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**BLA Clinical Review Memorandum**

Application Type	Efficacy Supplement -BLA
STN	125668/158
CBER Received Date	Dec 14,2020
PDUFA Goal Date	Oct 23, 2021
Division / Office	DCEPT/OTAT
Priority Review (Yes/No)	No
Reviewer Name(s)	Vijay Kumar, MD Medical Officer GMB1
Review Completion Date / Stamped Date	
Supervisory Concurrence	
Team Lead GMB1	Melanie Blank, MD
Branch Chief GMB1	Elizabeth Hart, MD
Division Director, DCEPT	Tejashri Purohit-Sheth, MD
Applicant	Octapharma
Established Name	Immune Globulin Subcutaneous (Human), 16.5% Liquid
(Proposed) Trade Name	Cutaquig
Pharmacologic Class	Immune Globulin Subcutaneous (human)
Formulation(s), including Adjuvants, etc.	Liquid; 0.165 g/mL solution for injection
Dosage Form(s) and Route(s) of Administration	16.5% IgG, 6 mL, 10 mL, 12 mL, 20 mL, 24 mL, 48 mL vials For subcutaneous use.
Dosing Regimen	Dosing Flexibility: Weekly; Biweekly; <1 week. When switching from IGIV to Cutaquig, start Cutaquig one week after last IGIV infusion. Initial weekly dose = previous IGIV dose (in grams) x 1.30/number of weeks between IGIV doses
Indication(s) and Intended Population(s)	Replacement therapy for primary humoral immunodeficiency (PI) in adults and children over 2 years of age.
Orphan Designated (Yes/No)	No

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GLOSSARY

AE	adverse event
AR	adverse reaction
BLA	biologics license application
CI	confidence interval
CMV	cytomegalovirus
CSR	clinical study report
CVID	common variable immunodeficiency
DCF	dosing conversion factor
eCRF	electronic case report form
FAS	full analysis set
FSR	Final Study Report
IGIV	Immune Globulin Intravenous (Human)
IGSC	Immune Globulin Subcutaneous (Human)
IP	Investigational Product
PID	primary (humoral) immunodeficiency
PK	pharmacokinetics
PMC	post marketing commitment
PMR	post marketing requirement
PP	per protocol
PREA	Pediatric Research Equity Act
PT	preferred term (MedDRA)
QoL	quality of life
SAE	serious adverse event
SAR	serious adverse reaction
SBI	serious bacterial infection
SC	subcutaneous
SOC	system organ class (MedDRA)
SS	safety analysis set
TEAE	treatment emergent adverse event
TEE	thromboembolic event
XLA	X-linked agammaglobulinemia

## 1. Executive Summary

Octapharma submitted an efficacy supplement for Cutaquig®, a 16.5% subcutaneous immune globulin product (IGSC), on December 14, 2020 for the treatment of primary humoral immunodeficiency (PID) in children. Cutaquig was initially approved for the treatment of PID in adults December 2018. At the time of approval, there were insufficient data to assess safety and efficacy in the pediatric population and there were no pediatric pharmacokinetic (PK) data. In accordance with the provisions of section 505B of the Food Drug and Cosmetic Act (21 U.S.C. 355c) (also referred to as the Pediatric Research Equity Act (PREA), the approval included a post-marketing requirement (PMR) to complete a pediatric study to assess PK, efficacy and safety in children 2-17 years of age.

To fulfill the PREA PMR and support the pediatric indication for PID, the Applicant provided pediatric data from 2 studies, pivotal study, SCGAM-01, and extension study, SCGAM-03. These studies provided ≥1-year of data in each of the 38 pediatric subjects and included a dedicated pediatric PK sub-study that included data in 19 children. The Applicant also proposed to change the conversion factor from 1.4 to 1.3 when converting subjects from intravenous immunoglobulin (IGIV) to Cutaquig based on population PK modeling data and to update adult safety data based on data from the extension study,.

PID represents a heterogeneous group of disorders resulting from largely inherited defects of the immune system. It is estimated that 1-2% of the population worldwide is affected.<sup>1</sup> The major 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. These disorders are marked by hypogammaglobulinemia which increases susceptibility to infections. Specifically, subjects with PI are at increased risk for recurrent, severe bacterial infections, especially respiratory tract infections. The mainstay of treatment is IGIV and IGSC, which provide antibodies to help serious bacterial diseases and is a mainstay of treatment.

SCGAM-01 was a pivotal phase 3, open label, multicenter, multinational, externally controlled study that was designed to evaluate the PK, efficacy, tolerability and safety of Cutaquig 16.5% in trial participants with PID. The study was initiated on 27-May-2014 and completed on 09-Jun-2020. The study duration was 15-months (3-month wash out from IV therapy + 12-month efficacy period for IGSC). Subjects were given the option to enroll in SGAM-03, the extension study. The studies were conducted in accordance with the “FDA guidance for industry: Safety, Efficacy, and Pharmacokinetic Studies to Support Marketing of Immune Globulin Intravenous (Human) as Replacement Therapy for Primary Humoral Immunodeficiency,” published June 2008.<sup>2</sup> The primary measure of efficacy is based on demonstrating prevention of serious bacterial infections (SBI) defined as bacteremia/sepsis, bacterial meningitis, osteomyelitis/septic arthritis, bacterial pneumonia, and visceral abscess. This endpoint is considered successful if the upper bound of the one-sided 99% confidence interval for the rate of SBIs is < 1.0 per subject-year of follow up. Accordingly, the primary efficacy endpoint for the pediatric subgroup

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<sup>1</sup> Modell V, Quinn J, Orange J, et al. Primary immunodeficiencies worldwide: an updated overview from the Jeffrey Modell Centers Global Network. *Immunol Res.* 2016;64:736-753.

<sup>2</sup> <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/safety-efficacy-and-pharmacokinetic-studies-support-marketing-immune-globulin-intravenous-human>

enrolled in study SCGAM-01 was demonstration of a SBI rate of < 1.0 per subject-year of follow up. The secondary efficacy endpoints included the annual rate of all infections; use of antibiotics; hospitalizations due to infection; and days missed from work/school/kindergarten/day care due to infections. Pharmacokinetic study endpoints measured area under curve (AUC), Maximum concentration (C<sub>max</sub>) and IG trough levels.

The weekly subcutaneous dose of Cutaquig used in the study was calculated by taking the subject's IGIV dose, dividing by the number of weeks of the IGIV inter-dose interval, and multiplying by 1.40. There were 38 pediatric subjects in Study SCGAM-01, ranging in age from 2 to 16-years of age. Twelve of the children who enrolled were in the 2 -<6-year-old range, 14 children were in the 6 -<12- year-old range, and 12 children were in the 12 -<17-year-old range. Nine were female and 29 were male. All were non-Hispanic and White. Most children (n=20; 52.6%) had Common Variable Immunodeficiency (CVID) as the etiology of their PID. Four adolescents withdrew (subject decision). There were no SBIs noted in children during the study and the results exceeded the minimum efficacy threshold outlined in the Agency guidance document.

In SCGAM-01, the annual rate of infections (non SBIs) in the pediatric population was 3.1 (2-sided 95% CI: 2.0,4.8). Systemic antibiotic use occurred in 24 (63.2%) of the pediatric subjects. The annual rate in days of antibiotic treatment/subject-year was 62.6 (2-sided 95% CI: 31.0, 126.4). Days out of work/school/kindergarten/day care due to infections in the pediatric population were 180 and the annual rate in days per subject-year was 5.2 (2-sided 95% CI: 2.8, 9.4). There was a total of 4 hospitalizations due to infections in the 38 pediatric subjects, accounting for 29 hospital days total, and the annual rate in days per subject-year was 0.8 (2-sided 95% CI: 0.3, 2.6).

The extension study, SCGAM-03, was conducted from 23-May-2016 to 05-Sep-2019 to monitor the longer-term safety, tolerability and durability of efficacy of Cutaquig in subjects with PID who had completed the SCGAM-01 trial (except for 6 de novo adults who were not enrolled in SCGAM-01). The results of the extension study, Study SCGAM-03, were similar to the pivotal study. Ten children were enrolled; 4 were female and six were male. The age distribution ranged from 6-15 years of age; 2 children were 2- ≤6 years of age, 4 children 6-<12 years of age, and 4 children 12 -<17 years of age. All Children (n=10;100%) had Common Variable Immunodeficiency (CVID) as the etiology of their PID. There were no SBIs in the extension study in the children. The secondary efficacy results were also similar to the SCGAM-01 study: The annual rate of infections (not SBIs) in the pediatric population was 2.0 (2-sided 95% CI: 0.9,4.8). Systemic antibiotic use occurred in 6 (60.0%) of the pediatric subjects. The annual rate in days of antibiotic treatment/subject-year was 70.6 (2-sided 95% CI: 22.7, 220.0). Days out of work/school/kindergarten/day care due to infections in the pediatric population were 75 and the annual rate in days per subject-year was 3.6 (2-sided 95% CI: 1.3, 10.3). There were no hospitalizations due to infections in the 10 pediatric subjects. Two children terminated the study early (one due to patient preference for IVIG, and one at the Applicant's discretion for IVIG following a pulmonary vein thrombosis).

The pharmacokinetic (PK) sub-study enrolled a total of 19 pediatric subjects. There were 5 subjects in the 2 -<6-year-old range, 8 subjects in the 6 -<12-year-old range, and 6 subjects in the 12-<17-year-old range. The actual dose converting factor (DCF) was 1.41 (1.21, 1.89). Using a Population PK model calculation, the DCF was determined in a statistically more advanced manner to be 1.33 for a median subject.

The PK study validated that the PK profile in children of all ages was similar to that of adults. The conclusion of the analysis was that children could be dosed using the same conversion factor as adults. Intra-subject serum IgG trough levels remained relatively constant throughout the study.

All 38 pediatric subjects were included in the pediatric safety analysis set. There were no deaths. Three non-infection SAEs were reported in children: seizure, status asthmaticus, and pulmonary embolism. All were considered unrelated or unlikely to be related to the product. The child with the pulmonary embolism had a previous history of deep vein thrombosis and family history of blood clots.

The most common adverse reactions were local reactions, occurring in 28 (74%) of subjects. No children <6 years experienced an infusion site reaction. Local reactions were mostly mild except for one moderate reaction in an adolescent subject. Other common reactions (occurring in > 5% of pediatric subjects) were asthma, cough, vomiting, nasal congestion, fever, headache, ALT increase, leukopenia, neutropenia, dermatitis, oropharyngeal pain, urticaria, AST increase, abdominal pain and ear pain. One adolescent had a positive Coombs test during the study, notably without hemolytic anemia.

The pediatric data collection was completed according to the agreed upon initial pediatric study protocol (iPSP). Based on a review of the clinical and PK data submitted in this supplement, the Division determined that the PREA post-marketing requirement (PMR) was fulfilled and the indication of PID should be expanded for children >2 years of age. The Pediatric Review Committee (PeRC) agreed with the Division's determination.

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1.1 Demographic Information: Subgroup Demographics and Analysis Summary

SCGAM01 – Pivotal Study

SCGAM01 study enrolled 75 subjects (36 females, 39 males). The youngest subject was 2 years and oldest was 75 years. All subjects were white and non-Hispanic, except for one adult subject who identified as “multiracial”. All children identified as non-Hispanic whites. Please see Table 1 for detailed information on sex by age and Table 2 for detailed information on age of subjects.

**Table 1: Demographic Data - SCGAM01- Sex Distribution**

Parameter Gender [N (%)]	Children ≥2 Years <6 Years N=12	Children ≥6 Years <12 Years N=14	Adolescents ≥12 Years <17 Years N=12	Adults ≥17 Years ≤75 Years N=37	Total All Subjects N=75
Female	1 (8.3%)	5 (35.7%)	3 (25.0%)	27 (73.0%)	36 (48.0%)
Male	11 (91.7%)	9 (64.3%)	9 (75.0%)	10 (27.0%)	39 (52.0%)

Reproduced from Table 7 Page 54 Source - CSR SCGAM01

**Table 2: Demographic Data - SCGAM01 - Age Distribution**

Parameter Age [Years]	Children ≥2 Years <6 Years N=12	Children ≥6 Years <12 Years N=14	Adolescents ≥12 Years <17 Years N=12	Adults ≥17 Years ≤75 Years N=37	Total All Subjects N=75
Mean (SD)	4.17 (1.12)	7.93 (1.44)	14.08 (1.38)	47.46 (13.62)	27.81 (21.91)
Median	4.50	8.00	14.00	46.00	16.00
Min, Max	2.0, 5.0	6.0, 10.0	12.0, 16.0	20.0, 73.0	2.0, 73.0

Reproduced from Table 7 Page 54 Source - CSR SCGAM01

*Reviewer’s Comment: It is notable that there were considerably more male (76%) than female children enrolled, but considerably more female (73%) than male adults. It is notable that there were no non-white children enrolled and only 1 non-white adult enrolled. This imbalanced demographic distribution does not represent the distribution of PID in the United States. However, based on knowledge about IGSC, this reviewer does not believe that demographic factors of the study population limit the interpretability of safety or efficacy results. It is difficult to make inferences based on demographic subgroups due to limited sample size.*

SCGAM03 -Extension study

SCGAM03 study enrolled 27 subjects (10 females, 17 males). The youngest subject was 6 years old, and oldest subject was 73 years old. Twenty-five subjects were white, and 2 subjects identified as “multiracial”; all subjects were non-Hispanic. All children belonged to white race. Table 3 provides detailed information on sex by age and Table 4 provides detailed information on age of subjects enrolled.

**Table 3: Demographic Data - SCGAM03-Sex Distribution**

Parameter Gender	Children ≥2 Years <6 Years N=2	Children ≥6 Years <12 Years N=4	Adolescents ≥12 Years <17 Years N=4	Adults ≥17 Years ≤75 Years N=17	All Subjects N=27
Male	2 (100.0%)	2 (50.0%)	2 (50.0%)	4 (23.5%)	10 (37.0%)
Female	0 (0%)	2 (50.0%)	2 (50.0%)	13 (76.5%)	17 (63.0%)

Reproduced from Table 11 Page 48 - Source CSR SCGAM03

**Table 4: Demographic Data - SCGAM03-Age Distribution**

Parameter Age (Years)	Children ≥2 Years <6 Years N=2	Children ≥6 Years <12 Years N=4	Adolescents ≥12 Years <17 Years N=4	Adults ≥17 Years ≤75 Years N=17	All Subjects N=27
Mean (SD)	6.50 (0.71)	9.00 (1.83)	14.25 (0.96)	56.12 (11.90)	39.26 (24.36)
Median	6.50	9.00	14.50	59.00	51.00
Min, Max	6.0, 7.0	7.0, 11.0	13.0, 15.0	25.0, 73.0	6.0, 73.0

Reproduced from Table 11 Page 48 - Source CSR SCGAM03

*Reviewer's Comment: The demographics of this extension study are comparable to the pivotal study. The limitations that impact the pivotal study apply to this study, but do not limit overall interpretability. The limited sample sizes for demographic subgroups do not allow for conclusions to be drawn regarding differences in safety or efficacy outcomes based on race, age or sex.*

## 1.2 Patient Experience Data

### Data Submitted in the Application

Check if Submitted	Type of Data	Section Where Discussed, if Applicable
<input checked="" type="checkbox"/>	Subject-reported outcome	6.1.8,6.1.11.2; 6.2.8,6.2.11.2
<input checked="" type="checkbox"/>	Observer-reported outcome	6.1.8,6.1.11.2; 6.2.8,6.2.11.2
<input checked="" type="checkbox"/>	Clinician-reported outcome	6.1.8,6.1.11.1
<input type="checkbox"/>	Performance outcome	
<input type="checkbox"/>	Subject-focused drug development meeting summary	
<input type="checkbox"/>	FDA Subject Listening Session	

<input type="checkbox"/>	Qualitative studies (e.g., individual Subject/caregiver interviews, focus group interviews, expert interviews, Delphi Panel)	
<input type="checkbox"/>	Observational survey studies	
<input type="checkbox"/>	Natural history studies	
<input type="checkbox"/>	Subject preference studies	
<input type="checkbox"/>	Other: (please specify)	
<input type="checkbox"/>	<b>If no Subject experience data were submitted by Applicant, indicate here.</b>	
<b>Check if Considered</b>	<b>Type of Data</b>	<b>Section Where Discussed, if Applicable</b>
<input type="checkbox"/>	Perspectives shared at Subject stakeholder meeting	
<input type="checkbox"/>	Subject-focused drug development meeting summary report	
<input type="checkbox"/>	FDA Subject Listening Session	
<input type="checkbox"/>	Other stakeholder meeting summary report	
<input type="checkbox"/>	Observational survey studies	
<input type="checkbox"/>	Other: (please specify)	

In Studies SCGAM-01 and SCGAM-03, the Applicant collected data from subjects and their caregivers on number of days of school/work/daily activities missed due to infections. This data was captured in a diary and reviewed by investigator site staff as secondary efficacy endpoints. The literature describes interference with daily life as meaningful for patients.

Clinician reported outcomes (CROs) included infections other than SBIs, duration of infections, duration of antibiotic use, and fever as secondary endpoints.

## 2. Clinical and Regulatory Background

### 2.1 Disease or Health-Related Condition(s) Studied

Primary humoral immunodeficiency (PI) is a heterogeneous group of disorders in which there is an intrinsic defect in the tissues, cells, and/or proteins of the immune system, in most cases due to a genetic defect, resulting in immune deficiency. It is estimated that 1-2% of the population worldwide is affected.

The major 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.

Many of these disorders are characterized by hypogammaglobulinemia and/or defective antibody production and, as a consequence, are clinically manifested as increased susceptibility to recurrent, severe respiratory tract and other infections (both viral and encapsulated bacterial in origin).

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

Replacement therapy with polyclonal human normal immunoglobulin is the cornerstone of management for significant primary antibody deficiency disorders. No viable alternatives exist to this essential, basic component of treatment, particularly in the context of severe, persistent, or recurrent bacterial infections. For most patients, replacement therapy is a lifelong requirement. Replacement therapy increases life expectancy and reduces the frequency and severity of infections. Subcutaneous and intravenous preparations are therapeutically equivalent.

Additional infection prevention measures include avoidance measures, vaccination, and prophylactic antibiotics. Treatment of infections often involves broad spectrum antimicrobials and prolonged treatment courses.

## 2.3 Safety and Efficacy of Pharmacologically Related Products

The FDA Guidance for Industry: “Safety, Efficacy, and Pharmacokinetic Studies to Support Marketing of Immune Globulin Intravenous (Human) as Replacement Therapy for Primary Humoral Immunodeficiency” (hereinafter referred to as the FDA Guidance for IGIV products) states that a statistical demonstration of a serious infection rate per person-year of less than 1.0 is adequate to provide substantial evidence of efficacy. Numerous marketed immune globulin products (both intravenously and subcutaneously administered) have demonstrated serious bacterial infection (SBI) rates of less than 1.0 per person-year. There are currently six licensed Immune Globulin Subcutaneous (Human) (IGSC) products in the U.S.: Cuvitru® (Baxalta US, Inc.), Hizentra® (CSL Behring), and Vivaglobin® (CSL Behring), Xembify® (Grifols USA), Hyqvia® (Baxter Healthcare Corporation, Baxter Bioscience), Cutaquig (Octapharma). All products are indicated for replacement therapy in patients with PID. Hyqvia is approved for use only in patients >12 years of age and, Cutaquig was approved for use only in patients >17 years of age. The other IGSC products listed above have been approved for use in children > 2 years of age.

The safety profile for immune globulins as a class is well-established. The incidence of adverse reactions (AR) reported in clinical studies supporting licensure varies according to the product, route of administration, and maximum infusion rate. In general, common ARs for immune globulins typically include local Infusion Associated Reactions (IARs) (i.e., swelling, redness, heat, discomfort at the injection site), headache, fatigue, nausea, diarrhea, vomiting, and/or pyrexia. IGIV products carry an obligate boxed warning for thrombosis, renal dysfunction, and acute renal failure. IGSC products carry an obligate boxed warning for thrombosis. Warnings and Precautions for this class of products include hypersensitivity/ anaphylaxis, aseptic meningitis, hemolysis, transfusion-related acute lung injury (TRALI) and transmission of infectious agents.

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

Cutaquig received first marketing authorization in Canada on February 15, 2018. FDA granted marketing approval for Cutaquig on December 12, 2018 for use in adults with PID. As of November 2020, Cutaquig has been licensed in 28 countries worldwide.

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

FDA approved Cutaquig for the treatment of adults with PID in December 2018. A PREA PMR was issued to study PK, safety and efficacy in children 2-17 years with PID. Specifically, the approval letter stated that the “deferred pediatric study (protocol SCGAM-01) for the treatment of primary humoral immunodeficiency in pediatric patients ages 2 to < 17 years of age...will provide pharmacokinetic data for at least two subjects ages 2 to < 6 years, at least six subjects ages 6 to < 12 years, and at least four subjects ages 12 to < 17 years of age, as well as safety and efficacy data for at least four subjects ages 2 to < 6 years, at least 10 subjects ages 6 to < 12 years, and at least six subjects ages 12 to < 17 years of age. The final report will compare efficacy and safety between pediatric age cohorts and between pediatric and adult subjects included in the study.” The final report was to be submitted by December 31, 2020, and it was submitted on December 14, 2020.

There were no meetings with the Agency to discuss this efficacy supplement.

## 2.6 Other Relevant Background Information

Not applicable

## 3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

### 3.1 Submission Quality and Completeness

The submission was adequately organized and integrated to accommodate the conduct a comprehensive clinical review without unreasonable difficulty. It was submitted electronically and formatted as an electronic Common Technical Document (eCTD) according to the FDA Guidance for Electronic Submissions. The submission contained the five modules in the recommended eCTD structure.

### 3.2 Compliance with Good Clinical Practices and Submission Integrity

The applicant affirms that the study was conducted in compliance with Good Clinical Practices and conforms with appropriate local laws and regulations and the Declaration of Helsinki.

Bioresearch Monitoring (BIMO) inspections were conducted at four (three U.S. sites and one foreign) clinical study sites for Study SCGAM-01 at the time of original BLA review. The inspections did not reveal any notable study conduct or data integrity issues. No additional sites were inspected during the review of the efficacy supplement.

### .3 Financial Disclosures

<b>Covered clinical study</b> (name and/or number): SCGAM01
Was a list of clinical investigators provided? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No (Request list from applicant)
Total number of investigators identified: <u>24</u>

Number of investigators who are sponsor employees (including both full-time and part-time employees): <u>0</u>
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u>
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? <input type="checkbox"/> Yes <input type="checkbox"/> No (Request details from applicant)  Is a description of the steps taken to minimize potential bias provided? <input type="checkbox"/> Yes <input type="checkbox"/> No (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): <u>0</u>  Is an attachment provided with the reason? <input type="checkbox"/> Yes <input type="checkbox"/> No (Request explanation from applicant)
<b>Covered clinical study</b> (name and/or number): SCGAM03
Was a list of clinical investigators provided? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No (Request list from applicant)
Total number of investigators identified: <u>8</u>
Number of investigators who are sponsor employees (including both full-time and part-time employees): <u>0</u>
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u>

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)

*Reviewer Comments: There were no apparent financial conflicts of interest that would impact data interpretability.*

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

##### 4.1 Chemistry, Manufacturing, and Controls

Cutaquig is a solution manufactured from human plasma. It contains 165 mg of protein/mL, of which  $\geq 96\%$  is IgG. The manufacturing process of Cutaquig is based on that of the U.S. marketed product, Octagam.

Cutaquig is manufactured by the cold-ethanol fractionation process followed by ultrafiltration and chromatography. Viral reduction steps include cold ethanol fractionation, solvent/detergent treatment, and pH 4 treatment. In addition, source plasma used to manufacture Cutaquig is tested for viral pathogens at both the donor and manufacturing [mini-] pool levels. None the less, despite these precautions, transmission of viruses remains a risk. The pH of the product is 5.0 to <sup>(b) (4)</sup> Maltose and polysorbate 80 serve as excipients.

Please refer to CMC reviewer's memo for additional product details.

##### 4.2 Assay Validation

N/A

##### 4.3 Nonclinical Pharmacology/Toxicology

Please refer to the nonclinical pharmacology/toxicology review from the initial BLA submission for details.

#### 4.4 Clinical Pharmacology

PK profiles for Cutaquig were evaluated for a subset of subjects (19 adults and 18 pediatric subjects) in Study SCGAM-01.

The applicant calculated the mean and median ratios of prior IGIV weekly-equivalent dose to Cutaquig dose for the subjects in the PK sub-study. Based on these analyses, for subjects switching from IGIV to IGSC, the dosage conversion factor (DCF) of 1.40 in the original label is being changed to 1.3.

The PK study validated that the PK profile in children of all ages was similar to that of the adults. The conclusion of the analysis was that children could be dosed using the same conversion factor as adults. Intra-subject serum IgG trough levels remained relatively constant throughout the study.

PK modeling supports alternative dosing schedules beyond the weekly dose tested in Study SCGAM-01.

Please refer to the clinical pharmacology memo for additional details.

##### 4.4.1 Mechanism of Action

Cutaquig contains a broad spectrum of IgG antibodies, some of which are directed towards infectious agents. Cutaquig distribution of IgG subclasses is proportional to that of human plasma. Administration of adequate doses of the product is intended to increase abnormally low IgG levels in PID to physiologic levels.

##### 4.4.2 Human Pharmacodynamics (PD)

Cutaquig contains primarily IgG antibodies, with an IgG subclass distribution that is similar to human plasma. Administration of the product increases IgG levels in a dose-dependent fashion.

##### 4.4.3 Human Pharmacokinetics (PK)

Please refer to the clinical pharmacology reviewer's memo for details. The primary PK endpoint was met, in that the ratio of the AUC at steady-state from weekly Cutaquig to the weekly-equivalent AUC from the prior IGIV administration fell within acceptable limits (2376 compared to 2441), taking variability into account.

#### 4.5 Statistical

The statistical reviewer confirmed the Applicant's primary efficacy analysis and supportive analyses that are being included in pediatric labeling.

Please refer to the statistical reviewer memo for additional details.

#### 4.6 Pharmacovigilance

The pharmacovigilance reviewer did not identify substantial issues at the time of original BLA review that necessitated additional risk management measures beyond standard pharmacovigilance measures. No pharmacovigilance review issues were identified during the review of this efficacy supplement.

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

### 5.1 Review Strategy

The reviewer focused on the pediatric data from SCGAM01, the pivotal study and SCGAM03, the extension study. The reviewer also reviewed the updated adult safety data and worked with the clinical pharmacologist to review the PK/PD data.

The reviewer also referred to the FDA Guideline for Industry: Safety, Efficacy, and Pharmacokinetic Studies to Support Marketing of Immune Globulin Intravenous (Human) as Replacement Therapy for Primary Humoral Immunodeficiency (<https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/ucm078526.pdf>). This reviewer also studied the labels and clinical review memos from commercially available subcutaneous immunoglobulin products.

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

The following materials from the application were considered during the review process:

1.2 Cover letter

1.3.4 Financial Certification and Disclosure

1.9.6 Other Correspondence Regarding Pediatric Exclusivity or Study Plans

1.14.1 Draft Labeling

2.7.3 Summary of Clinical Efficacy

2.7.3 Summary of Clinical Safety

2.7.6 Synopses of Individual Studies

5.2 Tabular listing of Clinical studies

5.3 Clinical Study Reports and Adverse Event datasets

### 5.3 Table of Studies/Clinical Trials

Summary of Clinical Studies Included in this Application are summarized in Table 7.

**Table 5: Synopses of Individual Studies – (b) (4) 16.5% (trade name Cutaquig)**

Adapted from Table 2.7.6.2-page 1 Source: Synopsis of Individual Studies

Study Reference investigator - source - year	Design	Number of subjects, age range, sex	Diagnosis / criteria for inclusion	Product(s), Dosage, Duration of Treatment	Efficacy results: Updated Efficacy Results limited to pediatric age group study participants. (The Efficacy results for study subjects ≥ 17 and ≤75 years of age was discussed in the original BLA approval memo).	Safety results Updated Safety Results limited to pediatric age group study participants. (The Safety results for study subjects ≥ 17 and ≤75 years of age was discussed in the original BLA approval memo).	Conclusions
SCGAM-01 Litzmann 2014-2020	Prospective, open-label, external controlled, single-arm, multi-center Phase 3 Study	<p>75 PID Subjects were enrolled in each of the following age groups:</p> <p>Younger children (≥2 and &lt;6 years) N=12 (1 Female; 11 Male)</p> <p>Older children (≥6 and &lt;12 years) N=14 (5 Female; 9 Male)</p> <p>Adolescents (≥12 and &lt;17 years) N=12 (3 Female; 9 Male)</p> <p>Adults (≥17 and ≤75 years) N=37 (27 Female; 10 Male)</p> <p>Age range: 2–73 52 % Male; 48% Female</p>	PID	(b) (4) 16.5% Weekly subcutaneous infusions during a 12-week wash in/ wash-out phase and 12 months efficacy phase. SC doses were given at 1.4 times the previous IGIV dose adjusted for weekly dosing.	<p>No SBIs were observed during the study in children.</p> <p>51 infections were reported in 11 young children. 48 of 51 were mild intensity. 35 infections were reported in 9 older children, all but 6 of which were mild intensity. 23 infections were reported in 8 patients in the adolescent age group; 14 were mild, 8 were moderate and 1 was severe. The rate of other infections per person-year were 4.19, 2.47, and 2.65 for younger children, older children and adolescents respectively. 10 younger children, 7 older children and 8 adolescents; required use of antibiotics with number of treatment days per person-year were 35.6, 63.6, and 139.3 respectively. There were 4 hospitalizations due to infection during the study, 1 in a young child (for 3 days), and 3 in adolescent patients (3, 10 and 13 days). Hospitalizations per person – year were 0.07, 0.0, and 0.28 for younger children, older children and adolescents respectively. The number (%) of children with absences from work/school were 7 (58.3%), 5 (35.7%), 4 (33.3%) for younger, older and adolescent age group children with per person year rates of 8.47, 2.97, and 4.04 respectively. There were no major changes in the mean and median CHQ - PF50 scores over time.</p>	<p>Overall, the 38 children in the Safety Analysis Set received 2213 infusions in the study., Number (%) of TEAEs excluding infections and infusion site reactions were reported in 9 (75.0%), 11 (78.6%) and 9 (75.0%) younger, older and adolescent children respectively. No TEAEs led to death or withdrawal from the study. 5 SAEs were reported in pediatric age group and were not related to the study medication. Infusion Site Reactions (%) were reported in 8 (66.7%), 11 (78.6%), 6 (50.0%) younger, older, adolescent children respectively. Of the 387 total reactions in pediatric age group, 374 (96%) were mild, 11 (3%) were moderate, 2 (&lt;1%) were severe in intensity.</p>	<p>The efficacy of (b) (4) in preventing the occurrence of SBIs in Subjects with PI was confirmed by a zero rate of SBIs in pediatric age group. Overall, the evaluation of AEs, infusion site reactions, routine laboratory examination, vital signs and physical examination showed that subcutaneous administration of study medication (b) (4) was generally well tolerated and safe in the pediatric population and comparable to data in the adult population.</p>

Study Reference investigator - source - year	Design	Number of subjects, age range, sex	Diagnosis / criteria for inclusion	Product(s), Dosage, Duration of Treatment	Efficacy results	Safety results	Conclusions
SCGAM-03 Melamed Gupta Rehman Kobayashi Geng Mandujano Ritchie 2016-2019	Prospective, open-label, noncontrolled single-arm, multicenter, safety follow-up Phase 3 Study	27 Subjects were enrolled in each of the following age groups:  Younger children (≥2 and <6 years) N=2 (0 Female;2 Male)  Older children (≥6 and <12 years) N=4 (2 Female;2 Male)  Adolescents (≥12 and <17 years) N=12 (2 Female;2 Male)  Adults (≥17 and ≤75 years) N=17 (13 Female;4 Male)  Age range: 2–73 37 % Male; 63% Female	PID	(b) (4) 16.5% Weekly subcutaneous infusions or every second week (±2 days) at the doubled weekly dose until 1) (b) (4) became commercially available in the USA 2) Applicant decided to terminate the trial, or 3) December 2020	The primary objective of this study was to assess the medium-to-long term safety and tolerability of (b) (4) : therefore, no primary efficacy analyses were performed. However, one SBI (in 1 adult) of the infection type bacteremia/sepsis that was not related to study drug was reported during the study. Total of 119 other infections were noted with 8, 12, 22, and 77 infections in younger children, older children, adolescents and adults respectively. Rate of infection (per person-year) were 1.59, 1.47, 2.9, and 2.3 in the 4 age groups respectively. There were 3 hospitalizations (all adults) due to infections. Antibiotics were used by 1, 2, 4, 13 study participants and days per person-year were 10.3, 73.4, 108.8, and 34.4 in 4 respective age groups. (Four subjects had antibiotic treatments of >100 days). Total number of days (rate) absent from work/school per person year were 4.7, 3.4, 3.2, and 1.6 in 4 respective age groups There were no major changes in the mean CHQ-PF50 scores over time, although the number of study participants completing the questionnaire was low at each timepoint.	All Subjects experienced at least 1 AE, including infections, during the study. Of the total 323 AEs reported during the study, 1/3rd (119 events) were infections. Excluding infections, 24 Subjects (88.9%) experienced 204 AEs; There were 16 SAEs reported among 7 Subjects during the study; none of these SAEs were considered related to study medication. Of the 94 Infusion Site Reactions, 54 were reported in adults including all 19 of severe intensity. No infusion associated reaction was reported in young children. In older children, all 27 reactions were mild intensity, whereas in adolescents of the 13 reactions, 11 were mild and 2 were moderate.	(b) (4) was effective in preventing the occurrence of serious bacteriology infections in Subjects with primary immunodeficiency disease during the extension study.. In conclusion, data from SCGAM-03, along with the data from the original Phase 3 study SCGAM- 01 indicate that (b) (4) administered by subcutaneous infusion is safe and effective for use in subjects with primary immunodeficiency diseases.

#### 5.4 Consultations

No consultations were needed or obtained for the review.

##### 5.4.1 Advisory Committee Meeting (if applicable)

An advisory committee meeting was not needed for the review, because the Review Team did not identify any scientific issues for which their input was warranted.

##### 5.4.2 External Consults/Collaborations

External consultants were not needed for the review and were therefore not obtained

#### 5.5 Literature Reviewed (if applicable)

Abolhassani H, Azizi G, Sharifi L, Yazdani R, et al Global systematic review of primary immunodeficiency registries. *Expert Rev Clin Immunol*. 2020 Jul;16(7):717-732.

Modell V, Quinn J, Orange J, et al Primary immunodeficiencies worldwide: an updated overview from the Jeffrey Modell Centers Global Network. *Immunol Res*. 2016 Jun;64(3):736-53.

### 6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

#### 6.1 Trial #1

SCGAM-01 is a phase 3 study to evaluate the pharmacokinetics, efficacy, tolerability and safety of subcutaneous human immunoglobulin (Cutaquig 16.5%) in subjects with primary immunodeficiency diseases.

##### 6.1.1 Objectives (Primary, Secondary, etc.)

###### 6.1.1.1 Primary Objectives:

- The first primary objective of the study was to assess the efficacy of Cutaquig in preventing SBI compared with historical control data.
- The second primary objective was to evaluate the PKs of Cutaquig and to compare the area under the curve (AUC) with that of IGIV.

###### 6.1.1.12 Secondary Objectives:

- To evaluate the tolerability and safety of Cutaquig.
- To determine the PK profile of Cutaquig.
- To assess the dosing conversion factor (DCF) when switching Subjects from IGIV treatment.
- To develop guidance and recommendations to support further adjustments of Cutaquig dosing based on the total IgG trough level.
- To assess the effect of Cutaquig on Quality of Life (QoL) measures

### 6.1.2 Design Overview

The study is a prospective, open-label, externally controlled, single-arm, multicenter Phase 3 study with a 12-week wash-in/wash-out period followed by a 12-month efficacy period.

There was also a PK sub study in the original submission, in which 37 adult Subjects underwent 3 PK assessments. In this submission, there were 19 pediatric subjects enrolled in a pediatric PK sub study. PK assessments were performed at three time points: (1) after the last administration of the previously used IGIV product prior to switching to Cutaquig (PKIV), (2) at the end of the wash-in/wash-out phase and (3) after 28 administrations of Cutaquig.

*Reviewer Comment: The single arm design with a natural history comparator is in alignment with FDA guidance document "Safety, Efficacy, and Pharmacokinetic Studies to Support Marketing of Immune Globulin Intravenous (Human) as Replacement Therapy for Primary Humoral Immunodeficiency" published in June 2008.*

*The 12-week wash in / wash out period was sufficient to transition study participants from IGIV to SCIV. 12- month efficacy was adequate to account for seasonal variation in infection rates.*

### 6.1.3 Population

#### 6.1.3.1 Inclusion Criteria:

Subjects who met all of the following criteria could be enrolled:

- Age of  $\geq 2$  years and  $\leq 75$  years.
- Confirmed diagnosis of PI as defined by European Society for Immunodeficiencies (ESID) and Pan-American Group for Immunodeficiency and requiring immunoglobulin replacement therapy due to hypogammaglobulinemia or agammaglobulinemia. The exact type of PI had to be recorded.
- Subjects with at least 6 infusions on regular treatment with any IGIV, thereof a minimum of the last 2 months on the same product prior to entering the study. Constant IGIV dose between 200 and 800 mg/kg body weight ( $\pm 20\%$  of the mean dose for the last 6 infusions).
- Availability of the IgG trough levels of 2 previous IGIV infusions before enrolment and maintenance of  $\geq 5.0$  g/L in the trough levels of these 2 previous infusions.
- Negative result on a pregnancy test (human chorionic gonadotrophin-based assay in urine) for women of childbearing potential and use of a reliable method of contraception for the duration of the study.
- For adult subjects: freely given written informed consent. For minor subjects: freely given written informed consent from parents/legal guardians and written informed assent from the child/adolescent in accordance with the applicable regulatory requirements.
- Willingness to comply with all aspects of the protocol, including blood sampling, for the duration of the study.

#### 6.1.3.2 Exclusion Criteria:

Subjects who met one (or more) of the following criteria were excluded from the study:

- Acute infection requiring IV antibiotic treatment within 2 weeks prior to and during the Screening period.
- Known history of adverse reactions to immunoglobulin A in other products.
- Subjects with body mass index (BMI) >40 kg/m<sup>2</sup>.
- Exposure to blood or any blood product or plasma derivatives, other than IGIV treatment of PI, within the past 3 months prior to first infusion of Cutaquig.
- Ongoing history of hypersensitivity or persistent reactions to blood or plasma derived products or any component of the investigational product (such as Polysorbate 80).
- Requirement of any routine premedication for IgG administration.
- History of malignancies of lymphoid cells and immunodeficiency with lymphoma.
- Severe liver function impairment (alanine aminotransferase [ALAT] 3 times above upper limit of normal).
- Known protein-losing enteropathies or proteinuria.
- Presence of renal function impairment (creatinine >120 µM/L or creatinine >1.35 mg/dL) or predisposition for acute renal failure (e.g., any degree of preexisting renal insufficiency or routine treatment with known nephritic drugs).
- Treatment with oral or parenteral steroids for ≥30 days or when given intermittently or as bolus at daily doses ≥0.15 mg/kg.
- Treatment with immunosuppressive or immunomodulatory drugs.
- Live viral vaccination (such as measles, rubella, mumps and varicella) within the last 2 months prior to first infusion of Cutaquig.
- Treatment with any IMP within 3 months prior to first infusion of Cutaquig.
- Presence of any condition, that is likely to interfere with the evaluation of study medication or satisfactory conduct of the trial.
- Known or suspected to abuse alcohol, drugs, psychotropic agents or other chemicals within the past 12 months prior to first infusion of Cutaquig.
- Known or suspected human immunodeficiency virus (HIV), hepatitis C virus (HCV) or hepatitis B virus (HBV) infection.
- Pregnant or nursing women.
- Planned pregnancy during course of the study.

*Reviewer Comment: Excluding subjects with other comorbid conditions who required premedication while receiving IGIV may have enriched the trial population for subjects who better tolerate immunoglobulin products, including Cutaquig.*

#### 6.1.4 Study Treatments or Agents Mandated by the Protocol

##### 6.1.4.1 Duration and Frequency of Infusion

Each Subject was treated with Cutaquig over a period of about 15 months (12-week wash-in/wash-out phase and 12-month efficacy phase). Each Subject who remained in the study for entire duration of 15 months received 64 Cutaquig SC weekly infusions. Cutaquig was administered subcutaneously every week (±2 days). A minimum time of 4 days had to be kept in between two single SC infusions.

##### 6.1.4.2 Dose Conversion

The equivalent monthly dose of IgG replacement therapy for PI, converting from IGIV to IGSC was determined in one of two ways:

- 1:1 dosing, wherein the monthly IGIV dose is split into four equal weekly IGSC infusions.
- AUC dosing, in which the IGSC dose is calculated from PK data to provide a monthly exposure to IgG equivalent to that with IGIV.

The former is common in Europe and Canada, while the latter is a requirement of the US FDA for IGSC labelling studies. For AUC dosing, the IGSC dose has been 1.3 or 1.5 times higher than the previous IGIV dose.

The Cutaquig dose was calculated as follows:

$$\text{Initial weekly dose (g)} = \frac{\text{previous IGIV dose (g)}}{\text{number of weeks between IGIV doses}} \times 1.4$$

Subjects participating in the PK sub study had an infusion of their previously used IGIV product during the study so that a PK profile could be obtained after the last administration of the previously used IGIV product prior to switching to Cutaquig. The same dose calculation method was used for all subjects throughout the study since interim PK data were not available during the study. Doses were supposed to be adjusted during the study for body weight fluctuations of >5%, but this did not always occur. Notwithstanding the instructions in the protocol to use a dosage conversion factor of 1.4 as shown in the equation above, the average ratio of Cutaquig dose to the weekly-equivalent prior IGIV dose used in the study was approximately 1.3.

#### 6.1.5 Directions for Use

##### Product Storage

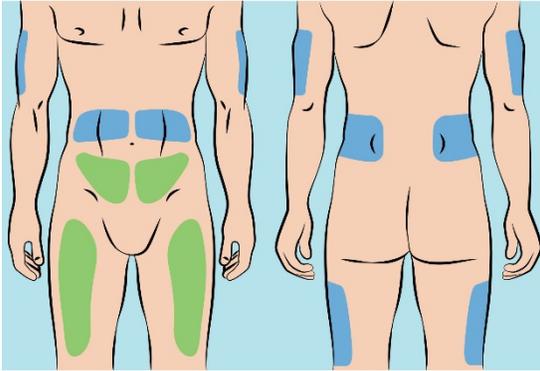
Cutaquig was delivered in glass vials; 1 mL contains: 165 mg protein of which ≥96% is human normal IgG. Each batch (lot) of Cutaquig is prepared from at least (b) (4) donations of human fresh frozen plasma. Information on the manufacturing process and viral safety can be found in the current clinical Investigator's Brochure. The batch numbers of the IMP were documented in the certificates of analysis, which are filed in the study master file. Cutaquig was to be stored and transported at +2°C to +8°C and protected from light. It was not to be frozen. Vials of Cutaquig had to be allowed to warm to room or body temperature prior to infusion.

##### Product Administration

The solution had to be clear or slightly opalescent. Each vial had to be examined visually for particulate matter and discoloration prior to administration. Solutions that were cloudy or had a deposit were not to be used. Thereafter, Cutaquig was infused subcutaneously using a syringe driver for precise infusion rates and standard infusion materials provided to the Subjects by the site. The correct amount of IgG taken from 12- or 48-mL vials of Cutaquig was infused with the aid of a syringe driver. The content of the vials had to be transferred into the syringes suitable for the syringe driver selected. Remaining solution in a vial had to be discarded. Cutaquig was not to be mixed with other medicinal products. Aseptic technique should be used when administering Cutaquig.

Infusion sites: The area of the body that could receive infusions were abdomen, front thigh, lower back and on each side. A maximum of six infusion sites were permitted for each administration. Infusion sites had to be at least two inches apart and had to be changed with each weekly administration.

**Figure 1: Sites of Infusion**



Source: Reproduced from Figure 5 – Prescriber Information

Subjects or their caregivers were trained at the study site for at least four Cutaquig infusions. Subsequently, Cutaquig could be administered at home. Administrations were given at the study site every four weeks.

#### Infusion Volume / site

Adult subjects

First administration: maximum of 15 mL/infusion site

Seventh administration onwards: volume could be gradually increased to a maximum of 25 mL/infusion site

25th administration onwards: volume could be increased to 35 mL/site

40th administration onwards: volume could be increased to 40 mL/site

Pediatric subjects aged  $\geq 5$  years old

Seventh administration onwards: volume could be gradually increased to a maximum of 25 mL/infusion site

25th administration onwards: volume could be increased to 30-35 mL/site

Pediatric subjects aged  $< 5$  years old

First administration: maximum of 10 mL/infusion site

Seventh administration onwards: volume could be gradually increased to a maximum of 10-15 mL/infusion site

25th administration onwards: volume could be increased to 20 mL/site

*Reviewer Comment: Maximum Volume (mL/site) varied in the study for each age group (15.5 mL/site for  $> 2$  to  $< 6$  years old), 29 mL/site for ages  $> 6$  to  $< 17$  years, and 40 mL/site for ages  $> 17$  years. (Source SCGAM 01 CSR pages 253, Table 14.1.6.2). This difference may impact the rate of infusion associated reactions (IAR).*

#### Infusion Rates

The maximum infusion rate for the first six infusions was 15 mL/hour/site; the maximum infusion rate was not to exceed a total of 30 mL/hour for all sites combined. For subsequent infusions, the flow rate could be gradually increased to 25 mL/hour/site. For the seventh to the 24th infusions, the maximum infusion rate was not to exceed a total of 50 mL/hour for all sites combined. For subsequent infusions, the maximum infusion rate could be increased to 80 mL/hour for all sites combined. Infusion rate adjustments were based on subject tolerability.

The maximum infusion volume per site and maximum flow rate per site were increased by amendment dated 03 March 2015. Protocol version 7 further increased the maximum volume to 40 mL per site and the total flow rate to a maximum of 100 mL per hour after the 40th SC product administration.

*Reviewer Comment: The maximum rate (mL/hr./site) also varied in the study for children and adults age groups (25 mL /hr./site for <=17 years old and 52 mL/hr./site for age >17 years old (Source: SCGAM 01 CSR pages 255-256, Table 14.1.6.2)*

#### IgG Monitoring

Serum IgG trough levels were monitored throughout the study. Subjects who did not participate in the PK sub study had trough levels measured at the following timepoints:

- Screening Visit
- Wash-in/Wash-out Period: Weeks 1, 2, 3, 4, 8, and 12
- Efficacy Period: Weeks 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 56, 60
- Termination Visit

Subjects participating in the PK sub study underwent 3 PK assessments: one after the last administration of the previously used IGIV product prior to switching to Cutaquig (PKIV), at the end of the wash-in/wash-out phase (PKSC1), and after 28 administrations of Cutaquig (PKSC2) As PK results were not available in time, the initial dose calculation was applied for all subjects. Throughout the study, appropriate dose levels were maintained by regular monitoring of IgG trough levels

During the efficacy period of the study, subjects' Cutaquig doses were individualized by titrating upward based on the difference in serum total IgG trough levels between the individual's measured value and the target value. The target trough IgG value was derived from the last IgG trough level obtained prior to switching to Cutaquig, using an equation. The subject's body weight was also used to calculate the Cutaquig dose. Investigators were provided with a dose adjustment tabulation to guide dose adjustments.

*Reviewer Comment: Determination of the pre-next-dose trough level of IgG is a standard method for calculating the correct dose for the individual subject. However, the individual practitioner may opt for higher trough level of >6g/L (which is the lower limit of normal range).*

#### 6.1.5 Permitted and Prohibited Treatments Mandated by the Protocol

- Cutaquig was not to be mixed with other medicinal products.
- Routine premedication to alleviate potential tolerability problems was not allowed during the study. However, subjects who experienced 2 consecutive treatment-emergent adverse events (TEAEs) that were likely to be prevented by premedication were permitted to receive antipyretics, antihistamines or antiemetic drugs. Non-steroidal anti-inflammatory drugs can affect renal function and were to be avoided. Local anesthetics to reduce pain associated with needle insertion were allowed.
- Treatment with any investigational product within 3 months prior to first infusion of Cutaquig was forbidden. Exposure to blood or any blood product or derivative, other than IGIV used for regular PI treatment, within the past 3 months prior to the first infusion of Cutaquig was forbidden. Administration of any blood or

plasma derived product was forbidden during the study and was only to be given for emergency reasons.

- Live viral vaccines were forbidden in the 2 months prior to first infusion of Cutaquig.
- Immunosuppressive and immunomodulatory drugs were also forbidden.

#### 6.1.6 Sites and Centers

In total, 24 sites were initiated, and subjects were enrolled at 20 study sites as follows: 2 sites in Poland, 4 sites in Czech Republic, 1 site in Hungary, 7 sites in the USA, 1 site in Canada, 3 sites in Slovakia and 2 sites in Russia.

##### 6.1.6 1 Investigator(s):

<u>Sites</u>	<u>Investigators</u>
Site 01 (Poland):	Grazyna Pulka
Site 02 (Poland):	Anna Pituch-Noworolska
Site 11 (Czech Republic):	Jiri Litzman
Site 12 (Czech Republic):	Ivana Malkusova
Site 13 (Czech Republic):	Radana Zachova
Site 14 (Czech Republic):	Jaromir Bystron
Site 32 (Hungary):	Gergely Krivan
Site 61 (Slovakia):	Peter Ciznar
Site 62 (Slovakia):	Katarina Gerecova
Site 63 (Slovakia):	Milos Jesenak
Site 41 (U.S.):	Isaac Melamed
Site 42 (U.S.):	Sudhir Gupta
Site 43 (U.S.):	Syed Rehman
Site 44 (U.S.):	Roger Kobayashi
Site 45 (U.S.):	Prescott Atkinson
Site 46 (U.S.):	Bob Geng
Site 47 (U.S.):	Jose Fernando Mandujano
Site 51 (Canada):	Bruce Ritchie
Site 61 (Slovakia)	Peter Ciznar
Site 62 (Slovakia)	Katarina Gerecova
Site 63 (Slovakia)	Milos Jesenak
Site 73 (Russia)	Anna Shcherbina
Site 75 (Russia)	Vadim Rassokhin

#### 6.1.7 Surveillance/Monitoring

For international study sites, study monitoring was performed by (b) (4) (b) (4), a contract research organization. Monitoring of the U.S. sites was organized internally by the Applicant. Local laboratories were used for routine laboratory analyses. Total serum IgG trough levels; PK measurements for total serum IgG; IgG subclasses; antigen-specific antibodies against Hemophilus influenza, cytomegalovirus (CMV), tetanus, and measles were performed by (b) (4) (b) (4) Streptococcus pneumoniae testing was performed by the (b) (4).

Safety assessments included vital signs, laboratory parameters (i.e., hematology, clinical chemistry, hemolysis markers, and viral markers), and AE monitoring.

The following assessments were performed at study site visits as outlined in the protocol schedule of assessments: laboratory parameters, weight, subject diary review, physical exam including vital signs, QoL assessments, local injection site reactions, urinalysis, and urine pregnancy test. Infusion details; infusion site reactions; adverse events; changes in concomitant medication; and results of physical exams, laboratory assessments, and vital signs were recorded in electronic case report forms (eCRFs) during the study.

A subject diary (non-electronic) was provided to each subject to document the following information during the study: date of infusion, volume and rate of infusion, infections, AEs, injection site reactions, temperature one-hour post-infusion, missed days from work or school, inpatient hospital stays, and changes in concomitant medications between study visits. Relevant data from the Subject diaries were transcribed onto eCRFs.

The Applicant established an IDMC for this study. During the study, the IDMC periodically reviewed relevant data, particularly with regard to TEEs and clinically significant hemolysis, and gave advice on the continuation, modification or termination of the study. A study-specific Charter defined in detail the composition, responsibilities and procedures of the IDMC was included in Appendix 16.1.1.2 of the study report.

#### 6.1.8 Endpoints and Criteria for Study Success

##### 6.1.8.1. Efficacy Endpoints

Primary efficacy endpoint:

- Rate of SBI (defined as bacteremia/sepsis, bacterial meningitis, osteomyelitis/septic arthritis, bacterial pneumonia and visceral abscess) per person-year on treatment.

Secondary efficacy endpoints:

- The annual rate of all infections of any kind or seriousness.
- Non-serious infections (total and by category).
- Time to resolution of infections.
- Use of antibiotics (number of days and annual rate).
- Hospitalizations due to infection (number of days and annual rate).
- Episodes of fever.
- Days missed from work/school/kindergarten/day care due to infections and their treatment.
- QoL assessments using the Child Health Questionnaire-Parent Form (CHQ-PF50) or SF-36 Health Survey.

##### 6.1.8.2. Pharmacokinetics (PK) Endpoints

The primary endpoint with respect to the PK investigations is the AUC from time 0 (start of the infusion) to the end of the nominal dosing period, standardized to 1 week (AUC<sub>T</sub>), at steady-state conditions.

Secondary PK endpoints:

- PK profiles of total IgG, of IgG subclasses (IgG1, IgG2, IgG3, IgG4) and of antigen specific antibodies against Hemophilus influenzae, Streptococcus

pneumoniae (types 4, 6B, 9V, 14, 18C, 19F, 23F), cytomegalovirus (CMV), tetanus and measles.

- Trough levels of serum total IgG (total and subclasses) throughout the study. Trough levels of specific antibodies against haemophiles influenzae, Streptococcus pneumoniae (types 4, 6B, 9V, 14, 18C, 19F, 23F), CMV, tetanus and measles throughout the study.
- Dose Conversion factor (DCF) IGIV to Cutaquig (based on the area under the concentration-time curve [AUC<sub>T</sub>]).

### 6.1.8 3. Safety Endpoints

Secondary safety endpoints:

- Occurrence of all treatment-emergent adverse events (TEAEs) throughout the entire 65-week treatment period starting with the first infusion of Cutaquig.
- Occurrence of temporally associated TEAEs.
- Proportion of infusions with at least one temporally associated AE.
- Occurrence of suspected adverse reactions (SARs).
- TEAEs by speed of infusion.
- Local injection site reactions.
- Vital signs (blood pressure, pulse, body temperature, respiratory rate).
- Laboratory parameters (hematology, clinical chemistry, markers for intravascular hemolysis and tests for viral safety).

### 6.1.9 Statistical Considerations & Statistical Analysis Plan

#### Efficacy:

Occurrence of SBI is presented as point estimates of the mean rates per person-year and associated confidence intervals (CIs). Based on historical data, a statistical demonstration of a serious infection rate per person-year less than 1.0 is adequate to provide substantial evidence of efficacy. Therefore, the null hypothesis to be tested was that the serious infection rate was greater than or equal to 1.0 per person-year, tested at the 1% level of significance. The null hypothesis was to be rejected if the upper 1-sided 99% confidence limit was less than 1.0. The rate of other infections was also calculated per person-year and presented with the upper limit of a one-sided 95% CI using a compound Poisson process model. The duration of infection was summarized by standard descriptive statistics by type of infection and by severity. In addition, 2 sensitivity analyses were added for the final analysis: the originally planned 2-sided 98% CI was calculated for the worse case that one bacterial infection would have been observed; secondly, the CI was calculated using a standard Poisson distribution instead of the compound Poisson process model.

Days of work/school missed, number and days of hospitalizations due to infections, the use of antibiotics and number of fever episodes are presented descriptively.

For the primary and secondary efficacy endpoints, an analysis using alternative age groups (2 to <12, 12 to <17, 17 to 65, and >65 years) and for male and female Subjects was done. For the analysis of antibiotic use, hospitalization and days absent from school/work upper limits of 1-sided 95% CIs were calculated.

The QoL data are presented descriptively by visit, along with the change from baseline (defined as the first infusion).

PK analysis plan:

PK parameters were analyzed descriptively for all IgG (total and subtypes) and antigen specific antibody assays. Individual PK profiles are presented graphically in Trellis plots (i.e., several plots with the same pairs of variables on one page) using a linear scale as well as a logarithmic scale for the plasma concentrations. Trough levels of all monitored IgG and antigen-specific parameters are summarized by infusion number and presented graphically as time profiles. In addition, the frequency of total IgG trough levels below 5.0 g/L are presented for each infusion.

The corrected DCF was derived from the observed AUC<sub>IV</sub> and AUC<sub>SC</sub> and the actual doses administered intravenously (at PK<sub>IV</sub>) and subcutaneously (at PK<sub>SC1</sub>), respectively, based on a linear least-square regression between AUC<sub>SC</sub> and Dose<sub>SC</sub>. In addition, an easy-to-use dose adjustment tabulation was derived to provide the investigators with guidance on dose adjustments based on the actual and target trough levels and the body weight of each individual Subject.

Safety:

The safety analysis comprised descriptive statistics, tabulations and listings of all TEAEs, safety laboratory results, viral markers, vital signs and physical examination findings. For each TEAE, the time relative to the start of the infusion was calculated and the TEAE was classified as temporally associated if the onset is during the infusion or within 72 hours after the end of the infusion. SARs are defined as all AEs that are either temporally associated or were at least possibly related to administration of Cutaquig or that have a missing or indeterminate causality assessment.

The number of infusions with at least one temporally associated AE over the total number of infusions was calculated for each subject and the ratio was presented, including the associated upper one-sided 95% confidence limit. All TEEs and all clinically significant cases of hemolysis that were assessed as probably or possibly related to Cutaquig were listed in full detail, together with all relevant laboratory parameters.

Descriptive summaries are presented for each of the primary and secondary variables. In general, summaries were completed for all subjects overall and by age group. Continuous, quantitative variable summaries include the number of subjects with non-missing values (N), mean, standard deviation, median, minimum and maximum, 1st and 3rd quartile.

Categorical, qualitative variable summaries include the frequency and percentage of Subjects who are in the particular category. In general, the denominator for the percentage calculation was based upon the total number of subjects in the analysis population unless otherwise specified.

In general, missing data was not imputed: calculations pertaining to person-year computations were based on observed values only

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

The following populations were considered for the statistical analysis:

The **Safety Analysis Set** consists of all subjects who received at least part of one infusion of *Cutaquig*.

The **full analysis set (FAS)** is defined according to the intention-to-treat principle and consists of all subjects of the Safety Analysis Set who satisfy all major eligibility criteria and for whom any post-baseline data are available; it is the set of eligible subjects with treatment effects measured.

The **per-protocol (PP) set** consists of all subjects of the FAS excluding those with major protocol violations which may have an impact on the analysis of the primary efficacy endpoint. This is the set of subjects who participated in the study as intended and for whom the primary efficacy endpoint can be evaluated as planned.

The **PK Evaluable Set 1** consists of all subjects who have concentration data for the pre-infusion trough levels and the AUC<sub>TIV</sub> and AUC<sub>TSC</sub> determinations prior to the switch to *Cutaquig* (PKIV) and after the 11th infusion of *Cutaquig* (PKSC1). Subjects with protocol violations or particular medical conditions likely to influence the trough levels and/or the AUC values were excluded from the PK Evaluable Set 1 to ensure the accuracy of the calculation of the corrected DCF.

The **PK Evaluable Set 2** for the assessment of bioavailability consists of all subjects who have sufficient concentration data to determine AUC<sub>TIV</sub> and AUC<sub>TSC</sub> prior to the switch to *Cutaquig* (PKIV) and after the 28th infusion of *Cutaquig* (PKSC2) respectively.

**Table 6: Study Subjects - Analysis Sets**

N (%)	Aged ≥2 to <6 y N=12	Aged ≥6 to <12 y N=14	Aged ≥12 to <17 y N=12	Aged ≥17 to ≤75 y N=37	Total N=75
Safety Analysis Set	12 (100.0)	14 (100.0)	12 (100.0)	37 (100.0)	75 (100.0)
In PK Sub study	5 (41.7)	8 (57.1)	7 (58.3)	19 (51.4)	39 (52.0)
Not in PK Sub study	7 (58.3)	6 (42.9)	5 (41.7)	18 (48.6)	36 (48.0)
Full Analysis Set	12 (100.0)	14 (100.0)	12 (100.0)	37 (100.0)	75 (100.0)
Per-protocol Analysis Set	12 (100.0)	14 (100.0)	9 (75.0)	36 (97.3)	71 (94.7)
PK Evaluable Set 1	5 (41.7)	8 (57.1)	6 (50.0)	18 (48.6)	37 (49.3)
PK Evaluable Set 2	5 (41.7)	8 (57.1)	6 (50.0)	18 (48.6)	37 (49.3)
Completed	12 (100.0)	14 (100.0)	8 (66.7)	34 (91.9)	68 (90.7)
Terminated early	0 (0)	0 (0)	4 (33.3)	3 (8.1)	7 (9.3)

**Efficacy Analysis Plan:**

All efficacy endpoints were analyzed on the basis of both the FAS and the PP analysis sets, to allow for an assessment of the robustness of the results with respect to protocol violations.

- The rate of SBI per person-year (bacterial pneumonia, bacteremia/sepsis, osteomyelitis/septic arthritis, visceral abscess, bacterial meningitis) during the treatment period with *Cutaquig* is presented as point estimates of the rate along with a two-sided 98% CI.
- The FDA Guidance for Industry suggests that, based on historical data, a statistical demonstration of a serious infection rate per person-year less than 1.0 is adequate to provide substantial evidence of efficacy. Therefore, the null

hypothesis was tested that the serious infection rate is greater than or equal to 1.0 per person-year, tested at the 1% level of significance.

- The duration of infection was summarized by standard descriptive statistics by type of infection and by severity. The individual characteristics of each infection, including the time to resolution was listed.
- The use of antibiotics was reported as a detailed list of all such medications and the number of subjects treated with antibiotics, the number of treatment episodes and the number of treatment days were tabulated
- All hospitalizations due to infections during the course of the study were listed with duration and reason; the numbers of subjects hospitalized, the number of hospitalizations and the number of days in hospital were tabulated and summarized descriptively.

#### **Safety Analysis Plan:**

All safety endpoints were analyzed on the basis of the Safety Set. adequate to provide substantial evidence of efficacy.

All medical history and reported AEs were coded according to Medical Dictionary for Regulatory Activities (MedDRA). For each TEAE, the time relative to the start of the infusion was calculated and the TEAE classified as temporally associated if the onset was during the infusion or within 72 hours after the end of the infusion.

All reported events were listed and tabulated in full detail, in particular the following key figures were presented for each age group and for the study as a whole:

- Total number of TEAEs reported.
- Number of temporally associated TEAEs.
- Number of SARs.
- Number and percentage of infusions temporally associated with one or more TEAE.
- Number of temporally associated TEAEs divided by the total number of infusions.
- Number of SARs divided by the total number of infusions.
- Infusion rate at the onset of temporally associated TEAEs (frequencies and percentages).

#### **Pharmacokinetics Analysis Plan.**

The PK analyses were based on the PK Evaluable Set 1, as it was identical to the PK Evaluable Set 2. The following PK parameters were analyzed descriptively for all IgG (total and subtypes) and antigen-specific antibody assays:

- Dose per kg.
- Maximum concentration [C<sub>max</sub>].
- Time to maximum concentration [T<sub>max</sub>].
- Minimum concentration [C<sub>min</sub>].
- Time to minimum concentration [T<sub>min</sub>].
- Elimination rate constant [ $\lambda_z$ ]. Half-life [T<sub>1/2</sub>].
- Specification of the data points used for determination of  $\lambda_z$  and, by extension, T<sub>1/2</sub>.
- Area under the concentration-time curve from time 0 [start of the infusion] to the time point of the last non-zero concentration [AUC<sub>0-last</sub>]

The upper limit of a one-sided 95% CI was calculated for the number of days in hospital per person-year using the compound Poisson process model. All episodes of fever were

listed. The numbers of subjects with at least one episode of fever during the course of the study and the number of episodes per person-year were presented. All absences from work or school were listed with duration and reason; the individual absence rates were summarized descriptively. The upper limit of a one-sided 95% CI was calculated for number of days absent from work/school per person-year using the compound Poisson process model. The QoL data were presented descriptively by visit, along with the change from baseline (defined as the first infusion).

#### 6.1.10.1.1 Demographics

##### **Subject Demographic Data**

The demographics of the study population are summarized in Table 9.

**Table 7: Demographic Data Full Analysis Set (n=75)**

Parameter	Children ≥2 Years	Children ≥6 Years	Adolescents ≥12 Years	Adults ≥17 Years	Total All Subjects N=75
	2-6 Years N=12	7-12 Years N=14	12-17 Years N=12	17-75 Years N=37	
<b>Gender [N (%)]</b>					
Female	1 (8.3%)	5 (35.7%)	3 (25.0%)	27 (73.0%)	36 (48.0%)
Male	11 (91.7%)	9 (64.3%)	9 (75.0%)	10 (27.0%)	39 (52.0%)
<b>Age [Years]</b>					
Mean (SD)	4.17 (1.12)	7.93 (1.44)	14.08 (1.38)	47.46 (13.61)	27.81 (21.91)
Median	4.50	8.00	14.00	46.00	16.00
Min, Max	2.0, 5.0	6.0, 10.0	12.0, 16.0	20.0, 73.0	2.0, 73.0
<b>ABO blood type [N (%)]</b>					
A	4 (33.3%)	4 (28.6%)	4 (33.3%)	18 (48.6%)	30 (40.0%)
AB	1 (8.3%)	1 (7.1%)	1 (8.3%)	3 (8.1%)	6 (8.0%)
B	4 (33.3%)	3 (21.4%)	1 (8.3%)	3 (8.1%)	11 (14.7%)
O	3 (25.0%)	3 (21.4%)	4 (33.3%)	12 (32.4%)	22 (29.3%)
Missing	0 (0%)	3 (21.4%)	2 (16.7%)	1 (2.7%)	6 (8.0%)
<b>Height [cm]</b>					
Mean (SD)	109.33 (9.71)	132.14 (10.33)	166.83 (8.99)	166.81 (9.90)	151.15 (24.63)
Median	108.00	132.00	165.00	164.00	160.00
Min, Max	95.0, 128.0	114.0, 149.0	157.0, 189.0	152.0, 190.0	95.0, 190.0
<b>Weight [kg]</b>					
Mean (SD)	19.99 (5.62)	32.02 (10.54)	58.01 (14.42)	68.74 (12.67)	52.37 (22.82)
Median	19.00	30.70	55.15	68.60	55.20
Min, Max	13.0, 32.5	16.0, 56.0	38.6, 86.4	44.3, 98.6	13.0, 98.6
<b>BMI [kg/m<sup>2</sup>]</b>					
Mean (SD)	16.28 (2.77)	17.91 (4.40)	20.78 (5.27)	24.64 (4.1)	21.43 (5.36)
Median	15.45	17.10	19.80	23.90	21.20

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Min, Max	13.2, 21.5	12.0, 27.8	13.7, 32.0	18.6, 40.0	12.0, 40.0
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#### 6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

##### Underlying Condition causing primary Immunodeficiency

The majority of subjects (56 subjects; 74.7%) had CVID and 6 subjects had X-linked agammaglobulinemia. Other immunodeficiencies reported in 13 subjects were:

- 2 subjects with hypogammaglobulinemia
- 2 subjects with Di George syndrome
- 1 subject each with:
  - Hyper IgM syndrome
  - X-linked hyper IgM syndrome
  - Agammaglobulinemia, not X-linked
  - IgG deficiency
  - Hypogammaglobulinemia IgG1
  - Selective deficiency of IgG1 and IgG2 with deficiency of specific antibodies
  - Nijmegen breakage syndrome
  - GATA2 deficiency
  - Wiskott-Aldrich syndrome

##### Baseline Clinical data:

The most common findings from the medical history (apart from immunodeficiency) were asthma (29 subjects [38.7%]), allergic rhinitis (23 subjects [30.7%]), gastroesophageal reflux disease (17 subjects [22.7%]) and chronic sinusitis (13 subjects [17.3%]).

All children and adolescents were non-smokers with zero alcohol consumption.

The distribution of ABO blood types, which is relevant to the risk of hemolysis from IgG products A and O were the most common blood types in children, and AB was the least common blood type.

Viral markers for HBsAg, HIV-1/2 antibody, HBV, HCV and HIV-1/2 viral load were negative at screening in all subjects tested. One child was positive for parvovirus B19 viral load at screening and 2 children were positive for hepatitis A virus viral load at screening

##### Prior IGIV Schedule

The most common previous IGIV schedule was a 4-weekly dosing (61 subjects: 81.3%).

#### 6.1.10.1.3 Subject Disposition

Four adolescents (Subject (b) (6) after 33 days, Subject (b) (6) after 56 days, Subject (b) (6) after 20 days and Subject (b) (6) after 215 days) and 3 adults (Subject (b) (6) after 224 days, Subject (b) (6) after 14 days and Subject (b) (6) after 271 days) withdrew from the study. For all but one subject, the reason for withdrawal was subject preference; two subjects specified that the SCIG infusion were too time-consuming as the reason they withdrew. Subject (b) (6) was withdrawn due to the subject's non-compliance.

**Table 8:Major Protocol Deviations Relating to Study Conduct (Safety Analysis Set, N=75)**

Type/ Nature of Protocol Deviation	Children ≥2 Years <6 Years N=12 N (%) n	Children ≥6 Years <12 Years N=14 N (%) n	Adolescents ≥12 Years <17 Years N=12 N (%) n	Adults ≥17 Years ≤75 Years N=37 N (%) n	Total All Patients N=75 N (%) n
Any Major Protocol Deviation	12 (100.0%) 23	11 (78.6%) 32	5 (41.7%) 12	24 (64.9%) 37	52 (69.3%) 104
Concomitant Medication	0 (0%) 0	1 (7.1%) 1	0 (0%) 0	0 (0%) 0	1 (1.3%) 1
Deviation from Study Protocol Procedures	9 (75.0%) 13	7 (50.0%) 15	4 (33.3%) 9	8 (21.6%) 11	28 (37.3%) 48
Dosing Error	4 (33.3%) 7	8 (57.1%) 12	2 (16.7%) 2	12 (32.4%) 13	26 (34.7%) 34
ICF Process or Signature/Version Issue	0 (0%) 0	1 (7.1%) 1	0 (0%) 0	0 (0%) 0	1 (1.3%) 1
Other	2 (16.7%) 2	0 (0.0%) 0	1 (8.3%) 1	4 (10.8%) 4	7 (9.3%) 7
Violation Of Inclusion/Exclusion Criteria	1 (8.3%) 1	3 (21.4%) 3	0 (0%) 0	7 (18.9%) 9	11 (14.7%) 13

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*Reviewer Comment: Protocol Deviations did not impact primary efficacy endpoint as there were no SBI reported during the study for either adult or pediatric population.*

### 6.1.11 Efficacy Analyses

#### 6.1.11.1 Analyses of Primary Endpoint(s)

No SBIs were observed during the study. There was 1 severe infection. A total of 231 infections were observed in 61 subjects in the primary observation period and 293 infections in 65 subjects over the total treatment period.

Upper respiratory tract infections were reported most frequently. The rate of other infections per person-year was 3.275 overall (upper 95% CI: 4.253). Three-quarters of the infections in the primary observation period were mild and one-quarter moderate in intensity; there was 1 severe infection. The median time to resolution of infections was 9 days, with longer times for moderate infections (14 days) than mild infections (8 days).

**Table 9:Summary of Other Infections- Rate of Other Infections per Person Year**

Number (%) of patients number of infections;	Children ≥2 Years <6 Years N=12	Children ≥6 Years <12 Years N=14	Adolescents ≥12 Years <17 Years N=12	Adults ≥17 Years 75 Years N=37	Total All Patients N=75
Any other infection	11 (91.7%) 51	9 (64.3%) 35	8 (66.7%) 23	33 (89.2%) 122	61 (81.3%) 231
Ear infections	1 (8.3%) 3	3 (21.4%) 3	1 (8.3%) 1	1 (2.7%) 1	6 (8.0%) 8
Eye infections	0 (0%) 0	0 (0%) 0	1 (8.3%) 1	1 (2.7%) 2	2 (2.7%) 3
Infections of the Gastrointestinal tract	3 (25.0%) 5	3 (21.4%) 4	1 (8.3%) 2	6 (16.2%) 8	13 (17.3%) 19
Infections of the Genitourinary tract	1 (8.3%) 1	2 (14.3%) 2	0 (0%) 0	8 (21.6%) 17	11 (14.7%) 20
Upper respiratory tract	10 (83.3%) 32	9 (64.3%) 16	6 (50.0%) 11	26 (70.3%) 76	51 (68.0%) 135
Lower respiratory tract	6 (50.0%) 10	4 (28.6%) 5	3 (25.0%) 4	6 (16.2%) 8	19 (25.3%) 27
Infections of the skin	0 (0%) 0	2 (14.3%) 2	1 (8.3%) 1	3 (8.1%) 3	6 (8.0%) 6
Infections not (elsewhere classified)	0 (0%) 0	3 (21.4%) 3	2 (16.7%) 3	6 (16.2%) 7	11 (14.7%) 13
Mild infections	11 (91.7%) 48	9 (64.3%) 29	8 (66.7%) 14	29 (78.4%) 79	57 (76.0%) 170
Moderate infections	2 (16.7%) 3	4 (28.6%) 6	6 (50.0%) 8	19 (51.4%) 43	31 (41.3%) 60
Severe infections	0 (0%) 0	0 (0%) 0	1 (8.3%) 1	0 (0%) 0	1 (1.3%) 1
Number of person-years exposure	12.16	14.16	8.66	35.54	70.53
Total number (rate) of other person-year	4.19	2.47	2.66	3.43	3.28

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### Time to Resolution of Infections

In the primary observation period, the median time to resolution of all infections was 9.00 days. The mean time to resolution was 20.98 days; the median time to resolution was longer for moderate infections (14.00 days) than for mild infections (8.00 days) in the primary observation period. Severe infections resolved in 21 days.

**Table 10: Time to Resolution of Other Infections**

Time to Resolution of Infections [Days]	Children ≥ 2 Years ≤ 6 Years N=12	Children ≥ 2 years ≤ 6 Years N=14	Children ≥ 2 years ≤ 6 Years N=12	Children ≥ 2 years ≤ 6 Years N=37	Children ≥ 2 years ≤ 6 Years N=75
n	51	35	23	122	231
Mean	19.20	27.06	24.74	19.28	20.98
(SD)	(37.13)	(53.62)	(63.82)	(33.55)	(41.42)

Median	8.00	11.00	11.00	9.50	9.00
Min, Max	1.0, 169.0	1.0, 292.0	2.0, 316.0	2.0, 232.0	1.0, 316.0

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### 6.1.11.2 Analyses of Secondary Endpoints

#### Use of Antibiotics

During the primary observation period 51 subjects (68.0%) used antibiotics and throughout the whole study, 54 (72.0%) subjects used antibiotics in 180 treatment episodes over 4796 treatment days.

The number of treatment episodes per person-year was 2.097 and the number of treatment days per person-year was 55.875 and were similar to the rates in the primary observation period.

**Table 11: Use of Antibiotics in the Primary Treatment Period**

Any Antibiotic	Children ≥2 Years <6 Years N=12	Children ≥6 Years <12 Years N=14	Adolescents ≥12 Years <17 Years N=12	Adults ≥17 Years ≤75 Years N=37	Total All Patients N=75
Patients with use of antibiotics [N (%)]	10 (83.3%)	7 (50.0%)	8 (66.7%)	26 (70.3%)	51 (68.0%)
Number of treatment episodes [n]	35	17	14	80	146
Number of treatment episodes per person-year	2.88	1.20	1.2	2.25	2.07
Number of treatment days [n]	434	900	1206	1514	4054
Number of treatment days per person-year	35.68	63.55	139.26	42.60	57.48
One-sided 95% CI – upper limit	76.79	168.90	321.78	75.30	85.87

Adapted from Table 12 Page 62 Source - CSR SCGAM01

#### Hospitalizations Due to Infection

There were 4 hospitalizations due to infection during the study, 1 in a young child and 3 in adolescent subjects, all in the primary observation period.

The young child spent 3 days in hospital due to infection and the 3 adolescent subjects spent 3, 10 and 13 days, respectively. The number of days in hospital per person-year in the primary observation period was 0.411 days.

#### Absences from Work or School Due to Infection

During the primary treatment period 24 subjects had 52 absences from work or school due to infections with a total of 252 days of absence. The rate of absence from work or school per person-year was 0.018, assuming 200 working/school days per year, with

similar rates for absences seen across the age groups, except for the younger children where higher rates were seen.

**Table 12: Absences from Work or School Due to Infections in the Primary Treatment Period**

Parameters	Children ≥2 Years <6 Years N=12	Children ≥6 Years <12 Years N=14	Adolescents ≥12 Years <17 Years N=12	Adults ≥17 Years ≤75 Years N=37	Total All Patients N=75
Number of patients with absences from work/school [N (%)]	7 (58.3%)	5 (35.7%)	4 (33.3%)	8 (21.6%)	24 (32.0%)
Total number of absences work/school	17	10	8	17	52
Total number (rate) of absences work/school per person-year	1.40	0.71	0.92	0.48	0.74
Total number of days absent from work/school	103	42	35	72	252
Total number of days (rate) absent from work/school per person-year	8.47	2.97	4.04	2.03	3.57
Rate of absence from work or school per person-year	0.04	0.02	0.020	0.01	0.02
One-sided 95% CI – upper limit	17.95	6.94	10.066	4.84	5.54

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Quality of Life -CHQ-PF50 Questionnaire

The QoL in children under 14 years of age is assessed using the CHQ-PF50 questionnaire, which consists of 50 items organized into 15 sub-scales: global health, physical functioning, role/social limitations due to emotional or behavioral difficulties, role/social limitations due to physical health, bodily pain and discomfort, behavior, global behavior, mental health, self-esteem, general health perceptions, change in health, emotional impact on parent, time, impact on parent, family activities and family cohesion. Overall, there were no major changes in the mean and median CHQ-PF50 scores over time. Mean SF-36v2 scores ranged between 42 and 53. The summary mental health score was 52.25 at the end of study visit and the physical health score was 48.51. Overall mean scores were stable or there were increases (i.e., improved QoL), albeit slight, between Week 1 and the end of study visit in mean scores for both summary scores (physical health and mental health) and also for all of the 8 scales.

6.1.11.3 Subpopulation Analyses

**Table 13: Infections – Comparison between Adults and Children**

Infection Types	Total (% of subjects)	Adults n (%)	Pediatrics n (%)
URI	77 (95.1)	39 (90.7)	38 (100)
Bronchitis	15 (18.5)	9 (20.9)	6 (15.8)
Pneumonia	1 (1.2)	0 (0)	1 (2.6)
UTI	13 (16.0)	11 (25.6)	2 (5.3)
Gastroenteritis	8(9.9)	2 (4.7)	6 (15.8)
Skin infection	9 (11.1)	4 (9.3)	5 (13.2)
Vulvovaginal Infection	5 (6.2)	5 (11.6)	0 (0)
Influenza	13 (16.0)	6 (14.0)	7 (18.4)
Abscess	4 (4.9)	3 (7.0)	1 (2.6)

Reviewer Comment: As expected, lower genitourinary

infections were more common in adults, while gastrointestinal and upper respiratory infections were more common in children.

#### 6.1.11.4 Dropouts and/or Discontinuations

Four (4) adolescents withdrew from the study (Subject (b) (6) after 33 days, Subject (b) (6) (after 56 days), Subject (b) (6) (after 20 days) and Subject (b) (6) (after 215 days) and 3 adults: Subject (b) (6) (after 224 days), Subject (b) (6) (after 14 days) and Subject (b) (6) (after 271 days).

For all but one subject, the reason for withdrawal from the study was the subject's decision (6 subjects; 8.0%); Subject (b) (6) was withdrawn due to the subject's non-compliance

#### 6.1.11.5 Exploratory and Post Hoc Analyses

No exploratory or Post Hoc analysis were performed.

#### 6.1.12 Safety Analyses

##### 6.1.12.1 Methods

###### Exposure to IP

Overall, the 75 subjects in the Safety Analysis Set received 4462 infusions in the study, with a mean of 59.49 infusions administered per subject (ranging from 2 to 65). In total 41,332 g (250,498 mL) was administered.

The average dose of Cutaquig used per subject was 0.187 g/kg in adult subjects, 0.150 g/kg in young children, 0.164 g/kg in older children and 0.170 g/kg in adolescents (0.174 g/kg overall). "If the investigator had assessed an AE as not being an infection but the PT [preferred term] indicated that the AE was an infection then the investigator's assessment could be overruled."

### 6.1.12.2 Overview of Adverse Events

Of the 75 Subjects in the Safety Analysis Set, 70 subjects (93.3%) experienced at least one AE, including infections, during the course of the study. If infections are excluded, 61 subjects (81.3%) experienced 310 events, thus 14 subjects only experienced AEs that were infections. In total, 603 AEs were recorded throughout the study, of which approximately half were infections (293 events). Eleven subjects (14.7%) had at least one systemic AE that the investigator considered to be related to study medication; 14 related events were reported in total. The majority of AEs (excluding infections) were mild in intensity (240/310; 77.4%), 63 (20.3%) were moderate and 7 (2.3%) were severe in intensity. All 12 SAEs were considered unrelated to study medication.

#### Infusion Associated Reactions:

The most common types of infusion site reactions were swelling, erythema, redness and pruritus.

Relative to the number of infusions, the incidence of temporally associated TEAEs was lowest at infusion rates of <70 mL/h and higher at flow rates between 70 and <90mL/h. Overall, 73.3% of subjects experienced infusion site reactions, with the highest incidences (78.6% and 81.1%, respectively) in older children and adult subjects. In three-quarters (77.7%) of infusions, there was no infusion site reaction, in one-fifth (20.1%) a mild reaction, in 2.1% a moderate reaction, and a severe reaction was observed in only 4 infusions.

The incidence of infusion site reactions was slightly higher during the first 4 training infusions; there were 63.1% of subjects with no reaction during the first 4 infusions which subsequently increased to ≥70% for the infusions given at site and just over 80% for the infusions given at home.

**Table 14: Summary of Category and Type of Infusion Site Reaction by Patient**

	Children ≥2 Years <6 Years N=12	Children ≥6 Years <12 Years N=14	Adolescents ≥12 Years <17 Years N=12	Adults ≥17 Years ≤75 Years N=37	Total All Patients N=75
Number of patients (%) number of infusion site reactions by category					
Skin lesions	6 (50.0%) 90	7 (50.0%) 32	4 (33.3%) 17	28 (75.7%) 342	45 (60.0%) 481
Space- occupying lesions	6 (50.0%) 84	11 (78.6%) 110	5 (41.7%) 58	21 (56.8%) 317	43 (57.3%) 569
Local sensation or perception	4 (33.3%) 27	5 (35.7%) 6	3 (25.0%) 6	16 (43.2%) 167	28 (37.3%) 206
Other	1 (8.3%) 1	3 (21.4%) 6	1 (8.3%) 2	10 (27.0%) 72	15 (20.0%) 81
Hematomas	3 (25.0%) 3	4 (28.6%) 9	1 (8.3%) 1	4 (10.8%) 6	12 (16.0%) 19
Procedural events	3 (25.0%) 3	0 (0%) 0	3 (25.0%) 3	2 (5.4%) 4	8 (10.7%) 10
Number of patients (%) number of infusion site reactions of ...					
Swelling	4 (33.3%) 71	6 (42.9%) 99	4 (33.3%) 38	16 (43.2%) 256	30 (40.0%) 464

Erythema	5 (41.7%)	80	1 (7.1%)	8	2 (16.7%)	7	20 (54.1%)	160	28 (37.3%)	255
Redness	3 (25.0%)	10	6 (42.9%)	20	3 (25.0%)	8	12 (32.4%)	159	24 (32.0%)	197
Pruritus	0 (0%)	0	2 (14.3%)	3	3 (25.0%)	3	11 (29.7%)	136	16 (21.3%)	142
Pain	4 (33.3%)	25	3 (21.4%)	3	2 (16.7%)	3	6 (16.2%)	11	15 (20.0%)	42
Oedema	1 (8.3%)	3	2 (14.3%)	2	1 (8.3%)	17	8 (21.6%)	47	12 (16.0%)	69
Mass	1 (8.3%)	1	3 (21.4%)	3	1 (8.3%)	1	6 (16.2%)	14	11 (14.7%)	19
Bruising	1 (8.3%)	1	4 (28.6%)	7	1 (8.3%)	1	3 (8.1%)	4	9 (12.0%)	13

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#### 6.1.12.3 Deaths

No deaths occurred in the study.

#### 6.1.12.4 Nonfatal Serious Adverse Events

Twelve SAEs were reported in 9 subjects (12.0%): 2 adults (5.4%), 3 adolescents (25.0%), 3 older children (21.4%) and 1 young child (8.3%) The SAEs were not considered to be related to Cutaquig. No action was taken with the study drug.

Seven non-infection related SAEs occurred. These included headache, spinal compression fracture, asthma, Asperger's disorder, seizure, pain, thyroid disorder, extremity pain. Those occurring in the pediatric population are described below:

- 5-year-old white male had Pain in Extremity, Tracheitis, Asperger's Disorder
- 10-year-old white male, was hospitalized with history of seizures, requiring adjustment of epileptic medications prior to discharge home the same day.
- 10-year-old white male was hospitalized for Asthma and RSV Bronchiolitis.
- 10-year-old white female experienced spinal compression fracture of the 6th thoracic vertebra related to trauma.

Five of the SAEs were infections (tracheitis, respiratory syncytial virus, abscess limb, Pneumocystis jiroveci infection and dental pulp osteomyelitis). Those that occurred in children are described below:

- 15-year-old white male had left calf abscess unrelated to site of infusion
- 16-year-old white male was hospitalized for Pneumocystis jiroveci infection
- 10-year-old white male was hospitalized for Asthma and RSV Bronchiolitis.

*Reviewer Comment: Narrative summaries of all SAEs were reviewed and adjudicated as not related to the product by the reviewer.*

#### 6.1.12.5 Adverse Events of Special Interest (AESI)

Six (6) adult subjects ((b) (6) ) and 1 adolescent (b) (6) had positive Coombs test during the study.

However, none of the subjects who had a confirmed positive Coombs' test also had a drop in hemoglobin of  $\geq 2$  g/dL and therefore there was no indication of intravascular hemolysis during the study.

There were no thromboembolic events, or cases anaphylaxis or of aseptic meningitis reported.

#### 6.1.12.6 Clinical Test Results

In general, subjects showed normal values of blood pressure, pulse rate and temperature during the study, with little fluctuation in mean values throughout the study. Eleven (11) subjects (14.7%) with 14 episodes of pyrexia during the study, of which 1 event in 1 adult was considered to be related to study medication. There was 1 TEAE of moderate sinus tachycardia in an adolescent (subject (b) (6)) at Week 52. Otherwise, there were no TEAEs related to changes in heart rate or blood pressure. The weight of the subjects did not vary markedly during the study.

Three subjects ((b) (6) ) had leucopenia with WBC ranging from 3.0-3.7. 3 subjects ((b) (6) ) had eosinophilia at various times during the study. Low Hb was noted in 2 subjects ((b) (6) - 10.8g/dl; (b) (6) - 9.1g/dl). Five (5) subjects had elevated transaminases (ALT- (b) (6) ); AST- (b) (6) ); 1 subject ((b) (6) ) had bilirubinemia (2.5mmol/dl) and 1 subject had high LDH (343).

#### Virology Testing

There were no positive results for HIV-1/2 antibody and viral load or for HCV viral load.

Eleven *subjects including* 1 young child, 2 older children and 2 adolescents had positive viral tests (Hepatitis A and 4 Parvovirus) during the study. All positive findings were graded as non-clinically significant by the investigator except for *subject* (b) (6) and *subject* (b) (6).

The positive result for HBsAg at the End of Study Visit (b) (6) in *subject* (b) (6), which was graded as clinically significant; HBV viral load was negative for this *subject* at this timepoint. The *subject* was re-tested approximately 1 month later (on (b) (6) ) and both HBsAg and HBV viral load were negative, as were all other virology tests. The negative HBV DNA test results (on (b) (6) ) and at repeat testing on (b) (6) ) in conjunction with a negative HBsAg test result (on (b) (6) ) exclude the possibility of an HBV infection.

Subject (b) (6) had an AE of HBV test positive with a positive PCR test at Week 64 (onset 4 days after the infusion) which resolved within 6 days (repeated PCR test was negative).

#### Concomitant Medications and Non-Drug Therapy

In total, 73 subjects (97.3%) used concomitant medication in this study and 26 (34.7%) used non-drug therapies (mainly surgery and dental work). The most common concomitant medications were antibacterial for systemic use taken by 53 subjects (70.7%), nasal preparations taken by 41 subjects (54.7%), drugs for obstructive airway

diseases taken by 38 subjects (50.7%), cough and cold preparations taken by 36 subjects (48.0%), antihistamines for systemic use and anti-inflammatory and antirheumatic products both taken by 34 subjects (45.3%) and analgesics taken by 31 subjects (41.3%).

#### 6.1.12.7 Dropouts and/or Discontinuations

No TEAEs led to dropout, discontinuation or death during the study.

#### 6.1.13 Study Summary and Conclusions

SCGAM-01 was an appropriately designed Phase III study to evaluate PK, efficacy, safety and tolerability of Cutaquig in children 2-17 years and adults with PID.

The study met its primary efficacy endpoint. The primary endpoint, annualized SBI rate was considered successful if the upper bound of the one-sided 99% CI for the rate of SBIs was <1 per subject year of follow-up. This rate was determined based on literature describing the historical frequency of SBI in children prior to immunoglobulin therapy. No child treated with Cutaquig had an SBI, and the upper-bound of the one-sided 99% CI was 0.13.

The outcomes of secondary efficacy endpoints were consistent with the product being effective. The annual rate of all infections per subject per year was 3.1 (95% CI 2, 4.8). This is slightly lower than the rates observed in adults. A total of 37% of children did not require systemic antibiotics. Only 4 children in the study were hospitalized due to infection, with annual rate of 0.8 days per subject year. Children in the study missed 5.2 days of school/daycare per subject per year due to infection. These findings are consistent with the product preventing bacterial infections and this treatment effect is similar to what is seen in other SCIG therapies approved for children with PID.

Subcutaneous infusion of *Cutaquig* resulted in flat PK profiles, consistent with gradual absorption, and with markedly lower fluctuations of C max at steady state, compared to IGIV dosing. The serum IgG trough levels were nearly constant during the course of the study and there were no subjects in the PK Evaluable Set 1 with IgG trough levels below 5 g/L. A DCF of 1.33 was determined by linear regression modelling; the actual dose increment (by a factor of 1.41) resulted in AUC values satisfying the criteria for bioequivalence.

Overall, Cutaquig was well tolerated in children. There were no deaths, cases of intravascular hemolysis, aseptic meningitis or renal failure in children. There was a single child who had a PE and superficial thrombosis that were attributed to underlying medical history rather than the product. The most common AEs were infusion site reactions, which were generally mild and less common in children than adults.

## 6.2 Trial #2

SCGAM-03 Clinical phase III is a study to monitor the safety, tolerability and efficacy of subcutaneous human immunoglobulin (Cutaquig) in subjects with primary immunodeficiency diseases who have completed the SCGAM-01 trial

### 6.2.1 Objectives

The primary objective of the study was to assess the medium-to-long-term safety and

tolerability of Cutaquig.

### 6.2.2 Design Overview

Study SCGAM-03 was designed as a prospective, open-label, non-controlled, single-arm, multicenter phase 3 safety follow-up study with observation of subjects receiving weekly or bi-weekly (every other week) doses of Cutaquig over a period of up to 4.5 years for subjects previously enrolled in Study SCGAM-01 (or 12 months for de novo subjects in Canada).

The study was conducted at study sites in the US that already participated in Study SCGAM-01 and at one study site in Canada that had participated in Study SCGAM-01. This Canadian site was allowed enroll 'de novo' subjects who did not participate in the SCGAM-03 trial but were on other IGSC treatment prior to entry however, no subjects who participated in the SCGAM-01 study at this Canadian site were enrolled in the SCGAM-03 study.

### 6.2.3 Population

#### Inclusion Criteria:

##### SCGAM-01 subjects Who Enrolled in US Study Sites

1. Completion of the main study SCGAM-01, with good tolerance of Cutaquig (as determined by the investigator).
2. For adult subjects: freely given written informed consent. For subjects below the legal age of majority freely given written informed consent from parents/legal guardians and written informed assent from the child/adolescent in accordance with local requirements.
3. For female subjects of child-bearing potential, a negative result in a urine pregnancy test conducted at the screening visit.
4. Willingness to comply with all aspects of the protocol, including blood sampling, for the duration of the study.

##### Canada Study Sites Enrolling De Novo Subjects

De novo subjects who were receiving IGSC treatment in Canada, but had not participated in the main study, were allowed to enter this study at Canadian Site #51 under the Canada specific protocol (version 05)

1C-a Age of  $\geq 18$  years and  $\leq 75$  years.

1C-b Confirmed diagnosis of PI as defined by ESID and PAGID and required immunoglobulin replacement therapy due to hypogammaglobulinemia or agammaglobulinemia. The exact type of PI was recorded.

1C-c Availability of the IgG trough levels of 2 previous IGSC infusions before enrollment, and maintenance of  $\geq 5.0$  g/L in the trough levels of these 2 previous infusions.

2. Freely given written informed consent.
3. For female subjects of child-bearing potential, a negative result in a urine pregnancy test conducted at the Screening Visit.
4. Willingness to comply with all aspects of the protocol, including blood sampling, for the duration of the study

#### Exclusion Criteria:

##### SCGAM-01 subjects enrolled at US Study Sites

Subjects who met any of the following criteria were not eligible for the study:

1. Subject being without any IgG treatment for period greater than 5 weeks between the last infusion of Cutaquig in the SCGAM-01 study and the first infusion of Cutaquig in the SCGAM-03 study
2. Exposure to blood or any blood product or derivative, other than IgG used for regular PID treatment, within the 3 months before the first infusion in this study
3. Planned pregnancy during the course of the study

#### De Novo subjects enrolled in Canada

Subjects who met any of the following criteria were not eligible for the study:

- 1C-a Acute infection requiring IV antibiotic treatment within 2 weeks prior to and during the Screening period
- 1C-b Known history of adverse reactions to immunoglobulin A (IgA) in other products
- 1C-c Subjects with body mass index >40 kg/m<sup>2</sup>
- 1C-d Ongoing history of hypersensitivity or persistent reactions to blood or plasma derived products, or any component of the investigational product (such as Polysorbate 80)
- 1C-e Requirement of any routine premedication for IgG administration
- 1C-f History of malignancies of lymphoid cells and immunodeficiency with lymphoma
- 1C-g Severe liver function impairment (alanine aminotransferase [ALT] 3 times above upper limit of normal)
- 1C-h Known protein-losing enteropathies or proteinuria.
- 1C-i Presence of renal function impairment (creatinine >120 µM/L or creatinine >1.35 mg/dL), or predisposition for acute renal failure (e.g., any degree of pre-existing renal insufficiency or routine treatment with known nephritic drugs)
- 1C-j Treatment with oral or parenteral steroids for ≥30 days or when given intermittently or as bolus at daily doses ≥0.15 mg/kg
- 1C-k Treatment with immunosuppressive or immunomodulatory drugs
- 1C-l Live viral vaccination (such as measles, rubella, mumps and varicella) within the last 2 months prior to first infusion of Cutaquig
2. Exposure to blood or any blood product or plasma derivatives, other than IGSC used for regular PID treatment, within the 3 months before the first infusion of Cutaquig in this study
3. Pregnant or nursing women or planned pregnancy during the course of the study.
4. Treatment with any investigational medicinal product within 3 months prior to first infusion of Cutaquig
5. Presence of any condition, that was likely to interfere with the evaluation of study medication or satisfactory conduct of the trial
6. Known or suspected to abuse alcohol, drugs, psychotropic agents or other chemicals within the past 12 months prior to first infusion of Cutaquig
7. Known or suspected HIV, HCV, or HBV infection

#### 6.2.4 Study Treatments or Agents Mandated by the Protocol

All subjects enrolled in the study were treated with Cutaquig administered subcutaneously every week (±2 days) or every second week (±2 days) at double the weekly dose. Each subcutaneous infusion was separated by a minimum of 4 days. IGSC infusions were administered at the study site or (self-administered) at home. Subjects entered the study at the same dose (in mg/kg) they were receiving at the Week 64 infusion of Study SCGAM-01. De novo subjects enrolled in Canada entered the study at the same dose (in mg/kg) they were receiving of their commercial IGSC product.

#### Selection of dose for each subject

Subjects entered the study at the same dose (in mg/kg) they were receiving at the Week 64 infusion of Study SCGAM-01. During the study, each subject's dose could be changed (individualized), if considered necessary by the investigator, by titrating upward or downward; this titration was based on the difference between each subject's measured serum total IgG trough levels while on Cutaquig and each subject's target serum total IgG trough level.

De novo subjects enrolled in Canada entered the study at the same dose (in mg/kg) they received with the previous IGSC product.

If, during the study, the subject's body weight changed by >5%, the dose was adjusted to keep it constant on a mg/kg body weight basis.

#### Timing of dose for each subject

Cutaquig was administered subcutaneously every week ( $\pm 2$  days) or every second week ( $\pm 2$  days) at the doubled weekly dose. Each subcutaneous infusion was separated by a minimum of 4 days.

IGSC infusions were administered at the study site or at home (either self-administered or administered with the assistance of a relative or caregiver).

### 6.2.5 Directions for Use

#### Preparation and Method of Administration

Cutaquig was administered the same way as in Study SCGAM-01.

#### IgG Monitoring

Throughout the study, appropriate dose levels were maintained by regular monitoring of serum IgG trough levels

During the efficacy period of the study, subjects' Cutaquig doses were to have been individualized by titrating upward based on the difference in serum total IgG trough levels between the individual's measured value and the target value. The target trough IgG value was derived from the last IgG trough level obtained prior to switching to Cutaquig, using an equation. The subject's body weight was also used to calculate the Cutaquig dose. Investigators were provided with a dose adjustment tabulation to guide dose adjustments.

### 6.2.6 Sites and Centers

#### Study Centers:

In total, 7 sites were initiated: 6 sites in the United States and 1 site in Canada. A total of 27 subjects were enrolled: 21 subjects at 6 sites in the US and 6 subjects at 1 site in Canada.

<u>Sites</u>	<u>Investigators</u>
Site 41 (U.S.):	Isaac Melamed
Site 42 (U.S.):	Sudhir Gupta
Site 43 (U.S.):	Syed Rehman
Site 44 (U.S.):	Roger Kobayashi
Site 45 (U.S.):	Prescott Atkinson
Site 46 (U.S.):	Bob Geng
Site 47 (U.S.):	Jose Fernando Mandujano
Site 51 (Canada):	Bruce Ritchie

### 6.2.7 Surveillance/Monitoring

For all study sites, monitoring was performed by Octapharma Hoboken, NJ 07030 USA. Study data management, statistics, and serious adverse event (SAE) reporting were delegated under an agreement of transfer of responsibilities to the external contract research organization (CRO), (b) (4) . (b) (4)

(b) (4)

All Octapharma procedures and policies were met by (b) (4) . discrepancies or exceptions were approved by Octapharma's Manager of Biometrics.

Study drug labelling and packaging was performed by Octapharma Dessau GmbH, Germany. (b) (4) was used for central storage and shipping study drug to clinical sites. Local laboratories were used for all routine laboratory analyses, including serum

immunoglobulin G (IgG) trough levels.

A data monitoring committee (DMC) was set up to independently monitor safety data.

### 6.2.8 Endpoints and Criteria for Study Success

#### Primary Endpoints

- Occurrence of all treatment-emergent AEs (TEAEs) throughout the entire treatment period starting with the first infusion of Investigational Medicine Product
- Occurrence of temporally associated TEAEs
- TEAEs by speed of infusion
- Local injection-site reactions
- Vital signs (blood pressure, pulse, body temperature, respiratory rate)
- Laboratory parameters (hematology, clinical chemistry, basic urinalysis, and tests for viral safety)

#### Secondary Endpoints

- QoL assessments using the Child Health Questionnaire-Parent Form (CHQ-PF50) from parent or guardian of Subjects <14 years of age and the Short Form Health Survey, 36 items (SF-36) in Subjects ≥14 years of age (Age refers to the age at enrollment into Study SCGAM-01, if applicable, so that each Subject continued using the same questionnaire as before.)
- Occurrence of SBIs
- Annual rate of all infections of any kind or seriousness
- Time to resolution of infections
- Use of antibiotics (number of days and annual rate)
- Total IgG trough levels

### 6.2.9 Statistical Considerations & Statistical Analysis Plan

#### Statistical Methods:

Because the primary objective of this study was to assess the safety and tolerability in medium-to-long-term administration of Cutaquig, no single parameter or measurement was chosen as a primary endpoint.

Descriptive summaries are presented for all primary and secondary variables.

Summaries are completed for all Subjects overall.

When appropriate, the analyses were stratified according to the age groups predefined in the main study:  $\geq 2$  years to  $< 6$  years,  $\geq 6$  years to  $< 12$  years,  $\geq 12$  years to  $< 17$  years,  $\geq 17$  years to  $\leq 75$  years.

In addition, the primary and secondary endpoints were investigated for the following subgroups: male versus female Subjects, and a different definition of age groups ( $\geq 2$  years to  $< 12$  years,  $\geq 12$  years to  $< 17$  years,  $\geq 17$  years to  $\leq 65$  years,  $> 65$  years).

#### 6.2.10 Study Population and Disposition

All 27 subjects enrolled in the extension study SCGAM03 received study treatment and 4 subjects terminated early from the study; 23 subjects (85.2%) completed the study. Four subjects were withdrawn from the study: subject (b) (6) per investigator discretion to change treatment, subject (b) (6) per investigator and subject's discretion to switch from IGSC to IGIV due to increase in autoimmune inflammation, subject (b) (6) per subject's discretion to withdraw, and subject (b) (6) per the Applicant's decision to discontinue subject due to diagnosis of pulmonary embolism, previous event of deep vein thrombosis, and a family history of blood clots.

The most frequently reported major protocol deviations (12 protocol deviations reported among 7 subjects) were due to dosing errors, including subjects using expired IMP at home infusions (5 deviations among 4 subjects), receiving an incorrect dose (5 deviations among 8 subjects), and missed doses (2 deviations among 1 subject) (Listing 16.2.2.1). No subjects were withdrawn from the study due to a protocol deviation or receiving an excluded concomitant medication.

#### 6.2.10.1 Populations Enrolled/Analyzed

##### **Safety analysis set:**

All subjects who received at least part of one infusion of Cutaquig within this extension study.

##### **Full analysis set (FAS):**

All subjects of the safety analysis set who satisfied all eligibility criteria and for whom any post screening data in this extension study were available.

##### **Per-protocol (PP):**

All subjects of the FAS excluding those with major protocol violations which may have impacted the analysis of the primary endpoints. This was the set of subjects who participated in the study as intended and for whom the primary endpoint was able to be evaluated as planned.

#### 6.2.10.1.1 Demographics

Overall, 10 male subjects and 17 female subjects participated in the study, with a higher proportion of women in the adult age group than in the younger age groups.

Mean age of subjects was 39.6 years (range 6-73 years). Almost all subjects were of white race 25/27 (Non-Hispanic ethnicity), the remaining 2 were listed as other/ multiple.

**Table 15: Demographics (Safety Analysis Set, N=27)**

Parameter	Children $\geq 2$ Years $< 6$ Years N=2	Children $\geq 6$ Years $< 12$ Years N=4	Adolescents $\geq 12$ Years $< 17$ Years N=4	Adults $\geq 17$ Years $\leq 75$ Years N=17	All Patients N=27
Age (Years)					

Mean (SD)	6.50 (0.71)	9.00 (1.83)	14.25 (0.96)	56.12 (11.90)	39.26 (24.35)
Median	6.50	9.00	14.50	59.00	51.00
Min, Max	6.0, 7.0	7.0, 11.0	13.0, 15.0	25.0, 73.0	6.0, 73.0
<b>Gender</b>					
Male	2 (100.0%)	2 (50.0%)	2 (50.0%)	4 (23.5%)	10 (37.0%)
Female	0 (0%)	2 (50.0%)	2 (50.0%)	13 (76.5%)	17 (63.0%)
<b>Race</b>					
White	2 (100.0%)	4 (100.0%)	4 (100.0%)	15 (88.2%)	25 (92.6%)
Other	0 (0%)	0 (0%)	0 (0%)	1 (5.9%)	1 (3.7%)
Multiple	0 (0%)	0 (0%)	0 (0%)	1 (5.9%)	1 (3.7%)
<b>Ethnicity</b>					
Not Hispanic or Latino	2 (100.0%)	4 (100.0%)	4 (100.0%)	17 (100.0%)	27 (100.0%)
<b>Height (cm)</b>					
Mean (SD)	119.50 (3.54)	137.50 (12.45)	166.75 (12.33)	165.18 (7.46)	157.93 (17.16)
Median	119.50	138.00	162.00	165.00	161.00
Range	117.0, 122.0	123.0, 151.0	158.0, 185.0	153.0, 180.0	117.0, 185.0
<b>Weight (kg)</b>					
Mean (SD)	23.50 (1.13)	37.78 (18.59)	76.78 (21.04)	72.05 (14.24)	64.07 (22.70)
Median	23.50	30.25	76.90	71.80	65.00
Min; Max	22.7, 24.3	25.6, 65.0	56.3, 97.0	47.7, 101.0	22.7, 101.0
<b>BMI (kg/m<sup>2</sup>)</b>					
Mean (SD)	16.55 (1.77)	19.28 (6.25)	27.35 (5.71)	26.44 (5.41)	24.78 (6.25)
Median	16.55	16.95	26.40	27.10	24.40
Min; Max	15.3, 17.8	14.7, 28.5	21.7, 34.9	17.5, 41.0	14.7, 41.0
<b>ABO Blood Group</b>					
A	1 (50.0%)	2 (50.0%)	2 (50.0%)	8 (47.1%)	13 (48.1%)
AB	0 (0%)	0 (0%)	1 (25.0%)	1 (5.9%)	2 (7.4%)
O	1 (50.0%)	2 (50.0%)	1 (25.0%)	8 (47.1%)	12 (44.4%)
<b>Type of PID</b>					
CVID	2 (100.0%)	4 (100.0%)	4 (100.0%)	14 (82.4%)	24 (88.9%)
Other	0 (0%)	0 (0%)	0 (0%)	3 (17.6%)	3 (11.1%)

Reproduced from Table 11 Page 48 Source - CSR SCGAM03

#### 6.2.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

##### Underlying Condition causing primary Immunodeficiency

The majority of subjects (24 subjects; 89%) had CVID. 3 de novo subjects in the adult group and included IgG1 subclass deficiency, and IgM syndrome as cause of PID.

##### Baseline Clinical Data:

The most common relevant medical history findings by preferred term (PT) (apart from CVID) were asthma (14 subjects [51.9%]), allergic rhinitis (12 subjects [44.4%]), gastroesophageal reflux disease (11 subjects [40.7%]), hypertension (8 subjects [29.6%]), chronic sinusitis (7 subjects [25.9%]), and drug hypersensitivity, depression, post menopause, and sinusitis (6 subjects each [22.2%]). There was 1 subject in age

group 2-6 years with Thalassemia beta, and 1 adult subject each with Factor V Leiden mutation, and hereditary spherocytosis.

The distribution of ABO blood types, which is relevant to the risk of hemolysis from IgG products, was as follows: 13 subjects with Type A, 2 subjects with Type AB, 12 subjects with Type O and no subjects with Type B. ABO blood type was missing for 6 subjects

The most frequently reported abnormal findings on physical examinations at screening were in the body system categories of abdomen with 2 subjects (7.4%) affected, and general appearance and integumentary with 1 subject (3.7%) in each category. All of these abnormalities were reported in the adult age group

#### Prior Medication Use Including Immunoglobulin Therapy

Subjects had previous IGSC therapy of either Cutaquig during their participation in SCGAM-01 study or had received another IGSC treatment (as did the 6 de novo Subjects enrolled in Canada).

Other prior medications were taken by 26 subjects (96.3%) with the most common being drugs for obstructive airway diseases in 16 subjects (59.3%), vitamins in 16 subjects (59.3%), and nasal preparations in 14 subjects (51.9%). Four subjects (14.8%) reported prior non-drug therapies. 7 adult females were on hormonal therapy.

#### Baseline Viral Marker and Urine Pregnancy Test Results

Results for HIV-1/2 and HCV tests were negative at screening for all subjects. Ten subjects (1 young child, 1 older child, 2 adolescents, and 6 adult subjects) had positive test results for HAV and 1 adult subject had a positive test result for HBV at screening. Urine pregnancy tests at screening for the 4 female subjects of childbearing potential were all negative

#### 6.2.10.1.3 Subject Disposition

All 27 subjects enrolled in the study received study treatment and 4 subjects terminated early from the study; 23 subjects (85.2%) completed the study.

Four subjects were withdrawn from the study:

- Subject (b) (6) per investigator discretion to change treatment
- Subject (b) (6) per investigator and subject discretions to switch from IGSC to IGIV due to increase in autoimmune inflammation
- Subject (b) (6) per subject discretion to withdraw
- Subject (b) (6) per the Applicant's decision to discontinue subject due to diagnosis of pulmonary embolism, previous event of deep vein thrombosis, and a family history of blood clots

#### Protocol Deviations:

The most frequently reported major protocol deviations (12 protocol deviations reported among 7 subjects) were due to dosing errors, including subjects using expired IMP at home infusions (5 deviations among 4 subjects), receiving an incorrect dose (5 deviations among 8 subjects), and missed doses (2 deviations among 1 subject) (Listing 16.2.2.1). No subjects were withdrawn from the study due to a protocol deviation or receiving an excluded concomitant. All 27 subjects enrolled in the study received study treatment and 4 subjects terminated early from the study; 23 subjects (85.2%) completed the study medication.

## 6.2.11 Efficacy Analyses

### 6.2.11.1 Analyses of Primary Endpoint(s)

#### Primary Efficacy Endpoint

The primary objective of this study was to assess the medium-to-long term safety and tolerability of Cutaquig; therefore, no primary efficacy analyses were performed.

However, the serious bacterial infection observed during the study stratified by age group is presented in table below. 1 SBI observed in an adult subject was Escherichia Coli Bacteremia.

**Table 16: Serious Bacterial Infection Rate: Bacteremia/Sepsis**

<b>Serious Bacterial Infections: Bacteremia/Sepsis</b>	<b>Children ≥2 Years &lt;6 Years N=2</b>	<b>Children ≥6 Years &lt;12 Years N=4</b>	<b>Adolescents ≥12 Years &lt;17 Years N=4</b>	<b>Adults ≥17 Years ≤75 Years N=17</b>	<b>Total N=27</b>
Number of person years exposure	5.05	8.02	7.58	33.44	54.09
Number of patients with SBIs	0 (0%)	0 (0%)	0 (0%)	1 (5.9%)	1 (3.7%)
Number of SBIs per patient:	0	4 (100%)	4 (100%)	16 (94.1%)	26 (96.3%)
	1	0 (0%)	0 (0%)	1 (5.9%)	1 (3.7%)

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### 6.2.11.2 Analyses of Secondary Endpoints

Secondary efficacy assessments included Quality of Life (QoL) assessments along with efficacy assessments including the annual rate of all infections of any kind or seriousness, time to resolution of infections, hospitalizations due to infections, episodes of fever, and antibiotic use. Missed days from work / school / kindergarten / day care were evaluated as a secondary target variable.

**Table 17: Rate of All Infections by Age Group**

<b>All infections</b>	<b>Children ≥2 Years &lt;6 Years N=2</b>	<b>Children ≥6 Years &lt;12 Years N=4</b>	<b>Adolescents ≥12 Years &lt;17 Years N=4</b>	<b>Adults ≥17 Years ≤75 Years N=17</b>	<b>Total N=27</b>
<b>Number of person-years exposure</b>	5.05	8.02	7.58	33.44	54.09
<b>Total Number of All infections</b>	8	12	22	77	119
Number of patients with all infections	2 (100.0%)	4 (100.0%)	4 (100.0%)	15 (88.2%)	25 (92.6%)
Total number of all infections per person-year	1.585	1.497	2.901	2.303	2.200

**Table 18:Types of Infections**

All infections	Children ≥2 Years <6 Years N=2 (subjects, %, total)	Children ≥6 Years <12 Years N=4 (subjects, %, total)	Adolescents ≥12 Years <17 Years N=4 (subjects, %, total)	Adults ≥17 Years ≤75 Years N=17 (subjects , %, total)	Total N=27 (subjects, %, total)
SBI – bacteremia / sepsis	0 (0%) 0	0 (0%) 0	0 (0%) 0	1 (5.9%) 1	1 (3.7%) 1
Upper respiratory tract infections	2 (100.0%) 5	3 (75.0%) 9	4 (100.0%) 13	11 (64.7%) 45	20 (74.1%) 72
Lower respiratory tract infections	1 (50.0%) 1	0 (0%) 0	3 (75.5%) 7	3 (17.6%) 5	7 (25.9%) 13
Infections of the skin	0 (0%) 0	1 (25.0%) 1	1 (25.0%) 1	5 (29.4%) 8	7 (25.9%) 10
Infections of the gastrointestinal tract	1 (50.0%) 2	1 (25.0%) 2	0 (0%) 0	4 (23.5%) 7	6 (22.2%) 11
Infections of the genitourinary tract	0 (0%) 0	0 (0%) 0	0 (0%) 0	6 (35.3%) 8	6 (22.2%) 8
Infections (not elsewhere classified)	0 (0%) 0	0 (0%) 0	0 (0%) 0	3 (17.6%) 3	3 (11.1%) 3
Ear infections	0 (0%) 0	0 (0%) 0	1 (25.0%) 1	0 (0%) 0	1 (3.7%) 1

Reproduced from Table 14 Page 55 Source - CSR SCGAM03

**Table 19:Use of Antibiotics**

Any Antibiotic	Children ≥2 Years <6 Years N=2	Children ≥6 Years <12 Years N=4	Adolescents ≥12 Years <17 Years N=4	Adults ≥17 Years ≤75 Years N=17	Total N=27
Number of person years exposure	5.05	8.02	7.58	33.44	54.09
Patients with use of antibiotics [N (%)]	1 (50.0%)	2 (50.0%)	4 (100.0%)	13 (76.5%)	20 (74.1%)
Number of treatment episodes	3	7	12	73	95
Number of treatment episodes per person-year	0.60	0.87	1.582	2.18	1.76
Number of treatment days	52	589	825	1151	2617
Number of treatment days per person-year	10.31	73.47	108.78	34.42	48.39

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**Hospitalization due to Infection.**

Two adult subjects were hospitalized for infection; 1 adult subject was hospitalized once for 3 days and 1 other adult subject was hospitalized twice; once for 2 days and once for

5 days for a total of 10 days of hospitalization among both subjects. The infections were Escherichia Bacteremia and an infected arthropod bite in adult subjects. No young children, older children, or adolescent subjects were hospitalized for infections. Overall, the total number of days in hospital per person-year overall due to an infection was 0.185 days two-sided 90% CI: 0.053, 0.647).

Absences from Work or School due to Infection

Absence rates on a per-person year basis were higher among children (2%) than among adolescent or adult subjects (1.6% and 1.0%, respectively); no absences from work or school due to an infection were reported among subjects over 65 years of age (which may reflect some subjects being retired). Absences were also summarized by male and female subjects for these alternative groups.

For male subjects, the absence rates per person-year due to infection were similar for children and adolescent subjects (1.5% and 1.8%, respectively); no absences were reported among male adult subjects or subjects over 65 years of age.

For female subjects, the absence rates per person-year were higher for children (females: 0.027; both genders 0.020) than the other age categories; however, overall, the absence rate for females was similar to that for both genders (females: 0.013; both genders: 0.012).

**Table 20: Absences from Work or School due to Infection**

<b>Absences from Work or School due to Infection</b>	<b>Children ≥2 Years &lt;6 Years N=2</b>	<b>Children ≥6 Years &lt;12 Years N=4</b>	<b>Adolescents ≥12 Years &lt;17 Years N=4</b>	<b>Adults ≥17 Years ≤75 Years N=17</b>	<b>Total N=27</b>
Number of person years exposure	5.05	8.02	7.58	33.44	54.09
Patients with absences work/school [N (%)]	2 (100.0%)	2 (50.0%)	2 (50.0%)	4 (23.5%)	10 (37.0%)
Total number of absences work/school	6	8	10	9	33
Total number (rate) of absences from work/school per person-year	1.19	0.99	1.31	0.26	0.61
Total number of days absent from work/school	24	27	24	55	130
Total number of days (rate) absent from work/school per person-year	4.75	3.37	3.16	1.64	2.40
Rate of absence from work/school per person-year	0.02	0.01	0.01	0.01	0.01

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**6.2.11.3 Subpopulation Analyses**

Age and Gender Differences

**Rate of all Infections:**

The rate was lowest for younger and older children at approximately 1.6 and 1.5 infections per person-year, respectively; the rates for adolescent and adult subjects were higher at approximately 2.9 and 2.3 infections per person-year, respectively. The rate of all infections was lower for male subjects than for female subjects (1.318 versus 2.806 per person-year, respectively)

**Use of Antibiotics:**

Adolescent subjects had the highest number of treatment days per person year, indicating that many were on long-term antibiotic therapy. One older child, 2 adolescent subjects and 5 adult subjects had >100 days in total of antibiotic use. Adult subjects (17 to 65 years of age) had the highest number of treatment episodes and treatment days per year and children had fewer treatment days or episodes on a per person-year basis than adolescent subjects.

Overall, male subjects had lower systemic antibiotic use than female subjects for both number of treatment episodes per person-year (males: 0.727, females: 2.463) and number of treatment days per person-year (males: 29.942, females: 61.041); these indicate that female subjects were administered systemic antibiotics more frequently and for longer periods of time

**6.2.11.4 Dropouts and/or Discontinuations**

Four subjects were withdrawn from the study:

Subject (b) (6) per investigator discretion to change treatment,  
Subject (b) (6) per investigator and subject's discretion to switch from IGSC to IGIV due to increase in autoimmune inflammation,  
Subject (b) (6) per Subject discretion to withdraw,  
Subject (b) (6) per Applicant decision to discontinue subject due to diagnosis of pulmonary embolism, previous event of deep vein thrombosis, and a family history of blood clots.

Early termination of study participation was not seen in children <12 years of age; however, seen in 2 out of 4 adolescents (50%), and 2 out of 17 adults (11.6%)

**6.2.11.5 Exploratory and Post Hoc Analyses**

No Exploratory or post hoc analysis was performed.

**6.2.12 Safety Analyses**

**6.2.12.1 Methods**

Overall, the 27 subjects in the Safety Analysis Set received 2777 infusions in the study and most infusions (98.7%) were given on a weekly basis. The total number of infusions administered per subject ranged from 17 to 169. The mean average actual dose of Cutaquig infused per subject was 0.127 g/kg in young children, 0.210 g/kg in older children, 0.160 g/kg in adolescent subjects and 0.166 g/kg in adult subjects

“If the investigator had assessed an AE as not being an infection but the PT [preferred term] indicated that the AE was an infection then the investigator’s assessment could be overruled.

### 6.2.12.2 Overview of Adverse Events

#### Infusion Site Reactions

Overall, 44.4% of subjects experienced infusion site reactions, with the highest incidences in older children (100%) and adolescent subjects (75.0%) (Table 30). No young children experienced an infusion site reaction.

Of the 12 subjects who experienced at least 1 infusion site reaction, 10 Subjects experienced infusion site reactions of mild intensity. One adolescent (25.0%) and 4 adult (23.5%) subjects experienced infusion site reactions of moderate intensity.

Three adult (17.6%) subjects experienced 19 infusion site reactions of severe intensity. Subject (b) (6) experienced severe swelling, induration, nodule mass, erythema, redness, pain, and warmth on the left and right abdomen at Week 28.

Subject (b) (6) experienced severe pruritus and redness on the left and right thighs at Week 32.

Subject (b) (6) experienced a total of 18 infusions with severe reactions including hives, swelling, and “other” (including wheals), all on the left and/or right abdomen from Week 8 through Week 79.

**Table 21: Summary of Category and Type of Infusion Site Reaction by Patient**

Number of patients (%) number of infusion site reactions by category	Children ≥2 Years <6 Years N=2	Children ≥6 Years <12 Years N=4	Adolescents ≥12 Years <17 Years N=4	Adults ≥17 Years ≤75 Years N=17	Total N=27
Conditions involving the skin	0 (0%) 0	4 (100.0%) 28	2 (50.0%) 10	4 (23.5%) 17	10 (37.0%) 55
Space consuming events	0 (0%) 0	2 (50.0%) 2	1 (25.0%) 10	2 (11.8%) 3	5 (18.5%) 15
Other	0 (0%) 0	0 (0%) 0	2 (50.0%) 12	2 (11.8%) 45	4 (14.8%) 57
Local sensation or perception	0 (0%) 0	0 (0%) 0	0 (0%) 0	3 (17.6%) 7	3 (11.1%) 7
<b>Number of patients (%) number of infusion site reactions of...</b>					
Redness	0 0 (0%)	25 2 (50.0%)	1 1 (25.0%)	7 2 (11.8%)	33 5 (18.5%)
Erythema	0 0 (0%)	3 2 (50.0%)	9 1 (25.0%)	3 2 (11.8%)	15 5 (18.5%)
Swelling	0 0 (0%)	2 0 (0%)	9 2 (50.0%)	3 1 (5.9%)	14 3 (11.1%)
Pruritus	0 (0%) 0	0 (0%) 0	0 (0%) 0	2 (11.8%) 6	2 (7.4%) 6

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Reviewer Comment: Infusion Associated Site reactions are dependent on flow rate and seen more commonly in adults compared to children as shown in table 24 below.

**Table 22: Infusion Rate at Onset of Temporally Associated Treatment Emergent Adverse Events (Safety Analysis Set, N=27)**

Parameter	Children ≥2 Years <6 Years (N=2) N (%)		Children ≥6 Years <12 Years (N=4) N (%)		Adolescents ≥12 Years <17 Years (N=4) N (%)		Adults ≥17 Years ≤75 Years (N=17) N (%)		Total (N=27) N (%)	
Total Number of:	Infusions	TA-TEAEs	Infusions	TA-TEAEs	Infusions	TA-TEAEs	Infusions	TA-TEAEs	Infusions	TA-TEAEs
<b>Infusion Flow Rate Category</b>	263 (100.0%)	2 (100%)	416 (100.0%)	7 (100.0%)	391 (100.0%)	13 (100.0%)	1707 (100.0%)	72 (100.0%)	2777 (100.0%)	94 (100.0%)
10 to <20 mL/h	59 (22.4%)	1 (50.0%)	0	0	0	0	0	0	59 (2.1%)	1 (1.1%)
20 to <30 mL/h	119 (45.2%)	1 (50.0%)	82 (19.7%)	1 (14.3%)	0	0	1 (0.1%)	0	202 (7.3%)	2 (2.1%)
30 to <40 mL/h	85 (32.3%)	0	241 (57.9%)	6 (85.7%)	47 (12.0%)	0	182 (10.7%)	6 (8.3%)	555 (20.0%)	12 (12.8%)
40 to <50 mL/h	0	0	93 (22.4%)	0	248 (63.4%)	9 (69.2%)	684 (40.1%)	28 (38.9%)	1025 (36.9%)	37 (39.4%)
50 to <60 mL/h	0	0	0	0	96 (24.6%)	4 (30.8%)	192 (11.2%)	3 (4.2%)	288 (10.4%)	7 (7.4%)
60 to <70 mL/h	0	0	0	0	0	0	196 (11.5%)	2 (2.8%)	196 (7.1%)	2 (2.1%)
70 to <80 mL/h	0	0	0	0	0	0	113 (6.6%)	4 (5.6%)	113 (4.1%)	4 (4.3%)
80 to <90 mL/h	0	0	0	0	0	0	136 (8.0%)	6 (8.3%)	136 (4.9%)	6 (6.4%)
90 to <100 mL/h	0	0	0	0	0	0	108 (6.3%)	22 (30.6%)	108 (3.9%)	22 (23.4%)
≥ 100 mL/h	0	0	0	0	0	0	95 (5.6%)	0	95 (3.4%)	0
Rate missing	0	0	0	0	0	0	0	1 (1.4%)	0	1 (1.1%)

Reproduced from Table 29 Page 81 Source - CSR SCGAM03

#### Treatment Emergent Adverse Events

The most commonly reported TEAEs (excluding infections and infusion site reactions) by SOC were gastrointestinal disorders (13 subjects, 48.1%), nervous system disorders (12 subjects, 44.4%), and respiratory system disorders (11 subjects, 40.7%).

Subject (b) (6) was discontinued per Applicant decision due to her diagnosis of pulmonary embolism (causally not related to the study drug), previous event of deep vein thrombosis, and a family history of blood clots.

No other AEs led to withdrawal of a subject from the study and there were no other significant TEAEs.

Commonly reported TEAEs (excluding infections and infusion site reactions) by PT were headache (5 subjects, 18.5%) along with asthma and back pain (4 subjects each, 14.8%). Other AEs were reported in <5% of subjects.

Of the total 204 TEAEs reported, 124 were mild, 60 were moderate, and 20 were of severe intensity.

*Reviewer Comment: Narrative summaries of all SAEs were reviewed and adjudicated as not related to the product.*

#### 6.2.12.3 Deaths

No deaths occurred during this study

#### 6.2.12.4 Nonfatal Serious Adverse Events

16 SAEs were reported among 7 subjects (25.9%): 4 adult subjects (23.5%), 2 adolescent subjects (50%), and 1 older child (25%).

Subject (b) (6) experienced severe muscle rupture and subdural hematoma (SAE).

Subject (b) (6) experienced severe diverticulitis (2 events, 1 SAE), arthralgia (2 events), irritable bowel syndrome (SAE), and osteoarthritis (SAE).

Subject (b) (6) experienced severe spinal column stenosis (SAE), spinal osteoarthritis (SAE), osteoarthritis, spondylolisthesis, and nerve compression.

Subject (b) (6) experienced severe asthma.

Subject (b) (6) experienced severe status asthmaticus (2 events, both SAEs).

Subject (b) (6) experienced severe pulmonary embolism (SAE), venous thrombosis limb, and autoimmune thyroiditis.

Subject (b) (6) experienced severe pleural effusion (SAE).

*Reviewer Comment: Narrative summaries of all SAEs were reviewed and adjudicated by this reviewer as not related to the product.*

#### 6.2.12.5 Adverse Events of Special Interest (AESI)

*Reviewer Comment: Narrative summary of the SAE in subject (b) (6) (withdrawn from the study by the applicant) was reviewed. The subject had a history of acute deep vein thrombosis of the popliteal vein on (b) (6) that was treated with Xarelto from 09-Jan-2018 until 18-May-2018. The subject had a family history of blood clots, as reported, her father has had two blood clots with negative work-up as for etiology. Subject was enrolled in the study on 05-Sept-2018. The subject had PE after week 26, after*

*superficial vein thrombosis involving right ante cubital vein. The subject was discontinued from the study by the sponsor Because of the subject's previous history of deep vein thrombosis (prior to study participation), family history of blood clots, it is possible that it was a contributing factor, but it is unlikely that that the product was solely responsible for this SAE.*

#### 6.2.12.6 Clinical Test Results

##### Clinical Hematology:

There were no marked changes from screening until the end of treatment visit in the median values for hematology parameters for any age group.

Subject (b) (6) (age 59) had low clinically significant leukocytes ( $2.5 \times 10^9/L$ ) and neutrophils ( $1.3 \times 10^9/L$ ) at center visit 10/Week 108, only, and low clinically significant platelets ( $125 \times 10^9/L$ ) at center visit 10/Week 108 and Center Visit 12/Week 132. All of these were abnormal but not clinically significant at end of the study.

Subject (b) (6) (age 64) had clinically significant low hemoglobin and hematocrit values at center visit 8/Week 84 ( $107 \text{ g/dL}$  and  $0.35 \text{ L/L}$ , respectively); at the end of study visit the hemoglobin value remained low and clinically significant ( $110 \text{ g/dL}$ ) and the hematocrit was normal.

##### Chemistries

Subject (b) (6) (age 59) also had high clinically significant ALT ( $46 \text{ U/L}$ ), AST ( $98 \text{ U/L}$ ), and LDH ( $239 \text{ U/L}$ ) values at center 104 visit 12/Week 132, only. At the end of study visit, ALT and LDH were normal, and AST was abnormal but not clinically significant.

Subject (b) (6) (age 64) had clinically significant high blood urea nitrogen and creatinine values at center visit 4/Week 36 ( $12.85 \text{ mmol/L}$  and  $131.72 \mu\text{mol/L}$ , respectively), which remained high and clinically significant at center visit 6/Week 60 ( $11.07 \text{ mmol/L}$  and  $93.70 \mu\text{mol/L}$ , respectively) at center visit 8/Week 84 ( $12.14 \text{ mmol/L}$  and  $106.96 \mu\text{mol/L}$ ), and at the end of study visit ( $10.35 \text{ mmol/L}$  and  $106.08 \mu\text{mol/L}$ ).

Subject (b) (6) (age 14) had clinically significant high ALT and AST at center visit 4/Week 36 ( $114 \text{ U/L}$  and  $90 \text{ U/L}$ , respectively), only; both were normal at end of study.

##### Virology Testing

There were no positive results for HIV-1/2 or HCV tests among any subjects.

Subject (b) (6) had a positive result for the HBV serology test at the end of study Visit. A repeat test for Hepatitis B DNA and Hepatitis B Core Immunoglobulin M (IgM), performed using polymerase chain reaction (PCR) technology, were negative.

#### 6.2.12.7 Dropouts and/or Discontinuations

Subject (b) (6) was discontinued per Applicant decision due to her diagnosis of pulmonary embolism (causally not related to the study drug), previous event of deep vein thrombosis, and a family history of blood clots.

#### 6.2.13 Study Summary and Conclusions

SCGAM-03 was designed as a prospective, open-label, non-controlled, safety follow-up study to the pivotal Phase 3 study (SCGAM-01) that evaluated the pharmacokinetic, efficacy and tolerability and safety of Cutaquig in subjects with primary immunodeficiency diseases.

Results from Study SCGAM-01 indicated that Cutaquig was effective in preventing the occurrence of serious bacteriological infections (SBIs) in subjects with primary immunodeficiency disease, IgG trough levels were above  $5 \text{ g/L}$  for all subjects,

and that subcutaneous administration of Cutaquig was generally safe and well-tolerated in that subject population.

Study had 1 serious bacterial infection, as defined in the FDA Guidance for IGIV, were reported during the trial. Based on older literature describing the natural history of PI, had the study subjects not received immunoglobulin replacement therapy, in a cohort of this size, a substantial number of SBIs would have been anticipated to have occurred over the 15-month observation period.

The rate of other infections per person-year was 2.2 overall (upper 90% CI: 3.583). Most infections (61.3%) were mild and 37.0% were moderate in intensity; there were 2 severe infections.

Overall, the median time to resolution of all infections was shorter for male than for female subjects (11.0 days and 12.5 days respectively); however, due to the low number of male subjects enrolled in the study gender comparisons may not be meaningful. There were 3 hospitalizations due to infection during the study; none of these infections were related to study drug.

No children or adolescents were hospitalized due to an infection.

Three episodes of fever were reported among 2 adult subjects (7.4%), resulting in 0.055 episodes of fever per person-year.

Three-quarters (74.1%) of subjects used antibiotics during the study and the majority of antibiotic use was systemic. The number of treatment episodes per person-year for all antibiotics was 1.756 and the number of treatment days per person-year was 48.386. The highest number of treatment episodes per person-year was by adult subjects and the highest number of days per person-year was by adolescent subjects.

Overall, 33 absences from work or school due to infections were reported among 10 subjects with a total of 130 days of absence. The rate of absence from work or school per person-year was 0.012, assuming 200 working/school days per year.

Overall, 44.4% of subjects experienced infusion site reactions, with the highest incidence in older children (100%), followed by adolescent (75.0%) and adult (29.4%) subjects; no young children experienced an infusion site reaction. In most (96.6%) infusions, there were no infusion site reactions; 2.0% had a mild reaction, and 0.7% each had moderate or severe reactions.

All subjects experienced at least 1 AE, including infections, during the study. If infections were excluded, 24 subjects (88.9%) experienced 204 AEs. 4 subjects (14.8%) experienced a mild, 13 subjects (48.1%) moderate and 7 subjects (25.9%) experienced severe TEAE. There were 16 SAEs reported among 7 subjects during the study; none of these SAEs were considered related to study medication.

No TEAEs led to death or withdrawal from the study, and no other significant AEs were Reported.

Overall median trough levels of IgG remained relatively constant during the study. Median trough levels were 12.50 g/L at Screening and 11.76 g/L at End of Study.

*Reviewer Comment: Study met its stated objective.*

## 7. INTEGRATED OVERVIEW OF EFFICACY

### 7.1 Indication #1

Replacement therapy for primary humoral immunodeficiency (PID) in children 2-17 years of age.

#### 7.1.1 Methods of Integration

The studies were analyzed separately rather than together as all subjects in SCGAM 03 were enrolled in SCGAM 01. An integrated efficacy analysis was not felt to be informative given the small sample size and variable duration of follow-up.

## 8. INTEGRATED OVERVIEW OF SAFETY

### 8.1 Safety Assessment Methods

The Applicant provided integrated safety data from the 2 clinical studies, SCGAM-01 and SCGAM-03.

### 8.2 Safety Database

#### 8.2.1 Studies/Clinical Trials Used to Evaluate Safety

Safety data from two prospective clinical trials (*SCGAM-01* and the follow-up *Study SCGAM-03*) conducted by Octapharma were submitted in application package to support expanding indication for use of Cutaquig in subjects with PID from adults to include the pediatric group > 2- <17 years of age.

#### 8.2.2 Overall Exposure, Demographics of Pooled Safety Populations

SCGAM 01: The study was conducted on 39 male subjects and 36 female subjects in the following age groups.

- 12 subjects  $\geq 2$  and <6 years of age (mean 4.2 years.)
- 14 subjects  $\geq 6$  and <12 years of age (mean 7.9 years)
- 12 subjects  $\geq 12$  and <17 years of age (mean 14.1 years.)
- 37 subjects  $\geq 17$  years of age (mean 47.5 years.)

The youngest was 2 years of age and oldest was 73 years. All subjects were White, except for one adult subject who was multiracial.

#### SCGAM 03:

Overall, 10 male subjects and 17 female subjects participated in the study, with a higher proportion of women in the adult age group than in the younger age groups. The youngest subject enrolled was 6 years old and the oldest was 73 years old. The mean age of the adult group was 56.1 years old. The majority of subjects (24 subjects, 88.9%) had common variable immunodeficiency (CVID) as their type of PID.

*Reviewer Comment: SCGAM 03 was a continuation study for US subjects who completed SCGAM01 study. Subjects in Canada were transitioned from another subcutaneous product. Of particular note, no pediatric subjects were enrolled at sites in Canada.*

### 8.2.3 Categorization of Adverse Events

All local infusion site reactions were deemed causally related to Cutaquig in this review. All AEs within 72 hours of Infusion were categorized as Temporally Associated Adverse Event (TAAE)

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

SCGAM 03 was a continuation study for US subjects who completed SCGAM01 study. Subjects in Canada were transitioned from another subcutaneous product. Of particular note, no pediatric subjects were enrolled at sites in Canada.

### 8.4 Safety Results

#### 8.4.1 Deaths

There were no deaths in any of the studies

#### 8.4.2 Nonfatal Serious Adverse Events

In the SCGAM 01 study, 12 SAEs were reported in 9 subjects (12.0%): 2 adults (5.4%), 3 adolescents (25.0%), 3 older children (21.4%) and 1 young child (8.3%) The SAEs were not considered to be related to Cutaquig. No action was taken with the study drug. SAE details are described under discussion of the study in section 6.1

In the SCGAM 03 study, 16 SAEs were reported among 7 subjects (25.9%): 4 adult subjects (23.5%), 2 adolescent subjects (50.0%), and 1 older child (25.0%). No action was taken with the study drug.

SAE details are described under discussion of the study in section 6.2.

#### 8.4.3 Study Dropouts/Discontinuations

In study SCGAM-01 there were no premature discontinuations of Cutaquig or withdrawals due to AEs.

In study SCGAM-03, one subject withdrew from the study “based on the Subject’s and investigator’s decision.”

#### 8.4.4 Common Adverse Events

The most common AEs across the two studies were infusion site reactions (erythema, swelling, redness, pruritis).

#### 8.4.5 Clinical Test Results

In the SCGAM01 study: 6 adult subjects (b) (6) and 1 adolescent (b) (6) had positive Coombs test during the study.

However, none of the subjects who had a confirmed positive Coombs’ test also had a drop in hemoglobin of  $\geq 2$  g/dL and therefore there was no indication of intravascular hemolysis during the study.

Three subjects (b) (6) had leucopenia with WBC ranging from 3.0-3.7. 3 subjects (b) (6) had eosinophilia at various times during the study. Low Hb was noted in 2 subjects (b) (6) - 10.8g/dl; (b) (6) - 9.1g/dl).

5 subjects had elevated transaminases. (ALT- (b) (6) ); AST- (b) (6), (b) (6)).

1 subject (b) (6) had bilirubinemia (2.5mmol/dl) and 1 subject had high LDH (343).

In the SCGAM03 study, 2 adult subjects had pancytopenia (subject (b) (6)), and anemia (Subject (b) (6))

3 subjects had increased transaminases (subjects (b) (6)).

1 adult subject (b) (6) had clinically significant increase in blood urea nitrogen to 131 µmol/L

No seroconversion for viral infections, positive Coomb's test were reported for the study.

#### 8.4.6 Systemic Adverse Events

The most frequent systemic adverse events were infections and headache, pyrexia, diarrhea, dermatitis, asthma, and excoriation

#### 8.4.7 Local Reactogenicity

in SCGAM 01, overall, 73.3% of subjects experienced infusion site reactions, with the highest incidences (78.6% and 81.1%, respectively) in older children and adult subjects. In three-quarters (77.7%) of infusions, there was no infusion site reaction, in one-fifth (20.1%) a mild reaction, in 2.1% a moderate reaction, and a severe reaction was observed in only 4 infusions.

In SCGAM03, overall, 44.4% of subjects experienced infusion site reactions, with the highest incidences in older children (100%) and adolescent subjects (75.0%).

No young children experienced an infusion site reaction.

Of the 12 subjects who experienced at least 1 infusion site reaction, 10 Subjects experienced infusion site reactions of mild intensity. One adolescent (25.0%) and 4 adult (23.5%) subjects experienced infusion site reactions of moderate intensity.

Three adult (17.6%) subjects experienced 19 infusion site reactions of severe intensity.

#### 8.4.8 Adverse Events of Special Interest

No aseptic meningitis, clinical hemolysis, or thromboembolic events (TEEs) were reported in studies SCGAM-01 or SCGAM-03.

No thromboembolic events (TEEs) were reported in study SCGAM-01

1 thromboembolic event (TEEs) was reported in study SCGAM-03 was related to intravenous access in the upper extremity.

### 8.5 Additional Safety Evaluations

#### 8.5.1 Dose Dependency for Adverse Events

Relationship of Infusion flow rate to AEs was noted during the study

#### 8.5.2 Time Dependency for Adverse Events

AEs that began within 72 hours of IP infusion were deemed suspected adverse reactions/adverse reactions regardless of investigator/applicant opinion otherwise

### 8.5.3 Product-Demographic Interactions

Age and Gender differences in infections, rate of antibiotic use is described in sections 6.1 and 6.2 for each individual study.

### 8.5.4 Product-Disease Interactions

Not analyzed

### 8.5.5 Product-Product Interactions

Not analyzed

### 8.5.6 Human Carcinogenicity

Human Carcinogenicity potential was not evaluated in the study. Human carcinogenicity with IGSC products has not been reported in literature.

### 8.5.7 Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Dosing errors (overdose) were recorded as protocol deviation, did not lead to clinical consequences. The IGSC product does not have withdrawal or rebound potential.

### 8.5.8 Immunogenicity (Safety)

Immunogenicity is not routinely assessed in IGSC studies and was not assessed in the three studies with the IP.

### 8.5.9 Person-to-Person Transmission, Shedding

Not applicable.

## 8.6 Safety Conclusions

No new safety signals were observed. The safety profile of Cutaquig appears qualitatively similar to that of other IGSC products licensed in the U.S.

## 9. ADDITIONAL CLINICAL ISSUES

### 9.1 Special Populations

There are insufficient data to conduct sub-group analyses.

#### 9.1.1 Human Reproduction and Pregnancy Data

No clinical studies were conducted in pregnant subjects. Hence, no human data are available to indicate the presence or absence of drug-associated risk.

#### 9.1.2 Use During Lactation

No clinical studies were conducted in lactating subjects. Hence, no human data are available to assess the presence or absence of Cutaquig® in human milk, the effects of Cutaquig® on the breast-fed child, and the effects of Cutaquig® on milk

production/excretion. Immunoglobulins, in particular IgA and IgM, are excreted into the milk.<sup>3</sup>

### 9.1.3 Pediatric Use and PREA Considerations

Pediatric data submitted were incomplete and inadequate to support a pediatric labeling claim at that time of the original BLA approval on Dec 12, 2018. The applicant conducted an assessment for pediatric Subjects older than 2 years old to less than 17 years of age in response to an outstanding PREA PMR this BLA.

Deferred Pediatric Study Timelines:

Final Protocol Amendment Submission: January 31, 2019

Study Completion Date: August 31, 2020

Final Report Submission Date: December 31, 2020

The applicant submitted an Efficacy Supplement to support the addition of the pediatric population to the indicated treatment of PI (originally approved for adults only). As shown in the table below, the new studies included more pediatric subjects than agreed upon in the iPSP/PMR.

**Table 23:Enrolled Pediatric Subjects - Actual (PMR)**

Age Range	Subjects (n) enrolled in Pharmacokinetic study (PMR Requirement)	Subjects (n) enrolled in Safety and Efficacy study (PMR Requirement)
>2 - <6 Years	5 (2)	12 (4)
>6 -<12 years	8 (6)	14 (10)
>12-<17 years	6 (4)	12 (6)

Efficacy was demonstrated because there were no SBIs noted in children during the study and the efficacy results exceed the minimum threshold outlined in the agency guidance document. The rate of other infections (classified as nonserious) per person-year was 3.275 overall (upper 95% CI: 4.253).

Three-quarters of the infections in the primary observation period were mild and one-quarter moderate in intensity with upper respiratory tract being reported most frequently. The median time to resolution of infections was 9 days, with longer times for moderate infections (14 days) than mild infections (8 days). There were 4 pediatric hospitalizations due to infections during the study; the number of days in hospital per person-year in the primary observation period was 0.411 days. Although the overall infection rate was comparable to those seen in adult population, upper respiratory and gastrointestinal

3 Hurley WL and Theil PK. Perspectives on Immunoglobulins in Colostrum and Milk. *Nutrients* 2011; 3:442-474

infections were more common in children and lower urogenital infections were more commonly observed in adults in the aggregated data from the two studies.

Safety: No deaths were reported. No treatment emergent adverse events led to withdrawal from the study or discontinuation of product. There were 10 serious adverse events (in the pediatric age group). The narrative summaries for the reported SAEs in the pediatric population were reviewed and adjudicated to be not related to product administration. No other concerning safety signals were noted. There were no treatment emergent adverse events leading to death or withdrawal from the study, however, 93% of subjects had at least one adverse event and the most common was infusion - associated reaction, occurring in 73.3% of subjects. The safety findings were similar across the different age ranges of children, and overall, the findings in the pediatric population appear similar to those seen in the adult population.

Pharmacokinetic Study results were comparable to adult data and no dosage changes were required by age group.

The pediatric data was presented to Pediatric Review Committee (PeRC) on July 20, 2021. The PeRC agreed with the assessment and fulfillment of the PREA PMR.

#### 9.1.4 Immunocompromised Subjects

Cutaquig® is indicated for primary immunodeficiency.

#### 9.1.5 Geriatric Use

There were only 3 geriatric subjects in this development program precluding any conclusions regarding efficacy and safety in this subpopulation.

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

N/A.

### 10. CONCLUSIONS

The applicant conducted pediatric PK, efficacy and safety studies in children 2-17 years of age to fulfill their PREA PMR obligations. The clinical studies were completed in accordance with FDA guidance "Safety, efficacy and PK studies to support marketing of IGIV (human) as replacement therapy for IGIV products" and the protocol was agreed upon with the Agency. A total of 38 children were enrolled in the pivotal study, SCGAM01, and 10 children were enrolled in SCGAM03, the extension study. Efficacy of Cutaquig in preventing SBI was demonstrated as there were no SBIs (99% upper one-sided CI 0.13), which is less than the pre-defined success criteria of <1.0 per subject-year of follow up based on historical data. The PK data and modeling confirmed a DCF of 1.3; pharmacokinetics was comparable between children and adults. Safety data demonstrated that Cutaquig was generally well tolerated in children. There were no new safety signals identified. Children had a similar safety profile to adults receiving Cutaquig and to children receiving other SCIGs. These studies and resulting data are sufficient to fulfill the PREA PMR and to expand the labeled indication to include children with PID who are at least 2 years of age.

## 11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

### 11.1 Risk-Benefit Considerations

The benefit-risk for Cutaquig in children 2-17 years of age with PID is favorable. Please see table below for detailed risk-benefit analysis.

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	<ul style="list-style-type: none"> <li>Primary Immunodeficiency (PID) represents a heterogeneous group of disorders resulting from inherited defects of the immune system. The major 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.</li> <li>Patients with PI are at increased risk for recurrent, severe respiratory tract infections (both viral and encapsulated bacterial in origin, particularly infections due to Pneumococcus and Hemophilus Influenza) as well as other infections.</li> </ul>	<ul style="list-style-type: none"> <li>PID are serious, chronic conditions associated with considerable morbidity and mortality.</li> <li>Immunoglobulin replacement therapy (administered by the intravenous or subcutaneous routes) has been shown to reduce the incidence of serious infections through provision of passive immunity.</li> </ul>
Unmet Medical Need	<ul style="list-style-type: none"> <li>Numerous marketed immune globulin products (both intravenously and subcutaneously administered) have demonstrated serious bacterial infection (SBI) rates of less than 1.0 per person-year. There are currently six licensed Immune Globulin Subcutaneous (Human) (IGSC) products in the U.S. for PID: Cuvitru® (Baxalta US, Inc.), Hizentra® (CSL Behring), and Vivaglobin® (CSL Behring), Xembify® (Grifols USA), Hyqvia® (Baxter Healthcare Corporation, Baxter BioScience), Cutaquig (Octapharma).</li> <li>Cuvitru, Hizentra, Vivaglobin and Xembify are approved for children &gt;2 years of age and Hyqvia is for adolescents (&gt;12 years of age).</li> </ul>	<ul style="list-style-type: none"> <li>Currently, there is no unmet medical need.</li> <li>There is potential for supply chain disruptions and shortages, so there is a public health benefit for having additional approved immunoglobulin replacement products on the market.</li> </ul>
Clinical Benefit	<ul style="list-style-type: none"> <li>SCGAM01: A prospective, open-label, single-arm, externally controlled, multicenter study that included 38 children (2-16 years) to assess efficacy, safety and PK over 12 months following a washout trial. The study design is consistent with FDA guidance for Immune Globulin products for PID. SCGAM03: A similarly designed extension study that included 10 children from SCGAM01.</li> <li>No serious bacterial infections (SBIs) were reported in any of the children, the upper bound of the 1-sided 99% confidence interval for the rate of SBI was &lt; 1 per subject/year of follow-up.</li> <li>Children treated with Cutaquig had similar rate of missed school/work/daycare, hospitalizations due to infections, antibiotic use and annual rate of infection to other IGSC approved for children.</li> <li>PK parameters were comparable between adults and children.</li> </ul>	<ul style="list-style-type: none"> <li>The product is effective at preventing SBIs in children 2-17 years old.</li> </ul>
Risk	<ul style="list-style-type: none"> <li>The most common AR in children treated with Cutaquig were infusion site reactions (erythema, swelling, pruritus), the majority of which were mild and occurred less frequently in children than adults.</li> <li>The most common systemic AR seen in &gt;5% of children were cough, vomiting, asthma, nasal congestion, fever, headache, ALT increased, leukopenia, neutropenia, dermatitis, urticaria, abdominal pain, AST increased, oropharyngeal pain and ear pain.</li> <li>There were no deaths, or AESI attributed to Cutaquig.</li> </ul>	<ul style="list-style-type: none"> <li>The infusion reactions were less common in pediatric population compared to adults, but in general the risks are similar between children in adults.</li> <li>Risks with Cutaquig are similar to other SCIG products</li> </ul>
Risk Management	<ul style="list-style-type: none"> <li>Subcutaneous immune globulin products carry an obligate boxed warning for thrombosis.</li> <li>Warnings and Precautions class labeling for SCIG include hypersensitivity and anaphylaxis, aseptic meningitis, renal dysfunction and acute renal failure, hemolysis, TRALI and transmission of infectious agents.</li> </ul>	<ul style="list-style-type: none"> <li>Labeling and routine pharmacovigilance are appropriate</li> <li>Patients should be monitored for signs and symptoms of hypersensitivity, thrombosis, aseptic meningitis, renal dysfunction, hemolysis, and TRALI</li> </ul>

		<ul style="list-style-type: none"><li>• Patients should be informed that Cutaquig is manufactured from human plasma and carries the risk of transmission of infectious agents</li></ul>
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### 11.2 Risk-Benefit Summary and Assessment

Given the substantial morbidity and mortality risk from SBI in PID, Cutaquig prevented SBI in children in an appropriately designed study and was generally well tolerated in children. The safety profile of Cutaquig in children is consistent with what was seen in adults and with other SCIG therapies. Therefore, we believe that Cutaquig has a favorable benefit-risk profile for children 2-17 years with PID.

### 11.3 Recommendations on Regulatory Actions

The Applicant has met the statutory standards and has provided substantial evidence of effectiveness and safety from a single adequate and well controlled study with confirmatory evidence from an extension study to support the expansion of the indication to pediatric patients. The clinical review team recommends approval of the sBLA to expand the indication for Cutaquig to patients 2 years old and above with PID and recommends considering the PREA PMR fulfilled.

### 11.4 Labeling Review and Recommendations

The primary changes to the label include:

- Updates to Indication and Usage (section 1) to expand the age to patients with PID who are 2 years of age and older.
- Updates to Dosage and Administration (sections 2.1 and 2.3) to provide details on the pediatric dose and modifications to the dose adjustment factor.
- Updates to Adverse Reactions (section 6), to include the new pediatric data and to update the adult safety information based on new data from the extension study.
- Updates to Pediatric Use (Section 8.4) to state safe and effective for children who are at least 2 years of age and provide general information to support use in children
- Updates to Clinical Studies (Section 14) to include new data from clinical studies, including pediatric data.

Please see label for additional details.

### 11.5 Recommendations on Post-marketing Actions

Routine pharmacovigilance is appropriate for this product. There is no need for any new PMCs/PMRs.