	2 (25.0)	4 (33.3)	9 (42.9)	3 (100.0)	19 (38.8)
Race	White	5 (100.0)	8 (100.0)	11 (91.7)	21 (100.0)	3 (100.0)	48 (98.0)
	Black/AA	0	0	0	0	0	0
	Asian	0	0	1 (8.3)	0	0	1 (2.0)
	Multiple	0	0	0	0	0	0
Ethnicity	Hispanic	0	0	0	0	0	0
	Not Hispanic	0	0	0	0	0	0

Adapted from Table 4, CSR, page 82 of 737, 23 Sep 2014

6.2.9.1.2 Medical/Behavioral Characterization of the Enrolled Population

The etiology of infusional TEAEs was confounded by pre-existing medical conditions or symptoms that mimic ARs associated with IgG treatment of PI, e.g., conditions such as headache (n=39 cases), sinusitis (n=31), pain (n=42), fatigue (n=16) and nausea (n=9) occurred at a high frequency (n) among enrollees (N=77).

6.2.9.1.3 Subject Disposition

Figure 4 shows the disposition of subjects in Epoch 1 (left side of tree) and Epoch 2 (right side of tree). Of the 55 subjects screened, 49 started Epoch 1, 48 continued into Epoch 2 and 45 completed the study (91.8%).

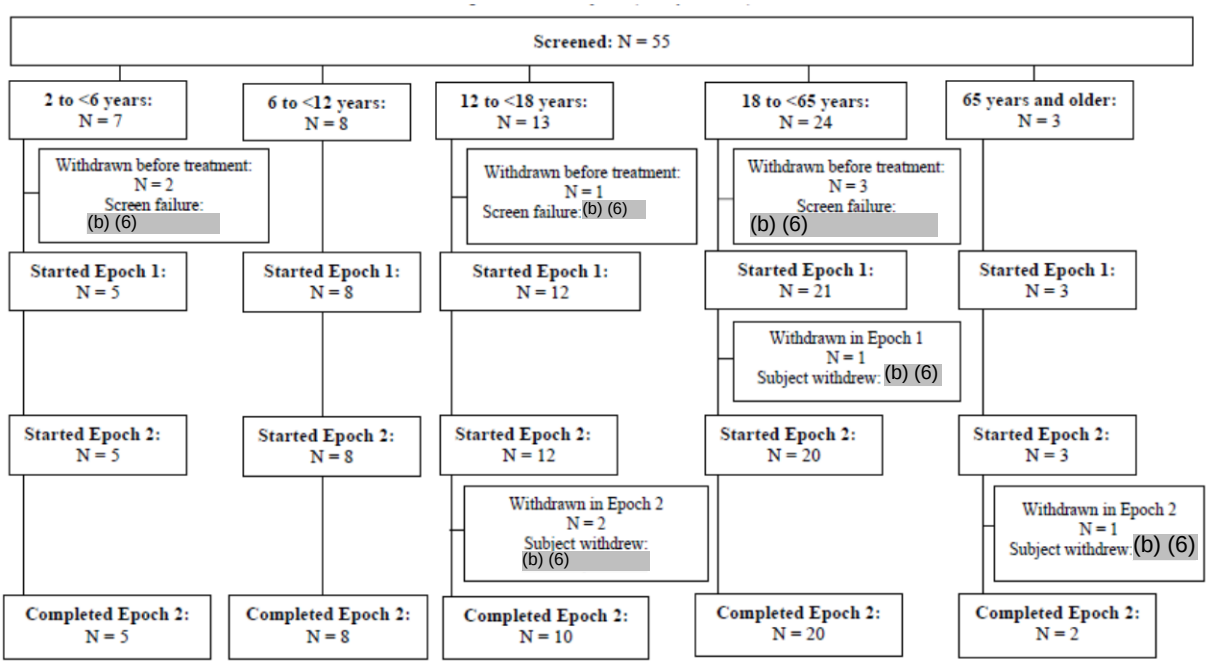

Figure 4: Disposition of subjects in Study 170903.
Source: Figure 1, CSR, page 49 of 737, 23 Sep 2014

6.2.10 Efficacy Analyses

6.2.10.1 Analyses of Primary Endpoint(s)

- The annual rate of SBIs for Cuvitru (point estimate: 0.022; upper limit of 99% CI: 0.049) was significantly lower than the FDA threshold (null hypothesis: SBI rate ≥1.0 per person year at the 1% level of significance). Significant values also were reported in the pediatric Cuvitru subpopulation: 0.06; upper limit of 99% CI: 0.17).

  Two SBIs were reported in one 9 year old White male subject (Subject (b) (6)). This subject had XLA, a more severe form of hypogammaglobulinemia, and experienced 1 SBI of bacterial pneumonia while receiving SUBCUVIA and a second one during treatment with Cuvitru (Epoch 2).

6.2.10.2 Analyses of Secondary Endpoints

- Total IgG trough levels
  Table 19 presents median total IgG trough levels for Cuvitru subjects in the aggregate as well as in subpopulation cohorts during the 6 week measurement period. All age cohorts demonstrated total IgG trough levels that were above the minimum therapeutic range (>5 g/L).

Table 19: Cuvitru Trough Levels During the 6-Week Measurement Period (Safety Set)

Population Cohort	N	Median Trough Level	95% CI
12 to < 18 years	11	8.1	7.7 to 11.7
18 to <65 years	20	8.6	7.6 to 9.9
≥65 years	2	6.64	NA
Total	46	8.48	7.9 to 9.9

Adapted from Table 10, CSR, page 88 of 737, 23 Sep 2014
NA=not applicable because of small sample size

- AUC
  The AUC of Cuvitru was 82% of the AUC of KIOVIG (90% CI: 77% - 88%). Median AUC per dose/body mass during Cuvitru administration was similar to the value calculated for SUBCUVIA and only slightly lower than the AUC per dose/body mass obtained for subjects treated with KIOVIG.
- Subject-reported outcomes (annualized)
  Table 20 shows annualized rate for secondary efficacy parameters.

Table 20: Annualized Subject Reported Outcomes (Safety Set)

Outcome	KIOVIG	SUBCUVIA	Cuvitru
Infection rates (% per subject	6.3	8.9	4.4
Days off school/work	10.7	50.4	15.6
Days on antibiotics	19.6	54.3	18.1
Number of hospitalizations	0.1	0.5	0.2
Number of acute physician/ED visits	5.1	7.6	3.8

Reviewer Comment
The incidence of subject-reported outcomes was similar between Cuvitru and KIOVIG, whereas corresponding values for SUBCUVIA were considerably higher.

6.2.10.3 Subpopulation Analyses

During Cuvitru administration at a dose equivalent to the previous SUBCUVIA or GAMMAGARD LIQUID IV dose, the annualized rate of infections per subject was

- 4.29 for subjects aged 2 to <6 years
- 4.21 for subjects aged 6 to <12 years
- 2.85 for subjects aged 12 to <18 years
- 5.52 for subjects aged 18 to <65 years
- 2.61 for subjects aged 65 years and above.

In all subgroups except subjects aged 2 to <6 years, annualized infection rates were higher during SUBCUVIA treatment than during Cuvitru administration.

6.2.10.4 Dropouts and/or Discontinuations

See Figure 4. Subjects were permitted to withdraw from further study participation for the following reasons:

- If the subject became pregnant. In this case, product exposure was to be discontinued. Attempts were to be made to follow her through completion of the pregnancy. The investigator was to record a narrative description of the course of the pregnancy and its outcome.
- The subject frequently (twice consecutively) missed administration of IP
- Use of other IGIV or IGSC products (for an exception see Protocol Amendment 5 version 3 Apr 2013, Section 10.4)
- Unacceptably severe allergic reaction related to IGSC, at the discretion of the investigator

6.2.10.5 Exploratory and Post Hoc Analyses

QoL

- Quality of life and treatment satisfaction scores obtained using the PEDS-QL questionnaire or the SF-36 survey and the EQ-5D Health Questionnaire were in the upper part of the possible score range indicating treatment satisfaction.
- The majority of subjects (42/48) stated that they preferred Cuvitru and would continue on this treatment, 1 preferred IGSC, 10% treatment, and 5 had a preference for IV administration.

6.2.11 Safety Analyses

6.2.11.1 Methods

The study comprised Epoch 1 and Epoch 2.

- Epoch 1
  Subjects were treated with KIOVIG for 13 weeks or SUBCUVIA for 12 weeks. Administration, dosage frequency, and dose were dependent on the pre-study treatment, although the dose range had to be within 0.3-1.0 g/kg BW/4 weeks.

  PK assessments were performed in subjects aged ≥12 years at the second to last KIOVIG infusion or at the last SUBCUVIA infusion. For subjects aged 2 to <12 years, only IgG trough levels were assessed in order to avoid multiple blood drawings.

  One week after the last KIOVIG (i.e., after infusion number 4 for the 4 week treatment interval or infusion number 5 for the 3 week treatment interval), Study Epoch 2 began. For subjects receiving SUBCUVIA during Epoch 1, subjects on a weekly treatment schedule began Epoch 2 one week after the last infusion and subjects on a biweekly schedule began Epoch 2 two weeks after the last infusion.

- Epoch 2
  Subjects received Cuvitru once every week for *51* weeks at the equivalent dose used during Epoch 1, adjusted to a weekly equivalent dose when necessary. If serum IgG

trough levels fell to ≤5 g/L, the dose was adjusted to maintain minimum trough levels (>5 g/L). The initial two infusions were started at 10 mL/h/infusion site and were increased stepwise if tolerated, to a maximum of 60 mL/h/infusion site.

After approximately 5 months in this study epoch, a PK assessment was performed in subjects aged 12 years and older. For subjects aged 2 to <12 years, IgG trough levels only were assessed.

6.2.11.2 Overview of AEs

SAEs

- No deaths were reported.

- A total of 12 SAEs occurred in 8 subjects and were assessed as *unrelated* to study product: 2 in the KIOVIG (6.1%) cohort, 2 in the SUBCUVIA (12.5%) cohort and 8 in the Cuvitru (12.5%) cohort, of which 2 were severe (acute MI and ventricular fibrillation), 5 were moderate and 1 was mild in intensity. See 6.2.11.4 for SAE NARRATIVES.

TEAEs

- Summary of TEAEs
  Table 21 presents an overview of TEAEs by subject.

Table 21: Subjects Experiencing TEAEs Regardless of Causality (Safety Analysis Set)

	KIOVIG N=33 (%)	**SUBCUVIA N=16 (%)**	**Cuvitru N=48 (%)**
Exposure duration	3 months		12 months
Number of subjects experiencing ≥1 TEAE	26 (78.8)	16 (100.0)	46 (95.8)
Number of subjects experiencing TEAEs by intensity			
Mild	26 (78.8)	15 (93.8)	45 (93.8)
Moderate	10 (30.3)	9 (56.3)	25 (52.1)
Severe	0 (0.0)	0 (0.0)	2 (4.2)
Number (%) of subjects experiencing TEAEs by age cohort (years)			
2 to <5	3 (60.0)	0 (0.0)	5 (100.0)
5 to <12	4 (66.7)	2 (100.0)	8 (100.0)
12 to <18	8 (80.0)	2 (100.0)	11 (91.7)
18 to <65	10 (90.9)	10 (100.0)	19 (95.0)
≥65	1 (100.0)	2 (100.0)	3 (100.0)
Number (%) of subjects experiencing infusional TEAEs within 72 hours	12 (36.4)	12 (75.0)	41 (85.4)

Adapted from Table 24 (page 261 of 737) and Table 31 (page 292 of 737), 23 Sep 2014

Table 22 presents a direct comparison of TEAEs associated with KIOVIG, SUBCUVIA, and Cuvitru using a ≥5% cut-off. Headache, the most common *systemic* TEAE, occurred twice as often in the KIOVIG and SUBCUVIA cohort as in the Cuvitru cohort. Of note, the most common local TEAE, infusion site erythema, was reported only in Cuvitru

subjects; other local TEAEs also occurred more frequently in Cuvitru subjects than in the other two cohorts.

Table 22: Incidence ≥5% for Causally Related and/or Temporally Associated TEAEs (Safety Analysis Set)♯

TEAEs	KIOVIG (%) N=33	SUBCUVIA (%) N=16	Cuvitru (%) N=48
Local adverse reactions	-	**2 (12.5)**	**18 (37.5))**
Infusion site erythema (including Injection site erythema)	-	-	10 (20.8)
Infusion site pain (including Infusion site discomfort and Injection site pain)	4 (12.1)	-	10 (20.8)
Infusion site pruritus (including injection site pruritus)		1 (6.3)	7 (14.6)
Systemic adverse reactions	**13 (39.4)**	**9 (56.3)**	**33 (68.8)**
Headache	6 (18.2)	3 (18.8)	14 (29.2)
Fatigue	3 (9.1)	1 (6.3)	6 (12.5)
Body temperature increased	2 (6.1)	-	-
Chills	2 (6.1)	-	-
Musculoskeletal chest pain, enteritis, abdominal pain upper, contusion, diarrhea, nausea, restless leg syndrome, urticaria, Vitamin D deficiency (each)	-	1 (6.3)	-

♯A hyphen (-) indicates the incidence ranged from 0 to <5%
*A subject may have experienced >1 TEAE
Adapted from Table 2, page 11 of 491, CSR, 23 Sep 2014, Information Request received 5 July 2016, and Information Request received 15 July 2016

Reviewer Comment

Data from Table 22 appear to show that the rate of local adverse reactions was 3-fold higher using Cuvitru *versus* SUBCUVIA (Hizentra). These data should be interpreted with caution, however, because subjects in the Cuvitru cohort were exposed to the product for 12 months *versus* 3 months for SUBCUVIA. Extrapolation of the SUBCUVIA data to 12 months computes to a 50% local adverse reaction rate, i.e., less than Cuvitru. In fact, the incidence of local adverse reactions using Cuvitru (study 170903: 37.5%; study 170904: 31.1%) is the *lowest* of currently licensed IGSC products: Cuvitru (pooled study data): 34.4%, Hizentra: 100%, HYQVIA: 51.9% and GAMUNEX-C: 75.0% (see Table 4).

Tolerance

At no time was an infusion interrupted or stopped for tolerability concerns or for AEs. Infusion rate reductions, however, were needed in 0.7 % of KIOVIG infusions (1/5 subjects aged 2 to <6 years) and 0.2% of Cuvitru infusions (2/4 Cuvitru (4% of Cuvitru enrollees) subjects in the 12 to <18 year cohort.[7]

7 No rate reductions were required for SUBCUVIA subjects.

6.2.11.3 Deaths

No deaths occurred during the study.

6.2.11.4 Nonfatal Serious AEs

SAEs (N=12) occurred in 8 subjects during Epoch 1 and Epoch 2. Two SAEs were severe in nature (NSTEMI and ventricular fibrillation), 9 were of moderate in severity (lymphadenopathy, forearm fracture, bacterial pneumonia (2), thoracic vertebral fracture, enteritis, chronic sinusitis, brain stem infarction and rhinorrhea) and 1 was mild (nasal septum deviation).

NARRATIVES

- **Subject** (b) (6) was a 9 year old child with XLA who experienced bacterial pneumonia during initial treatment with SUBCUVIA. His medical history was notable for chronic cough (2003), chronic bronchitis (2005), and pneumonia (2008 and 2010). Four days after the subject had received his first dose of SUBCUVIA therapy on 20 Feb 2012, he experienced high fever, chills, rigors, productive cough and thoracic pain. Three days later he underwent a chest X-ray that showed pulmonary infiltrates and consolidation. He was diagnosed with bacterial pneumonia and treated with antibiotics. The subject was discharged on 1 Mar 2012. The investigator assessed the event as serious and not causally related to the product.

  Reviewer Comment
  The temporal relationship between pneumonia onset and initiation of SUBCUVIA therapy four days earlier suggests the possibility of therapeutic failure.

- **Subject** (b) (6) was a 17 year old female with CVID who experienced exacerbation of chronic maxillary sinusitis during participation in Epoch 2 (Cuvitru). Her medical history was notable for rhinitis (2011) and acute exacerbations of chronic maxillary sinusitis (2011, 2012) of moderate severity. On 28 Feb 2012, she experienced an acute exacerbation of chronic maxillary sinusitis. Her otolaryngologist elected to perform endoscopic sinus surgery (FESS) operation. By 1 Mar 2012, she had recovered from the event and was discharged home. The investigator assessed the exacerbation as serious and not causally related to the product.

  Reviewer Comment
  This subject had a positive medical history for chronic maxillary sinusitis and a nadir total IgG level nadir of 8.1 at Epoch 2 Infusion 51. The exacerbation was unrelated but represented a treatment failure.

- **Subject** (b) (6) was a 9 year old (at Screening) child with XLA who experienced bacterial pneumonia during initial treatment with SUBCUVIA. His medical history was notable for chronic cough (2003), chronic bronchitis (2005), and pneumonia (2008 and 2010). Four days after the subject had received his first dose of

SUBCUVIA therapy on 20 Feb 2012, he experienced high fever, chills, rigors, productive cough and thoracic pain. Three days later he underwent a chest X-ray that showed pulmonary infiltrates and consolidation. He was diagnosed with bacterial pneumonia and treated with antibiotics. The subject was discharged on 1 Mar 2012. The investigator assessed the event as serious and not causally related to the product.

Reviewer Comment
In addition to the pneumonia indicating therapeutic failure associated with Cuvitru, the temporal relationship between pneumonia onset and initiation of SUBCUVIA therapy four days earlier aslo suggests the possibility of therapeutic failure.

- **Subject** (b) (6) was a 17 year old White male with CVID who experienced asymptomatic left axillary lymphadenopathy shortly after receiving his 2nd dose of KIOVIG administered IV (Epoch 1). Surgical removal was performed to rule out lymphoma on 20 Feb 2013 and he was discharged the next day without any signs of malignancy. The investigator assessed the event as serious and not causally related to the product.

Reviewer Comment
I concur with the investigator's assessment of causality.

- **Subject** (b) (6) was a 62 year old White male with CVID who had completed Study 170903 after receiving Cuvitru and subsequently experienced (*a*) an NSTEMI on 23 Feb 2014 and (*b*) a left brainstem infarction the next day. His medical history was notable for hypertension and 3-vessel coronary artery disease. He received his weekly Cuvitru dose on 24 Feb 2014. He underwent minimally invasive heart surgery on 5 Mar 2014 and during the procedure, an external pacemaker was applied. The next day he experienced an episode of ventricular fibrillation. Following resuscitation, he was diagnosed with trochlear nerve paralysis due to infarction of the mesencephalon and thalamus. Dislodgment of a pre-existing atherosclerotic plaque during resuscitation was the presumed etiology of his paralysis. He was discharged from the hospital on 1 May 2014. The investigator reported the event was serious and not causally related to the product.

Reviewer Comment
I concur with the investigator's assessment of causality.

- **Subject** (b) (6) was 40 year old White male with CD40 ligand deficiency who experienced nasal septum deviation following initiation of Cuvitru administration on 29 Dec 2011 (Epoch 2). His medical history was notable for impaired nasal breathing due to nasal septum curvature as well as CVID, chronic sinusitis, infectious mononucleosis, pneumococcal pneumonia, splenectomy, and pneumonia. The subject also suffered from chronic sinusitis prior to study screening and was planning to undergo corrective nasal septum surgery. There was no worsening of the nasal septum deviation during the study. He was hospitalized on 26 Sep 2012 and underwent nasal septum surgery. He remained for 3 days and was released on 29 Sep

2012. The investigator assessed the event as serious (due to the need for surgery) and not causally related to the product.

Reviewer Comment
I concur with the investigator's assessment of causality. The patient's nasal septum curvature and related symptoms predated his entry into the study and there was no worsening of the nasal septum deviation during the day.

- **Subject** (b) (6) was a 6 year old White male with XLA who experienced chronic rhinorrhea while receiving Cuvitru in Epoch 2. In Jan 2013, he experienced dry cough and rhinorrhea without bacterial infection. Prick test was negative and pulmonary HRCT confirmed minor bronchiectasis. On 14 May2013, he was diagnosed with chronic rhinitis. An adenoidectomy was performed uneventfully on 20 Jun2013. He was discharged the next day without any symptoms. The investigator assessed the event as serious (due to the need for hospitalization) and not causally related to the product.

  Reviewer Comment
  I concur with the investigator's assessment of causality.

- **Subject** (b) (6) was a 46 year old White female with CVID who experienced acute gastroenteritis while receiving Cuvitru in Epoch 2. Her medical history was notable for pneumonia, giardiasis, celiac disease grade II, sinusitis, diarrhea, and penicillin and Tobramycin allergy. On 23 Jan2012 she experienced vomiting and diarrhea and was admitted to hospital. The investigator assessed the event as serious (due to the need for hospitalization) and not causally related to the product.

  Reviewer Comment
  My assessment is that gastroenteritis was possibly related to Cuvitru.

- **Subject** (b) (6) was a 61 year old White male with CVID who experienced thoracic vertebral body fractures while receiving SUBCUVIA in Epoch 1. His medical history was notable for chronic rhinitis (since 1985), chronic sinusitis (since 1978), chronic bronchitis (1985 to 2005), acute purulent bronchitis (2012), hypertension (since 1998), chronic diarrhea (1996 to 2002), osteoporosis (since 1995), and muscular weakness in both legs. On 12 Jan 2013 he fell from a ladder and landed on his back, which resulted to a vertebral body fracture. He was hospitalized but no neurological deficiencies observed. The subject was confined to bed and conservative treatment was planned. The investigator assessed the event as serious (due to the need for hospitalization) and not causally related to the product.

  Reviewer Comment
  I concur with the investigator's assessment of causality.

- **Subject** (b) (6) was a 14 year old White male with CVID who experienced a left forearm fracture during skating while receiving KIOVIG in Epoch 1. His medical

history was unremarkable except for PI (CVID). The investigator assessed the event as serious (due to the need for hospitalization) and not causally related to the product.

Reviewer Comment
I concur with the investigator's assessment of causality.

6.2.11.5 AEs of Special Interest (AESI)

With the exception of potential hemolysis, no AESIs were reported in Study 170903. Adults and adolescent subjects (N=36) were tested pre- and post-infusion for hemolysis; 16.7% (6/36) experienced a decline in hemoglobin of ≥2.0 g/dL (Subjects (b) (6)), but none of the reductions was confirmed to be due to a hemolytic reaction. Table 24 shows that at no time was there a concordance of other laboratory tests, e.g., Coombs' test, haptoglobin, LDL, hemosiderin, confirming a diagnosis of hemolysis.

Table 24: Potential Hemolysis Defined as Decline in Hemoglobin ≥2 g/dL

Subject No.	Visit	Coombs'	Nadir Hb (g/L)	Hp* (g/L)	LDH (U/L)	Urine Hemosiderin
(b) (6)						
	Screen	Negative	143	1.40	157	Positive
	SCV 43	Unknown	123	1.54	120	Unknown
(b) (6)						
	Screen	Negative	147	0.85	176	Negative
	SCV21	Negative	129	0.79	149	Negative
(b) (6)						
	Screen	Negative	150	1.74	155	Positive
	Unscheduled	Unknown	80	2.01	180	Unknown
(b) (6)						
	Screen	Negative	138	0.67	191	Negative
	Unscheduled	Unknown	124	1.23	219	Unknown
(b) (6)						
	Screen	Unknown	123	1.07	133	Negative
	SCV 9	Unknown	104	0.34	122	Unknown
(b) (6)						
	Screen	Negative	129	0.94	178	Negative
	IVSCV 3	Negative	83	1.94	104	Negative

Adapted from Listing 30, CSR Appendix 16.2.7, page 378 of 395,
**#SCV = Subcutaneous visit; IVSCV = Intravenous or subcutaneous visit; Hp = haptoglobin*

6.2.11.6 Clinical Test Results

Aside from potential hemolysis, no clinically meaningful grade 3 or grade 4 chemistry value toxicities were reported. No signs of infections were found for HIV, Hepatitis B or Hepatitis C viruses.

6.2.11.7 Dropouts and/or Discontinuations

See 6.2.9.1.3.

6.3 STUDY 160601

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

6.3.1 Objectives

- Primary

Evaluate tolerability and pharmacokinetics (bioequivalence) of GAMMAGARD LIQUID administered SC compared with the pharmacokinetics of GAMMAGARD LIQUID given IV.

- Secondary

Evaluate efficacy in terms of acute serious bacterial infections.

6.3.2 Design Overview

Prospective, open-label, historically-controlled, multicenter study comprising 4 Parts plus an optional Study Extension Part as described in Table 25.

Table 25: Study 160601 Design

	Study Part 1	Study Part 2	Study Part 3a	Study Part 3b	Extension
Route of Administration	IV	SC	SC	SC	SC
Administration intervals	3 or 4 weeks	Weekly	Weekly	Weekly	Weekly
Dose	300-1000 mg/kg depending on pre-study dose	Subjects on 4-week interval in Study Part 1: 130% of the 4-week IV dose divided by 4 Subjects on 3-week interval in Study Part 1: 130% of the 3-week IV dose divided by 3	Adjusted Dose calculated from PK derived from the first 15 subjects aged ≥12 years in Study Part 1 and Study Part 2.	Adjusted Dose as in Study Part 3a (if trough level increase was within 15% of the expected increase) or the Individually Adapted Dose (if the increase in trough levels was not within 15% of the expected increase).	Same dose as in Study Part 3b
PK evaluation*	After IV infusion No. 4 (for 3-week interval) or after IV	After SC infusion No. 8	No PK evaluation	After SC infusion No. 8, at Adjusted or Individually	Not applicable

	infusion No. 3 (for 4-week interval)			Adapted Dose	
Trough levels	At each infusion	At SC infusions 1, 5 and 9	At SC infusions 1 and 5	At SC infusions 1, 5, and 9 and End-of-Study Visit.	Prior to Infusion 1

* PK evaluation was performed in subjects aged ≥12 years only to avoid frequent blood samples in small children
Adapted from Table 9.1-1, CSR, page 29 of 152, 14 Apr 2010

Study Part 1
All subjects received GAMMAGARD LIQUID administered intravenously every 3 or every 4 weeks for 12 weeks at the dose and schedule that they were on prior to the study (300 to 1,000 mg/kg/4 weeks). Trough levels were evaluated before every infusion in all subjects. Blood for PK analysis was taken from all subjects aged ≥12 years after the third or fourth IV infusion, depending on the treatment interval. Subjects began SC treatment 1 week after a further regular IV treatment, i.e., fourth or fifth infusion) given at the end of the PK evaluation.

Study Part 2
All subjects received GAMMAGARD LIQUID administered subcutaneously weekly at a dose 130% of the weekly equivalent of the IV dose administered in Study Part 1 for a minimum of 12 weeks. Trough levels were evaluated monthly and blood for full PK analysis was taken from all subjects aged ≥12 years following the eighth infusion.

All subjects participated in Study Part 2 for a minimum period of 12 weeks and until the first 15 subjects aged ≥12 years had completed the PK assessment and the results were available. The PK analysis was used to determine the "Adjusted Dose" (ratio of the weekly IV dose) to be administered in Study Part 3a for all subjects, including subjects aged 2 to <12 years.

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

Study Part 3a
All subjects were treated subcutaneously with GAMMAGARD LIQUID for 6 weeks using the Adjusted Dose (as a ratio of the weekly IV dose). This Adjusted Dose was calculated based on the PK assessments from the first 15 subjects aged ≥12 years in Study Parts 1 and 2.

To determine whether each subject received an adequate dose, trough levels were determined at Week 5 (after four weekly infusions in Study Part 3a) and subject trough levels on SC (Study Part 3a) and IV treatment (Study Part 1) were compared within the next 2 weeks. During this period, the subject received another 2 infusions of the Adjusted

Dose. If the increase in trough levels was not within 15% of the expected increase, the dose was individually adapted ("Individually Adapted Dose") using an Individual Adaptation Factor read from the nomogram derived from the analysis of the first 15 PK subjects in Study Part 2.

Study Part 3b

All subjects received weekly SC infusions of GAMMAGARD LIQUID for 12 weeks. The dose was determined as follows:

- If the increase in trough levels was within 15% of the expected increase over the trough level determined in Study Part 1, the subject received the same dose (Adjusted Dose) as during Study Part 3a
- If the increase in trough levels was not within 15% of the expected increase over the trough level in Study Part 1, the subject received the Individually Adapted Dose Following Infusion No. 8, blood sampling for a full PK analysis was done in all subjects aged 12 years and older.

Study Extension Part

At the end of Study Part 3b, all subjects were offered the opportunity to enter into a Study Extension Part to capture safety and tolerability data. The duration of the Study Extension Part was estimated to be no more than 5 months.

6.3.3 Population

Safety Population: The Full Safety Dataset (**FSDS**) comprised subjects (N=49) who received study drug. Of the 49, 38 were naïve to IGSC replacement therapy, 14 in the age 2 to <12 year cohort and 24 in the age ≥12 year cohort. See Figure 5.

Study Part 1

- Subjects aged ≥2 years (≥12 years: N=23, with at least 4 subjects aged 12 to <16 years; 2 to <12: N=12), treated with IGIV, 10% at 3-week and 4-week infusion intervals
- Subjects aged ≥12 years for PK assessment

Study Part 2

- Subjects aged ≥2 years treated with IGSC, 10% at 130% of the IV dose divided by IGIV frequency
- Subjects aged ≥12 years for PK assessment after SC infusion #8.

Study Part 3a

- Subjects aged ≥ 2 years treated with IGSC, 10% at Adjusted Dose calculated from PK of first 15 subjects in in Study Part 1 and Part 2.
- No PK assessments

Study Part 3b

- Subjects aged ≥2 years treated with IGSC, 10% at the Adjusted Dose or at the Individually Adapted Dose, depending on whether trough levels collected in Study Part 3a were within 15% of the expected increase (Adjusted Dose) or not (Individually Adapted Dose).
- Subjects aged ≥12 years for PK assessment after SC infusion #8

Extension Study

- Subjects aged ≥2 years treated with same dose as in Study Part 3b
- Subjects aged ≥12 years for PK assessment after SC infusion #8

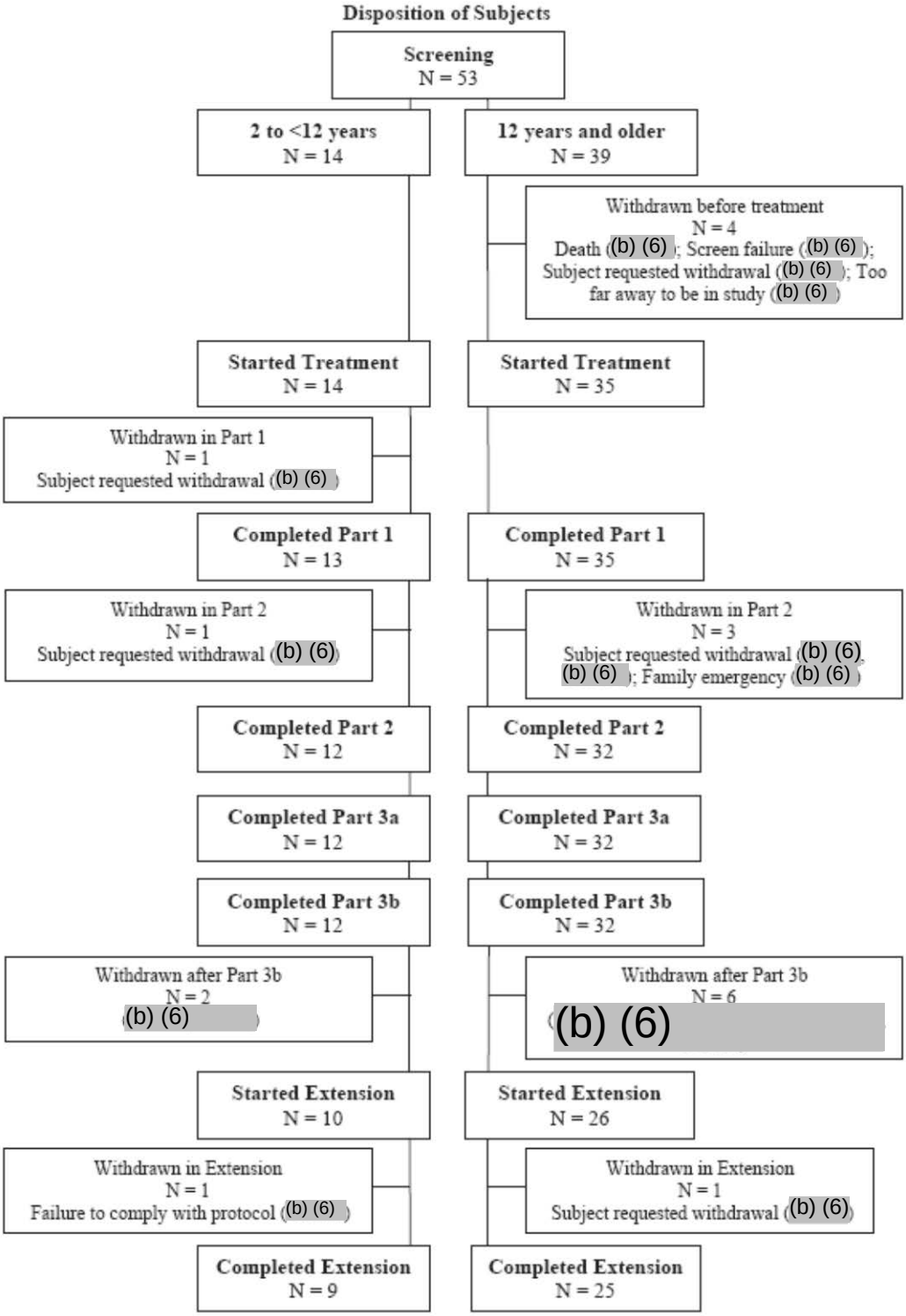

Figure 5: Disposition of subjects in Study 160601.

6.3.4 Study Treatments or Agents Mandated by the Protocol

Study Part 1: **GAMMAGARD LIQUID (IV administration)**
Study Parts 2, 3a, 3b, Study Extension: **GAMMAGARD LIQUID (SC administration)**

6.3.5 Sites and Centers

34 - Isaac Melamed, 1st Allergy & Clinical Research Center, Centennial CO
39 - Mark Stein, Allergy Associates of the Palm Beaches, North Palm Beach FL
40 - Richard Wasserman, Pediatrics Allergy/Immunology Assoc, Dallas TX
50 - Lisa Kobrynski, Emory Children's Center, Atlanta GA
52 - Rebecca Buckley, Duke University Medical Center, Durham NC
53 - Robert L. Roberts, UCLA Medical Center, Los Angeles CA
54 - Steven D. Strausbaugh, University Hospitals of Cleveland, Cleveland OH
55 - Andrew Grant, University of Texas Medical Branch, Galveston TX
58 - John M. Routes, Medical College of Wisconsin, Milwaukee WI

6.3.6 Surveillance/Monitoring

Safety assessments included monitoring of vital signs, laboratory parameters and AE reporting using accepted standard methods for safety evaluation at the time of the study. Infections were reported as a separate variable. Serious acute bacterial infections, i.e., bacteremia/sepsis, bacterial meningitis, osteomyelitis/septic arthritis, bacterial pneumonia and bacterial visceral abscess were diagnosed according to the Guidance for Industry, November 2005.

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.

A urinalysis was performed at baseline, at the first visit in each study part and at end of study.

6.3.7 Endpoints and Criteria for Study Success

Pharmacokinetics
Primary Endpoint

- In subjects aged 12 years and older: bioavailability defined as 80% to 125% of the AUC for intravenous administration compared with subcutaneous administration at an Adjusted/Individually Adapted Dose, as measured by the area under the IgG concentration versus time curve (AUC) per week.
- In subjects aged 2 to <12 years, bioavailability as measured by trough levels of IgG

Secondary Endpoint

- In subjects aged 12 years and older
  - Trough levels of IgG, and levels of antibody to *tetanus, Haemophilus influenza (H. influenza), measles* and *hepatitis B* for IV and SC treatment in Study Parts 1, 2, 3a and 3b
  - 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

Primary Endpoint

- SBI and TEAE infections (reported as the monthly rate of infections per subject).

Safety

Primary Endpoint

- Tolerability, i.e., ability to tolerate GAMMAGARD LIQUID administered intravenously or subcutaneously. Separate analyses were to be performed for IV and SC administrations in all study parts (1, 2, 3a 3b, and Study Extension Part).

Secondary endpoints

- Infusional TEAEs
- Related TEAEs
- Frequency of dose adjustments based on IgG trough levels <4.5 g/L IgG
- Proportion of subjects reporting ≥1 moderate or severe infusional AEs
- Number and rate of TEAEs categorized by preferred terms, seriousness, relatedness to the investigational product, and severity
- Proportion of infusions associated with ≥1 related or infusional (with and without excluding infection) TEAEs
- Proportion of infusions associated with systemic infusional TEAE
- Proportion of infusions associated with local infusional AEs

6.3.8 Statistical Considerations & Statistical Analysis Plan

Point estimates and 95% CIs for the annual SBI rates were calculated using a Poisson model. See the biostatistical review memo.

6.3.9 Study Population and Disposition

Inclusion Criteria

1. Written informed consent obtained from either the subject or the subject's legally acceptable representative prior to any study-related procedures and study product administration; when appropriate, the assent of the minor child was also to be obtained.
2. Diagnosis of a PI disorder as defined by World Health Organization criteria1 for which the subject had been receiving a regular Ig 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.
3. Aged 2 years and older.
4. Serum trough level of IgG >4.5 g/L at the last documented determination.
5. Negative serum pregnancy test for any female subject of childbearing potential.
6. Female subjects of childbearing potential agreed to practice birth control measures for the duration of the 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. ALT or AST >2.5 times 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 times the upper limit of normal for age and gender.
5. Malignancy other than adequately treated basal cell or squamous cell carcinoma of the 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, nephritic syndrome, severe lung disease).
8. Anemia that would preclude phlebotomy for laboratory studies.
9. Received any blood or blood product other than an IGIV, IGSC, immune serum globulin (ISG) preparation, or albumin within the 6 months prior to study enrollment.
10. Ongoing history of hypersensitivity or persistent reactions (urticaria, breathing difficulty, severe hypotension, or anaphylaxis) following IGIV, IGSC and/or ISG infusions.
11. IgA deficiency and known anti-IgA antibodies.
12. Receiving antibiotic therapy for the treatment of infection within 7 days prior to enrollment.
13. Participating in another clinical study involving an investigational product or device - with the exception of Baxter Study 160603 – within 28 days prior to study enrollment.
14. Bleeding disorders or on anti-coagulation therapy

6.3.9.1 Populations Enrolled/Analyzed

- Full Safety Dataset (N=49): subjects who received at least one dose of any study drug, regardless of whether they met (N=45) or did not meet (N=4) all enrollment criteria[8]
- Subjects Naïve to Subcutaneous Administration (N=38)
- Subjects With Prior Experience with Subcutaneous Administration (N=11)

8 The 4 subjects not meeting all enrollment criteria were naïve to IGSC replacement at time of enrollment. Three did not satisfy the WHO criteria for PI, including one who did not have PI but a secondary immune deficiency that was diagnosed after inclusion in the study. The fourth subject had been receiving antibiotic therapy for an infection within7 days prior to enrollment.

6.3.9.1.1 Demographics

Table 26: Study 160601 Population Demographics (Safety Analysis Dataset)

Parameter	Category	Age 2 to <12 Years N=14 (%)	Age ≥12 Years N=35 (%)	Total N=49 (%)
Gender	Male	8 (57.1%	19 (54.3%)	27 (55.1%)
	Female	6 (42.9%)	16 (45.7%)	22 (44.9%)
Race	White	13 (92.9%)	33 (94.3%	46 (93.9%
	Black/AA	1 (7.1%)	1 (2.9%)	2 (4.1%)
	Asian	0	0	0
Ethnicity	Hispanic	0	1 (2.9%)	1 (2.9%)
	Not Hispanic	0	0	0

Adapted from Table 14.1.2-1, CSR, page 87 of 152, 14 Apr 2010

6.3.9.1.2 Medical/Behavioral Characterization of the Enrolled Population

The etiology of infusional TEAEs was confounded by pre-existing medical conditions or symptoms that mimic ARs associated with IgG treatment of PI, e.g., headache, sinusitis, pain, fatigue, and nausea.

6.3.9.1.3 Subject Disposition

Of the 53 subjects screened for the study, 4 withdrew before treatment. Reasons for withdrawal were death (Subject (b) (6)), screen failure (b) (6)), subject request ((b) (6)), and subject request due to long commute to study site ((b) (6)). Nine study sites enrolled 49 subjects who received IgG (FSDS). Of these, 14 were aged 2 to <12 years and 35 were ≥12 years old.

6.3.10 Efficacy Analyses

6.3.10.1 Analyses of Primary Endpoint

PK bioequivalency between IGSC, 10% and IGIV, 10% was demonstrated by an AUC of 95.2% (90% confidence interval: 92.3% to 98.2%) that was within the prespecified 80% to 125% margins of equivalence.

The annual SBI rate while on SC treatment with IGIV, 10% was 0.067 (99% upper confidence limit: 0.134). This CI is substantially lower than the goal of achieving a rate of <1 serious bacterial infection per person-year.

6.3.10.2 Analyses of Secondary Endpoints

- PK
  Table 27 presents PK data from the FSDS for Part 1 (GAMMAGARD LIQUID IV), Part 2 (GAMMAGARD LIQUID SC) and Part 3b (GAMMAGARD LIQUID SC, adjusted dose) indicating minimum therapeutic trough levels (>5 g/L) were achieved.

Table 27: PK Parameters for Subjects in the PKIV and PKSC Aged 12 Years and Older

Study Part	Parameter	N	Median	95% CI for Median
Study Part 1	C max (g/L)	32	22.7	21.0 to 25.0
	C min (g/L)	32	10.1	9.4 to 12.4
	AUC (g*days/L)	32	384	347 to 432
	AUC per week	32	97.3	91.8 to 113.8
	Cl (mL/kg/day)	32	1.36	1.23 to 1.43
	Initial half-life (days)	32	9.6	5.5 to 25.8
	Terminal half-life (days)	32	33.1	28.7 to 41.4
Study Part 2	C max (g/L)	31	14.5	12.3 to 16.4
	T max (days)*	31	4.7	3.0 to 4.9
	C min (g/L)	31	12.5	11.3 to 14.2
	AUC (g*days/L)	31	94.3	83.8 to 106.3
	Cl (mL/kg/day)	31	1.87	1.61 to 2.04
Study Part 3b	C max (g/L)	32	14.1	12.5 to 16.3
	T max (days)	32	2.9	1.2 to 3.2
	C min (g/L)	32	12.6	10.6 to 14.0
	AUC (g*days/L)	32	94.6	80.4 to 106.9
	Cl (mL/kg/day)	32	2.0	1.84 to 2.12

Adapted from Table 14.2.2.2-1, CSR, page 1 of 60,
*Time to Tmax

- IgG and IgG subclass levels

For both age categories analyzed (2 to <12 years and 12 years and older) and for subjects who received IV treatment in Study Part 1 at 3-week as well as for subjects treated at 4-week intervals, IgG trough levels (C min) were higher during weekly SC replacement than during IV replacement in Study Part 1.

- Specific antibody levels

Anti-*tetanus* antibody levels were higher during weekly SC treatment than in the IV treatment period. Similar outcomes were reported for the following:

- Anti-*H. Influenza* antibody: 2.03 ug/mL and 3.150 ug/mL in the 3-week and 4-week IV treatment periods, respectively *vs.* 2.81 ug/mL and 3.29 in the SC treatment period [protective level: >200 ug/mL]
- Anti-*hepatitis-B* antibody: 202.89 IU/mL and 282.05 IU/mL *vs.* 314.10 IU/mL and 385.20 IU/mL in the SC treatment period [protective level: >10 IU/mL)
- Anti-measles antibody titers [protective titers: >1:8] were reported as ≥1:32, rendering further analysis unnecessary.

6.3.10.3 Subpopulation Analyses

The size of the pediatric and geriatric cohorts were too small to permit meaningful analyses.

6.3.10.4 Dropouts and/or Discontinuations

Of the 49 FDSD subjects, 5 terminated the study prematurely: 4 were naïve to IGSC and one (400014) had previously been exposed to IGSC therapy. Overall, 89.8% of subjects (44/49) in the FSDS completed Study Parts 2 through 3b. One pediatric subject and 3 subjects aged ≥12 years terminated the study prior to completion of Study Part 2. A total of 69.4% of subjects in the FSDS (34/49) completed the Study Extension Part.

Study Part 1: Subject (b) (6), a 6 year old White female, requested withdrawal because the upcoming SC treatment schedule conflicted with her vacation plans. Subject (b) (6), a 7 year old White female, was withdrawn by the subject's parent after completion of Study Part 1 but before transitioning to SC replacement.

Study Part 2: Of the 47 subjects who continued into Study Part 2, 3 adults ((b) (6)) requested withdrawal during that epoch. Reasons for discontinuation included: subject did not wish to continue with study ((b) (6)), family emergency ((b) (6)), and subject stated that the quality of life had decreased on SC treatment and complained of increased fatigue and general malaise ((b) (6)). Subject (b) (6) reported one instance each of mild fatigue and moderate malaise which were possibly related to the use of the investigational product in Study Part 2.

Study Part 3: Of the 44 subjects who completed Study Part 2, none withdrew during Study Part 3.

Study Extension Study: Of the 44 subjects who completed Study Part 3, 2 pediatric subjects ((b) (6)) and 6 subjects aged ≥12 years ((b) (6)) did not participate in the Study Extension Part, leaving 36 subjects who elected to continue into the Extension Part. One 10 year old White male ((b) (6)) and one 14 year old White male ((b) (6)) terminated participation prematurely.

6.3.10.5 Exploratory and Post Hoc Analyses

Not applicable.

6.3.11 Safety Analyses

6.3.11.1 Methods

Duration of exposure to IGSC, 10% was ≥53 weeks in 26 subjects, 30 to 52 weeks in 17 subjects, and 0 to 29 weeks in 4 subjects.

- In Study Part 1, most subjects received 4 IV infusions of product.
- In Study Part 2, the number of SC infusions administered per subject ranged from 1 to 18, with the majority of subjects (N=25) receiving 12 infusions.
- In Study Part 3a, the majority of subjects received 6 SC infusions; 2 subjects received 7 infusions and 1 received 8 infusions.
- In Study Part 3b, all but 5 subjects received 12 SC infusions; 3 received 15 SC infusions, 1 received 11 infusions and 1 received 14 SC infusions.

- The number of SC infusions administered during the Study Extension Part ranged from 1 to 36 with the majority of subjects receiving between 20 and 30 infusions.

Median maximum infusion rates of 20.0 mL/h and of 30.0 mL/h were achieved for IGSC infusion in the 2 to <12 years and ≥12 years, The proportion of infusions in the entire SC treatment period for which the infusion rate had to be reduced and/or the infusion had to be interrupted or discontinued for tolerability reasons was 0.2%.

6.3.11.2 Overview of AEs

- SAEs

A total of 4 unrelated SAEs were reported (see 6.3.11.4).

- TEAEs

Overall, 226 TEAEs were reported during IV administration (Study Part 1) and 634 TEAEs during SC administration (Study Parts 2, 3a, 3b, and Extension). Of these 860 TEAEs, 85 (9.9%) were considered related to the use of the Investigational product during IV administration and 150 (17.4%) were considered related during SC administration. By frequency, the six TEAEs most commonly reported in the IV cohort were headache (n=30, including 3 severe cases), chills (n=13), vomiting (n=9), pyrexia (n=6), increase heart rate (n=5), and nausea (n=5). Corresponding TEAEs in the SC cohort were infusion site pain (n=-22), headache (n=20, including 1 severe case), infusion site hematoma (n=13), increased heart rate (n=9), fatigue (n=8) and increased blood pressure.

Table 28 shows that the proportion of GAMMAGARD LIQUID subjects who experienced TEAEs was similar for subjects aged <12 years *vs.* ≥12 years regardless of route of administration. An indirect comparison between GAMMAGARD LIQUID and Cuvitru when administered subcutaneously shows that the incidence of local adverse reactions was lower (<20%) using 10% GAMMAGARD LIQUID than 20% Cuvitru (34%; see Table 3); systemic adverse reactions occurred at a slightly lower frequency with subcutaneous GAMMAGARD LIQUID (34-61%) compared with subcutaneous Cuvitru (74%; Table 3).

Table 28: No. of Subjects With TEAEs Regardless of Causality (Safety Analysis Set)

Classification	Part 1 N=49	Part 2 N=47	Part 3a N=44	Part 3b N=44	Extension N=36
	IV Administration	SC Administration			
No. of subjects with TEAEs					
<12 years of age	12 (85.7)	11 (91.7)	8 (66.7)	10 (83.3)	10 (100.0)
≥12 years of age	32 (91.4)	31 (88.6)	22 (68.8)	25 (78.1)	22 (84.6)
No. (%) of subjects with TEAEs by intensity					
<12 years of age					
Mild	5 (35.7)	6 (50.0)	4 (33.3)	3 (25.0)	6 (60.0)
Moderate	8 (57.1)	6 (50.0)	5 (41.7)	8 (66.7)	7 (70.0)
Severe	4 (28.6)	2 (16.7)	8 (66.7)	0 (0.0)	1 (10.0)
≥12 years of age					
Mild	10 (28.6)	21 (60.0)	11 (34.4)	10 (31.3)	8 (30.8)

Moderate	23 (65.7)	16 (45.7)	14 (43.8)	19 (59.4)	15 (57.7)
Severe	4 (11.4)	1 (2.9)	22 (68.8)	1 (3.1)	3 (11.5)
Local adverse reactions	2 (4.1)	16 (34.0)	6 (13.6)	7 (15.9)	6 (16.7)
Systemic adverse reactions	31 (63.3)	26 (55.3)	15 (34.1)	20 (45.5)	22 (61.1)

Adapted from Table 14.3.2-1, CSR, page 1 of 82, 14 Apr 2010 and Response to Information Request, 3 May 2016

- Infusional TEAEs

The incidence of moderate or severe infusional TEAEs (i.e., occurring within 72 hours) during SC administration was highest in subjects aged 2 to <12 years (0.92) and lower in subjects aged 12 to <16 (0.50) and adults (0.58).

- Tolerability

The infusion rate had to be reduced, interrupted and/or stopped in 16.3% (2 to < 12 years: 21.4%; ≥12 years: 14.3%) of subjects during IGIV and 4.3% (2 to <12 years: 16.7% in Study Part 2 and 0% in Study Extension Part; ≥12 years: 0%) of subjects during IGSC. During the entire SC treatment period, 0.2% of infusions required a reduction of the infusion rate and/or interruption or discontinuation of infusion for tolerability reasons

- AEs of Special Interest (AESI)

There were no AESI.

6.3.11.3 Deaths

No deaths were reported.

6.3.11.4 Nonfatal Serious AEs

A total of 4 SAEs were reported:

- 2 (sinusitis and convulsions) in Study Part 1
- 1 (cholecystitis due to gallstones) in Study Part 2
- 1 (chest pain) in Study Part 3b.

All 4 SAEs were considered unrelated to the use of the investigational product by the investigator.

NARRATIVES

- **Subject** (b) (6) was a 40 year old White female who presented at the emergency room with abdominal pain. Examination revealed that the subject had two gallstones. On 22 MAR 2008 she underwent a cholecystectomy. The subject had received GAMMAGARD LIQUID subcutaneously on 7 MAR 2008.

  Her medical history was significant for PI, recurrent sinusitis, recurrent UTI, chronic fatigue, migraine headaches, depression, irritable bowel syndrome, fibromyalgia, osteoarthritis, common variable immune deficiency, corrective

mandible surgery, Cesarean section (x 2), tubal ligation, endoscopy, colonoscopy, endometrial ablation, ruptured cervical disc, GERD, and insomnia.

The subject had no gallbladder issues prior to the event and had no further issues following surgery. The reporting investigator considered the events to be moderate in severity and unrelated to the investigational product.

Reviewer Comment
I concur with the investigator's assessment of causality.

- **Subject** (b) (6) was a 15-year-old African-American male who did not receive treatment in the context of the study, withdrew his consent and is not included in the FSDS.

  He was screened and enrolled during a routine GAMMAGARD LIQUID infusion visit on 26 FEB 2008 which had to be stopped because he developed a sickle cell pain crisis (severe back and leg pain). IV fluids, Tylenol, and Benadryl were administered. Naprosyn was also given. The pain decreased and the subject was discharged home.

  Due to increasing pain later that day, he was admitted to the hospital on 27 FEB 2008. He 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 rate of infusion and exacerbated by upper respiratory infection (URI). He had been on chronic IGIV infusions but usually received another product rather than GAMMAGARD LIQUID.

  Medical history included sickle cell disease and pain crises, hypo-gammaglobulinemia, acute chest syndrome, IGIV treatment since 1996 but without an IGIV-related crisis in the past. The investigator judged the event to be moderate in severity and initially considered the SAE to be possibly related to the use of GAMMAGARD LIQUID. The investigator subsequently changed his assessment to unrelated to investigational product since the subject's mother had URI at the time of the event and viral infections may trigger sickle cell pain.

  Reviewer Comment
  I concur with the investigator's assessment of causality.

- **Subject** (b) (6) was a 5-year-old Caucasian female subject was hospitalized on 4 APR 2008 for sinusitis after a sinus CT on 3 APR 2008 had suggested an acute infection. On 9 APR 2008, the subject recovered and was discharged from hospital. The subject had received GAMMAGARD LIQUID intravenously on 26 MAR 2008.

Medical history of the subject included chronic sinusitis. The reporting Investigator believed the event was moderate in severity and unrelated to the investigational product. No action was taken on the investigational product or trial procedure.

Reviewer Comment
I concur with the investigator's assessment of causality, although this does represent a treatment failure.

- **Subject** (b) (6) was a 42-year-old Caucasian female subject developed chest pain after IGSC administration. The last administration of GAMMAGARD LIQUID intravenously before the event was on 1 Sep 2008. She was not feeling well on the evening of 3 Sep 2008 and went to the emergency room. She was admitted on 4 Sep 2008 to rule out a blood clot in the left arm. She was discharged on the same day and was considered recovered. Per the discharge summary, she presented with chest pain at the site of her Mediport (left side). Medical history included asthma, umbilical hernia repair, cholecystectomy, and gastric bypass. Family history included diabetes mellitus and increased clot production.

  The reporting investigator believed the event was severe and unlikely related to the investigational product or trial procedure and provided the subject's Mediport in the left chest as an alternative etiology. No action was taken on the investigational product.

  Reviewer Comment
  I concur with the investigator's assessment of causality.

- **Subject** (b) (6) was a 19-year-old Caucasian male who had a seizure on 27 Feb 2008 requiring hospitalization. He had received GAMMAGARD LIQUID intravenously in the context of Study 160601 on 4 Feb 2007. He was treated with Depakote and Keflex. On 29 FEB 2008 he was released from the hospital. He had been diagnosed with a seizure disorder 4 years previously and had been taken off anti-epileptic medications a year prior to the SAE.

  The investigator judged this SAE to be of moderate severity and unrelated to GAMMAGARD LIQUID therapy. No action was taken on the investigational product.

  Reviewer Comment
  I concur with the investigators' assessment.

6.3.11.5 AEs of Special Interest (AESI)

No AESI were reported.

6.3.11.6 Clinical Test Results

A toxicity assessment of hemoglobin, WBC, neutrophil count, lymphocyte count, and chemistry values in the FSDS showed that none of the values determined at baseline or during the study surpassed Grade 1. Decreases in hemoglobin of >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 these subjects had appreciable changes in LDH at the same time and no corresponding AEs were reported in these subjects.

6.3.11.7 Dropouts and/or Discontinuations

See 6.3.10.4.

7. INTEGRATED OVERVIEW OF EFFICACY

7.1 Indication #1

Replacement therapy for primary humoral immunodeficiency (PI) in adult and pediatric patients two years of age and older.

7.1.1 Methods of Integration

The Integrated Summary of Efficacy (ISE) was based on data from the two efficacy studies, Study 170904 and the "No dose adjustment study" 170903, supported by data from Study 160601.

Due to differences in doses and /or product concentrations administered in the three studies and different analyses performed, comparison of efficacy results across studies is limited.

- In Study 170904, subjects aged 2 years and older received Cuvitru at a dose adjusted to achieve the bioavailability of GAMMAGARD LIQUID administered IV. Subjects received a weekly dose equivalent to 145% of their GAMMAGARD LIQUID IV dose in Epoch 2, which was adapted/individually adjusted for bioavailability in Epoch 3 and Epoch 4.
- In Study 170903, subjects aged 2 years and older received Cuvitru at the weekly equivalent of KIOVIG (GAMMAGARD LIQUID) administered IV. The study consisted of 2 Epochs.
- Study 160601, subjects aged 2 years and older received GAMMAGARD LIQUID administered SC at a dose adjusted to achieve the bioavailability of GAMMAGARD LIQUID administered IV.

7.1.2 Demographics and Baseline Characteristics

Table 29 shows that (*a*) most enrolled subjects were White, with minimal representation of minorities, (*b*) median age was higher in Study 170904 than in the other studies and (*c*) there was varying preponderance of male subjects in each study.

Table 29: Demographic Characteristics of the BLA Study Population

Parameter	170904	170903	160601
Subjects administered an IGSC product	74	48	47
Age			
Median	36	17	20
Min; Max	3; 83	2; 67	3; 77
Gender			
Male [N (%)]	40 (51.9)	30 (61.2)	27 (55.1)
Female [N (%)]	37 (48.1)	19 (38.8)	22 (44.9)
Race			
White [N (%)]	70 (90.9)	48 (98.0)	46 (93.9)
Black/African	3 (3.9)	0	2 (4.1)
American [N	5 (6.5)	0	1 (2.0)
(%)]	2 (2.6)	1 (2.0)	0
Hispanic/Latino	2 (2.6)	0	0
[N (%)]			
Asian [N (%)]			
Multiple [N			
(%)]			

Adapted from Table 3, ISE, page 20 of 48, 11 Aug 2015

Table 30 presents demographic age characteristics for three pediatric subpopulations.

Table 30: Demographic Characteristics by Pediatric Age Cohort (Safety Analysis Set)

Study No.	No. of Subjects	<6 Years N (%)	6 to <12 Years N (%)	12 to <16 Years N (%)	Pediatric Subjects Receiving Cuvitru N (%)
160601	49	3 (6.1)	9 (18.4)	4 (8.2)	-
170903	49	5 (10.2)	8 (16.3)	5 (10.2)	18 (36.7)
170904	77	1 (1.3)	14 (18.2)	6 (7.8)	21 (27.3)
Total	175	9 (5.1)	31 (17.7)	15 (8.6)	39 (22.3)

Adapted from Table 3, ISS, page32 of 1575, 11 Aug 2015

7.1.3 Subject Disposition

Cuvitru was administered in clinical study 170903 and 170904 to 122 subjects, 112 of whom completed the study and 10 discontinued for various reasons, as depicted in Table 31.

Table 31: Disposition of Subjects Receiving Cuvitru by Study (Safety Analysis Set)

Category	170904	170903	Total
Subjects Administered Cuvitru	74	48	122
Subjects Completed Study	67	45	112
Subjects Discontinued Due to:	7	3	10
AE	1	0	1
Physician's decision	1	0	1
Subject's decision	5	3	8
Other	0	0	0

Adapted from Table 1, ISS, page 2 of 1575, 11 Aug 2015

7.1.4 Analysis of the Primary Endpoints

As depicted in Table 32, the point estimate of the annualized SBI rate was 0.01 (upper limit of 99% CI: 0.02) during Cuvitru administration in Study 170904 (Epoch 2 to Epoch 4), well below the threshold needed to reject the null hypothesis of SBI rate ≥1.0 per person year at the 1% level of significance. Similar outcomes were reported in Study 170903.

Table 32: Analysis of SBI by Study and Population Cohort (Safety Analysis Set)

Study	Population	Epoch	Product	Point Estimate	Upper Limit 99% CI	p-value
170904						
	Aggregate	1	GAMMAGARD LIQUID IV	0.00	0.23	NA
		2-4	Cuvitru	0.01	0.02	<0.0001
	Age <16 y	1	GAMMAGARD LIQUID IV	0.00	0.77	NA
		2-4	Cuvitru	0.00	0.16	NA
170903		2-4	GAMMAGARD LIQUID IV			
	Aggregate	1	GAMMAGARD LIQUID IV	0.00	0.55	NA
		1	SUBCUVIA	0.27	0.85	0.006
		2	Cuvitru	0.02	0.05	<0.0001
	Age <16 y	1	GAMMAGARD LIQUID IV	0.00	1.23	NA
		1	SUBCUVIA	1.45	8.26	NA
		2	Cuvitru	0.06	0.17	<0.0001

Adapted from Tables 1 and 2, pages 10 and 14, ISE, 11 Aug 2015 and IR response generated on 17 Jun 2016
NA=not applicable

7.1.5 Analysis of Secondary Endpoints

- Cuvitru total trough levels
  Study 170903: 8.26 g/L (median, 95% CI: 7.3 to 9.0)
  Study 170904: 15.2 g/L (median, 95% CI: 13.6 to 15.7)

  Reviewer Comment
  Dosing in Study 170903 was fixed at 145% of trough levels observed using GAMMAGARD LIQUID administered IV. Since doses were not adjusted or individualized as they were in Study 170904, differences in trough levels between this study and Study 170904 are not unexpected. In both studies, there is no evidence that subjects were at risk of achieving subtherapeutic levels at any time.

- Trough levels of specific antibodies
  In all 3 studies, trough levels of specific antibodies against *Clostridium tetani*, *Haemophilus influenzae b*, or *hepatitis B* antigens were maintained when switching to Cuvitru (Studies 170904 and 170903) or GAMMAGARD LIQUID

administered SC (Study 160601). These levels were significantly higher than the generally accepted minimum protective titers of 0.015 IU/mL for anti-C*lostridium tetani* toxoid antibody, 0.15µg/mL for *Haemophilus influenza* and > 12 mIU/mL for *Hepatitis B* Ags.

- Infections and other subject-reported outcomes
  Table 33 lists clinical outcome parameters. Where the study was not designed to capture this information, NA (not applicable) is indicated in the table.

Table 33: Annualized Rates for Secondary Endpoints (Infections and Subject-Reported Outcomes) by Study

		Study 170904 Rate per Year		Study 170903 Rate Per Year		Study 160601 Rate Per year	
Parameter	**Product**	**Point Estimate**	**95% CI**	**Point Estimate**	**95% CI**	**Point Estimate**	**95% CI**
Number of infections	Cuvitru	2.4	1.9 to 3.0	4.4	3.4 to 5.6	NA	NA
Days off school/work		1.2	0.7 to 1.8	15.6	10.1 to 22.8	NA	NA
Days on antibiotics		57.6	40.7 to 78.6	18.1	13.0 to 24.4	NA	NA
Number of hospitalizations		0.02	0.01 to 0.04	0.2	0.08 to 0.26	NA	NA
Days in Hospital		0.1	0.05 to 0.20	1.7	0.7 to 3.2	NA	NA
Acute physician visits		0.9	0.5 to 1.3	3.8	2.6 to 5.3	NA	NA
Number of infections	GAMMAGARD LIQUID IV	3.9	2.8 to 5.2	6.3	4.2 to 9.0	5.1	3.7 to 6.9
Days off school/work		3.2	1.9 to 5.0	10.7	5.3 to 18.8	4.6	2.6 to 7.3
Days on antibiotics		63.2	43.4 to 88.3	19.6	12.6 to 28.8	43.1	25.8 to 66.8
Number of hospitalizations		0.05	0.02 to 0.10	0.1	0.04 to 0.26	-	-
Days in Hospital		0.2	0.1 to 0.4	0.1	0.04 to 0.26	0.7	0.3 to 1.2
Acute physician visits		1.7	1.0 to 27.	5.1	3.0 to 8.1	2.7	1.6 to 4.1
Number of infections	GAMMAGARD LIQUID SC	NA	NA	NA	NA	4.1	3.2 to 5.1
Days off school/work		NA	NA	NA	NA	4.0	2.5 to 6.1
Days on antibiotics		NA	NA	NA	NA	50.2	33.4 to 71.9
Number of hospitalizations		NA	NA	NA	NA	-	-
Days in Hospital		NA	NA	NA	NA	0.05	0.02 to 0.09
Acute physician visits		NA	NA	NA	NA	4.7	3.5 to 6.3
Number of infections	SUBCUVIA	NA	NA	8.9	6.4 to 12.1	NA	NA
Days off school/work		NA	NA	50.4	19.6 to 103.4	NA	NA
Days on antibiotics		NA	NA	54.3	31.4 to 86.3	NA	NA
Number of hospitalizations		NA	NA	0.5	0.2 to 1.3	NA	NA
Days in Hospital		NA	NA	2.4	0.7 to 5.9	NA	NA
Acute physician visits		NA	NA	7.6	3.6 to 13.8	NA	NA

NA=not applicable; - = not captured per protocol

Point estimate values ≤0.1 carried to two decimal places

Adapted from Table 4, ISE, page 23 of 48, 15 July 2015 and 21 July 2016 (Information Request)

Reviewer Comment

The incidence of favorable subject-reported outcomes in the Cuvitru and KIOVIG cohorts were similar, whereas the incidence of favorable outcomes was much lower in the SUBCUVIA cohort. The reason for this anomaly is not clear.

7.1.7 Subpopulations

Study 170904

During Cuvitru administration, the annualized rate of all infections per subject was

- 0.00 (95% CI: 0.00 to 4.61) for subjects aged 2 to <5 years
- 1.72 (95% CI: 0.85 to 3.05) for subjects aged 5 to <12 years
- 2.00 (95% CI: 0.70 to 4.35) for subjects aged 12 to <16 years
- 2.62 (95% CI: 1.91 to 3.50) for subjects aged 16 to <65 years
- 2.91 (95% CI: 1.67 to 4.65) for subjects aged 65 years and above.

In all subgroups except geriatrics, annualized infection rates were higher during GAMMAGARD LIQUID IV treatment, 3.86 (95% CI: 2.77 to 5.22), than with Cuvitru.

Study 170903

During Cuvitru administration, at a dose equivalent to the previous SUBCUVIA or GAMMAGARD LIQUID IV dose, the annualized rate of infections per subject was

- 4.29 for subjects aged 2 to <6 years
- 4.21 for subjects aged 6 to <12 years
- 2.85 for subjects aged 12 to <18 years
- 5.52 for subjects aged 18 to <65 years
- 2.61 for subjects aged 65 years and above.

In all subgroups except subjects aged 2 to <6 years, annualized infection rates were higher during SUBCUVIA treatment than during Cuvitru administration.

7.1.8 Persistence of Efficacy

Long-term efficacy data on Cuvitru are not yet available.

7.1.9 Product-Product Interactions

IgG products may reduce the effect of some live virus vaccines such as measles, rubella, mumps and chicken pox. The studies in this submission did not directly address this issue.

7.1.11 Efficacy Conclusions

Outcomes from Studies 170904 and 170903 support the efficacy of Cuvitru as replacement therapy for PI in adult and pediatric patients aged ≥2 years.

8. INTEGRATED OVERVIEW OF SAFETY

8.1 Safety Assessment Methods

Safety data were assessed from two clinical studies in which subjects were exposed to Cuvitru.

8.2 Safety Database

8.2.1 Studies/Clinical Trials Used to Evaluate Safety

Study 170904 using Cuvitru in the U.S. and Canada
Study 170903 using Cuvitru in Europe
Study 160601 using IGSC, 10% (supportive)

All three studies evaluated subjects aged ≥2 years. .

8.2.2 Overall Exposure, Demographics of Pooled Safety Populations

Cuvitru was administered subcutaneously to 122 subjects, 74 in Study 170904 and 48 in Study 170903; IGSC 10% was administered to 47 subjects in Study 160601, increasing the total to 169. Of the 122 subject who received Cuvitru, 112 completed the study and 10 discontinued – 1 discontinued due to an AE (Subject (b) (6), 1 due to the physician's decision, and 8 subjects decided to discontinue participation in the study). Table 33 shows that over half of the subjects were adults.

8.2.3 Categorization of AEs

All AEs were coded according to the Medical Dictionary for Regulatory Activities (MedDRA).

8.3 Caveats Introduced by Pooling of Data Across Studies/Clinical Trials

Different doses and/or product concentrations were administered in the three studies.

8.4 Safety Results

8.4.1 Deaths

There were no deaths in any study.

8.4.2 Nonfatal Serious AEs

10 SAEs were reported in 8 subjects (6.6%): 2 subjects in Study 170904 and 6 subjects in Study 170903. None of the SAEs was related to the product.

SAE intensity

- Mild in one subject aged 16 to <65 years

- Moderate in 5 subjects (1 subject aged <6 years, 1 subject aged 6 to <12 years, 2 subjects aged 16 to <65 years, and 1 subject aged ≥65 years)
- Severe in 2 subjects (1 subject aged 16 to <65 years and 1 subject aged ≥65 years)
- As shown in Table 33, 10 SAEs occurred in association with infusion of Cuvitru: 2 SAEs in Study 170904 and 8 in Study 170903.[9] None of the SAEs was related to the product by the investigator.

Table 33: SAEs Reported in Cuvitru 20% Subjects (Safety Set)

Trial	Subject	Preferred Term	Intensity	Relationship to IGSC 20%*	Status
170904	(b) (6)	Lung adenocarcinoma	Severe	Unrelated	Unresolved
	(b) (6)	Pneumonia	Moderate	Unrelated	Resolved
170903	(b) (6)	Acute Myocardial Infarction	Severe	Unrelated	Resolved
		Ventricular fibrillation	Severe	Unrelated	Resolved
		Brain stem infarction	Moderate	Unrelated	Resolved
	(b) (6)	Enteritis	Moderate	Unrelated	Resolved
	(b) (6)	Chronic sinusitis	Moderate	Unrelated	Resolved
	(b) (6)	Pneumonia bacterial	Moderate	Unrelated	Resolved
	(b) (6)	Rhinorrhea	Moderate	Unrelated	Resolved
	(b) (6)	Nasal septum deviation	Mild	Unrelated	Resolved

*Applicant's/Investigator's assessment. See my review comment, below.

NARRATIVES
For SAE narratives, see 6.1.11.4 for Study 170904 and 6.2.11.4 for Study 170903.

8.4.3 Study Discontinuations Due to TEAEs

- **170904**: GAMMAGARD LIQUID Subject (b) (6) experienced a mild intensity headache SAE; Cuvitru Subject (b) (6) experienced mild cases of diarrhea, dizziness and fatigue, assessed by the applicant/investigator as unrelated to the product.

- **170903**: Cuvitru Subject (b) (6) reported 3 infusion site pain TEAEs of mild intensity and discontinued from the study.

- **160601**: Subject (b) (6) withdrew after complaining of increased fatigue and malaise, as well as infusion site erythema, infusion site irritation, infusion site pain (all mild).

9 SAEs also occurred in *non*-Cuvitru cohorts.
- In Study 170904, one SAE (mild headache) occurred in the GAMMAGARD LIQUID cohort.
- In Study 170903, two moderate SAEs (lymphadenopathy and forearm fracture) occurred in the KIOVIG cohort and 2 moderate SAEs (bacterial pneumonia and thoracic vertebral fracture) occurred in the SUBCUVIA cohort.
- In Study 160601, two SAEs (sinusitis and convulsions occurred in the GAMMAGARD LIQUID IGIV cohort and two SAEs (cholecystitis due to gallstones and one episode of chest pain) in the GAMMAGARD LIQUID IGSC cohort.

8.4.4 TEAEs

As presented in Table 34, a total of 1389 TEAEs were associated with 6675 Cuvitru infusions administered in Study 170904 and 170903 (N=122). Overall, (*a*) 91% of subjects experienced a TEAE, most of which were mild or moderate in intensity; (*b*) 78% experienced a temporally related (72 h) TEAE; (*c*) 29% experienced local TEAEs; and (*d*) 22% experienced systemic TEAEs.

Table 34: TEAEs in Cuvitru Studies 170904 and 170903 (Safety Set)

	Total	<6	6 to <12	12 to <16	16 to <65	≥65
TEAEs by intensity and age cohort (years)						
No. of subjects	111 (91)					
Mild	64	3	17	7	31	6
Moderate	65	2	4	6	45	8
Severe	4	-	-	-	3	1
TEAEs temporally related (72 h)						
No. of subjects affected	95 (78)					
No. of infusions associated (%)	739 (53)					
No. of pediatric subjects affected (%)	27 (69)					
No. of TEAEs in pediatric subjects	423					
Local TEAEs						
No. of subjects affected (%)	35 (29)					
No. of infusions associated (%)	229					
No. of pediatric subjects affected (%)	14 (42)					
No. of TEAEs in pediatric subjects	423					
Systemic TEAEs						
No. of subjects affected (%)	27 (22)					
No. of infusions associated (%)	165					
No. of pediatric subjects affected (%)	4 (24)					
No. of pediatric TEAEs	18					

Table 35 presents specific TEAEs that were causally related *and/or* temporally associated to the product, representing (in the reviewer's opinion) the cohort most closely mimicking patient-reported outcomes.[10] It shows that the incidence of local and systemic TEAEs overall was higher with Cuvitru than with IGIV. Note that some subjects were counted more than once because they experienced local and systemic TEAEs.

10 The Integrated Summary of Safety tables categorize the data as causally related and temporally associated, causally related, and temporally associated.

Table 35: Incidence ≥5% for Causally Related and/or Temporally Associated (72 h) TEAEs Associated with Cuvitru (Safety Analysis Set)

Adverse Event	Study 170903 (N=48) Subjects Affected n (%)	Study 170904 (N=74) Subjects Affected n (%)	Studies 170903, 170904 (N=122) Subjects Affected n (%)
Local TEAEs	18 (37.5)	23 (31.1)	41 (33.6)
Infusion/injection site pain/discomfort	10 (20.8)	15 (20.3)	25 (20.5)
Infusion/injection site erythema	10 (20.8)	8 (10.8)	18 (14.8)
Infusion/injection site pruritus	7 (14.6)	4 (5.4)	11 (9.0)
Systemic TEAEs	33 (68.8)	41 (55.4)	74 (60.7)
Headache	14 (29.2)	10 (13.5)	24 (19.7)
Diarrhea	9 (18.8)	5 (6.8)	14 (11.5)
Nausea	2 (4.2)	9 (12.2)	11 (9.0)
Fatigue	6 (12.5)	5 (8.1)	12 (9.8)

8.4.5 Clinical Test Results

- Potential hemolysis

  In **170904**, laboratory values for all subjects who received at least one product infusion were assessed for potential hemolysis. Six (7.8%) subjects experienced a decline in hemoglobin of ≥2.0 g/dL (Subjects (b) (6)). The fall in hemoglobin could not be confirmed to be due to a study-drug induced hemolytic reaction. At no time was there a concordance of other laboratory tests (e.g., Coombs' test, free hemoglobin, haptoglobin, low-density lipoprotein [LDL], urine hemosiderin) confirming a diagnosis of hemolysis

  In **170903,** adults and adolescent subjects (36) were tested pre- and post infusion for signs of potential hemolysis; 16.7% (6/36) of them experienced a decline in hemoglobin of ≥2.0 g/dL (Subjects (b) (6)). The fall in hemoglobin could not be confirmed as due to a product-induced hemolytic reaction. At no time was there a concordance of other laboratory tests (e.g., Coomb's test, haptoglobin, LDL, urinary hemosiderin) confirming a diagnosis of hemolysis.

  In **160601**, decreases in hemoglobin after administration of the investigational product of more than 2.0 g/L, which might have been 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). However none of these subjects had appreciable changes in LDL at the same time.

- Clinical Chemistry

  No clinical chemistry values during the three studies were attributed grade 4 or grade 3 toxicity level.

- No signs of infections were found for human immunodeficiency virus (HIV), hepatitis B virus (HBV) or hepatitis C virus (HCV).

8.4.7 Local Reactogenicity

- Infusions tolerated without TEAE
  - **170903 and 170904**: During Cuvitru administration, 6856/6857 infusions were tolerated without need for a dose reduction due to a TEAE.
  - For all studies, 9145/9151 SC infusions were tolerated without need for a dose reduction due to a TEAE.
- Infusions requiring adjustment due to tolerability concerns
  - **170904**: The infusion rate was reduced for 5/4327 (0.1%) of infusions, and 3/4327 (< 0.1%) of infusions were interrupted or stopped due to tolerability concerns or TEAEs.
  - **170903**: The rate of infusion had to be reduced due to tolerability concerns or TEAEs in 5/2338 (0.2%) of infusions with Cuvitru. No infusion had to be interrupted or stopped for tolerability concerns or for an AE at any time during Cuvitru administration.
  - 160601: No subjects over 12 years of age had an infusion interrupted or stopped for tolerability concerns or for TEAEs.
- Subjects with infusions requiring adjustment due to tolerability concerns
  - **170904**: The infusion rate had to be reduced for tolerability concerns or for TEAEs in 4 subjects and interrupted for tolerability concerns or TEAEs in 1 subject (1.4 %), and for 1 subject (1.4%) (aged 8 years) an infusion had to be stopped.
  - **170903**: The rate of infusion had to be reduced due to tolerability concerns or TEAEs in 2 subjects (4.2%) under Cuvitru administration. No subject had to have an infusion interrupted or stopped for tolerability concerns or for TEAEs at any time.
  - 160601: Two (4.3%) subjects (all aged 2 to <12 year old) required a reduction in infusion rate.

8.4.8 AEs of Special Interest (AESI)

AEs of Special Interest include hemolysis, thrombosis, renal failure, anaphylaxis, aseptic meningitis, and risk of transfusion-transmitted disease, such as variant Creutzfeldt-Jakob disease (vCJD). No AESI were reported in this study.

8.5 Additional Safety Evaluations

N/A.

8.5.1 Dose Dependency for AEs

See 8.4.7.

8.5.2 Time Dependency for AEs

See 8.4.4.

8.5.3 Product-Demographic Interactions

Small sample size precluded assessment of product-demographic interactions.

8.5.4 Product-Disease Interactions

Ig products can interfere with the immune response to live viral vaccines such as measles, mumps, rubella and varicella. This is noted in the package insert.

8.5.5 Product-Product Interactions

Not formally studied.

8.5.6 Human Carcinogenicity

Not applicable.

8.5.7 Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Not applicable.

8.5.8 Immunogenicity (Safety)

No anti-drug antibodies or hypersensitivity reactions were observed.

8.5.9 Person-to-Person Transmission, Shedding

Not applicable.

8.6 Safety Conclusions

The overall safety profile of Cuvitru has been sufficiently demonstrated for adults and pediatric subjects greater than 2 years of age with primary humoral immunodeficiency.

9. ADDITIONAL CLINICAL ISSUES

9.1 Special Populations

Not applicable.

9.1.1 Human Reproduction and Pregnancy Data

No clinical studies in pregnant subjects have been conducted.

9.1.2 Use During Lactation

No clinical studies in lactating subjects have been conducted.

9.1.3 Pediatric Use and PREA Considerations

An agreed initial PSP was submitted on 17 April 2015 and accepted by FDA on 13 May 2015. A partial waiver of the requirement for pediatric assessments for children aged 0 to <2 years was granted.

9.1.4 Immunocompromised Patients

Not applicable.

9.1.5 Geriatric Use

Small sample size precluded assessment of safety in the geriatric population.

9.2 Aspect(s) of the Clinical Evaluation Not Previously Covered

Package Insert
Each of the clinical study reports in this submission included two sets of safety tables. One set reported adverse reactions, including infectious adverse reactions, regardless of incidence; the second set was identical to the first except that infectious adverse reactions were excluded.

Unless noted otherwise, safety tables listed in this memo include all adverse reactions, including infections. Adverse reaction tables presented in Section 6.1 of the draft package insert, however, explicitly exclude infections (denoted by an asterisk in the table). A telecon was held with the applicant on 19 May 2016 to discuss revising the safety tables to include infections. During the telecon (and subsequently in efficacy information amendment 1.11.3), the applicant claimed that none of the package inserts for marketed Ig products includes infections in their labeling.

Investigation by this reviewer (Table 36) shows that CSL Behring and Baxalta explicitly exclude infections in Section 6.1 of their package inserts whereas other manufacturers do not. Since precedence exists, safety data tables in the draft package insert that exclude infections are acceptable.

Table 36: Exclusion of Infections in Package Inserts of Licensed Ig Products

Proprietary Name	Manufacturer	Infections Explicitly Excluded in Section 6.1
BIVIGAM 10%	Biotest	No
Flebogamma 10% DIF	Grifols	No
GAMMAGARD LIQUID	Baxalta	No*
GAMUNEX-C 10%	Grifols	No
Hizentra 20%	CSL Behring	Yes
HYQVIA 10%	Baxalta	Yes
Octagam 10%	Octapharma	No
Privigen 10%	CSL Behring	Yes

*Section 6.1 of the GAMMAGARD LIQUID PI does not explicitly indicate exclusion of infections but no infections are listed (Table 6. Adverse Reactions Occurring in ≥5% of Subjects)

10. Conclusions

Apart from a lower incidence of local TEAEs, Cuvitru was comparable to other IGSC products licensed for treatment of PI. It is concluded that clinical benefit exceeds risk.

11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

11.1 Risk-Benefit Considerations

The risks associated with use of Cuvitru for the treatment of PI are small and far outweighed by the benefit. Compared indirectly against existing IGSC products, the incidence of local ARs was noticeably lower; systemic ARs occurred at a frequency similar to existing products.

11.2 Risk-Benefit Summary and Assessment
Benefit outweighs the risks.

11.3 Discussion of Regulatory Options
The regulatory options for this application are approval or a complete response letter, which is inappropriate in this reviewer's judgment.

11.4 Recommendations on Regulatory Actions
I recommend approval of this application.

11.5 Labeling Review and Recommendations
The applicant has responded to labeling revisions requested by FDA.
I recommend that the labeling be approved.

11.6 Recommendations on Postmarketing Actions
None (other than routine surveillance appropriate for the product class).

Table 37: Risk-Benefit Assessment

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Current treatment of PI using IGIV is safe and effective. Administration is required every 3-4 weeks.	• IGIV is effective in reducing SBI
Unmet Medical Need	• Effective treatment already is available	• Not an unmet medical need
Clinical Benefit	• Clinical benefit of Cuvitru was investigated in subjects (N=122), including pediatric subjects 2-12 years of age (N=28) and 12-16 years of age (N=11), in an open-label, single-arm, phase 3 study at 14 centers in the US and one site in Canada.	• Cuvitru was effective in reducing the number of SBI to <1% per year.
Risk	• Class effects associated with Cuvitru appear to result primarily from the immunoglobulin component. Serious risks include thrombosis and renal dysfunction (including acute renal failure) and are listed in a Box Warning in the PI. Other risks include hypersensitivity (anaphylaxis) in patients with a history of anaphylaxis or those with antibodies against IgA (contraindication), fluid overload, aseptic meningitis, hemolysis, and, theoretically, CJD agent	• Clinical benefit exceeds risk.
Risk Management	• Patients should be made aware of potential signs/symptoms of hypersensitivity, renal failure, aseptic meningitis, hemolysis, TRALI, and thrombosis.	• Injections should be administered by infusion pump and patients monitored for signs of hypersensitivity and fluid overload.