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Division / Office	DHRR/OBRR
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Priority Review	No
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Review Completion Date / Stamped Date	
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Applicant	Baxalta USA Inc.
Established Name	Immune Globulin Subcutaneous (Human), 20% Solution
(Proposed) Trade Name	Cuvitru
Pharmacologic Class	Immune Globulin Subcutaneous (Human), 20% Solution
Formulation(s), including Adjuvants, etc	
Dosage Form(s) and Route(s) of Administration	(b) (4) (median; 95% CI: (b) (4)) Subcutaneous
Dosing Regimen	0.30-1.0 g/kg BW /4 weeks
Indication(s) and Intended Population(s)	Replacement therapy for primary humoral immunodeficiency (PID) in adult and pediatric patients two years of age and older

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GLOSSARY

ASBI	acute serious bacterial infection
BW	body weight
CMC	Chemistry, Manufacturing and Controls
CI	confidence interval
Ig	immunoglobulin
IgG	immunoglobulin G
IGI, 10%	immune globulin infusion (human), 10% solution
IGIV, 10%	IGI,10%, administered IV
IGSC, 10%	IGI,10%, administered SC
IGSC, 16%	IGI,16% administered SC
IGSC, 20%	IGI,20% for SC administration
IP	investigational product
IV	intravenous
MedDRA	Medical Dictionary for Regulatory Activities
PID	primary immunodeficiency
SC	subcutaneous
VASBIs	validated acute serious bacterial infections

1. EXECUTIVE SUMMARY

This BLA submission is for immune globulin infusion 20% solution, for subcutaneous administration (IGSC, 20%). It is essentially the same as Baxter's currently licensed GAMMAGARD LIQUID, Immune Globulin Infusion (Human), 10% Solution (IGI, 10%) product, which was approved by the FDA on April 27, 2005 (BLA 125105) for the treatment of various immune deficiencies including primary immunodeficiency (PID). However, the concentration of this product is 20% rather than 10% and the route of administration is only subcutaneous.

Pivotal study 170904 is a prospective, open-label, non-controlled, multicenter, global study to evaluate the efficacy, safety, tolerability, and PK characteristics of IGSC, 20% in subjects with PID in the USA and Canada. The study consisted of four epochs. In Epoch 1 subjects received IGI, 10% intravenously (IGIV, 10%) and complete PK assessment. In Epoch 2, subjects received IGSC, 20% subcutaneously at a dose adjusted to 145% of the IGIV, 10% dose. In Epoch 3, subjects were treated with IGSC, 20% for 3 months at the "Adjusted Dose". In Epoch 4, subjects were infused with IGSC, 20% at the "Individually Adapted Dose". Efficacy, safety and tolerability were determined throughout Epochs 2 to 4 (12 months). The primary efficacy endpoint was the rate of acute serious bacterial infections (ASBI) meeting the FDA Guidance for Industry (2008)[i] criteria for IGIV products. The point estimate of the annualized rate of validated ASBIs among 74 subjects (including 21 children of <16 years old at screening) was 0.012 (upper limit of 99% CI: 0.024). These annual rates of validated ASBI were statistically significantly lower than 1.0 validated ASBIs / year, ($p<0.0001$), the FDA threshold for efficacy as stated in the guidance.

The rate of temporally-associated adverse events (TAAEs) (adverse events that begin during the infusion or within 72 hours of completion of the infusion) per infusion was 0.079 (343 TAAEs in 4327 infusions). The upper one-sided 95% confidence limit of observed proportion of infusions with TAAEs was 0.086 which met the FDA Guidance for Industry success criterion of < 0.4.

Study 170903 is a Phase 2/3, prospective, open-label, non-controlled, non-randomized, multi-center European study using IGSC, 20% to evaluate efficacy, safety, tolerability, and PK parameters of IGSC, 20% in subjects with PID. The primary efficacy endpoint was the same as in Study 170904. In Study 170903, 48 subjects received IGSC, 20%. The median age was 17 years (range: 2-67 years). In this 2-part ("epoch") study, subjects received IGSC, 20% during Epoch 2 at a dose equivalent to that administered for IGIV, 10% or IGSC, 16% during Epoch 1. Efficacy, safety and tolerability were determined in Epoch 2. Efficacy was assessed based on the rate of validated acute serious bacterial infections (VASBIs) defined as the mean number of validated ASBIs per subject per year in the intent-to-treat population (ITT). The point estimate of the annual rate of VASBIs was 0.022 (upper limit of 99% CI: 0.049) during IGSC, 20% treatment (Epoch 2). A total of 454 TAAEs were reported in 48 subjects during IGSC, 20% treatment. The rate per infusion of TAAEs was 0.193 (total of 2349 infusions). The upper one-sided 95% confidence limit of observed proportion of infusions with TAAEs was 0.210 which met the FDA Guidance for Industry success criterion of < 0.4.

In total, 122 subjects were exposed to IGSC, 20% in two clinical trials in subjects with PID. The treatment of IGSC, 20% was successful in both studies. The annual ASBI rates were statistically significantly lower than 1.0 ASBIs / year, ($p<0.0001$). A total of 797 TAAEs were reported in 122 subjects during IGSC, 20% treatment. The rate of TAAEs per infusion was 0.12 of 6675 infusions across IGSC, 20% Studies 170903 and 170904. The upper one-sided 95% confidence limit of observed proportion of infusions with temporally associated AE was 0.13 which met the success criterion of < 0.4.

The statistical results of Studies 17094 and 170903 appear to support the use of IGSC, 20% in subjects with PID for control of SBIs.

2. CLINICAL AND REGULATORY BACKGROUND

2.1 Disease or Health-Related Condition(s) Studied

PIDs are disorders that result in increased susceptibility to recurrent infections, secondary to the underlying defects in humoral and/or cell-mediated immunity. Considered rare diseases until recently, PIDs may affect up to 1/1200 people worldwide according to current estimates. The number of known PID defects has increased in the last 20 years and the World Health Organization currently recognizes more than 220 different disorders that meet the definition of PID. The best-described PIDs include X-linked agammaglobulinemia, common variable immune deficiency disease, selective IgA deficiency, severe combined immune deficiency, chronic granulomatous disease, Wiskott-Aldrich syndrome, X-linked hyper IgM syndrome, DiGeorge syndrome, IgG

subclass deficiency, ataxia telangiectasia, leukocyte adhesion deficiency, and complement deficiencies.

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

Therapeutic options for the treatment of infections in PID include standard antibiotic treatment and administration of Immunoglobulin G (IgG) as a replacement therapy. Antibody replacement can be accomplished either intramuscularly, intravenously (IV) or subcutaneously (SC). Therapeutic options for treatment of PID itself include transplantation of bone marrow- derived stem cells and gene therapy.

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

The proposed product, IGSC, 20% is essentially the same as Baxter's currently licensed GAMMAGARD LIQUID, Immune Globulin Infusion (Human), 10% Solution (IGI, 10%) product.

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

The IGI, 10% product was approved by the FDA on April 27, 2005 (BLA 125105) for the treatment of various immune deficiencies including PIDs, and approved July 22, 2011 for the subcutaneous route of administration (BLA 125105/708). However, the concentration of this product is 20% rather than 10% and the route of administration is only subcutaneous.

On August 13, 2010, Baxter had a Pre-IND meeting with FDA to outline the clinical development program for Baxter's Phase 2/3 clinical study entitled "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." Subsequently IND 14505 was filed September 30, 2010 and the clinical study was initiated in January 2013.

In the December 9, 2014 response to a CMC Type C meeting request, FDA also requested that Baxter submit a pediatric study plan outlining their development plan for the IGSC, 20% product. Baxalta submitted the agreed-upon initial pediatric study plan on April 17, 2015.

A Type B pre-BLA meeting was scheduled for April 30, 2015. FDA responded to Baxalta's questions on April 24, 2015. Concerning the SAP, the FDA advised the applicant to provide analyses on both a per-subject and per-infusion basis for the proportion of adverse reaction (ARs) and suspected adverse reactions (SAR) [ARs + SARs].

2.6 Other Relevant Background Information

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The submission was adequately organized for conducting a complete statistical review without unreasonable difficulty.

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

5.1 Review Strategy

The applicant submitted data from one completed pivotal study (IND 14505; Study 170904), one European study 170903, and one supportive study 160601. Study 160601 used IGI, 10% as opposed to IGSC, 20%. Because of this difference, only pivotal study 170904 and supportive study 170903 are reviewed in this memo.

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

The following documents (and module number) in BLA 125596 were reviewed:

1.14 Labeling
1.2 Cover Letter
2.2 Introduction
2.5 Clinical Overview
2.7.3 Summary of Clinical Efficacy
2.7.4 Summary of Clinical Safety
2.7.6 Synopsis of Individual Studies
5.2 Tabular Listing of all Clinical Studies
5.3.5.2 170904 Clinical Study Report
5.3.5.2 170903 Clinical Study Report
5.3.5.3 Integrated summary of efficacy
5.3.5.3 Integrated summary of safety

5.3 Table of Studies/Clinical Trials

Table 1. Design of Completed Clinical Studies Presented in the Submission

Study number /Report	IP	Study type	Subject population	Subjects exposed to IP	Doses administered (g/kg)
170904	IGSC, 20% IGIV, 10%	Phase 2/3 Efficacy, PK, Tolerability and Safety	Subjects aged 2 years and older, with PIDD	77[iii]	- IGSC, 20%: 145% of the weekly dose equivalent of IGIV, 10% or adjusted dose based on individual PK - IGIV, 10%: 0.30-1.0 g/kg BW /4 weeks
170903	IGSC, 20% IGSC, 16% IGIV, 10%	Phase 2/3 Efficacy, PK, Tolerability and Safety	Subjects aged 2 years and older, with PIDD	49[iv]	0.30-1.0 g/kg BW /4 weeks
160601	IGSC, 10% IGIV, 10%	Phase 2/3 Efficacy, PK and Tolerability	Subjects aged 2 years and older, with PIDD	49[v]	- IGSC, 10%: 130% of the weekly dose equivalent of IGIV, 10% or adjusted dose based on individual PK - IGIV, 10%: 0.30-1.0 g/kg BW /4 weeks

BW = body weight; PK = pharmacokinetic; PID = Primary immunodeficiency; SC = subcutaneous; IV = intravenous;

[iii] In Study 170904, 77 subjects were treated with any investigational product; 74 subjects received IGSC, 20%. Two subjects were discontinued for non-compliance and one subject experienced an AE that led to discontinuation during Epoch 1.

[iv] In Study 170903, 49 subjects were treated with any investigational product; 48 subjects received IGSC, 20%. One subject became pregnant and withdrew during Epoch 1;

[v] In Supportive Study 160601, 49 subjects were treated with any investigational product; 47 subjects received IGSC, 10%.

Source: BLA 125596, Module 2.5 Clinical Overview, Table 1

6. Discussion of Individual Studies/Clinical Trials

6.1 Trial #1

Study 170904

6.1.1 Objectives (Primary, Secondary, etc)

Primary Objective

To demonstrate the efficacy of IGSC, 20% in preventing the development of ASBIs in subjects with PID as defined by the FDA Guidance for Industry (2008)[i].

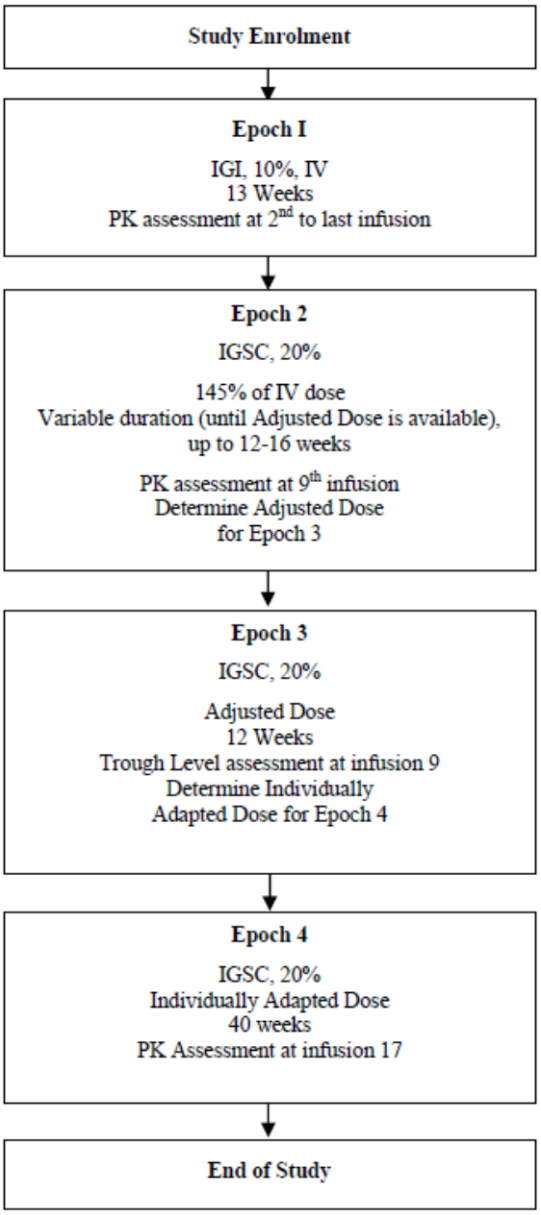
Secondary Objectives

To evaluate the safety, tolerability, and PK characteristics of IGSC, 20% in subjects with PID and assess quality of life and treatment satisfaction.

6.1.2 Design Overview

Study 170904 is a prospective, open-label, non-controlled, multicenter, global study consisting of 4 epochs. In Epoch 1 (duration 13 weeks) subjects received IGI, 10% intravenously (IGIV, 10%). All subjects aged ≥12 years completed a PK assessment. In Epoch 2 (duration 12-16 weeks), subjects received IGSC, 20% subcutaneously at a dose adjusted to 145% of the IGIV, 10% dose. The first 15 subjects aged ≥12 years completed a PK assessment. Based on the results from PK and trough level assessments in Epochs 1 and 2, this dose was adjusted (the "Adjusted Dose" for Epoch 3; duration 12 weeks) and then individually adapted (for Epoch 4; duration 40 weeks) as described in Section 6.1.4. Efficacy, safety and tolerability were determined throughout Epochs 2 to 4. Treatment in Epoch 3 started as soon as the Adjusted Dose became available. Consequently, later enrolling subjects who completed Epoch 1 after the Adjusted Dose was available, directly went into treatment with the Adjusted Dose (Epoch 3). The overall study design and schedule is presented in Figure 1.

Figure 1. Study Design



Source: BLA 125596, Module 2.3.5.2 Full Clinical Study Report 170904, Figure 9-1

6.1.3 Population

Subjects had a documented diagnosis of a form of PID involving defective antibody formation and requiring gammaglobulin replacement. Subjects were 2 years or older at the time of screening, and had a minimum body weight of 13 kg. Subjects had a serum trough level of IgG > 500 mg/dL at screening.

6.1.4 Study Treatments or Agents Mandated by the Protocol

IGSC, 20% was administered by SC infusion (regulated via pump) once every week. In Epoch 2 subjects received 145% of their IGIV, 10% dose used in Epoch 1 (adjusted to a weekly equivalent dose). Based on the PK data from Epoch 1 and Epoch 2, the IGSC,

20% dose that would, on average, provide equivalent IgG exposure as IGIV, 10% administration ("Adjusted Dose") was calculated. In Epoch 3, subjects were treated with IGSC, 20% at the "Adjusted Dose". Since this Adjusted Dose represented the average dose-response of only 15 subjects, the possibility that some subjects could be over- or under-dosed, could not be excluded. Thus, for each subject an "Individually Adapted Dose" of IGSC, 20% was determined by the investigator using a nomogram to compare the trough level attained in Epoch 3 to the expected trough level increase calculated from the PK comparison of Epochs 1 and 2. In Epoch 4, subjects were infused with IGSC, 20% at the "Individually Adapted Dose".

For subjects with a body weight >= 40 kg, up to 60 mL was to be administered per infusion site if well tolerated. For subjects with a body weight <40 kg it was recommended that for the initial two infusions the volume be limited to 20 ml per infusion site, but if well tolerated the volume was to be increased to a maximum of 60 ml for subsequent infusions. When two or more SC infusion sites were to be used during an infusion, each site had to be at least 10 cm (4 inches) apart. Multiple infusion sites could be used simultaneously. The number of infusion sites depended on the subject's total dose in mL; there was no maximum to the number of infusion sites. The number of sites to be used was calculated by dividing the total volume to be infused by the maximum volume/site to be infused.

6.1.6 Sites and Centers

The study was conducted in 14 centers located in the United States of America and one center in Canada.

6.1.8 Endpoints and Criteria for Study Success

Primary Efficacy Endpoint:
Rate of validated ASBIs defined as the mean number of validated ASBIs per subject per year. ASBIs included bacteremia/sepsis, bacterial meningitis, osteomyelitis/septic arthritis, bacterial pneumonia, and visceral abscess that were caused by a recognized bacterial pathogen.

The observation period for each subject started with the day of the first IGSC, 20% infusion in Epoch 2 and ended with the day of the End of Study visit (including start and end day). The length of the observation period was expressed in years by dividing the number of days in the observation period by the average length of the year in the Gregorian calendar (365.2425 days).

The study is considered a success if the upper limit of an exact one-sided 99 % confidence interval (CI) for the rate is < 1, or alternatively, if the annual validated ASBI rate is less than 1.0 at the 0.01 level of significance.

Secondary Efficacy Endpoints:
1. Annual rate of all infections per subject
2. Annual rate of sinus infections per subject

3. Annual rate of fever episodes per subject
4. Annual rate of days off school/work or days unable to perform normal daily activities due to illness or infection per subject.
5. Annual rate of days on antibiotics per subject
6. Annual rate of hospitalizations for illness or infection per subject
7. Annual rate of days of hospitalizations for illness or infection per subject
8. Annual rate of acute (urgent or unscheduled) physician visits, or visits to the Emergency Room for illness or infection per subject.

(Selected) Safety Endpoints:

1. All SAEs and AEs
a. Number of SAEs and AEs (including and excluding infections) regardless of relationship to the investigational product(s) divided by the number of subjects
b. Number of SAEs and AEs (including and excluding infections) regardless of relationship to the investigational product(s) divided by the number of infusions

2. TAAEs
a. Number of AEs (including and excluding infections) that begin during or within 72 hours of completion of infusion divided by the number of subjects
b. Number of AEs (including and excluding infections) that begin during or within 72 hours of completion of infusion divided by the number of infusions. The success criterion is an upper one-sided 95% confidence limit less than 0.4 for the observed proportion of infusions with TAAEs.
c. Number of AEs (including and excluding infections) that begin during or within 24 hours of completion of infusion divided by the number of subjects
d. Number of AEs (including and excluding infections) that begin during or within 24 hours of completion of infusion divided by the number of infusions
e. Number of AEs (including and excluding infections) that begin during or within 1 hour of completion of infusion divided by the number of subjects
f. Number of AEs (including and excluding infections) that begin during or within 1 hour of completion of infusion divided by the number of infusions

Quality of life and treatment satisfaction:

1. Quality of Life
a. Pediatric Quality of Life Inventory (PEDS-QLTM) (observer: parent) for the age group 2 to 4 and 5 to 7 years[ii]
b. PEDS-QLTM (observer: subject) for the age group 8 to 12, and 13 years (use 13 to 18 years form) [ii]
c. Short-Form 36v2 (SF-36v2) for the age group 14 years and older[iii]

2. Life Quality Index
a. Life Quality Index (LQI); for the age group 2 to 12 years the observer was a parent, for the age group 13 years and older the observer was the subject. [iv]

3. Treatment Satisfaction
a. Treatment Satisfaction Questionnaire for Medication (TSQM); for the age

group 2 to 12 years the observer was a parent, for the age group 13 years and older the observer was the subject. [v]

Reviewer Comment: Because quality of life is covered in the clinical review, my review is focused on safety, efficacy, and not on quality of life metrics.

6.1.9 Statistical Considerations & Statistical Analysis Plan

Sample Size:
The sample size, based on the ASBI rate, was determined using a single sample comparison against a fixed value of ASBI of 0.65/year. It was estimated that a sample size of 59 subjects could provide of 85% power to reject the null hypothesis of a serious infection rate greater or equal 1.0. Allowing for a dropout rate of 15%, and to accommodate the requirements for approximately 30 SC naïve subjects and approximately 16-20 subjects with PID aged 2 to <16 years (including approximately 4-6, each, in the age groups 2 to < 5 years and 5 to <12 years, as well as 6-8 in the age group 12 to < 16 years), 70 subjects were planned to be enrolled into the study.

Analysis Populations:
The safety population includes all subjects who received at least one infusion of the study drug during Epoch 1 through Epoch 4. The efficacy population includes all subjects who received IGSC, 20% during Epoch 2 through Epoch 4.

Analysis of the Primary Endpoint:
The rate of validated ASBIs and the 99% upper confidence limit for the validated ASBI rate was calculated using a Poisson regression model accounting for the length of the observation periods per subject. A SAS PROC GENMOD assuming the Poisson distribution for the number of ASBI with the logarithm as link function was used. The model included the natural logarithm of the length of the observation period in years as an offset option to account for the different lengths of the observation periods per subject.

Analyses of Secondary Endpoints:
Rates of infection, fever episodes, days on antibiotics, off work/school/daily activity, hospitalizations, and acute physician visits were calculated using a Poisson regression model accounting for observation time and are presented as point estimates and 95% confidence intervals.

Analyses of Safety Endpoints:
Descriptive statistics were used for the analysis of safety for Epoch 1 and the combined Epochs 2, 3, and 4 separately. The upper one-sided 95% confidence limit of observed proportion of infusions with TAAEs for combined Epochs 2, 3, and 4 was calculated using a logistic regression model.

Handling of Dropouts or Missing Data:
Statistical techniques were not used to identify and exclude any observations as outliers

from the analyses. If any data were considered spurious, e.g. for lack of biological plausibility, this was documented to include the reason for exclusion and the analyses from which the data points were excluded.

Reviewer Comment: This was the applicant's proposal for handling missing data. For dropouts, the Poisson regression model incorporated an offset variable to account for the different lengths of the observation periods per subject.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

Populations Enrolled/Analyzed

Of the 86 subjects screened for the study, 77 subjects started Epoch 1. Of these 77 subjects, the 74 subjects started Epoch 2 and Epoch 3. Therefore, the safety population includes 77 subjects and efficacy population includes 74 subjects.

6.1.10.1.1 Demographics

Of the 77 treated subjects (51.9% male, 48.1% female), the majority were White/Caucasian (90.9%) and not of Hispanic or Latino ethnicity (93.5%) (Table 2). The median age of treated subjects was 36.0 years (range: 3-83 years). Twenty-three subjects were < 16 years of age and 9 subjects were ≥ 65 years of age. The median weight was 68.20 kg (range: 13.20-161.80 kg) and the median height 164.60 cm (range: 106.50-195.6 cm) (Table 3).

Table 2 Demographic and Baseline Characteristics (subjects started Epoch 1)

Parameter	Category	Subjects Aged 2 to <5 Years[a] N = 1 n (%)	Subjects Aged 5 to <12 Years[a] N = 14 n (%)	Subjects Aged 12 to <16 Years[a] N = 8 n (%)	Subjects Aged 16 to <65 Years[a] N = 45 n (%)	Subjects Aged 65 Years and Older[a] N = 9 n (%)	Total N = 77 n (%)
Sex	Male	1 (100.0)	13 (92.9)	7 (87.5)	18 (40.0)	1 (11.1)	40 (51.9)
	Female	0 (0.0)	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 or African American	0 (0.0)	2 (14.3)	1 (12.5)	0 (0.0)	0 (0.0)	3 (3.9)
	Asian	0 (0.0)	2 (14.3)	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.6)
	Multiple	0 (0.0)	1 (7.1)	0 (0.0)	1 (2.2)	0 (0.0)	2 (2.6)
Ethnicity	Hispanic or Latino	0 (0.0)	0 (0.0)	1 (12.5)	4 (8.9)	0 (0.0)	5 (6.5)
	Not Hispanic or Latino	1 (100.0)	14 (100.0)	7 (87.5)	41 (91.1)	9 (100.0)	72 (93.5)

[a]Age at screening.
Source: Adapted from BLA 125596, Module 2.3.5.2 Full Clinical Study Report 170904, Table 4

Table 3. Demographic and Baseline Characteristics (Safety Analysis Set)

Parameter*	Statistics	Subjects Aged 2 to <5 Years*	Subjects Aged 5 to <12 Years*	Subjects Aged 12 to <16 Years*	Subjects Aged 16 to <65 Years*	Subjects Aged 65 Years and Older*	Total
Age [Years]	N	1	14	8	45	9	77
	Min	3	6	12	16	66	3
	Median	3.0	8.0	13.0	48.0	69.0	36.0
	Max	3	11	15	63	83	83
Weight [kg]	N	1	14	8	45	9	77
	Min	13.2	19.6	39.9	42.2	48.0	13.2
	Median	13.20	25.85	50.50	76.00	68.20	68.20
	Max	13.2	56.1	80.0	161.8	113.4	161.8
Height [cm]	N	1	14	8	45	9	77
	Min	106.5	111.8	147.2	144.5	132.1	106.5
	Median	106.50	127.90	158.80	167.60	167.60	164.60
	Max	106.5	158.8	173.0	195.6	188.0	195.6

Source: "BLA 125596, 2.3.5.2 Full Clinical Study Report 170904, Table 5"

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

The majority of the subjects had a significant medical history of eye, ears nose and throat infections (83.1%) and more than half of respiratory infections (62.3%).

"Common variable immunodeficiency" was the most commonly diagnosed PID (32.5% of subjects), followed by "Specific antibody deficiency" (23.4% of subjects) (Table 4).

Table 4. Primary Immunodeficiency Diagnosis (Safety Analysis Set)

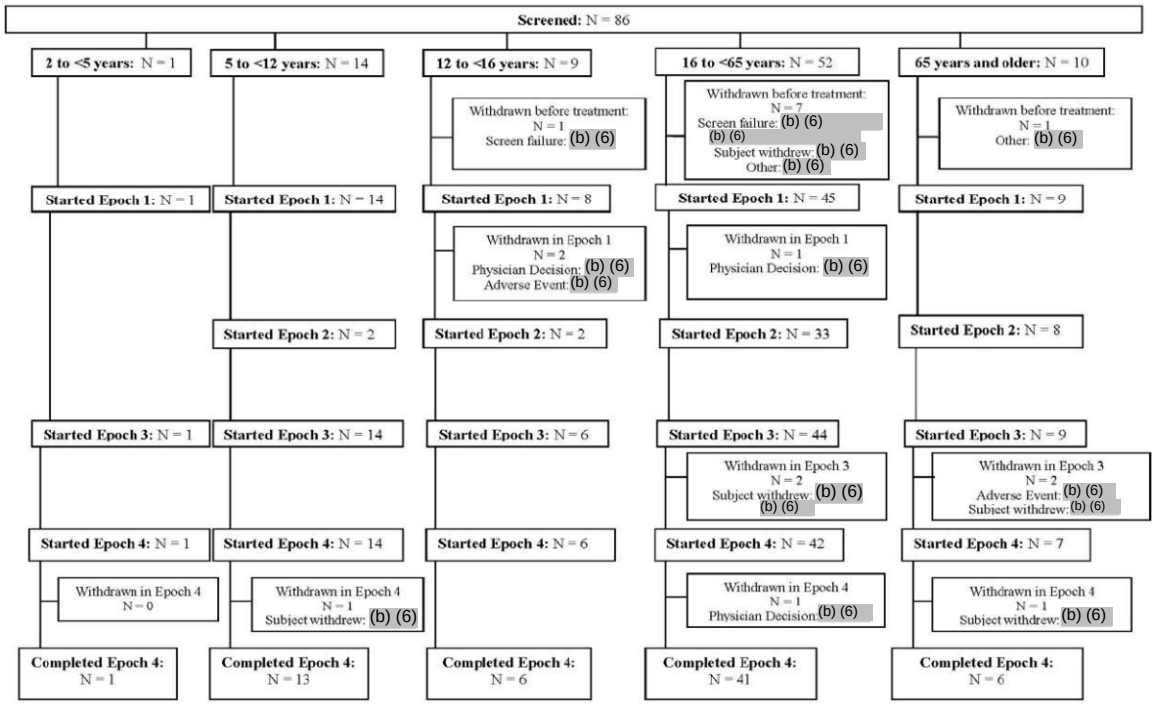
System Category	n of N (%)
CONGENITAL AGAMMA - XLA	8 of 77 (10.4)
AGAMMAGLOBULINEMIA - AR	2 of 77 (2.6)
X-LINKED HYPER IGM (XHIM)	1 of 77 (1.3)
HYPER-IGM - AR	1 of 77 (1.3)
SEVERE COMBINED IMMUNE DEFICIENCY	1 of 77 (1.3)
COMMON VARIABLE IMMUNE DEFICIENCY	25 of 77 (32.5)
SPECIFIC ANTIBODY DEFICIENCY	18 of 77 (23.4)
SPECIFIC ANTIBODY DEFICIENCY WITH IGG SUBCLASS DEFICIENCY	6 of 77 (7.8)
SPECIFIC ANTIBODY DEFICIENCY WITH LOW IGG	9 of 77 (11.7)
SPECIFIC ANTIBODY DEFICIENCY: WITH HYPOGAMMUGLOBENEMIA	1 of 77 (1.3)
ATAXIA TELANGIECTASIA	1 of 77 (1.3)
OTHER: BRUTON'S XLINKED AGAMMAGLOBULINEMIA	1 of 77 (1.3)
OTHER: FAMILIAL TACI MUTATION C.512>G	1 of 77 (1.3)
OTHER: IGG1 AND IGG3 SUBCLASS DEFICIENCY WITH LOW IGG	1 of 77 (1.3)
OTHER: SPECIFIC ANTIBODY DEFICIENCY WITH IGG SUBCLASS DEFICIENCY	1 of 77 (1.3)
Total	77 of 77 (100.0)

Source: BLA 125596, Module 2.3.5.2 Full Clinical Study Report 170904, Table 7

6.1.10.1.3 Subject Disposition

The disposition of the 86 subjects who were screened for eligibility to participate in this study is shown in Figure 2.

Figure 2. Disposition of Subjects



Source: BLA 125596, Module 2.3.5.2 Full Clinical Study Report 170904, Figure 1

Of the 86 subjects screened for the study, 77 subjects started Epoch 1, 74 subjects received IGSC, 20% and 67 subjects completed the study. Of the 74 subjects treated with IGSC, 20%, 45 participated in Epoch 2 (IGSC, 20% treatment at 145% of IGIV, 10% dose) and 29 went from Epoch 1 directly on to Epoch 3. All 74 subjects received IGSC, 20% at the adjusted dose during Epoch 3 and 70 subjects went on to Epoch 4 (individually adapted IGSC, 20% dose) (Table 5).

Table 5. Subject Disposition

Category	Subjects Aged 2 to <5 Years[a] N (%)	Subjects Aged 5 to <12 Years[a] N (%)	Subjects Aged 12 to <16 Years[a] N (%)	Subjects Aged 16 to <65 Years[a] N (%)	Subjects Aged 65 Years and Older[a] N (%)	Total N (%)
Enrolled subjects (i.e. subjects who signed the informed consent)	1 (100.0)	14 (100.0)	9 (100.0)	52 (100.0)	10 (100.0)	86 (100.0)
Screen failures	0 (0.0)	0 (0.0)	1 (11.1)	5 (9.6)	0 (0.0)	6 (7.0)
Subjects treated with any Study Drug (i.e. in Safety Analysis Set)	1 (100.0)	14 (100.0)	8 (88.9)	45 (86.5)	9 (90.0)	77 (89.5)
Subjects treated with IV 10 %	1 (100.0)	14 (100.0)	8 (88.9)	45 (86.5)	9 (90.0)	77 (89.5)
Subjects treated with SC 20 %	1 (100.0)	14 (100.0)	6 (66.7)	44 (84.6)	9 (90.0)	74 (86.0)
SC 20 % 145% IV	0 (0.0)	2 (14.3)	2 (22.2)	33 (63.5)	8 (80.0)	45 (52.3)
SC 20 % adjusted	1 (100.0)	14 (100.0)	6 (66.7)	44 (84.6)	9 (90.0)	74 (86.0)
SC 20 % individualized	1 (100.0)	14 (100.0)	6 (66.7)	42 (80.8)	7 (70.0)	70 (81.4)
Subjects discontinued study	0 (0.0)	1 (7.1)	3 (33.3)	11 (21.2)	4 (40.0)	19 (22.1)
Subjects completed study	1 (100.0)	13 (92.9)	6 (66.7)	41 (78.8)	6 (60.0)	67 (77.9)

[a]Age at screening.
Source: BLA 125596, Module 2.3.5.2 Full Clinical Study Report 170904, Table 1

Of the 19 screened subjects who did not complete the study, 9 subjects were withdrawn from the study before treatment (Figure 1): 6 subjects due to screen failure, one subject withdrew consent and 2 subjects had their participation terminated per decision of Baxalta's Medical Director because the first infusion would not have been within 30 days of the screening visit. In Epoch 1, 2 subjects were discontinued for non-compliance and one subject experienced an AE that lead to discontinuation. During IGSC, 20% treatment, 7 subjects terminated their study participation. The reasons for discontinuation were consent withdrawn by 5 subjects, 1 subject experienced an AE and 1 subject experienced non-compliance.

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoint(s)

One validated ASBI of pneumonia was reported in a 78-year old subject who had specific antibody deficiency while receiving IGSC, 20% during Epoch 4. The point estimate of the annualized rate of validated ASBIs was 0.012 (upper limit of 99% CI: 0.024). This annual rate of validated ASBI is statistically significantly lower than 1.0 validated ASBIs / year ($p<0.0001$), thus meeting the success criterion.

6.1.11.2 Analyses of Secondary Endpoints

All of these results are from when IGSC, 20% was administered.
1. The annualized rate of all infections per subject was 2.41 (95% CI: 1.89 to 3.03).
2. The annualized rate of sinus infections per subject was 0.69 (95% CI: 0.50 to 0.93).
3. The annualized rate of fever episodes per subject was 0.13 (95% CI: 0.08 to 0.21).
4. The annualized rate of days that subjects were not able to attend school/work or to perform normal daily activities due to illness/infection was 1.16 (95% CI: 0.70 to 1.79) per subject.
5. The annualized rate of days on antibiotics per subject was 57.59 (95% CI: 40.71 to 78.59).
6. The annualized rate of hospitalizations per subject was 0.02 (95% CI: 0.01 to 0.04).
7. The annualized rate of days in hospital per subject was 0.11(95% CI: 0.05 to 0.20).
8. The annualized rate of acute (urgent or unscheduled) physician visits per subject was 0.86 (95% CI: 0.54 to 1.28).

6.1.11.3 Subpopulation Analyses

The single ASBI, a validated pneumonia was reported in the oldest (78-year old) white male subject. There were no ASBIs experienced during the course of this study among all other subpopulations.

6.1.11.4 Dropouts and/or Discontinuations

Estimated or derived data were not used to deal with missing data. The analyses of annualized SBI rate were done per subject-year for all 74 subjects exposed to IGSC, 20%, and thus included an adjustment for length of time each subject was followed. Therefore no imputation of missing data for early terminations was performed. Because the

observed performance was well below the threshold in the FDA guidance and the relatively short observation period of early terminations (≤100 days, Listing 8, Validated Acute Serious Bacterial Infections), it seems unlikely that the seven subjects who dropped out ((b) (6)) would have impacted meeting the success criteria.

6.1.12 Safety Analyses

6.1.12.3 Deaths

No deaths occurred during the study.

6.1.12.4 Nonfatal Serious Adverse Events

Two SAEs occurred in two subjects during the IGSC, 20% treatment. One was severe in nature (lung adenocarcinoma in 67 year old white female); one was of moderate severity (pneumonia in 78 year old white male). Neither SAE was assessed as related to IGSC, 20%.

6.1.12.5 Adverse Events of Special Interest (AESI)

A total of 343 AEs (including infections) that occurred during IGSC, 20% treatment, were assessed as causally related to IGSC, 20% treatment and/or temporally-associated with IGSC, 20%. Of them 54 (3.86 per subject) were in children between 5 and <12 years of age, 24 (4.0 per subject) were in children between 12 and <16 years of age, 220 (5.0 per subject) were in subjects between 16 and <65 years of age, and 45 (5.0 per subject) were in subjects 65 years of age and older (Clinical Study Report, Table 61). The rate per infusion of TAAE was 0.079 (343 TAAEs in 4327 infusions). The upper one-sided 95% confidence limit of observed proportion of infusions with TAAEs was 0.086 which met the success criterion of < 0.4.

6.2 Trial #2

Study 170903

6.2.1 Objectives (Primary, Secondary, etc)

Primary Objective:
To evaluate the efficacy of IGSC, 20% in subjects with PID.

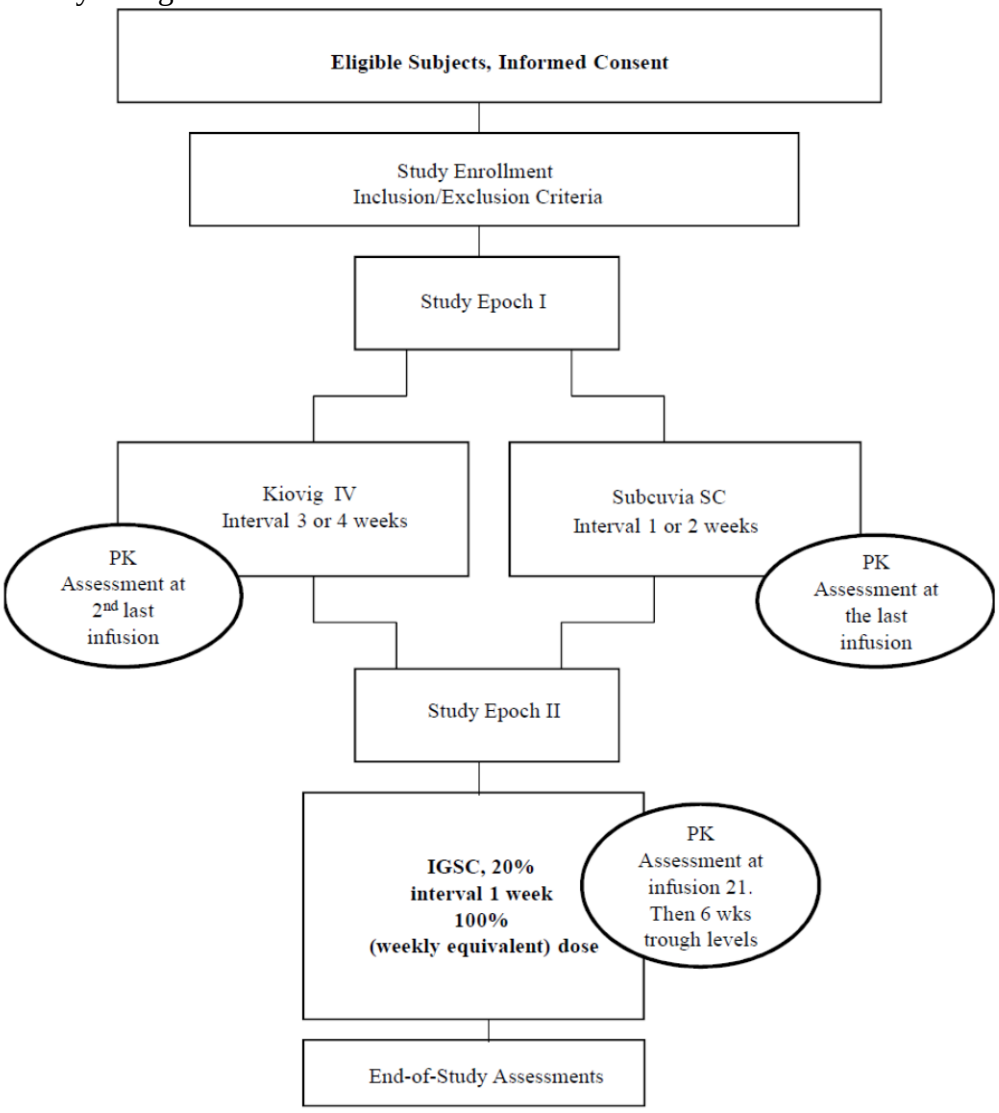
Secondary Objectives:
To evaluate the safety, tolerability, and PK characteristics of IGSC, 20% in subjects with PID.

6.2.2 Design Overview

This was a Phase 2/3, prospective, open-label, non-controlled, non-randomized, multi-center, 2-part (“epoch”) study. Subjects received IGSC, 20% during Epoch 2 at a dose equivalent to that administered for IGIV, 10% or IGSC, 16% during Epoch 1. Subjects received either IGIV, 10% at a 3 or 4-week interval for 13 weeks or IGSC, 16% every

week or every other week for 12 weeks. When switching to study Epoch 2, subjects received IGSC, 20% weekly, at the same dose as in Epoch 1 (adjusted to a weekly-equivalent dose in case of an interval change) for 51 weeks. The overall duration of the study was 33 months from study initiation (first subject in) to study completion (last subject out). The duration of study participation for each subject was approximately 16 months (up to 1 month from enrollment to first infusion, approximately 3 months in Epoch 1, approximately 12 months in Epoch 2). The overall study design and schedule is presented in in Figure 3.

Figure 3. Study Design



KIOVIG (IGIV, 10%), SUBCUVIA (IGSC, 16%)
Source: BLA 125596, Module 2.3.5.2 Full Clinical Study Report 170903, Figure 9.2-1

6.2.3 Population

Male and female subjects, aged 2 years or older, with documented diagnosis of a form of PID involving antibody formation and requiring gammaglobulin replacement were included in the study. Age was defined as the age at screening. Subject had a serum trough level of IgG > 5 g/L at screening.

6.2.4 Study Treatments or Agents Mandated by the Protocol

In Epoch 1, KIOVIG was administered by IV infusion (regulated via a pump) once every 3 or 4 weeks. Previous IV immunoglobulin treatment could be used to guide infusion rates but the maximum rate of administration should not exceed 6 mL/kg BW/hr. It was recommended that the first infusions be administered at a slower rate than had been used prior to enrollment in the study. SUBCUVIA was administered by SC infusion (regulated via a pump), once every 7 or 14 days. Previous SC immunoglobulin treatment was used to guide the volume/site, number of sites, and the rate of administration. The dose in Epoch 1 depended on the pre-study dose, but was required to be within 0.3-1.0g/ kg BW/4weeks.
In Epoch 2, subjects were administered SC infusion of IGSC, 20% once every week for 51 weeks with the same dose as that used during Epoch 1 (adjusted to a weekly equivalent dose if necessary). If serum trough levels of IgG fell to 5 g/L or below, the subject's dose was to be adjusted to maintain minimum trough levels (>5 g/L). If an infusion was well tolerated, up to 60 mL was administered per infusion site. For subjects with a BW of <40 kg it was recommended that for the initial two infusions the volume be limited to 20 mL per infusion site, to be increased to 40 mL and if tolerated then increased to 60 mL, if well tolerated. The initial two infusions were started at 10 mL/hr/infusion site, and were to be increased stepwise if well tolerated, with rate increments at the discretion of the investigator, to a maximum of 60 mL/hr/infusion site.

6.2.6 Sites and Centers

The study was conducted in 16 centers located in Austria, Belgium, Germany, Hungary, the Netherlands, Sweden, and UK.

6.2.8 Endpoints and Criteria for Study Success

Primary Efficacy Endpoint:
The primary efficacy endpoint was the mean number of validated ASBI per subject per year during Epoch 2. ASBI includes bacteremia / sepsis, bacterial meningitis, osteomyelitis / septic arthritis, bacterial pneumonia, and visceral abscess. ASBI per subject per year was expressed in years by dividing the number of days in the observation period by the average length of the year in the Gregorian calendar (365.2425 days).

The study is considered a success if the upper limit of an exact one-sided 99 % CI for the ASBI rate is < 1, or alternatively, if the annual validated ASBI rate is less than 1.0 at the 0.01 level of significance.

Secondary Efficacy Endpoints:
1. The annual rate of all infections per subject

2. The annual rate of sinus infections per subject
3. The annual rate of fever episodes per subject
4. Days off school/work due to illness/infection or to perform normal daily activities due to illness/infection
5. Days on antibiotics
6. Number of hospitalizations and length of stay (in days)
7. The annualized rate of acute (urgent or unscheduled) physician visits due to illness/infection

(Selected) Safety Endpoints:
1. All AEs
a. Annual rate of serious adverse events (SAEs), related and not related
b. Rates of AEs (including and excluding infections) defined as number of AEs categorized by Medical Dictionary for Regulatory Activities (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

2. TAAEs
a. Number of AEs (including and excluding infections) that begin 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 begin during or within 72 hours of completion of infusion divided by the number of infusions. The success criterion for this proportion is that the upper one-sided 95% confidence limit of the observed rate of infusions with TAAEs is less than 0.4.

6.2.9 Statistical Considerations & Statistical Analysis Plan

Sample Size:
The applicant estimated that a sample size of 43 subjects provided 84% power to reject the null hypothesis of a serious infection rate greater or equal to1.0 by means of a one-sided test, Type I error of 0.01, and assuming an ASBI rate of 0.6/year. Allowing for a dropout rate of 10%, 47 subjects should be dosed in the study.

Analysis Populations:
The safety population includes all subjects who received at least one infusion of the study drug during Epoch 1 and Epoch 2. The efficacy population includes all subjects who received IGSC, 20% during Epoch 2.

Primary Efficacy Analysis:
The ASBI rate and the 99% upper confidence limit for the ASBI rate was calculated using a Poisson regression model accounting for the length of the observation periods per subject. A generalized linear model assuming the Poisson distribution for the number of ASBI with the logarithm as the link function was used. The Poisson model included the natural logarithm of the length of the observation period in years as an offset to account for the different lengths of the observation periods per subject. To handle over-dispersion,

the exponential distribution dispersion parameter was assumed to be given by the deviance divided by the degrees of freedom and all statistics were adjusted accordingly. The statistical programs used in these calculations were identical to the programs used in Study 170904.

Handling of Missing Data:
The applicant's only plan for handling missing data was the use of an offset variable in the Poisson regression model to account for the different lengths of the observation periods per subject.

6.2.10 Study Population and Disposition

6.2.10.1 Populations Enrolled/Analyzed

Forty nine subjects were included in the safety population and 48 subjects were included in the efficacy population.

6.2.10.1.1 Demographics
Of the 49 treated subjects (61.2% male, 38.8% female), the majority (98.0%) were White/Caucasian (Table 6). The median age was 17 years (range: 2-67 years).

Table 6. Demographic and Baseline Characteristics (Safety Analysis Set)

Parameter	Category	Subjects Aged 2 to <6 Years[a] N = 5 n (%)	Subjects Aged 6 to <12 Years[a] N = 8 n (%)	Subjects Aged 12 to <18 Years[a] N = 12 n (%)	Subjects Aged 18 to <65 Years[a] N = 21 n (%)	Subjects Aged 65 Years and Older[a] N = 3 n (%)	Total N = 49 n (%)
Gender	Male	4 (80.0)	6 (75.0)	8 (66.7)	12 (57.1)	0 (0.0)	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)
	Asian	0 (0.0)	0 (0.0)	1 (8.3)	0 (0.0)	0 (0.0)	1 (2.0)

[a]Age at screening.
Source: Adapted from BLA 125596, Module 2.3.5.2 Full Clinical Study Report 170903, Table 4

6.2.10.1.2 Medical/Behavioral Characterization of the Enrolled Population
More than half of the subjects had a previous significant medical history of eye, ears nose and throat infections (69.4%) or respiratory infections (65.3%).

"Common variable immunodeficiency" was the most commonly diagnosed PID (65.3% of subjects), followed by "X-linked agammaglobulinemia" (18.4% of subjects) (Table 7).

Table 7. Primary Immunodeficiency Diagnosis (Safety Analysis Set)

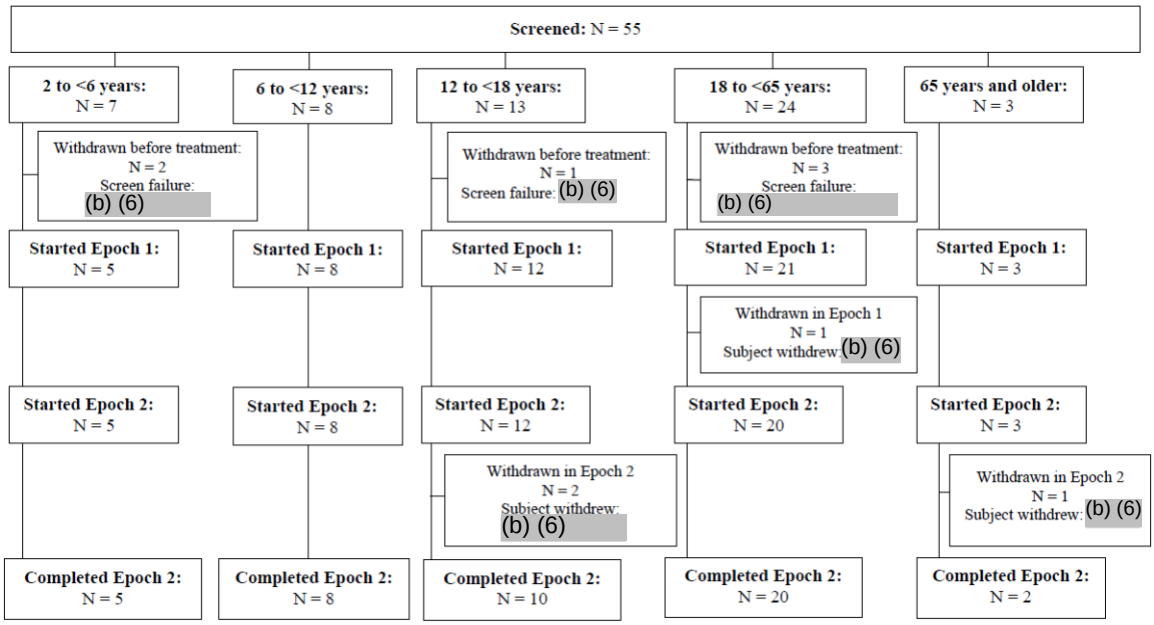
System Category	n of N (%)
COMMON VARIABLE IMMUNODEFICIENCY (CVID)	32 of 49 (65.3)
X-LINKED AGAMMAGLOBULINEMIA (XLA)	9 of 49 (18.4)
AUTOSOMAL RECESSIVE HYPOGAMMAGLOBULINEMIA	1 of 49 (2.0)
HYPER IGM	2 of 49 (4.1)
ISOLATED IGG SUBCLASS DEFICIENCY	2 of 49 (4.1)
SPECIFIC ANTIBODY DEFICIENCY	3 of 49 (6.1)
OTHER:CD 40 LIGAND DEFICIENCY	1 of 49 (2.0)
OTHER:IGM AND IGG DEFICIENCY	1 of 49 (2.0)
Total	49 of 49 (100.0)

Source: BLA 125596, Module 2.3.5.2 Full Clinical Study Report 170903, Table 7

6.2.10.1.3 Subject Disposition

The reasons for discontinuation during Epoch 2 were pain during and after administration of the study medication for one subject aged 16 years), for another subject withdrew full consent because coming to the site was too time- and effort-consuming (aged 65 years) and the third subject was no longer willing to administer IGSC, 20% and as a result withdrew full consent (aged 16 years). The disposition of the 55 subjects who were screened for eligibility to participate in this study is shown in Figure 4. Forty five subjects completed the study.

Figure 4. Disposition of Subjects



Source: BLA 125596, Module 2.3.5.2 Full Clinical Study Report 170903, Figure 1

6.2.11 Efficacy Analyses

6.2.11.1 Analyses of Primary Endpoint(s)

One ASBI of bacterial pneumonia was reported in a nine-year old subject during IGSC, 20% treatment (Epoch 2). The point estimate of the annual rate of ASBIs was 0.022 (upper limit of 99% CI: 0.049) . This annual ASBI rate was statistically significantly lower than 1.0 ASBIs / year, ($p<0.0001$), thus meeting the success criterion.

6.2.11.2 Analyses of Secondary Endpoints

1. The annualized rate of all infections per subject was 4.38.
2. The annualized rate of sinusitis/bacterial sinusitis per subject was 0.15/0.02. The annualized rate of acute sinusitis per subject was 0.09 and the annualized rate of chronic sinusitis per subject was 0.02.
3. The annualized rate of fever episodes per subject was 0.88.
4. The annualized rate of days that subjects were not able to attend school/work or to perform normal daily activities due to illness/infection per subject was 15.55.
5. The annualized rate of days on antibiotics per subject was 18.11.
6. The annualized rate of hospitalizations per subject was 0.15.
7. The annualized rate of acute (urgent or unscheduled) physician visits per subject was 3.77.

6.2.11.3 Subpopulation Analyses

A total of one VASBI was reported in one 9-year old, male, white subject among 29 white male subjects (3.5%) and among 48 white subjects (2%) in Epoch 2.

6.2.11.4 Dropouts and/or Discontinuations

No imputation of missing data for early terminations was performed. Different lengths of observation for the primary efficacy endpoint were accounted for in the Poisson regression model via an offset. The mean duration of treatment with IGSC 20% was 347 days, SD = 48.4, min = 127 and max = 399 (Clinical Study Report, Table 41), while the maximal duration of treatment of dropouts and discontinuations was ≤100 days (Lising 8). For the three subjects who dropped out (see Section 6.2.10.1.3), the reasons for discontinuing were unlikely to impact efficacy. Furthermore, the dropouts were unlikely to influence the study outcome because only one ASBI was observed among the 45 subjects who completed the study, yielding a result well below the efficacy criterion.

6.2.12 Safety Analyses

6.2.12.3 Deaths

No subject died during the study.

6.2.12.4 Nonfatal Serious Adverse Events

A total of 12 SAEs occurred in 8 subjects in the safety population. Of them, four SAEs occurred in Epoch 1 and eight SAEs in Epoch 2:

- 5 years, Male, White, rhinorrhea (Epoch 2)
- 9 years, Male, White, pneumonia bacterial twice (Epoch 1 and Epoch 2)
- 13 years, Male, White, forearm fracture (Epoch1)
- 16 years, Male, White, lymphadenopathy (Epoch1)
- 18 years, Female, White, chronic sinusitis (Epoch 2)
- 39 years, Male, White, nasal septum deviation (Epoch 2)
- 46 Female, White, enteritis (Epoch 2)
- 60 years, Male, White, brain stem infarction (Epoch 2), acute myocardial infarction (Epoch 2), ventricular fibrillation (Epoch2), thoracic vertebral fracture (Epoch1).

All SAEs had resolved at the time of study completion. Of all SAEs reported during this study, none were deemed by the investigator or the sponsor to be related to any of the IPs and none led to study discontinuation.

6.2.12.5 Adverse Events of Special Interest (AESI)

A total of 454 TAAEs were reported in 2349 infusions during IGSC, 20% treatment, yielding a rate of TAAEs per infusion of 0.193. The upper one-sided 95% confidence limit of the observed proportion of infusions with TAAEs was 0.210 which met the success criterion of < 0.4.

8. INTEGRATED OVERVIEW OF SAFETY

8.2 Safety Database

8.2.1 Studies/Clinical Trials Used to Evaluate Safety

This submission integrates clinical data relevant to the safety and tolerability of IGSC, 20% in subjects with PID aged 2 years and older who participated in clinical studies 170904 and 170903.

8.2.2 Overall Exposure, Demographics of Pooled Safety Populations

The Safety Analysis Dataset comprised all subjects who received at least one IGSC infusion in either one of the studies included in this analysis. IGSC, 20% was administered to 122 subjects over a median (range) of 365 (30 - 629) exposure days (mean ± SD: 387.3 ± 100.6 days). The median (range) weekly dose of IGSC, 20% was 0.17 (0.08 – 0.46) g/kg/week (Table 8).

Table 8. Summary of Exposure to SC 20% (Studies 170903, 170904: Safety Analysis Set)

Statistics	Exposure days [days]	Number of Infusions	IGI Dose [g]	IGI Dose/Body Weight [g/kg]	IGI Dose/Body Weight/Week [g/kg/week]
N	122	138	6856	6856	6856
Mean	387.3	49.7	12.37	0.186	0.1858
SD	100.6	19.6	6.675	0.07783	0.07789
Min	30	3	2.6	0.076	0.076
Q1	358	51	6.4	0.123	0.123
Median	365	51	11.3	0.173	0.171
Q3	414	56	17.4	0.231	0.231
Max	629	88	30	0.462	0.462

Source: BLA 125596, Module 2.3.5.2 Integrated Summary of Safety for IGSC, 20%, Table 10

The demographics in the combined studies 170903 and 170904 were as follows:

- Age – The median (range) age was 32.0 (2-83) years. Most subjects were adults aged 16 to < 65 years (71/122, 58.2%), followed by children aged 6 to <12 years (22/122, 18.0%), 12 to < 16 years (11/122, 9.0%), and < 6 years (6/122, 4.9%). The proportion of subjects in each age category was similar in each of the two studies in this pooled analysis set.
- Sex – Slightly more males (68/122, 55.7%) than females (54/122, 44.3%) were treated.
- Race – Most subjects (114/122, 93.4%) were White; 3 subjects (2.5%) were Black or African American, 3 subjects (2.5%) were Asian, and 2 subjects (1.6%) were of multiple races.
- Ethnicity – Hispanic or Latino subjects comprised 4.1% (5/122) of the population.

8.4 Safety Results

8.4.1 Deaths

No subject died during IGSC, 20% treatment in studies 170904 and 170903.

8.4.2 Nonfatal Serious Adverse Events

In Study 170904, two SAEs were reported under IGSC, 20% treatment: one was severe in nature (lung adenocarcinoma) in Subject ((b) (6)) and one was moderate (pneumonia) in Subject ((b) (6)). Both were deemed unrelated to IGSC, 20% administration by the investigator. Both subjects chose to complete the study. One Subject experienced SAE under IV 10% treatment. It was deemed by the investigator as related to IGIV, 10% infusion and led to one subject (Subject (b) (6)) discontinuation. In Study 170903, eight SAEs were reported in six subjects during IGSC, 20% treatment. Two SAEs were severe in nature (acute myocardial infarction and ventricular fibrillation), five were moderate (enteritis, chronic sinusitis, bacterial pneumonia, brain stem infarction and rhinorrhea)

and one was mild (nasal septum deviation). All were deemed unrelated to IP and all had resolved at the time of study completion. Two SAEs, were reported under IGIV, 10% treatment and two other SAEs under IGSC, 16% treatment. Both SAE were deemed unrelated to IP.

8.6 Safety Conclusions

10. CONCLUSIONS

10.1 Statistical Issues and Collective Evidence

A total of 122 subjects have been exposed to IGSC, 20% in two clinical trials in subjects with PID (pivotal Study 170904 in North America, and Study 170903 in Europe). In Study 170904, IGSC, 20% was administered at a dose adjusted to achieve the bioavailability of IGIV, 10%. In Study 170903, IGSC, 20% was administered at the same dose (i.e., g/kg BW/week) as IGIV, 10% or IGSC, 16%.

In Study 170904, the annualized rate of validated ASBIs was 0.012 (upper limit of 99% CI: 0.024). In Study 170903, the point estimate of the annualized rate of validated ASBIs was 0.022 (upper limit of 99% CI: 0.049). Both studies met the success criteria of the upper 99% confidence limit <1.

The rate of TAAEs per infusion was 0.12 of 6675 infusions across IGSC, 20% treatment in Studies 170903 and 170904. The upper one-sided 95% confidence limit of observed proportion of infusions with TAAEs was 0.13 which met the success criterion of < 0.4.

10.2 Conclusions and Recommendations

There were no statistical issues in this submission. The confidence intervals were calculated correctly. Data from the IGSC, 20% clinical development program support the safe administration of IGSC, 20% in adult and pediatric patients with PID. In both clinical studies, the annualized rate of ASBIs for subjects administered IGSC, 20% was substantially lower than 1.0 ASBI/year, the threshold specified as providing substantial evidence of efficacy by the EMA Guidelines and the FDA Guidance for Industry.

[i] Safety, Efficacy, and Pharmacokinetic Studies to Marketing of Immunne Clobulin Intravenous (Human) as Replacment Therapy for Primary Humoral Immunodeficiency. FDA Guidance for Industry (2008)

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